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Pyrolytic and Photolytic Decomposition of Trityl β-Naphthoate[1]

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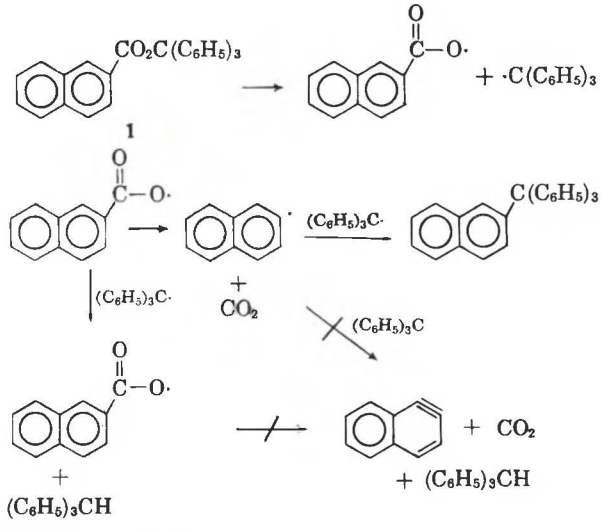
Pyrolysis of trityl β-naphthoate was investigated over the range 250–350° in a static system. Although the decomposition was examined after long time intervals, the process was essentially complete within an interval of 1.5 hr. Both acyl–oxygen and alkyl–oxygen bond severance occurred as evidenced by the major products, β-naphthoic acid, β-naphthoic anhydride, triphenylmethane (tritane), and two polymers, one a hydrocarbon and the other a polyester. Minor products observed were carbon dioxide, carbon monoxide, water, naphthalene, benzophenone, 9-phenylfluorene, and an unknown gas. Oxidation of the melt resulted in a marked increase in benzophenone. Although photolysis of the ester in an oxygen atmosphere resulted in limited decomposition, benzophenone was identified in the photolysate. A radical mechanism is postulated to explain the data.

As part of a program to elucidate the chemistry of aroyloxy radicals generated under pyrolytic conditions, trityl β-naphthoate was considered important since little has been published on β-naphthoxyloxy radicals. In view of the preference of trityl radical to abstract hydrogen rapidly at elevated temperatures,[3] naphthyne was envisioned as a possible intermediate *via* removal of the α-hydrogen and loss of carbon dioxide.[4,5] Moreover, trityl β-naphthalene is a conceivable product since the homolog, trityl benzoate, is recorded to decompose at 235° with tetraphenylmethane formed in moderate yields.[6,7] The simplicity of decomposition as depicted in Scheme I was not observed, however.

Trityl β-naphthoate (1) was prepared by an extension of the method described previously.[8] Recently we reported the pyrolysis of several trityl alkyl carboxylates from which acyl–oxygen and alkyl–oxygen bond cleavages were observed.[3] Thermal decomposition of 1 was conducted in a static system over the range 250–350° under nitrogen. It was discovered that the ester decomposed completely within 1.5 hr. near 350°.

SCHEME I



Major products were β-naphthoic acid, β-naphthoic anhydride, tritane, and two polymers (A and B). Small amounts of several other compounds also were observed as shown in Table I.

Molecular models indicate the ester to be quite hindered with carbonyl oxygen atom in close proximity to an orthohydrogen on the phenyl ring of the trityl moiety. High yields of β-naphthoic acid suggest cleavage of ester in such a manner that the acid is formed rapidly. A concerted mechanism for the decomposition is conceivable as shown, although initial homolytic alkyl–oxygen fission is possible perhaps to give radical pairs. β-Naphthoyloxy radical has been reported as unstable in boiling carbon tetrachloride.[6] In regard to the thermal stability of β-naphthoyloxy radical, pyrolysis of β-naphthoyl peroxide occurred vigorously.

(1) (a) We gratefully acknowledge the generous support of the National Science Foundation, Grant 19733; (b) the paper was presented in part at the Southwest Regional Meeting of the American Chemical Society, Dec., 1963, Houston, Tex.

(2) Dow Chemical Company Predoctoral Fellow, 1963-1964.

(3) K. D. Berlin, L. H. Gower, B. S. Rathore, G. P. Sturm, J. W. White, J. B. Richards, and M. Peterson, *J. Org. Chem.*, **28**, 2039 (1963).

(4) A discussion of possible benzyne-type intermediates in ester pyrolysis can be found in the literature [P. E. Reininger and P. D. Ritchie, *J. Chem. Soc.*, 2678 (1963)].

(5) It is recorded that β-naphthoyl peroxide decomposes in carbon tetrachloride to give several decarboxylated naphthalene derivatives [see M. S. Kharasch and R. L. Dannley, *J. Org. Chem.*, **10**, 406 (1945)].

(6) E. Jones and P. D. Ritchie, *J. Chem. Soc.*, 4141 (1960).

(7) Noteworthy is the isolation of tetraphenylmethane (20–30%) from the reaction of trityl radical with benzoyl peroxide [see G. S. Hammond, J. T. Rudesill, and F. J. Modic, *J. Am. Chem. Soc.*, **73**, 3929 (1951)].

(8) K. D. Berlin, L. H. Gower, J. W. White, D. E. Gibbs, and G. P. Sturm, *J. Org. Chem.*, **27**, 3595 (1962).

TABLE I

PYROLYSIS OF TRITYL β-NAPHTHOATE (UNDER NITROGEN)[a]

Products	Wt., g.	Mole % of ester
Carbon dioxide	0.0799	3.63
Carbon monoxide, Naphthalene, Water, Unknown gas	0.1723	
β-Naphthoic acid	5.8795	68.4
β-Naphthoic anhydride	0.865	10.6
Tritane	4.6672	38.2
9-Phenylfluorene	0.1938	1.6
Benzophenone	0.0073	0.008
Polymer A	2.137	17.4
Polymer B	4.80	
Tar	0.683	
	19.485	
Wt. of ester	20.700	

[a] Temperature, 345–350°; time, 1.5 hr.

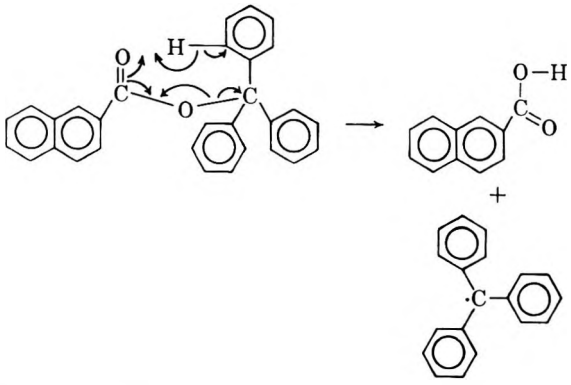
TABLE II

PYROLYSIS OF β-NAPHTHOYL PEROXIDE[a]

Products	Wt., g.	Mole % of peroxide
Carbon dioxide	0.1225	27.8
β-Naphthoic acid	0.768	44.6
Naphthalene	Traces	
Residue	0.510	
	1.4005	
Wt. of peroxide	1.710	

[a] Temperature, 107–109°; time, 10 min.

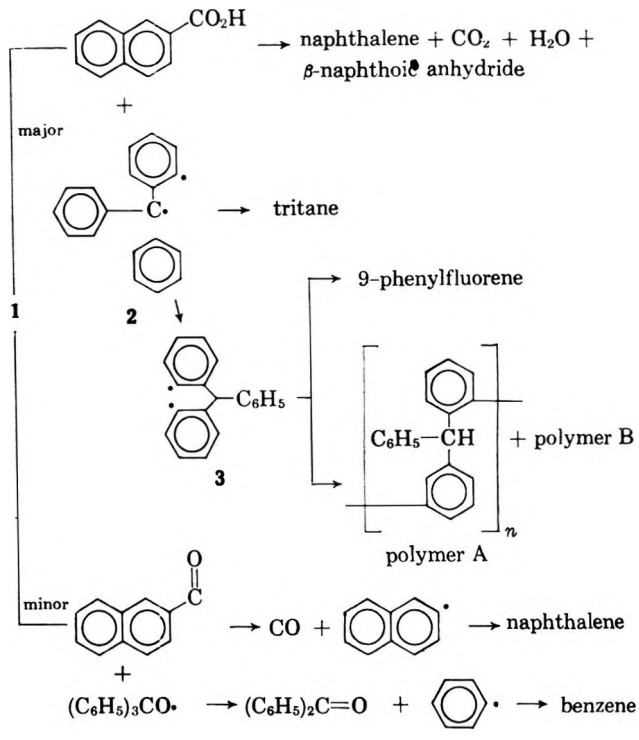
109° to yield β-naphthoic acid and carbon dioxide (Table II). Apparently β-naphthoyloxy radicals decay by removing a hydrogen from the naphthalene ring in a fast reaction. Consequently, the reactivity of this aroyloxy radical would be enhanced at pyrolysis temperature as would the rate of decarboxylation. Since very little carbon dioxide is evolved, it is doubtful that



naphthoyloxy radicals are entirely free, and hence formation of a biradical and naphthoic acid is proposed as the mechanism rather than the cleavage of the ester into β-naphthoyloxy and trityl radicals. A biradical intermediate has been postulated previously from the decay of trityl radical.[9] It is suggested that a similar highly reactive biradical 2 is formed which rearranges to another biradical 3. Intramolecular coupling of this biradical would give 9-phenylfluorene or the former could polymerize to polymer A. Scheme II is proposed to account for most of the products. Tar also is obtained, and very probably its precursor may furnish

(9) R. L. Letsinger, R. Collat, and M. Magnusson, *J. Am. Chem. Soc.*, **76**, 4185 (1945).

SCHEME II



hydrogen for trityl radicals to give tritane. Formation of naphthoic anhydride, naphthalene, carbon dioxide, and water is thought to result from secondary pyrolysis of β-naphthoic acid.[10] This conclusion is supported by the fact that pyrolysis of β-naphthoic acid gave identical products in nearly proportionate mole ratios with 69% recovery of the acid (Table III).

TABLE III

PYROLYSIS OF β-NAPHTHOIC ACID[a]

Products	Wt., g.	Mole % of acid
Naphthalene, Carbon dioxide, Water	0.146	
β-Naphthoic anhydride	1.040	24.4
β-Naphthoic acid	3.106	69.0
	4.292	
Wt. of acid	4.502	

[a] Temperature, 345–355°; time, 1.5 hr.

Elemental analysis of polymer A confirmed its hydrocarbon skeleton with an empirical formula of $C_{19}H_{14}$. Strong absorption in the infrared at 700 and 745 cm.$^{-1}$ implies the presence of mono- and *ortho*-substituted phenyl groups.

A comparison of the ultraviolet spectrum of polymer A with that of 9-phenylfluorene and 2,2′-dimethylbiphenyl showed remarkable similarities as might be expected (Table IV). Additional support for the postulated structure of polymer A was gained by examination of the n.m.r. spectrogram which displayed a complex multiplet at δ 7.18 and a singlet at 5.46. The latter is nearly identical with the field position of the tertiary hydrogen in tritane.

(10) Decarboxylation of β-naphthoic acid by distillation with barium hydroxide has been reported by M. Merz [*Z. Chem.*, **12** 72 (1869)]. However, a survey of the literature revealed that pyrolysis of β-naphthoic acid by itself or its esters has not been studied previously.

TABLE IV

A COMPARISON OF ULTRAVIOLET SPECTRA[a]

Polymer A	9-Phenylfluorene	2,2′-Dimethylbiphenyl
240	236	230 9
269	268	264
280	276	273

[a] Values are given in mμ.

Polymer B did not give consistent analytical results even with samples that had been fractionated repeatedly. Infrared absorption at 1739 cm.$^{-1}$ suggests a carbonyl group, but it is apparently hindered since the polymer resisted boiling alkali, Girard T reagent, and boiling alkaline potassium permanganate. Certainly, if it is an ester function it is not on a terminal position, since it is saponified rapidly by dilute base.

In an effort to learn the fate of tritane in the presence of β-naphthoyloxy radical, the hydrocarbon was heated at 145° in the presence of β-naphthoyl peroxide.[11] Although decarboxylation and formation of naphthoic acid were recorded, nearly 90% tritane could be recovered. Minor products detected were tritanol, β-naphthyl β-naphthoate, and trityl peroxide (Table V).

TABLE V

PYROLYSIS OF β-NAPHTHOYL PEROXIDE WITH TRITANE[a]

Products	Wt., g.	Mole % of peroxide
Carbon dioxide	0.136	30.9
β-Naphthoic acid	0.525	30.5
Tritanol	0.05	
Trityl peroxide	Traces	
β-Naphthyl β-naphthoate	0.05	
Benzophenone	Trace	
Naphthalene	Trace	
Tritane	2.14	87.7%
Residue	0.08	(Recovered)
Wt. of peroxide	1.71	
Wt. of tritane	2.44	

[a] Temperature, 142–145°; time, 60 min.

Formation of peroxide probably occurs through oxidation of trityl radical. The infrared spectrum of the small residue was identical in nearly all respects with the residue obtained from static pyrolysis of β-naphthoyl peroxide. It was noted that this residue possessed a different structure from that of polymer A or B. However, the data indicate that tritane is attacked by the β-naphthoyloxy radical which may account to a small extent for the product distribution in the pyrolysate of **1**.

Photolysis of **1** in boiling benzene with an oxygen stream directed into the solution resulted in partial decomposition of the ester to give tritanol, benzophenone, and β-naphthoic acid. Oxidation of the ester **1** at 350° resulted in a remarkable increase in the yield of benzophenone compared to the static pyrolysis under nitrogen. Clearly these products suggest initial homolytic fission in the ester.

Both polymer A and 9-phenylfluorene were conspicuously absent from the oxidation at high temperature. However, a new material, polymer C, was isolated from the pyrolysate. Formation of polymer C *via* oxidation of polymer B determined the origin of the former (Table VI). The similarities between the photolytic and pyrolytic decompositions of **1** suggest a radical pathway of decay following initial homolysis of the alkyl–oxygen bond.

TABLE VI

PYROLYSIS OF TRITYL β-NAPHTHOATE (IN OXYGEN)[a]

Products	Wt., g.	Mole % of ester
Carbon dioxide	0.075	7.35
Naphthalene, Water	0.065	
β-Naphthoic acid	2.601	65.3
β-Naphthoic anhydride	0.380	10.0
Tritane	1.620	28.9
Benzophenone	0.445	10.55
Polymer C	2.601	
Insoluble residues	0.310	
	8.097	
Wt. of ester	9.5795	

[a] Temperature, 345–355°; time, 1.5 hr.

Experimental[12]

Preparation of Trityl β-Naphthoate (1).—Trityl bromide (16.1 g., 0.05 mole) and sodium β-naphthoate (10.9 g., 0.056 mole) in 70 ml. of benzene were boiled for 39 hr. The contents were filtered while hot, and the filtrate was concentrated to an oil. About 15 ml. of isopropyl ether was added and the contents were concentrated again. A pale yellow solid was obtained which was washed with about 25 ml. of isopropyl ether containing 2 ml. of triethylamine: yield 17.7 g. (86.7%), m.p. 146–149°. Recrystallization from isopropyl ether raised the melting point to 149–150°; infrared spectrum (KBr): 3030, 1724, 1282, 781, 763, 743, and 714–689 cm.$^{-1}$ (broad).

Anal. Calcd. for $C_{30}H_{22}O_2$: C, 86.95; H, 5.31. Found: C, 86.59; H, 5.39.

Pyrolysis of Trityl β-Naphthoate in Nitrogen.—The pyrolysis was studied in a static system using a salt bath (potassium nitrate, sodium nitrate mixture) preheated to 350° and which was removed at the end of the heating period (1.5 hr.). On cooling, the contents set to a hard solid mass which was dissolved in 200–300 ml. of carbon tetrachloride, and the solution was poured into 500 ml. of Skelly F. The contents were then concentrated to dryness. The yellow mass obtained was extracted with Skelly F in a Soxhlet extractor.

The Skelly F extract contained tritane, benzophenone, 9-phenylfluorene, and polymer A, all of which were separated by chromatography on acid-washed alumina. 9-Phenylfluorene was identified by its infrared spectrum.[13] Extraction of the residue with sodium bicarbonate removed the free acid. The new residue obtained was essentially polymer B and β-naphthoic anhydride with small amounts of tritane, benzophenone, 9-phenylfluorene, and polymer A. This residue was further fractionated by extraction with Skelly B. The Skelly B insoluble solid softens at 260° and turns brown near 270–280° with no sharp melting point. Extraction of this residue with methanol gave only a tar that was absorbed by charcoal. Reprecipitation of this solid from a carbon tetrachloride solution with ethanol gave fractions which melted above 300°. Concentration of the Skelly B extract gave lower melting fractions of polymer B (identical infrared spectra), which were filtered. The filtrate was then evaporated to dryness and the residue was extracted with methanol. Evaporation of the methanolic extract to dryness gave a semi-

(11) Wieland has studied the pyrolysis of benzoyl peroxide in the presence of tritane and observed the formation of benzoic acid, trityl benzoate, and carbon dioxide in high yield [see H. Wieland, T. Ploetz, and H. Indest, *Ann.*, **532**, 179 (1937)].

(12) Carbon dioxide was determined by absorption in an ascarite tube. Vapor phase chromatographic (v.p.c.) analyses were done on a Wilkens Model A-550 Hy Fi hydrogen flame unit using a column of silicone rubber, 10% on Chromosorb W., 80–100 mesh, 8 ft. × ¼ in. Infrared spectra were recorded on a Beckman IR-5 instrument. N.m.r. spectra were recorded on a Varian A-60 high resolution spectrometer. Tetramethylsilane was used as an internal standard with its scale as 0 in δ units. Skelly F is petroleum ether, b.p. 35–45°. Skelly B is petroleum ether, b.p. 60–70°. Microanalyses were done by Midwest Microlab, Inc., Indianapolis, Ind.

(13) An authentic sample was kindly supplied by Mr. James Rea, Department of Chemistry, University of Missouri, Columbia, Mo.

solid residue. This was treated with Girard T reagent to remove benzophenone. The residual material was refluxed with aqueous sodium hydroxide (25 ml. of 10% solution) to hydrolyze the anhydride or any ethyl or methyl ester that might have formed during the work-up. Acidification with concentrated hydrochloric acid gave β-naphthoic acid. The base-insoluble portion was chromatographed over alumina to yield tritane, 9-phenylfluorene, and polymer A. The products are listed in Table I.

Polymer A.—This material was soluble in ethanol and could be separated into different fractions by fractional precipitation from an ethanolic solution with water. Melting ranges of fractions varied from 80–144°. The polymer softened to a glassy bead which could be tapped from the melting point capillary tube. Molecular weight determination[14] on a fraction with melting range of 132–144° gave values of 598–600 in benzene solution; infrared spectrum (KBr): 3030, 1600, 1492, 1449, 1034, 744, and 700 cm.$^{-1}$.

Anal. Calcd. for an empirical formula $C_{19}H_{14}$: C, 94.01; H, 5.78. Found: C, 93.66; H, 5.78.

Polymer B.—Fractions with melting ranges varying from 150–300° were isolated during the work-up; infrared spectrum (KBr): 3030, 1739, 1600, 1492, 1449, 1279, 1187, 1034, 744, and 700 cm.$^{-1}$.

Anal. Found for fraction melting at 233–252°: C, 88.96; H, 5.18. Found for fraction melting above 300°: C, 91.75; H 5.25.

Pyrolysis of Trityl β-Naphthoate Using Oxygen.—Pyrolysis was effected in the same system as above with the exception that oxygen was bubbled into the melt. Traces of naphthalene were detected as sublimate in the condenser. After cooling, the residue was dissolved in benzene and extracted with cold sodium bicarbonate to remove the free acid. The anhydride was hydrolyzed and removed by boiling the solution with aqueous sodium hydroxide solution. V.p.c. analysis of the solution showed only benzophenone and tritane as the volatile components. Benzophenone was leached by treatment with Girard T reagent, and tritane was isolated by chromatography on alumina. The final residue was chiefly polymer C. Table VI contains all products.

Pyrolysis of β-Naphthoic Acid.—β-Naphthoic acid was pyrolyzed in the same system. After removal of the free acid by extraction with cold sodium bicarbonate, the residue was characterized and shown to be β-naphthoic anhydride, m.p. 136–137°, lit.[15] m.p. 133–134°.

Pyrolysis of β-Naphthoyl Peroxide.[16]—The flask containing the peroxide was heated cautiously to 107° in an oil bath. The contents softened slightly and decomposed vigorously after heating at 107–109° for 10 min. Heating was stopped and the oil bath was removed. β-Naphthoic acid was extracted with base and left an orange solid containing a trace of naphthalene and an unknown substance which showed carbonyl absorption at 1724 and 1695 cm.$^{-1}$ in the infrared spectrum. This material resisted all attempts at purification by recrystallization or sublimation. Table II shows all products.

Pyrolysis of β-Naphthoyl Peroxide with Tritane.—The two components in the molar ratio 1:2 were carefully powdered and transferred to the pyrolysis flask. The contents slowly were heated to 142° over a period of 1 hr. during which time some effervescence was observed. Further heating for 1 hr. was done at 142–145°. After removal of the acid, the base-insoluble residue was chromatographed over alumina. The various products are listed in Table V.

Photolysis of Trityl β-Naphthoate.—Photolysis of the ester in benzene with oxygen bubbling into the solution was studied over a period of 72–93 hr. A type 30620 Hanovia lamp (140 watts) was used. The infrared spectrum of the crude photolysate indicated β-naphthoic acid. The contents then were refluxed with a solution of 5 g. of sodium hydroxide in 50 ml. of water. The nonacid portion was found to be tritanol containing a small quantity of benzophenone as identified by v.p.c.

(14) We acknowledge our thanks to Dr. Paul O. McCoy, Department of Chemistry, University of Oklahoma, Norman, Okla., for the molecular weight determination.

(15) O. Hausamann, *Ber.*, **9**, 1515 (1876).

(16) Crude peroxide melting at 120–125° was used. Pure peroxide decomposes explosively at 138°.

Multinuclear Ferrocenes. III. Acetylation of Biferrocenyl[1-3]

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Received October 16, 1963

Acetylation of biferrocenyl with acetic anhydride in the presence of polyphosphoric acid provides all three possible monoacetylbiferrocenyl position isomers as well as three isomeric diacetylbiferrocenyls. Structure assignments for all products are made on the basis of n.m.r. analysis, while previous infrared and ultraviolet spectral correlations for disubstituted ferrocenes are examined. In spite of the fact that the ferrocenyl group has been established as a strong electron donator, competitive acetylation of ferrocene and biferrocenyl in the present work shows that biferrocenyl is less susceptible to electrophilic substitution than is ferrocene. This apparent inconsistency is explicable in terms of a rapid equilibrium in which the iron atom of one ferrocene nucleus in biferrocenyl is bonded to electrophile, thus deactivating the molecule.

With the availability of methods of synthesis much better than that used in its initial preparation,[4] notably the Ullmann-type coupling of iodoferrocene,[5,6] study of biferrocenyl became a practical undertaking, and we began investigations into the chemistry of this molecule. Since the biferrocenyl molecule may be viewed as a ferrocene nucleus bearing a ferrocenyl substituent, we were interested initially in learning its reactivity relative to ferrocene itself as well as the possibility of obtaining information regarding the existence of any preferred pattern of orientation during electrophilic substitution.

Results and Discussion

A. Relative Reactivity.—In several instances the ferrocenyl group has been shown to possess strong electron-donating ability. Thus, ferrocenylbenzoic acids and ferrocenylphenols are weaker acids than benzoic acid and phenols, respectively, and *m*- and *p*-ferrocenylanilines are stronger bases than aniline itself.[7] The remarkable stability of a ferrocenylcarbinyl

(1) Previous paper: S. I. Goldberg and R. L. Matteson, *J. Org. Chem.*, **29**, 323 (1964).

(2) We are pleased to acknowledge generous support of this work by the National Science Foundation, Grant G-24083. We also wish to express additional thanks to that agency for the 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 J. S. Crowell, University of South Carolina, 1963.

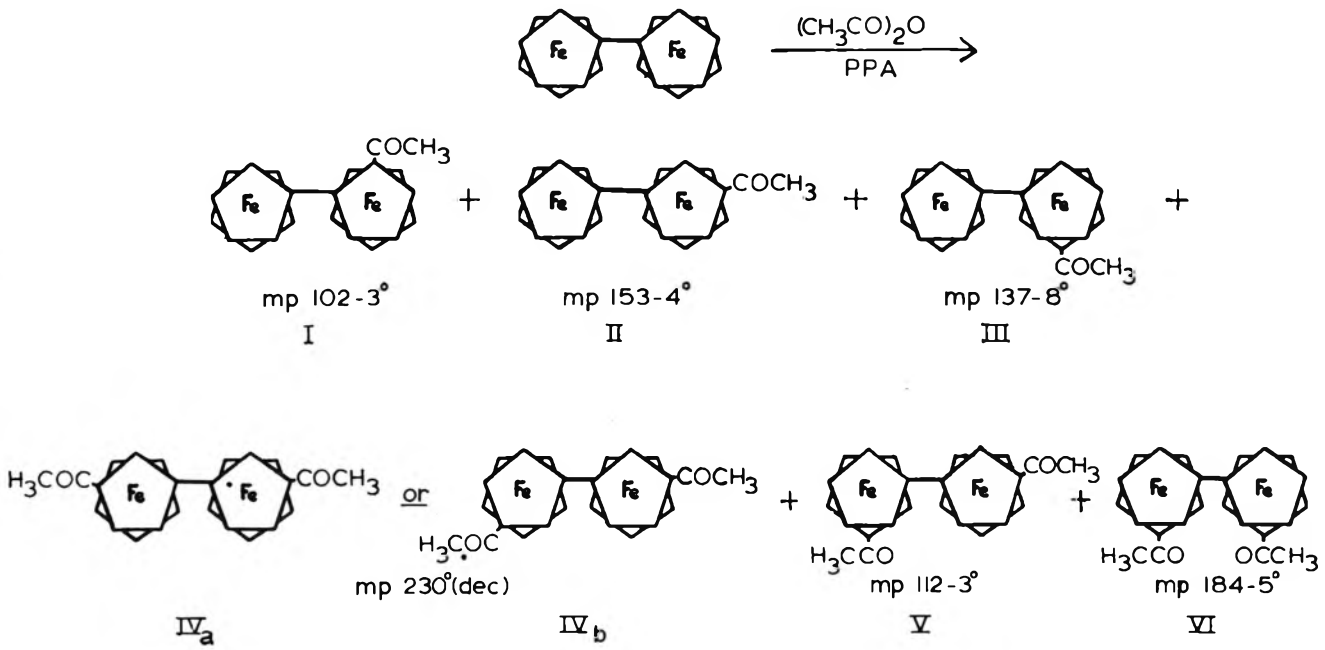
(4) S. I. Goldberg and D. W. Mayo, *Chem. Ind.* (London), 671 (1959).

(5) E. G. Perevalova and O. A. Nesmeyanova, *Dokl. Akad. Nauk SSSR*, **132**, 1093 (1960).

(6) M. D. Rausch, *J. Org. Chem.*, **26**, 1802 (1961).

(7) A. N. Nesmeyanov, E. G. Perevalova, and R. V. Golovnya, *Dokl. Akad. Nauk SSSR*, **103**, 81 (1958); *cf.* A. N. Nesmeyanov, *Proc. Roy. Soc.* (London), **246**, 495 (1958).

SCHEME I

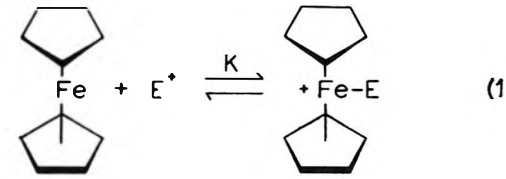


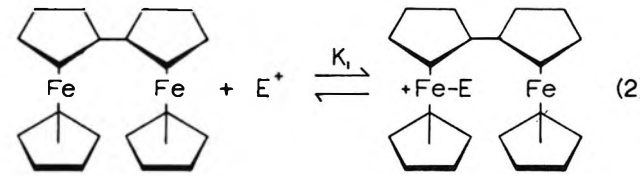
carbonium ion[8] also may be taken as an indication of the strong electron-donating ability of the ferrocenyl group; and the fact that the oxidation potential of biferrocenyl falls in between that of ethylferrocene and methoxyferrocene[9] is also in accord with this view. It was, therefore, expected that biferrocenyl would be found to be more susceptible to electrophilic substitution than ferrocene, and we were surprised to find this expectation not to be met by experimental trial.

Equal molar amounts of ferrocene and biferrocenyl were allowed to compete for a molar equivalent amount of acetyl chloride in the presence of aluminum chloride under mild conditions. Careful work-up of the reaction mixture provided 92% recovery of biferrocenyl, but only 64% recovery of ferrocene. In addition, it was shown that acetylferrocene comprised 61% (by weight) of the acetylated material obtained from the reaction.

A further indication of the greater substitution ability of ferrocene is the fact that 51% of biferrocenyl was recovered from the acetylation mixture of acetic anhydride and polyphosphoric acid under conditions in which ferrocene gives rise to 71% yield of acetylferrocene.[10]

Thus, in spite of the fact that the ferrocenyl group is strongly electron donating, a ferrocene nucleus bearing a ferrocenyl group (biferrocenyl) undergoes electrophilic substitution to a lesser extent than does ferrocene. Yet, this is not inconsistent, when viewed in terms of an interpretation (eq. 1 and 2) which recognizes the strong electron-donating ability of the ferrocenyl group, in that biferrocenyl is *more* susceptible to electrophilic attack than ferrocene, but initial attack is on *iron*,[11a] and the biferrocenyl nucleus is rendered less prone to substitution on carbon. Since attack on iron is presumably an equilibrium step,[11a] the rate of substitution on carbon will be governed by the equilibrium concentration of uncharged species. In other words, because of the greater nucleophilic character of biferrocenyl, K_1 would be expected to be larger than K, and the results of the competition experiment may be explained by the presence of a greater concentration of uncharged ferrocene available for electrophilic attack on carbon.





B. Substitution Products of Biferrocenyl.—While treatment of biferrocenyl with acetic anhydride in the presence of polyphosphoric acid during 10 min. in a boiling water bath afforded incomplete reaction of biferrocenyl (51% recovery of starting material), a variety of acetylated products was obtained.[11b] The mixture of products was submitted to elution chromatog-

(8) E. A. Hill and J. H. Richards, *J. Am. Chem. Soc.*, **83**, 4216 (1961).

(9) E. G. Perevalova, A. N. Nesmeyanov, and S. P. Gubin, Abstracts A, XIXth International Congress of Pure and Applied Chemistry, London, 1963, p. 187.

(10) P. J. Graham, R. V. Lindsey, G. W. Parshall, M. L. Peterson, and G. M. Whitman, *J. Am. Chem. Soc.*, **79**, 3416 (1957).

(11) (a) M. Rosenblum and J. O. Santer, *ibid.*, **81**, 5517 (1959); T. J. Curphey, J. O. Santer, M. Rosenblum, and J. H. Richards, *ibid.*, **82**, 5249 (1960); A. Berger, W. E. McEwen, and J. Kleinberg, *ibid.*, **83**, 2274 (1961); W. F. Little, R. A. Berry, and P. Kannan, *ibid.*, **84**, 2525 (1962); M. Rosenblum, J. O. Santer, and W. G. Howells, *ibid.*, **85**, 1450 (1963). (b) NOTE ADDED IN PROOF.—Since submission of this paper an account of the work of A. N. Nesmeyanov, V. N. Drozd, V. A. Sazonova, V. I. Romanenko, A. K. Prokof'ev, and L. A. Nikonova [*Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 667 (1963)] has appeared [*Chem. Abstr.*, **59**, 7556*E* (1963)] containing a report of results obtained from acetylation of biferrocenyl. The Russian authors observed only three acetylation products: 3-acetylbiferrocenyl, 1′,6′-diacetylbiferrocenyl (compounds II and VI of the present investigation—both previously obtained by independent synthesis[1]), and a triacetylbiferrocenyl, m.p. 143–144°

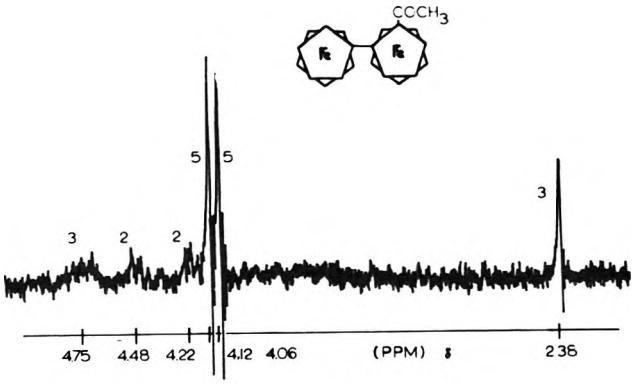


Figure 1

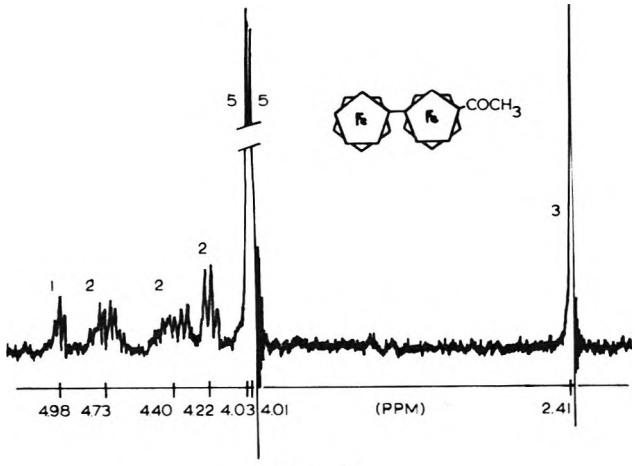


Figure 2

raphy on alumina, and each product was recrystallized to constant melting. Relatively easy separation of the monoacetylated products (I–III) from the diacetylated products (IV–VI) was obtained during column chromatography, but separation among the individual isomers of each group required very careful column development and elution. (See Scheme I.)

The first isomer to be eluted and the least abundant was assigned structure I, 2-acetylbiferrocenyl,[12] by means of comparison of the n.m.r. spectrum determined from it with that of the second eluted isomeric monoacetylated product, 3-acetylbiferrocenyl (II). In each spectrum (Fig. 1 and 2, respectively), the presence of two five-proton signals near δ 4, unsubstituted cyclopentadienyl ring, and one three-proton singlet near δ 2.4, methyl group in acetyl function, showed that each isomer possessed only one acetyl group (confirmed by combustion analysis) and that the acetyl group was contained in one of the directly bonded cyclopentadienyl of the biferrocenyl nucleus. The choice between the two isomeric possibilities was decided by the fact that the n.m.r. spectrum of the isomer melting at 153–154° (second to be eluted) gave rise to a low field one-proton triplet (δ 4.98) that must be due to a proton flanking the acetyl group but remote from the ring assembly, C-1. The lowest field signal present in the n.m.r. spectrum obtained from the isomer melting at 102–103° (first to be eluted) is a three-proton multiplet centered at δ 4.75 which must include the proton flanking the acetyl group and must be remote from C-1. Since the acetyl group may be expected to exert a greater deshielding effect on an adjacent proton when it is more remote from C-1, the higher melting isomer which gives rise to the lower field signal is assigned structure II, 3-acetylbiferrocenyl. This analysis is also consistent with the fact that the signal due to the methyl protons of the acetyl function of the higher melting isomer (II) occurs at slightly lower field (δ 2.41) than it does (δ 2.38) in the n.m.r. spectrum obtained from the lower melting isomer (I).

The remaining monoacetyl isomer, m.p. 137–139° (third to be eluted) was assigned structure III, 1′-acetylbiferrocenyl. This material was shown to be identical with 1′-acetylbiferrocenyl, previously synthesized by an independent route, and the n.m.r. spectrum determined from III, as well as its analysis, are included in a separate account[1] of that work.

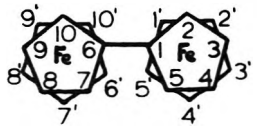
There have been several attempts to establish empirical generalizations based on properties of isomeric disubstituted ferrocenes. Among these is the order of elution of isomeric disubstituted ferrocenes from alumina which has been observed[13,14] to be 1,2- first, 1,1′- second, and 1,3- third. It will be noted that this sequence was not observed in the present work. This generalization, therefore, appears to be limited to disubstituted isomers possessing only one ferrocene nucleus. Empirical correlations based on infrared absorption also have been examined with the compounds encountered in this work. Utility of the reliable 9–10 rule[13,14–17] is extended by the present investigation to include substituted biferrocenyls: all of the compounds possessing at least one unsubstituted cyclopentadienyl ring (I, II, III, IV, and V) exhibit bands near 9 and 10 μ in their infrared spectra.

While correlation of infrared spectra of bands in the 10.9–11.3-μ region advanced by Rosenblum[18] as an aid in distinguishing between 1,2- and 1,3-disubstituted ferrocenes does not appear to be applicable in the present work, a similar correlation of bands in the region 1270–1300 cm.$^{-1}$ [13,16,19,20] appears to include the monoacetyl isomers, I and II.

Thus, 2-acetylbiferrocenyl (I) possesses a band at 1270 but not near 1290 cm.$^{-1}$, while 3-acetylbiferrocenyl (II) gives rise to a doublet of equal intensity at 1304 and 1292 cm.$^{-1}$ with no absorption near 1270 cm.$^{-1}$.

It is significant that the correlation of ultraviolet absorption in the region near 220 mμ previously suggested[13] for substituted acylferrocenes is applicable here. 3-Acetylferrocene (II) displays the longest wave-

(12) In order to designate the individual isomers unambiguously, the numbering system shown below for biferrocenyl has been proposed.[1]



(13) K. L. Rinehart, Jr., K. L. Motz, and S. Moon, *J. Am. Chem. Soc.*, **79**, 2749 (1957).

(14) M. Rosenblum, W. G. Howells, A. K. Banerjee, and C. Bennett, *ibid.*, **84**, 2726 (1962).

(15) M. Rosenblum, Doctoral dissertation, Harvard University, 1953.

(16) M. Rosenblum and R. B. Woodward, *J. Am. Chem. Soc.*, **80**, 5443 (1958).

(17) A. N. Nesmeyanov, L. A. Kazitsyna, B. V. Lokshin, and V. D. Vilchevskaya, *Dokl. Akad. Nauk SSSR*, **125**, 1037 (1959).

(18) M. Rosenblum and W. G. Howells, *J. Am. Chem. Soc.*, **84**, 1167 (1962).

(19) K. L. Rinehart, Jr., and K. L. Motz, *Chem. Ind.* (London), 1150 (1957).

(20) K. L. Rinehart, Jr., D. E. Bublitz, and D. H. Gustafson, *J. Am. Chem. Soc.*, **85**, 970 (1963).

length maxima in this region, while 2-acetylferrocene (I) possesses the shortest (Fig. 3). It does not appear, however, that either the infrared correlation or the ultraviolet correlation is applicable to the isomeric diacetylated biferrocenyls obtained in this work.

Of the three isomeric diacetylbiferrocenyls obtained, the first eluted from alumina decomposed over a temperature range starting at about 230°. The n.m.r. spectrum determined from this material (Fig. 4) displayed a ten-proton singlet at δ 4.07, showing the presence of two unsubstituted cyclopentadienyl rings. The fact that the methyl groups of the two acetyl functions gave rise to a singlet signal (δ 2.42) indicated that the acetyl groups were equivalent, and the two-proton signal (probably a triplet) at δ 5.00 also meant that each acetyl group was located β to the ring assembly atoms of the biferrocenyl nucleus. This analysis, therefore, limits the structure possibilities to either 3,9-diacetylbiferrocenyl (IVa) or 3,8-diacetylbiferrocenyl (IVb). While it is not possible to distinguish between these two structures at the present time, the four-proton triplet at δ 4.80, in either case, must arise from the four protons which flank the ring assembly atoms.

The n.m.r. spectrum (Fig. 5) determined from the second diacetyl isomer eluted from alumina (m.p. 111–112°) shows the presence of one unsubstituted cyclopentadienyl ring (five-proton singlet at δ 4.02) and the presence of two nonequivalent acetyl groups. The three-proton singlet at δ 2.18 is due to an acetyl group present in a nondirectly bonded cyclopentadienyl ring (signal at δ 2.15 for acetyl groups in III and VI), while the lower field, three-proton singlet must be due to the acetyl group present in a bonded cyclopentadienyl ring and located β to the ring assembly atom because of the presence of the one-proton triplet at δ 4.98. This isomer is, therefore, assigned the structure of 3,6′-diacetylbiferrocenyl (V).

The last of the isomeric diacetyl biferrocenyls, m.p. 183–185°, to elute from alumina proved to be identical with 1′,6′-diacetylbiferrocenyl (VI), previously synthesized.[1]

While any attempt to correlate spectral properties with structure for these disubstituted isomers would be premature since the three isomers obtained here represent only a small fraction of the number of disubstituted biferrocenyls possible, it may be significant to note that adsorbability on alumina appears to increase with the degree of substitution in the nondirectly bonded cyclopentadienyl rings of biferrocenyl.

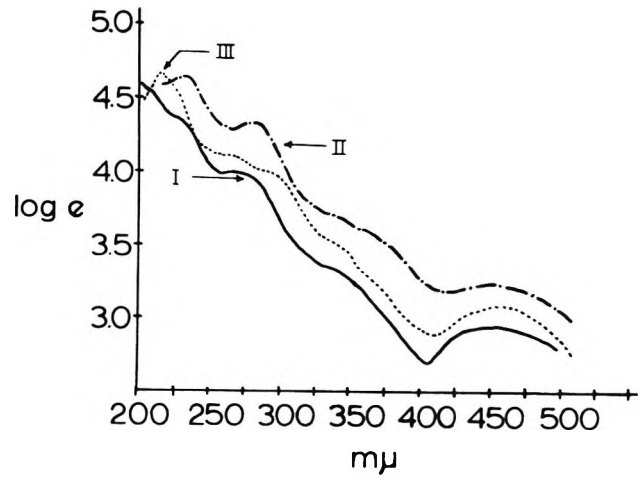


Figure 3

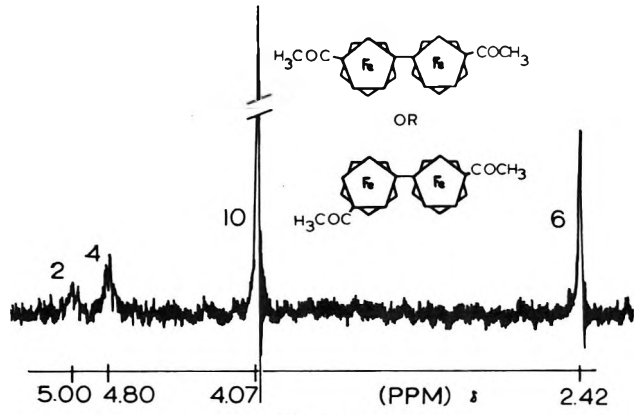


Figure 4

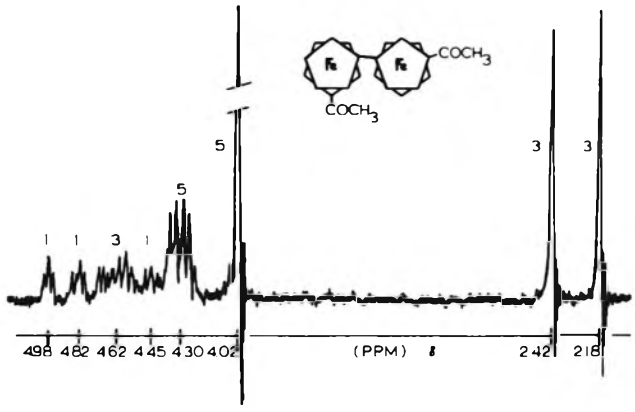


Figure 5

Experimental

Temperature measurements are reported uncorrected. N.m.r. spectra were determined with a Varian A-60 spectrometer at 60 Mc. with a room temperature probe, employing chloroform solvent containing approximately 5% (v./v.) tetramethylsilane as internal standard. Ultraviolet spectra were obtained in 95% ethanol with a Cary Model 14 recording spectrophotometer, while infrared spectra were determined in carbon tetrachloride solution, usually 5% (wt./wt.), with a Perkin-Elmer Model 21 recording spectrophotometer.

Combustion analyses were carried out by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

The biferrocenyl used in this work was prepared[21] by a procedure previously described.[1]

All column elution chromatography was carried out with Merck acid-washed alumina and purified elution solvents. The column chromatograms were wrapped with aluminum foil to protect them from light during development and elution.

Competitive Acetylation of Biferrocenyl and Ferrocene.—Ferrocene (186 mg., 1.00 mmole) and biferrocenyl (370 mg., 1.00 mmole) were dissolved in 100 ml. of dry methylene dichloride, and the resulting solution was cooled to approximately 0° by means of an external ice bath. While the solution was maintained under an atmosphere of purified nitrogen and agitated by means of a magnetically operated stirrer, a mixture of acetyl chloride (134 mg., 1.00 mmole) and anhydrous aluminum chloride (120 mg., 1.00 mmole), contained in 13 ml. of methylene dichloride, was added slowly to the cold, red solution during a 30-min. period. The reaction mixture immediately assumed a deep violet coloration upon initial introduction of the acid chloride–aluminum chloride addend.

After addition, the reaction was allowed to warm slowly (~1 hr.) to room temperature, and stirring was continued during an

(21) We wish to acknowledge the very able assistance of Miss Patricia Mobley and Mr. John Alford in preparation of the biferrocenyl.

additional hour at room temperature. After the mixture was poured quickly onto 100 ml. of crushed ice and the ice was allowed to melt, the resulting hydrolysate was phase separated. The light blue aqueous phase was treated with ascorbic acid to discharge the blue color and then extracted with three 10-ml. portions of methylene dichloride. Combination, drying, and evaporation of all the methylene dichloride solutions yielded 583 mg. of a solid, orange-red material which was submitted to chromatography on 30 g. of Merck acid-washed alumina. Development with hexane gave rise to a large, yellow, diffuse band, which was eluted with hexane, and a smaller, orange-red area, which was eluted with ethyl acetate. Evaporation of the hexane eluent gave 504 mg. of orange solid which, by means of fractional crystallization from hexane,[1] was shown to consist of 339 mg. (92% recovered) of biferrocenyl and 119 mg. (64% recovered) of ferrocene.

Evaporation of the ethyl acetate eluent yielded 67 mg. of light red solid which was chromatographed on alumina. Development with ether produced a mobile salmon-colored band and several slower moving, darker red bands. The large, salmon-colored band was collected in ether and evaporated to 41 mg. of red, needle-shaped crystals of acetylferrocene, m.p. 84–87° (lit.[22] m.p. 85–86°), which was not depressed upon admixture melting with authentic acetylferrocene. This material also gave rise to an infrared spectrum (carbon tetrachloride) superimposable upon that determined from authentic acetylferrocene.

Acetylation of Biferrocenyl.—Biferrocenyl (20.0 g., 54.1 mmoles) was suspended and partially dissolved in a mixture containing 80 ml. of acetic anhydride and 20 ml. of polyphosphoric acid (two parts 85% orthophosphoric acid and one part phosphorus(V) oxide by weight). The heterogenous reaction mixture was flushed with nitrogen and then immersed in a hot water bath (~95°) for 10 min. during which time the flask was constantly swirled. At the end of the 10-min. heating period, enough crushed ice was added to cause the temperature of the reaction mixture to fall rapidly to about 15°. After neutralization of the cooled reaction mixture by addition of saturated aqueous sodium carbonate solution, all of the solid material present was washed onto a Büchner funnel and sucked as dry as possible. The solid residue was triturated with three 25-ml. portions of ether, leaving 8.5 g. of biferrocenyl as residue. An additional 1.7 g. of recovered biferrocenyl was obtained from elution chromatography (see below), bringing the total recovered starting material to 10.2 g. (51%). The combined ether extracts were dried over anhydrous magnesium sulfate, filtered, and evaporated to an orange-red, solid residue. An infrared spectrum (carbon tetrachloride) determined from this crude mixture indicated the presence of acetylation product (broad band near 6 μ). The material then was submitted to a slow, careful chromatographic separation on alumina.

Chromatographic Separation of Biferrocenyl Acetylation Mixture.—The solid, ether-soluble residue described above was dissolved in a minimum volume of hot chloroform and transferred to a column containing 600 g. of Merck acid-washed alumina. The column of alumina, 3 ft. high and 1 in. in diameter, previously was carefully packed in hexane solution. The dark red chloroform solution was run onto the top of the alumina column in a narrow uniform band, and development of the column was begun with hexane. The initially narrow band of material widened quickly while the chloroform was washed through, but then only slow and steady movement of a diffuse, yellow band, which had developed out of the dark red solution, was observed. Elution with hexane was continued until all of the mobile, yellow region was collected.

Evaporation of the hexane eluent yielded an additional 1.7-g. portion of unreacted biferrocenyl which was identified by means of a mixture melting point with authentic biferrocenyl.

Development of the column then was continued with 1:1 (v./v.) hexane–benzene. The remaining material separated into two major regions: a dark orange band moving downward just perceptively and a red region remaining stationary. Continued elution with 1:1 hexane–benzene eventually gave rise to a separation of the mobile, orange area into two component orange bands.

2-Acetylbiferrocenyl (I).—Just before any of the material in the faster-moving, orange band had reached the end of the column, there was collected a volume (~300 ml.) of faintly yellow eluent. The yellow material in the eluent was not visible on the column. Evaporation of the eluting solvent mixture, followed by recrystallization of the residue from hot hexane, gave rise to 13 mg. (0.12% yield[23]) of an orange-red crystalline material, m.p. 102–103°, which was assigned the structure of **2-acetylbiferrocenyl (I)** on the basis of the spectral data (see text) determined from it.

Anal. Calcd. for $C_{22}H_{20}Fe_2O$: C, 64.12; H, 4.89. Found: C, 63.81; H, 5.1[illegible].

3-Acetylbiferrocenyl (II).—Elution of the column was continued with 1:1 hexane–benzene, and the faster-moving, orange band was collected. The eluting solvent mixture was evaporated *in vacuo*, and the crystalline, orange residue obtained was recrystallized from hot hexane to yield 70 mg. (0.64% yield[23]) of **3-acetylbiferrocenyl (II)** as needle-shaped crystals, m.p. 153–154° (see text for discussion of structural assignment).

Anal. Calcd. for $C_{22}H_{20}Fe_2O$: C, 64.12; H, 4.89. Found: C, 63.82; H, 5.[illegible]4.

1'-Acetylbiferrocenyl (III).—The slower-moving, orange band was eluted next with the same solvent mixture, 1:1 hexane–benzene. Evaporation of the eluent to dryness *in vacuo* provided a crystalline, orange residue. Recrystallization of this material from hot hexane solution gave 550 mg. (5.1% yield[23]) of pure **1'-acetylbiferrocenyl (III)** as dark orange, needle-shaped crystals, m.p. 137–138°, which was undepressed upon melting in admixture with 1'-acetylbiferrocenyl previously obtained by means of an independent synthesis.[1] For additional comments concerning the structural assignment and spectral properties of this compound, see ref. 1.

Anal. Calcd. for $C_{22}H_{20}Fe_2O$: C, 64.12; H, 4.89. Found: C, 64.23; H, 4.[illegible].

3,9- or 3,8-Diacetylbiferrocenyl (IVa or IVb).—Since very little development of the red region at the top of the column occurred during the large volume of solvents used for elution of unreacted biferrocenyl and the monoacetylbiferrocenyls, the eluting solvent was changed to pure benzene. Column development with this solvent caused a diffuse, light red band to move slowly out of the major dark red area. This band was collected in eight fractions of approximately equal volume, and each fraction was evaporated to dryness *in vacuo*. Crystallization and recrystallization of the combined residues obtained from the first three fractions gave 100 mg. (0.85% yield[23]) of **3,9- or 3,8-diacetylbiferrocenyl** as yellow crystals which were observed to decompose steadily over the temperature range 230–250°, when melting was attempted. See text for spectral data and discussion concerning the two structural possibilities for this compound.

Anal. Calcd. for $C_{24}H_{22}Fe_2O_2$: C, 63.47; H, 4.88. Found: C, 63.55; H, 4.9[illegible].

3,6'-Diacetylbiferrocenyl (V).—The small amount of material left in the mother liquors of the crystallizations of the combined residue obtained from the first three fractions described above was added to the combined residues provided by evaporation of the remaining benzene eluents. This material was crystallized and recrystallized from a benzene–hexane mixture to give rise to 700 mg. (5.8% yield[23]) of **3,6'-diacetylbiferrocenyl (V)** as red, needle-shaped crystals, m.p. 112–113°. See text for spectral data pertinent to the structural assignment made to this compound.

Anal. Calcd. for $C_{24}H_{22}Fe_2O_2$: C, 63.47; H, 4.88. Found: C, 63.86; H, 4.89

1',6'-Diacetylbiferrocenyl (VI).—While elution with pure benzene gave rise to the diffuse, light red band described above, the slower-moving, darker red band remained close behind and appeared to be homogenous throughout its movement down the column. The major portion of this band was eluted from the column with 20:1 (v./v.) benzene–ether which carried it off the column a little faster than did pure benzene. The crystalline residue obtained from the eluents was recrystallized from hot benzene to yield 200 mg. (1.8% yield[23]) of **1',6'-diacetylbiferrocenyl (VI)** as dark red, needle-shaped crystals which melted at 184–185°, undepressed on admixture with 1',6'-diacetylbiferrocenyl previously prepared by an independent route.[1] For spectral data and addition comments regarding the structural assignment to this material, see ref. 1.

Anal. Calcd. for $C_{24}H_{22}Fe_2O_2$: C, 63.47; H, 4.88. Found: C, 63.41; H, 4.5[illegible]

(22) A. N. Nesmeyanov, E. G. Perevalova, R. V. Golovnya, and O. A. Nesmeyanova, *Dokl. Akad. Nauk SSSR*, **97**, 459 (1954).

(23) Yield calculation was based on 9.8 g. of unrecovered biferrocenyl.

Wittig Cyclization and Base-Induced Elimination in the Reactions of Some ω-Benzoylalkyltriphenylphosphonium Salts[1]

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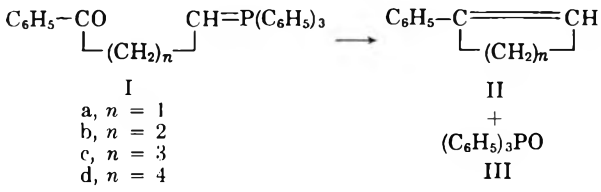
Received September 19, 1963

The reactions of four ω-benzoylalkyltriphenylphosphonium salts with organolithium reagents have been studied. An internal Wittig reaction leading to the formation of 1-phenylcyclohexene is observed with the 5-benzoylpentyl salt, but only β-elimination of triphenylphosphine is observed in the reactions of the 1-phenylcyclobutene precursor. The β-elimination of triphenylphosphine from phosphonium salts also has been observed in reactions of two 2-benzoylethyl salts. The study indicates that the formation of cyclopentenes and cyclohexenes constitutes a lower limit on Wittig cyclization reactions.

The intermolecular Wittig reaction between a bisphosphorane and a dicarbonyl compound has been utilized in a number of instances for the synthesis of medium and large ring cycloalkenes,[2] but relatively few studies of the simpler intramolecular cyclizations of ω-oxoalkylphosphoranes have been carried out.[3] Two studies of the reactions of the simplest models, ω-benzoylalkyltriphenylphosphoranes (I), have been reported. Bieber and Eisman have shown that Ic, formed by the



I
a, $n = 1$
b, $n = 2$
c, $n = 3$
d, $n = 4$

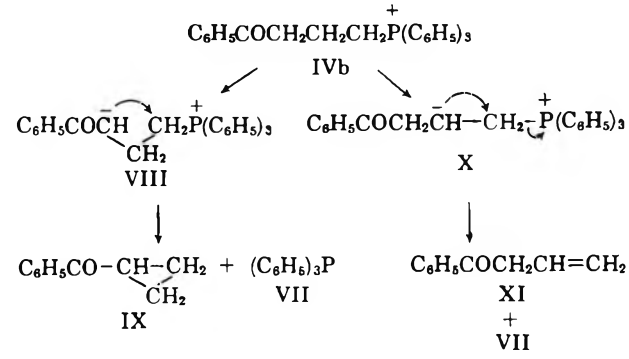
II
+
$(C_6H_5)_3PO$
III

action of sodium ethoxide on the corresponding phosphonium salt (IVc), undergoes intramolecular cyclization to yield 1-phenylcyclopentene (IIc) and triphenylphosphine oxide (III).[4] A different reaction course was observed with Ia which underwent intermolecular reaction (cyclodimerization) with the formation of 1,4-diphenylcyclohexadiene (V) rather than the cyclopropene (IIa).[5] Since the formation of a dimeric product in the latter reaction indicated the internal Wittig reaction to be subject to ring size limitations, the reactions of Ib and Id (cyclobutene and cyclohexene precursors) have been examined.

1-Phenylcyclohexene (IId) was prepared by treating a suspension of (5-benzoylpentyl)triphenylphosphonium iodide (IVd) in benzene with *n*-butyllithium and refluxing the resulting phosphorane (Id) solution for 13 hr. IId was isolated in 9.6% yield; reaction residues were shown to contain III and IVd.

In the reactions of Ib, neither the expected cycloalkene, 1-phenylcyclobutene (IIb), nor the cyclic diene, 1,5-diphenylcyclooctadiene-1,5 (VI), was detected as a product. The formation of VI might be anticipated by a cyclodimerization process analogous to the formation of V. Treatment of IVb, (3-benzoylpropyl)triphenylphosphonium chloride, with phenyllithium led to the isolation of triphenylphosphine (VII), III, biphenyl, and polymeric material. The use of *n*-butyllithium as base for the generation of Ib led to the isolation of VII (25%), III, unchanged IVb, and polymeric material. Since biphenyl was not isolated in the latter reaction, it is assumed that it was formed during the preparation of phenyllithium. A sample of the latter reaction mixture was examined by g.l.c. and shown to contain no detectable amount of IIb by comparison with the g.l.c. behavior of an authentic sample[6] of IIb.

Since neither IIb nor VI was detected in the reactions of Ib, it appears that polymerization of Ib and elimination of VII from IVb are the major reactions. Elimination of triphenylphosphine from IVb could occur by either of two processes: intramolecular displacement of VII from the inner salt VIII to yield a cyclopropane derivative (IX),[7] or simple β-elimination from the inner salt (X) to yield 3-butenophenone (XI). The inner



salts VIII and X could be formed by either the direct attack of base on IVb or by equilibration processes between Ib and IVb. A g.l.c. analysis of the products from the reaction of IVb showed the absence of any detectable amount of VIII,[8] indicating that the probable major process is β-elimination. XI may rearrange to the more stable α,β-unsaturated isomer,[9] crotonophenone (XII), in the strongly basic reaction mixture; neither XI nor XII was detected as reaction product, but might be anticipated to undergo polymerization. Intermolecular reaction of Ib would account for the formation of III and would lead to a polyolefin.

(1) This study was supported in part by grants from the National Science Foundation (G-11280) and the National Institute of Allergy and Infectious Diseases, U. S. Public Health Service (E-2359).

(2) For a summary of leading references, see C. E. Griffin and J. A. Peters, *J. Org. Chem.*, **28**, 1715 (1963); C. E. Griffin, K. R. Martin, and B. E. Douglas, *ibid.*, **27**, 1627 (1962).

(3) Other intramolecular Wittig cyclizations are reported by H. J. Bestmann and O. Kratzer, *Angew. Chem. Intern. Ed. Engl.*, **1**, 511 (1962); G. Markl, *ibid.*, **1**, 511 (1962); H. O. House and H. Babad, *J. Org. Chem.*, **28**, 90 (1963).

(4) T. I. Bieber and E. H. Eisman, *ibid.*, **27**, 678 (1952).

(5) C. E. Griffin and G. Witschard, *ibid.*, **27**, 3334 (1962).

(6) A. Burger and R. Bennet, *J. Med. Pharm. Chem.*, **2**, 687 (1960).

(7) The formation of mesityl 2-phenylcyclopropyl ketone by a similar internal displacement of VII from an intermediate analogous to VIII formed in the reaction of methylenetriphenylphosphorane and benzalacetomesitylene has been reported; *cf.* J. P. Freeman, *Chem. Ind.* (London), 1254 (1959).

(8) We are indebted to Dr. J. B. Plumb for carrying out this analysis.

(9) The rearrangement of XI to XII has been demonstrated by R. M. Horowitz and T. A. Geissman [*J. Am. Chem. Soc.*, **72**, 1518 (1950)].

A number of simple β-eliminations of VII from phosphonium salts have been reported previously[10]; in these examples, activation of the β-proton toward the attack of base has been provided by the direct or vinylogous attachment of phosphonium,[10a,d] cyano,[10b] carbethoxy,[10c] carboxylate,[10e] and acyl[10f] groups at the β-carbon. In the β-elimination of VII from IVb, the β-proton is not subject to conventional activation since the β-substituent (in IVb) is a phenacyl group. Thus, the present case represents an example of β-elimination in a salt possessing a minimal degree of activation. Cleavage of phosphonium salts lacking β-proton activation is well-known and follows a different course; the action of hydroxide[11a] and alkoxide[11b] ions on these salts has been shown to produce III and alkanes. In the cleavages, attack of base occurs on the phosphorus atom to yield intermediates which subsequently fragment to III. In the reactions under consideration in this study, attack by base (phenyl- or butyllithium) on phosphorus would not be energetically favorable and abstraction of a β-proton with elimination of VII in analogy to Hofmann eliminations would be feasible.

In order to investigate the possible occurrence of β-elimination in structures more favorable toward this process than IVb, the reaction of IVa with bases was reinvestigated; it was reported previously that VII,

$$C_6H_5COCH_2\overset{+}{C}H_2P(C_6H_5)_3$$
IVa

as well as V and III, was detected in the reaction of IVa with phenyllithium.[5] The reaction of IVa with *n*-butyllithium led to the formation of triphenylphosphine (50%) and III (40%). In IVa, β-elimination would be more highly favored than in IVb, since, in the former compound, the β-hydrogen is activated by the benzoyl group. Elimination would lead to the formation of acrylophenone which was not isolated, but the ready polymerization of this compound has been demonstrated.[12]

β-Elimination of VII was demonstrated cleanly in the reaction of phenyllithium and (2-benzoyl-1-phenylethyl)triphenylphosphonium bromide (XIII). Triphenylphosphine (53%) and the elimination product, chalcone (XIV, 48%), were the only products isolated;

$$C_6H_5COCH_2CH(C_6H_5)\overset{+}{P}(C_6H_5)_3 + n\text{-}C_4H_9Li \longrightarrow$$
XIII

$$C_6H_5COCH{=}CHC_6H_5 + VII$$
XIV

no dienes were detected. In the case of XIII, simple cyclization to the cyclopropene and cyclodimerization would be unfavorable processes because of probability and steric factors. The preferred elimination process would be facilitated by the activation of the β-hydrogen by the benzoyl group and the stability of the α,β-unsaturated ketone formed on elimination. No III was detected in this reaction indicating that even the intermolecular Wittig reaction leading to polymer has been suppressed in favor of elimination.

The results of this study indicate that the effective lower limit for Wittig cyclizations of ω-oxoalkylphosphoranes is in the cyclopentene series and that β-elimination of VII can occur readily in phosphonium salts possessing sufficient β-hydrogen activation.

Experimental[13]

(5-Benzoylpentyl)triphenylphosphonium Iodide (IVd).—6-Bromocaproic acid was prepared by the hydrolysis of 6-bromocapronitrile (Columbia Organic Chemicals Co.) with refluxing 48% hydrobromic acid. The acid was isolated in 46% yield by distillation, b.p. 120–130° (1 mm.), lit.[14] b.p. 165–170° (20 mm.). The acid was converted to the corresponding chloride by treatment with excess thionyl chloride at 80° for 1 hr.; distillation gave the product in 92% yield, b.p. 84–90° (2.5 mm.). 6-Bromocaprophenone was prepared by a conventional Friedel–Crafts procedure from the acid chloride, anhydrous benzene, and aluminum chloride with a reaction period of 30 min. The product, isolated in 61% yield by distillation, had b.p. 150–154° (0.7 mm.), lit.[15] b.p. 124° (0.05 mm.). Quaternization was achieved by refluxing a mixture of 16.5 g. (0.063 mole) of triphenylphosphine and 16.0 g. (0.063 mole) of the bromo ketone in 50 ml. of N,N-dimethylformamide for 68 hr.; no solid was formed on cooling. The solvent was removed under reduced pressure and the oily residue was washed with petroleum ether (b.p. 30–60°) and added to 600 ml. of hot aqueous potassium iodide. A viscous oil separated on cooling and was crystallized by the addition of ether to give 21.4 g. (60%) of IVd, m.p. 158–159° (recrystallized from ethanol–ether).

Anal. Calcd. for $C_{30}H_{30}IOP$: C, 63.83; H, 5.36; P, 5.49. Found: C, 63.88, 63.76; H, 5.39, 5.28; P, 5.32, 5.47.

The infrared spectrum of IVd showed bands at 3067 w, 2941 s, 2882 wm, 1669 m, 1585 w, 1433 ms, 1109 s, 994 wm, 746 m, 719 s, and 690 s cm.$^{-1}$.

1-Phenylcyclohexene (IId).—A suspension of 18.8 g. (0.033 mole) of IVd in 190 ml. of anhydrous benzene was treated with a solution of 0.033 mole of *n*-butyllithium in hexane; the reaction mixture was refluxed for 13 hr., allowed to cool, and quenched with 50 ml. of water. The organic layer was dried over sodium sulfate, concentrated on a steam bath, and distilled to give 0.50 g. (9.6%) of IId, b.p. 90.5–93.5° (1.5 mm.), lit.[16] b.p. 126–128° (16 mm.). The observed ultraviolet and infrared spectra of IId agreed with the values reported by Mixer and Young.[17] A brown solid which separated during the course of the reaction was shown to consist of III and unchanged IVd by examination of its infrared spectrum.

(3-Benzoylpropyl)triphenylphosphonium Chloride (IVb).—A mixture of 100 g. (0.55 mole) of γ-chlorobutyrophenone, 158 g. of triphenylphosphine, and 200 ml. of toluene was refluxed for 15 hr. After cooling, the solvent was removed under reduced pressure and the red residue was crystallized by trituration with a small amount of acetone to give 80 g. (33%) of IVb, m.p. 184.5–186° (recrystallized from acetone–petroleum ether).

Anal. Calcd. for $C_{28}H_{26}ClOP$: C, 75.59; H, 5.89; P, 6.96; Cl, 7.97. Found: C, 73.76, 73.57; H, 6.01, 6.16; P, 6.82; Cl, 7.74, 7.79.

The infrared spectrum of IVb had bands at 3030 w, 2899 m, 1678 s, 1600 m, 1486 wm, 1437 s, 1404 w, 1369 m, 1297 w, 1206 wm, 1136 w, 1109 s, 1026 w, 996 m, 980–973 w, 945 w, 752 ms, 722 s, and 690 s cm.$^{-1}$.

Reaction of (3-Benzoylpropyl)triphenylphosphonium Chloride (IVb) with Base.—A mixture of 4.44 g. (0.01 mole) of IVb and 0.012 mole of *n*-butyllithium in 500 ml. of benzene was refluxed for 20 hr., cooled, and quenched with water. The organic layer was separated and concentrated on a steam bath. The residue

(10) (a) G. Wittig, H. Eggers, and P. Duffner, *Ann.*, **619**, 10 (1958); (b) H. Hoffmann, *Chem. Ber.*, **94**, 1331 (1961); (c) A. Aksnes, *Acta Chem. Scand.*, **15**, 438 (1961); (d) J. A. Ford, Jr., and C. V. Wilson, *J. Org. Chem.*, **26**, 1433 (1961); (e) D. B. Denney and L. C. Smith, *ibid.*, **27**, 3404 (1962); (f) H. J. Bestmann, F. Seng, and J. Schulz, *Chem. Ber.*, **96**, 465 (1963).

(11) (a) M. Zanger, C. A. Vander Werf, and W. E. McEwen, *J. Am. Chem. Soc.*, **81**, 3806 (1959); (b) M. Grayson and P. T. Keough, *ibid.*, **82**, 3919 (1960).

(12) J. F. Norris and H. B. Couch, *ibid.*, **42**, 2329 (1920).

(13) All melting points are uncorrected; microanalyses were performed by Galbraith Laboratories. Infrared spectra were recorded on Perkin-Elmer Model 21 and Beckman IR-8 spectrophotometers, and ultraviolet spectra were recorded on a Cary Model 14 spectrophotometer.

(14) C. S. Marvel, D. W. MacCorquodale, F. E. Kendall, and W. A. Lazier, *J. Am. Chem. Soc.*, **46**, 2838 (1924).

(15) G. C. Coker, British Patent 830,519; *Chem. Abstr.*, **54**, 18,567 (1960).

(16) C. C. Price and J. V. Karabinos, *J. Am. Chem. Soc.*, **62**, 1160 (1940).

(17) R. Y. Mixer and W. G. Young, *ibid.*, **78**, 3379 (1956).

was dissolved in benzene and chromatographed on a 40-cm. Florisil column; elution with benzene led to the isolation of VII (25%), III (26%), and a brown oil which was shown to contain unchanged IVb. The organic layer from a similar reaction was examined by quantitative g.l.c.[18] and no peaks corresponding to either IIb or phenyl cyclopropyl ketone (IX) were observed; an unidentified peak with a retention time of 22 min. was the only peak observed. Under the conditions employed, authentic samples of IIb and IX had retention times of 48 and 27 min., respectively.

When this reaction was carried out with phenyllithium as base, but under otherwise identical conditions, the only materials isolated were biphenyl and unchanged IVb.

Reaction of (2-Benzoylethyl)triphenylphosphonium Bromide (IVa) with *n*-Butyllithium.—The reaction of IVa (0.011 mole) and *n*-butyllithium (0.015 mole) was carried out in the same manner as in the preceding experiment. Chromatographic separation on a Florisil column led to the isolation of VII (50%) by elution with benzene and III (40%) and IVa (5%) by elution with acetone.

(2-Benzoyl-1-phenylethyl)triphenylphosphonium Bromide (XIII).—A mixture of 60 g. (0.208 mole) of β-bromo-β-phenylpropiophenone, prepared by the method of Kashiwagi,[19] 54.4 g. (0.208 mole) of triphenylphosphine, and 200 ml. of anhydrous benzene was refluxed for 3 hr. On cooling two layers formed; the viscous orange layer was heated on a steam bath with 200 ml. of acetone. XIII (87 g., 76%) was obtained when the solution was cooled; XIII was recrystallized from acetone and melted at 149.5–151.0°.

Anal. Calcd. for $C_{33}H_{28}BrOP$: C, 71.86; H, 5.12. Found: C, 71.42, 71.61; H, 5.39, 5.24.

The infrared absorption spectrum of XIII had bands at 1678 m, 1600 w, 1449 w, 1437 ms, 1325 w, 1212 ms, 1190 w, 1106 s, 996 w, 976 w, 917 w, 750 s, 727 s, 702 ms, and 690 ms cm.$^{-1}$.

Reaction of (2-Benzoyl-1-phenylethyl)triphenylphosphonium Bromide (XIII) with Phenyllithium.—A mixture of 11.0 g. (0.02 mole) of XIII, 0.025 mole of phenyllithium, and 1.3 l. of anhydrous toluene was refluxed for 24 hr., cooled, and concentrated under reduced pressure to a volume of 15 ml. The residue was chromatographed on a 60-cm. neutral alumina column; elution with petroleum ether gave 2.78 g. (53%) of VII and elution with ethyl acetate gave 2.00 g. (48%) of chalcone (XIV). No other materials could be isolated from the column. The infrared spectrum of the residue indicated the presence of XIII, but gave no indication of III. XIV was identified by mixture melting point and infrared spectra comparisons with an authentic sample.

(18) Gas-liquid chromatography was carried out on an F and M Model 500 gas chromatograph using a 21-ft. Apiezon L column (16.9% on Chromosorb W, 110–120 mesh) at a column temperature of 200°, an injection port temperature of 245°, and a flow rate of 24.3 ml./min. (helium).

(19) H. Kashiwagi, *Bull. Soc. Chem. Japan*, **26**, 355 (1953).

The Preparation of Olefins by Pyrolysis of Carbalkoxyphosphonium Salts[1,2]

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It has been found that phosphonium salts, $R_3P^+CH_2CO_2R'X^-$, decompose at convenient rates at temperatures between 130 and 225°. The products of these decompositions are carbon dioxide, $R_3P^+CH_3\ X^-$, and an olefin derived from R'. Salts have been prepared and decomposed where R' is a primary, secondary, or tertiary alkyl group. In most cases it was possible to isolate pure terminal olefins from decomposition of salts, R' = 1°. Where isomer formation was possible, *i.e.*, R' = 2°, 3°, the ratio of isomers was determined in many cases. A definite tendency to form the thermodynamically most stable olefins was noted. Olefins from several systems were found to be those arising from carbonium ion rearrangements.

Because of the general availability of alcohols, methods for their conversion to olefins have been the subject of constant investigation. In particular, mild methods have been sought. Pyrolytic decomposition of esters and xanthates has often been used.[5]

It is the purpose of this report to present a new and synthetically useful pyrolytic method for the conversion of an alcohol to an olefin. This work received its stimulus from the casual observations of Michaelis and Gimborn[6a] and Piaux.[6b] Michaelis and Gimborn found that triphenylcarbethoxymethylphosphonium chloride (I) slowly decomposes on heating at 100° to give triphenylmethylphosphonium chloride. They speculated, and quite reasonably so, that ethylene and carbon dioxide were the other products. Piaux found that

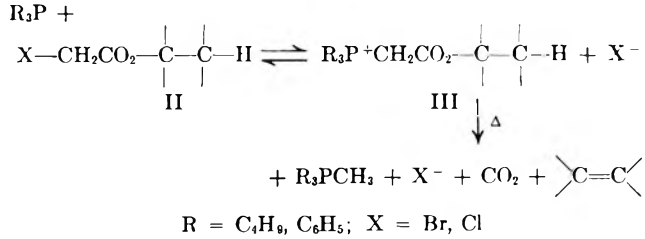
$$\underset{I^-}{(C_6H_5)_3P^+CH_2CO_2C_2H_5} + Cl^- \longrightarrow (C_6H_5)_3P^+CH_3 + Cl^-$$

heating phenyldimethylcarbethoxymethylammonium iodide yielded phenyltrimethylammonium iodide.

The initial phase of this investigation was directed at establishing the course of decomposition of salts of this type. Having found that olefins were formed, the later work has been directed towards extending the reaction to systems which would establish its generality and limitations. The results of these experiments are now being reported.[7] Consideration of mechanism and related matters, in particular the solvolysis of these salts, will be discussed in a subsequent report.

Results and Discussion

It has been found that a wide variety of α-halo esters (II)[8] react with tributyl or triphenylphosphine to give salts (III). Heating of these salts at temperatures between 130 and 225° leads to decomposition with



R = C_4H_9, C_6H_5; X = Br, Cl

(1) Research supported by the National Science Foundation.

(2) A preliminary account appeared in *J. Am. Chem. Soc.*, **83**, 3336 (1961).

(3) Rutgers Research Council Faculty Fellow, 1963–1964.

(4) National Science Foundation Cooperative Graduate Fellow in Chemistry, 1960–1961.

(5) C. H. DePuy and R. W. King, *Chem. Rev.*, **60**, 431 (1960).

(6) (a) A. Michaelis and V. Gimborn, *Ber.*, **27**, 272 (1894); (b) L. Piaux, *Compt. rend.*, **190**, 645 (1930).

(7) For some interesting olefin-forming pyrolytic decompositions of phosphorus-containing compounds, see H. E. Baumgarten and R. E. Allen, *J. Org. Chem.*, **26**, 1533 (1961); W. J. Bailey, W. M. Muir, and F. Marktscheffel, *ibid.*, **28**, 2150 (1963).

(8) In general, α-bromoacetates were used. These were prepared in high yield by esterification with α-bromoacetic acid or, in the case of acid-sensitive alcohols, α-bromoacetyl bromide was used.

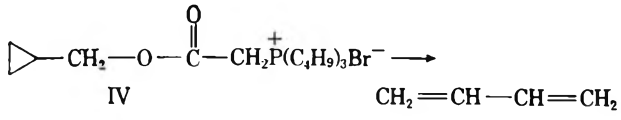
the production of carbon dioxide, a phosphonium halide, and an olefin derived from the alkoxy group of the salt (III).[9,10] It has been found that in general it is not necessary to isolate and purify the salts before pyrolysis. Indeed, the simplest and most generally applicable procedure developed involves mixing of the ester and tributylphosphine with cooling followed by heating at the appropriate temperature.

Decomposition of Primary Salts.—The salt from *n*-octyl bromoacetate and tributylphosphine was heated at 170° (bath) for 4 hr. to give a 72% yield of a mixture of octenes which was shown to consist of 60% 1-octene and 40% isomers. Repetition of this experiment at 110 mm., conditions under which the olefin was removed as formed, yielded 1-octene which was at least 96% pure.

Decomposition of the salt from tributylphosphine and *n*-butyl bromoacetate at 165° gave a mixture of butenes, 96% 1-butene, 3% *trans*-2-butene, and 1% *cis*-2-butene. Repetition of the experiment at 195° yielded 1-butene contaminated with *ca.* 1% of the isomeric 2-butenes. The total yields of olefins were not determined accurately but appeared to be excellent (*ca.* 90%).

Pyrolysis of the salt from tributylphosphine and 2-phenylpropyl bromoacetate at 210° yielded 74% of α-methylstyrene. Rearranged olefin, propenylbenzene, was not found in the product.

Decomposition of the cyclopropylcarbinyl salt (IV) at 155 and 200° yielded butadiene. It is not known whether methylenecyclopropane was formed and then isomerized to butadiene or whether rearrangement was synchronous with decomposition of IV.



IV $CH_2=CH-CH=CH_2$

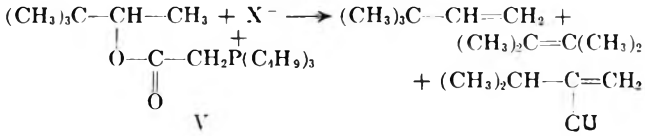
Decomposition of the *n*-decyl salt at 190° yielded 67% of mixed decenes. The composition of the olefin mixture was not determined nor was the reaction conducted under reduced pressure.[11]

The results of these experiments indicate that decomposition of primary salts has considerable merit as a means of introducing a terminal double bond. It is clear, though, that isomerization can occur if the olefin is not removed from the reaction mixture rapidly. There is some indication (cyclopropylcarbinyl system) that this may not always be possible.

Decomposition of Secondary Salts.—Decomposition of the 2-octyl salt at 190° yielded 76% mixed octenes, 2-heptyl at 280° yielded 76% mixed heptenes, and 1,2-diphenylethyl at 145° gave 90% *trans*-stilbene.

Pyrolysis of the salt from tributylphosphine and *sec*-butyl bromoacetate gave at 158 and 170° a mixture of butenes, whose composition varied little with the difference in pyrolysis temperature. The mixture consisted of 33% 1-butene, 48% *trans*-2-butene, and 19% *cis*-2-butene. The yields were excellent.

Both the chloride and bromide salts (V) were prepared and decomposed under a variety of conditions. In all cases, rearranged olefins, tetramethylethylene

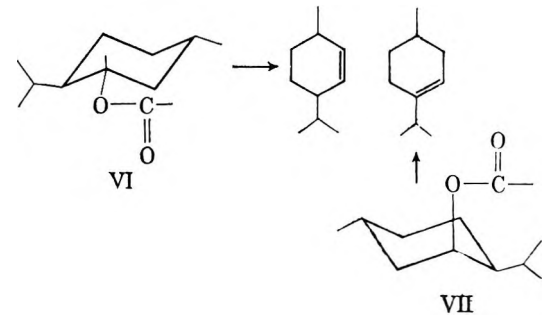


V CU

and 2,3-dimethyl-1-butene, were formed. The total yields were high. Pyrolysis of the bromide at 210° gave 92% of crude product which consisted of 82% of *t*-butylethylene, 11% tetramethylethylene, and 7% 2,3 dimethyl-1-butene. Other experiments gave good yields of mixed olefins but the per cent of unrearranged olefin was less than that obtained above.

The results of these experiments with secondary systems demonstrate that olefins can be obtained without difficulty; however, the possibility of skeletal rearrangement, presumably by a carbonium ion mechanism, detracts from its general application. In this sense acetate pyrolysis is considerably more specific; for example, the *t*-butylmethylcarbinyl system yields only *t*-butylethylene.[5] The mixture of isomers obtained from the *sec*-butyl system differs considerably from those found from acetate and xanthate pyrolyses and is considerably closer to the thermodynamic equilibrium mixture.[5]

Decomposition of Secondary Cycloalkyl Salts.—Decomposition of the cyclohexyl salt yielded 57% cyclohexene.[12] Decomposition of the *l*-menthyl (VI) and *d*-neomenthyl (VII) salts under a variety of conditions yielded a mixture of 2- and 3-menthenes. The 3-menthene invariably constituted at least 90% of the mixture. In one attempt to decompose VI at 120°



VI VII

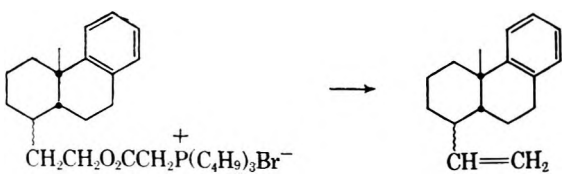
(0.01 mm.), the components, *i.e.*, ester and phosphine, distilled, thus demonstrating the reversibility of salt formation.

The salts from *cis*- and *trans*-2-phenylcyclohexanol were decomposed at 195° (*ca.* 0.5 mm.). The *trans* isomer yielded a mixture of 65% 1- and 35% 3-phenylcyclohexene while the *cis* led to 83% 1- and 17% 3-phenylcyclohexene. In a control experiment, 3-phenyl-

(9) For ease of discussion, salts derived from esters whose alkyl moiety is primary will be called primary salts, secondary salts, etc.

(10) Detailed descriptions of all of the experiments are available in the dissertations of C. J. R. and J. J. V., Rutgers, The State University, 1962. These theses are available on microfilm from University Microfilms, Ann Arbor, Mich.

(11) Recently Professor R. A. Barnes and E. P. Lira have pyrolyzed both diastereoisomeric salts illustrated under vacuum at 220°. Decomposition occurred in *ca.* 3 min. with the production of the terminal olefins in 80–90% yield.

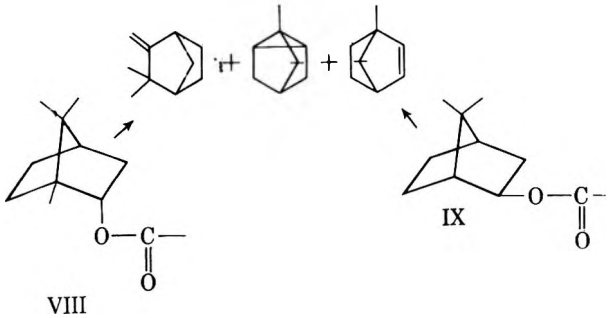


(12) Low yields are thought to be due mainly to mechanical losses and the relatively small amount of material decomposed in some cases.

cyclohexene was added to a reaction mixture and heated under reflux (180°) for 1 hr. The recovered olefin was essentially pure 3-phenylcyclohexene.

The results of these experiments and those in the menthyl series indicate that decomposition of the *d*-neomenthyl and *cis*-2-phenylcyclohexyl salts is not occurring by a *cis* elimination mechanism such as is proposed for the decompositions of acetates and xanthates.[5,13]

Decomposition of the bornyl (VIII) and isobornyl (IX) chlorides and bromides at 200° at atmospheric



VIII IX

pressure and 100 mm. led to mixtures of camphene, tricyclene, and bornylene. In general, only traces of bornylene were formed; however, with the bornyl salts at 100 mm., 4–7% bornylene was formed. Camphene constituted 82–87% of the product and tricyclene 13–18%.

Decomposition of Tertiary Salts.—Little work was done with tertiary systems. It was found that the salt from *t*-amyl chloroacetate and tributylphosphine decomposed at 136° to give 60% mixed olefins, 32% 2-methyl-1-butene, and 68% 2-methyl-2-butene. It is interesting to note that this ratio of isomers is entirely different from that found by acetate pyrolysis, 76% 2-methyl-1-butene and 24% 2-methyl-2-butene.[5]

Experimental[14]

Materials.—Tributylphosphine was obtained from FMC Co. It was fractionated, b.p. 124° (21 mm.), and stored in a serum-capped bottle under nitrogen. Triphenylphosphine was obtained from M & T Chemical Company. It was recrystallized from ethanol before use and had m.p. 81–82°. The alcohols used to prepare the esters were either available commercially or were synthesized by methods reported in the literature. In all cases their properties agreed well with those reported. Conventional esterification techniques proved satisfactory for the preparation of most α-halo esters. With tertiary and acid-sensitive alcohols the α-halo acid halide and pyridine were used. Most new α-halo esters were analyzed and gave satisfactory analytical results. In some cases where only small quantities of alcohol were available this was not done. The infrared spectra of all the esters were in agreement with the assigned structures.

Olefin Analysis.—The ratio of isomers of the olefins obtained from the pyrolyses was determined by g.l.p.c. except for the phenylcyclohexenes where ultraviolet measurements were employed. The identification of the various isomers by g.l.p.c. was conducted in the main by comparing retention times with those of known samples. These materials were either available commercially or were prepared by known methods. The per cent of each isomer present in the pyrolysates was determined by measuring and averaging the area under the curves obtained from three or more chromatograms. In all cases it was assumed that the thermal conductivities of the isomers were the same.

Decompositions.—The salts were formed at the outset of this work by reaction with triphenylphosphine. These materials were usually crystalline and easily purified. Most of the later work involved *in situ* formation of the salt by the cautious addition with cooling and stirring of tri-*n*-butylphosphine to the α-halo ester. A one-piece distillation head was attached and the salt was pyrolyzed by immersing the flask in a Wood's metal bath at the appropriate temperature. In cases of small quantities of salt the decompositions were often conducted in a molecular still. Several representative decompositions are described below.

• The salt from *sec*-butyl bromoacetate, 19.0 g. (0.10 mole), and tributylphosphine, 20.2 g. (0.01 mole), was pyrolyzed at 170°. The distillate was collected in a Dry Ice-cooled receiver. After 4 hr. distillation ceased. The mixture of butenes was analyzed by g.l.p.c. with a 2,5-hexanedione column at room temperature.

2-Phenylpropyl bromoacetate (5.0 g., 0.0201 mole) was allowed to react with 4.1 g. (0.0201 mole) of tributylphosphine. The salt was heated for 1 hr. at 210° (bath). No distillate was observed. The pressure was lowered to 20 mm. and 2.0 g. (74%) of material distilled. The infrared spectrum showed no trace of alcohol or ester and it was identical with that of α-methylstyrene. G.l.p.c. analysis confirmed the infrared analysis. With a 2-ft. silicone gum rubber column at 70° α-methylstyrene had a retention time of 4.0 min. and propenylbenzene 5.8 min. Only α-methylstyrene was found in the distillate.

The salt from 5.0 g. (0.0216 mole) of bornyl chloroacetate and 4.3 g. (0.0216 mole) of tributylphosphine was pyrolyzed in a molecular still at 200° (block) and 100 mm. After 4 hr., 2.1 g. (68%) of material was collected. The infrared spectrum of the product, when compared to that of an authentic sample of commercial camphene, showed it to be mainly camphene. The spectrum had a peak at 717 cm.$^{-1}$ which was not present in the commercial camphene. This band has been ascribed to bornylene.[15] G.l.p.c. analysis indicated three components with retention times of 5.0, 5.4, and 6.8 min. on a 15-ft. Carbowax column at 155°. The later two components appear in commercial camphene in the ratio 1:10. It was on this basis that the 5.4-min. component was assigned to tricyclene and the 6.4-min. component to camphene.

(13) This conclusion depends on there being little isomerization of the least-substituted olefin under the conditions of the experiment. The control experiment supports this.

(14) Analyses were by G. Robertson, Florham Park, N. J. The infrared spectra were obtained with Perkin-Elmer Model 21 or 137 instruments. Ultraviolet spectra were obtained with a Cary Model 11MS. Melting points and boiling points are uncorrected.

(15) J. McKenna and J. B. Slinger, *J. Org. Chem.*, **23**, 2759 (1958).

Tri-*t*-butyl Phosphite and Some of Its Reactions

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Tri-*t*-butyl phosphite, m.p. 4–5°, obtained in high conversion, was characterized by H^1 and P^{31} nuclear magnetic resonance (n.m.r.) and infrared spectroscopy. It reacted spontaneously with methyl bromide and methyl iodide to yield (in addition to the Michaelis–Arbuzov product, di-*t*-butyl methylphosphonate) di-*t*-butyl phosphonate as the major product. It reacted also with hexachlorocyclopentadiene to yield 5-*t*-butylpentachlorocyclopentadiene. Several quadruply connected derivatives were prepared and characterized by n.m.r. and infrared spectroscopy. The high reactivity of tri-*t*-butyl phosphite is attributed to both inductive and steric influences resulting from the presence of the three *t*-butoxy groups.

The need of tri-*t*-butyl phosphite, $(t\text{-}C_4H_9O)_3P$ (I), of known purity arose in the course of a separate investigation. Perusal of the literature indicated, however, a controversial background for this compound which has not been isolated and characterized in pure form.[2] P^{31} n.m.r. spectroscopy, shown to be uniquely apt for distinguishing between and characterizing various classes of phosphorus compounds,[3a] appeared to offer a convenient method to analyze both qualitatively and quantitatively for (and hence to follow the fate of) I in its formation and in its reactions.

A preliminary experiment, in which the literature procedure[2b,f,g] was followed, indicated that the reaction betwen phosphorus trichloride, *t*-butyl alcohol, and triethylamine, carried out between 0 and 5°, yielded, after filtration, a solution in which the precipitation of the amine hydrochloride continued during the time that the filtrate warmed up to room temperature. In subsequent experiments carried out under similar conditions, the reaction mixture was kept, therefore, at room temperature for 12–24 hr. before filtration. The weights of both the amine hydrochloride and of the residue, obtained after the evaporation of the solvent *in vacuo* at or below room temperature, indicated an essentially quantitative formation of I, which was characterized by H^1 n.m.r., P^{31} n.m.r., and infrared spectroscopy, refractive index, and melting point.

Although proven to be very reactive, a sample of the phosphite was kept under nitrogen at 25° for days and at *ca.* 0° for weeks without any noticeable decrease in the assay as indicated by P^{31} n.m.r. spectroscopy. When heated, however, above 50° *in vacuo*, a rapid evolution of isobutylene occurred so that, after 2 hr. at 80° and 50 mm., an essentially quantitative yield of di-*t*-butyl phosphonate, $(t\text{-}C_4H_9O)_2P(O)H$ (II), was obtained. The rapid decomposition above 50° indicates that distillation[2b,d,f,g] of the crude phosphite is not a suitable method of purification and that any operation at elevated temperature results in rapid decrease in the assay of the sample.

While handling I exposed to air, the ready formation of a crystalline crust was noted, which was identified as tri-*t*-butyl phosphate[2f,g,h] (III), m.p. 72–74°. When air was introduced in I at room temperature, a spontaneous exothermic reaction started and III was obtained in high yield. The ready formation of III contrasts with the resistance of triethyl phosphite to oxidation by air.[2f,g]

Both sulfur and selenium reacted exothermally with I and yielded the corresponding adducts, O,O,O-tri-*t*-butyl phosphorothioate, $(t\text{-}C_4H_9O)_3PS$ (IV), and O,O,O-tri-*t*-butyl phosphoroselenoate, $(t\text{-}C_4H_9O)_3PSe$ (V). On heating above 80°, IV started to decompose and yielded O,O-di-*t*-butyl thiolphosphate, $(t\text{-}C_4H_9O)_2P(O)SH$ (VI), m.p. 90–93°.

The high reactivity of I was indicated also by its participation at room temperature in the Michaelis–Arbuzov reaction. When the theoretical amount of methyl iodide was added to I at 5–10°, formation of white crystals was noted, the amount of which increased as the temperature rose owing to the mildly exothermic nature of the subsequent reaction. Soon (in about 15–20 min.), the crystals began to disappear, and after 30–40 min. a pale yellow solution resulted and the P^{31} n.m.r. showed it to be a mixture of II (major) and the Michaelis–Arbuzov product, di-*t*-butyl methylphosphonate (VII), $CH_3P(O)(O\text{-}t\text{-}C_4H_9)_2$. The structure of VII was proven, in addition to H^1 and P^{31} n.m.r. and infrared spectroscopy, also by its synthesis from sodium di-*t*-butyl phosphite and methyl iodide. I yielded VII spontaneously when brought into contact with methyl bromide also but not, under similar conditions, with methyl chloride.

The formation of II in major proportion in the reaction of I with methyl iodide requires some comment. The precipitation of the transient white crystals safely can be attributed to the formation of the phosphonium adduct[3b] (VIII).

$$(C_4H_9O)_3P: + CH_3I \longrightarrow \underset{\text{VIII}}{(C_4H_9O)_3P^+—CH_3\ I^-} \qquad (1)$$

The decay of VIII to VII takes place probably by an SN1 route[4] (eq. 2), which can be assisted by the partici-

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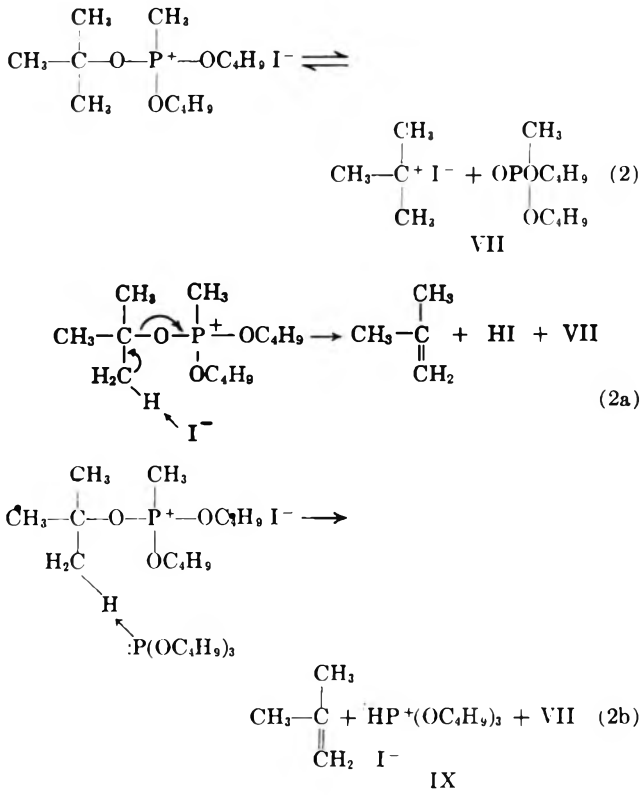
(2) (a) T. Milobendzki and A. Sachnowski, *Chem. Polski*, **16**, 34 (1917); (b) G. M. Kosolapoff, *J. Am. Chem. Soc.*, **74**, 4953 (1952); (c) W. Gerrard, M. J. D. Isaacs, M. Machell, K. B. Smith, and P. L. Wyvill, *J. Chem. Soc.*, 1920 (1953); (d) R. W. Young, *J. Am. Chem. Soc.*, **75**, 4620 (1953); (e) H. Goldwhite and B. C. Saunders, *J. Chem. Soc.*, 2409 (1957); (f) J. R. Cox, Jr., and F. H. Westheimer, *J. Am. Chem. Soc.*, **80**, 5441 (1958); (g) J. R. Cox, Jr., Ph.D. thesis, Harvard University, 1959; (h) J. R. Cox, Jr., M. G. Newton, and O. B. Ramsay, Abstracts, Joint Southeastern-Southwestern Regional Meeting of The American Chemical Society, New Orleans, La., Dec., 1961.

(3) (a) N. Muller, P. C. Lauterbur, and J. Goldenson, *J. Am. Chem. Soc.*, **78**, 3557 (1956); J. R. Van Wazer, C. F. Callis, J. N. Shoolery, and R. C. Jones, *ibid.*, **78**, 5715 (1956); H. Finegold, *Ann. N. Y. Acad. Sci.*, **70**, 875 (1958); R. A. Y. Jones and A. R. Katritzky, *Angew. Chem.*, **74**, 60 (1962); L. C. D. Groenweghe, L. Maier, and K. Moedritzer, *J. Phys. Chem.*, **66**, 901 (1962). (b) Low solubility of phosphonium salts in nonpolar solvents, such as ether, is well-known and contrasts with the good solubility of the related triply and quadruply connected uncharged structures in the same solvent. For instance, in the preparation of the methiodide of triphenyl phosphite, *i.e.*, $CH_3P^+(OC_6H_5)_3I^-$, ether is used to elute the unconverted starting materials [S. R. Landauer and H. N. Rydon, *J. Chem. Soc.*, 2224 (1953)].



pation of the halide (eq. 2a) or of the phosphite (I) (eq. 2b).

Decay of IX probably follows a route similar to the decay of VIII by eq. 2, 2a, or 2b.

$$IX \longrightarrow II + \text{coproducts} \qquad (3, 3a, 3b)$$

Consumption of I by one of the coproducts of eq. 2a, HI, can also take place.[5] This step also results in the formation of IX.

Compound I reacted readily also with hexachlorocyclopentadiene and yielded 5-*t*-butylpentachlorocyclopentadiene (X)[4] and di-*t*-butylphosphorochloridate, $(t\text{-}C_4H_9O)_2P(O)Cl$ (XI), identified by P^{31} n.m.r. The H^1 and P^{31} n.m.r. frequencies of the phosphorus compounds listed are presented in Table I.

TABLE I

P^{31} AND H^1 N.M.R. CONSTANTS

	Compound	δ_{P31}, p.p.m.[a]	J_{H-P}, c.p.s.	δ_{H^1} (t-C_4H_9), p.p.m.[b]
I	$(t\text{-}C_4H_9O)_3P$	−138.2		1.34
II	$(t\text{-}C_4H_9O)_2P(O)H$	+3.8	678	1.45[c]
III	$(t\text{-}C_4H_9O)_3PO$	+13.3		1.46
IV	$(t\text{-}C_4H_9O)_3PS$	−41.2		1.53
V	$(t\text{-}C_4H_9O)_2PSe$	−31.1		1.57
VI	$(t\text{-}C_4H_9O)_2P(O)SH$	−25.0		1.54
VII	$(t\text{-}C_4H_9O)_2P(O)CH_2$	−21.2	17.3	1.44[d]
XI	$(t\text{-}C_4H_9O)_2P(O)Cl$	+5.8		
XII	$(t\text{-}C_4H_9O)_2PCl$	−170.3		

[a] External (capillary), 85% H_3PO_4 reference. [b] Downfield from internal tetramethylsilane reference. [c] δ_{H-P} = 6.61 p.p.m.; J_{P-H} = 676 c.p.s. [d] δ_{CH_3P} = 1.26 p.p.m.; J_{P-H} = 17.4 c.p.s.

The high reactivity of I is probably the result of two major influences: the inductive effect of the *t*-butyl groups and the steric conditions around both the phosphorus and the central carbon atom in the *t*-butyl groups. The effect of the electron-releasing *t*-butyl substituent *via* induction in organic reactions has been studied extensively and interpreted.[6] The P^{31} n.m.r. shifts support the specific role attributable to the *t*-butyl group in increasing the electron density on the site of substitution and suggest that, compared with the normal alkyl analogs, the *t*-butyl increases the electron density on phosphorus *via* the linking oxygen, as indicated by the more effective shielding (high-field shift) in the n.m.r. of the derivatives of I.[7] The high electron density around the phosphorus thus is partly responsible for the enhanced nucleophilicity of I, as, for instance, reflected by the Michaelis–Arbuzov reaction.

Analysis of P^{31} n.m.r. data on I and related structures indicates considerable steric congestion in the trivalent species.[7] Although measurements of bond angles of the organic P(III) esters are not reported in the literature, the interpretations of n.m.r. chemical shifts are compatible with structures in which the esters of phosphorous acid primarily utilize p-orbitals[7] and hence have bond angles not far from the theoretical value of 90°. When the substituents are bulky, as in the case of *t*-butyl, steric congestion arises and the repulsion between the substituent groups results in widening of the bond angles,[7] which occurs through increased utilization of sp^3-orbitals.[8] The enhanced reactivity of I over its straight chain analogs thus is partly attributable to the "abortive bond"[8] formed by the inclusion of the unshared pair of electrons of the phosphorus in the sp^3 hybrid and to the decrease of strain in the transformation of I into quadruply connected, tetrahedral structures, which are known to have expanded bond angles close to the theoretical value of 109° 28′.

Much of the chemistry of I is attributable to the ready detachment of this bulky substituent as a *t*-butyl carbonium ion. The ease with which SN1 or SN1 type of reactions (eq. 2–3b) takes place[2e,9] is due to the formation of $(CH_3)_3C^+$, which eliminates isobutylene and makes the step, when carried out at or above room temperature and in an open system, essentially irreversible.[10]

Experimental

N.m.r. Spectra.—Proton spectra were obtained with an A-60 n.m.r. spectrometer, manufactured by Varian Associates, Palo Alto, Calif., using tetramethylsilane as internal reference. P^{31} measurements were made on a Varian Associates HR-60 high-resolution spectrometer equipped with a Model V-4311 fixed-frequency RF unit, operating at 24.288 Mc. in a magnetic field of 14,092 gauss. Referencing was done by an audio-side-band

(4) The transfer of *t*-butyl in preference to ethyl was demonstrated in the alkylation of hexachlorocyclopentadiene by *t*-butyl diethyl phosphite [V. Mark, *Tetrahedron Letters*, 295 (1961)] and interpreted as taking place *via* an SN1 route [V. Mark, Abstracts, 139th National Meeting of the American Chemical Society, St. Louis, Mo., March 1961, p. 46-O].

(5) For a study of the dealkylation of tributyl phosphite by hydrogen halides, see W. Gerrard and E. G. G. Whitebread, *J. Chem. Soc.*, 914 (1952).

(6) See, for example, C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell Univ. Press, Ithaca, N. Y., 1953, pp. 64–71, and several pertinent chapters listed in the Index.

(7) V. Mark and J. R. Van Wazer, a correlation of molecular structure with the n.m.r. shifts of phosphorus compounds having tertiary alkyl substituents will be published separately.

(8) J. R. Van Wazer, "Phosphorus and Its Compounds," Interscience Publishers, Inc., New York, N. Y., 1958, pp. 70, 53.

(9) For a comparison and a contrasting of the hydrolysis of tri-*t*-butyl phosphate with the primary trialkyl phosphates (in which the P–O, and not the C–O, bonds are cleaved), see ref. 2h.

(10) The formation of isobutylene was actually observed in the Michaelis–Arbuzov reactions of I.

modulation technique, using (as an external reference) 85% phosphoric acid in a sealed 1.0-mm.-o.d. capillary tube inserted in the sample. Peak-position measurements could be reproduced to within ±0.1 p.p.m. Positive shifts (δ) are upfield.

Tri-*t*-butyl Phosphite (I).—To a three-necked flask equipped with a Hershberg stirrer, dropping funnel, thermometer, and a vent line leading to a nitrogen atmosphere, there was charged a solution of 74.1 g. (1.0 mole) of *t*-butyl alcohol and 111.3 g. (1.1 moles) of triethylamine in 400 ml. of anhydrous ether. The solution was cooled to +2 to +5°, after which a solution of 45.8 g. (0.33 mole) of phosphorus trichloride in 100 ml. of anhydrous ether was added at such a rate as to keep the temperature of the resultant slurry around +5°. After the addition was completed in about 2 hr., the slurry was stirred for an additional hour at +2 to +5°. A filtered sample of a parallel experiment taken at this time deposited, on warming to room temperature, triethylamine hydrochloride. The P^{31} n.m.r. of a sample stripped of the solvent and triethylamine below +5° indicated the presence of di-*t*-butyl phosphorochloridite, $(t\text{-}C_4H_9O)_2PCl$ (XII), $\delta = -170.3$ p.p.m.) and of I ($\delta = -138.2$ p.p.m.).

The ice bath was removed and the slurry was kept at room temperature (24°) for 12–18 hr. Filtration through a sintered-glass funnel and rinsing of the filter cake (which, after drying, weighed 136.2 g., 99%) yielded a clear solution. After stripping of the solvent *in vacuo* at 5–15°, a pale yellow oil was obtained, $n^{25}D$ 1.4205, the weight (80.6 g.) of which indicated a 96.7% conversion. P^{31} n.m.r. of the sweet smelling oil showed a composition of 90% of I and 10% of II. The yield of I accordingly was 87%. The oil solidified at 0° to a white crystalline mass. The large crystals, which had a feather-like structure, melted at 4–5°. Infrared maxima of the oil were 3.35 (s)[11] C–H; 6.82 (w), 7.21 (m), and 7.34 (s) *t*-C_4H_9; 7.91 (m) P=O, due to the presence of II; 8.04 (m); 8.52 (s); 9.67 (m); 10.10 (s) P–O–C; 10.58 (s); 11.04 (s); 12.40 (m); 13.68 (w); and 14.56 (m) μ. The n.m.r. data are summarized in Table I.

Di-*t*-butyl Phosphonate (II).—Considerable frothing began when a sample of I (17.7 g.) was heated to 50–60° at 20–30 mm. After the gas evolution subsided, the pale yellow oil (which now weighed 14.3 g.) was fractionated to yield II as a colorless liquid, b.p. 42° at 0.4 mm., $n^{23}D$ 1.4186.[2c,d,e] The infrared maxima checked with those reported.[2d,e]

Tri-*t*-butyl Phosphate (III).—The introduction of air into I (8.0 g.) caused a mildly exothermic reaction, in the course of which the temperature rose to 35°. In about 1 hr., the sample solidified. Recrystallization from pentane yielded large colorless plates of II, m.p. 72–74° (lit.[2f,g] m.p. 71–75°). Infrared maxima were 3.33 (s) C–H; 6.73 (m), 7.14 (s), and 7.26 (s) *t*-C_4H_9; 7.88 (s) P=O; 8.47 (m); 9.60 (s); 10.06 (s) P–O–C; 10.88 (m); 12.02 (w); 12.32 (w); 13.28 (w); 14.12 (m); 14.50 (w); and 15.28 (w) μ.

Anal. Calcd. for $C_{12}H_{27}O_4P$: C, 54.11; H, 10.22; P, 11.59. Found: C, 53.9; H, 10.2; P, 11.4.

O,O,O-Tri-*t*-butyl Phosphorothioate (IV).—The addition of sulfur powder to a solution of 14.6 g. of I in 30 ml. of ether was accompanied by an exothermic reaction in which the sulfur was consumed. The solution was allowed to stand with excess sulfur overnight, after which filtration and evaporation of the solvent *in vacuo* yielded IV in form of a pale yellow oil (16.0 g.), $n^{25}D$ 1.4482. P^{31} n.m.r. ($\delta = -41.2$ p.p.m.) confirmed the structure and indicated the presence of small amounts (~5%) of II and III. Infrared maxima were 3.36 (s), 6.82 (m), 7.21 (s), 7.35 (s), 8.05 (s), 8.58 (s), 9.68 (s), 10.16 (s), 10.95 (s), 12.17 (s), 13.56 (s), 14.16 (w), and 14.57 (m) μ.

O,O-Di-*t*-butyl Phosphorothioic Acid (VI).—Distillation of IV (14.6 g.) was only partly successful. Although pure IV was obtained as a colorless oil, b.p. 80° at 0.4 mm., the bulk of the sample decomposed with strong gas evolution when the pot temperature surpassed 85°. Even during the decomposition of the sample, a solid began to separate in the flask and, at the end of the reaction, the entire content of the flask solidified to an off-white solid, which weighed 5.7 g. Recrystallization from ether yielded white crystals, m.p. 90–93° (decomposition with gas evolution), which were identified as O,O-di-*t*-butyl phosphorothioic acid, $(t\text{-}C_4H_9O)_2P(O)SH$, by P^{31} n.m.r. ($\delta = -25.0$ p.p.m.), elemental analysis (Calcd. for $C_8H_{19}O_3PS$: C, 14.17. Found: S, 13.6.), and infrared analysis. The latter showed the following maxima in a Nujol mull: 3.4 (s, broad); 4.2 (m, broad) probably sh; 6.79 (m), 7.10 (w), and 7.25 (m) *t*-C_4H_9; 8.14 (s, broad) hydrogen-bonded P=O; 8.60 (s); 9.88 (s) P–O–C; 10.80 (s); and 12.3 (m) μ.

O,O,O-Tri-*t*-butyl Phosphoroselenoate (V).—The addition of selenium in excess to a solution of 2.5 g. of I in 5 ml. of ether was exothermic and yielded V in form of a colorless oil. The structure of V was identified by its P^{31} n.m.r. frequency ($\delta = -31.1$ p.p.m.), which showed the presence of II and III only in small amounts (~10%) in the sample.

Di-*t*-butyl Methylphosphonate (VII). **A.** ***Via* the Michaelis–Arbuzov Reaction.**—To an ice-cold sample of crystalline I (31.8 g., 0.127 mole) there was added, without solvent, 20.0 g. (0.141 mole) of methyl iodide. The crystals dissolved readily, but in about 6 min. a precipitate of smaller crystals began to separate, the amount of which increased for about 10 min. more, parallel with a spontaneous increase in temperature to 29°. In another 5 min., the crystals began to dissolve and, in about 20 min. more, a clear solution resulted while the temperature decreased to 22°. P^{31} n.m.r. of the sample gave the following pattern: a quadruplet at -21.2 ± 0.1 p.p.m. (about 5%), $J \approx 17.3$ c.p.s.; the doublet of II at -10.4 and $+17.4$ p.p.m., $J = 678$ c.p.s. (about 90%); and the singlet of III (about 5%) at $+13.6 \pm 0.1$ p.p.m.

Essentially the same results were obtained when methyl bromide (excess) was added at 0° to I. Transient formation of a white, crystalline precipitate was noted again during the mildly exothermic reaction. No reaction was observed within a 1-hr. test period when methyl chloride was introduced into I at 20 to 25°.

B. ***Via* the Michaelis–Becker Reaction.**—The sodium salt of II was prepared in the form of a thick paste by refluxing 16.2 g. (0.0835 mole) of II with 1.92 g. (0.0835 g.-atom) of sodium in 120 ml. of dry dioxane, with the aid of a Hershberg stirrer. After the paste was cooled to room temperature, 50 ml. of ether was added to give a stirrable mixture, and 15.0 g. (0.106 mole) of methyl iodide was added dropwise to keep the strongly exothermic reaction below 30°. After the addition was completed (in 30 min.), the slurry was refluxed for 1 hr., filtered, and the ether was removed by distillation. Pentane (30 ml.) was added to the resulting oil and the solution was washed three times with water in order to remove the dioxane. Drying of the solution and evaporation of the pentane yielded a colorless oil (8.3 g.), the P^{31} n.m.r. of which exhibited the same quadruplet as under A (about 60%), and also the doublet of II (about 40%). The quadruplet accordingly belongs to di-*t*-butyl methylphosphonate (VII), and this assignment is confirmed also by H^1 n.m.r. (see Table I). The yield of VII in the Michaelis–Becker reaction is accordingly 29% but can be increased, if care is taken to completely transform II into its sodium salt. Attempted fractionation was not successful in separating VII from II, owing apparently to close boiling points of the two compounds (49° at 1 mm.). Vapor phase chromatography (14 ft. × 1/4 in., 5% Dow Corning 550 silicon on T-6 firebrick) was equally unsuccessful and runs at column temperatures between 190 and 50° indicated thermal decomposition.

Infrared maxima attributable to VII were 3.34 (s), 6.24 (w), 6.67 (w), 7.08 (w), 7.20 (m), 7.31 (s), 7.68 (m), 7.96 (s), 9.12 (s, broad), 9.90 (s, broad), 11.60 (m, broad), 12.55 (s, broad), 13.04 (m), 13.28 (w), 13.63 (w), and 15.12 (w) μ.

5-*t*-Butylpentachlorocyclopentadiene (X).—To a solution of 12.5 g. (0.05 mole) of I in 80 ml. of ether, there was added dropwise, in the course of 20 min., a solution of 13.6 g. (0.05 mole) of hexachlorocyclopentadiene in 20 ml. of ether. During the resulting exothermic reaction, the temperature rose to 32° and the solution acquired a pale brown color. Evaporation of the solvent under vacuum yielded a light brown oil, the P^{31} n.m.r. of which indicated the presence of di-*t*-butyl phosphorochloridate, $(t\text{-}C_4H_9O)_2P(O)Cl$ (XI), as the major component (about 70%) in addition to II and III, which were present to about 20 and 10%, respectively. Hydrolysis and chromatography over alumina yielded X (m.p. 62–63°)[4] in 40% yield (5.9 g.).

(11) s = strong, m = medium, w = weak.

Heterocyclic Diamides of Phosphorus from Imidazole and Pyrrole. Synthesis and Utilization in Polymerization Reactions[1]

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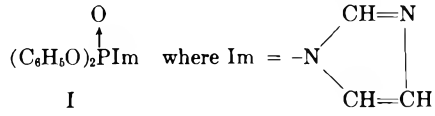
Diimidazol-1-ylphenylphosphine oxide (DIPPO) has been prepared and shown to react transamidatively with monoamines and diamines. With the latter, polymeric products were obtained. The polymer obtained from DIPPO and 5,5′-bibenzimidazole is thermally stable to about 360°. Diimidazol-1-yl-N-methyl-N-phenylphosphinic amide and imidazol-1-yl-N-methyl-N-phenylphenylphosphinic amide were found to be exceptionally inert toward hydrolysis and nucleophilic substitution reactions. Dipyrrol-1-ylphenylphosphine oxide has been prepared and found less reactive than DIPPO. It yielded an oligomer with 5,5′-bibenzimidazole.

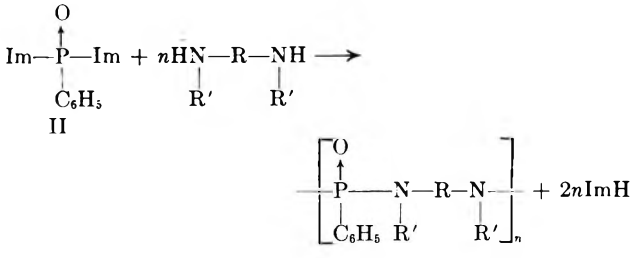
Baddiley and co-workers[3] have reported the synthesis of diphenyl imidazol-1-ylphosphonate (I) and have



I

described its reactions with amines and alcohols to form the corresponding amides and esters. Staab[4] reported the synthesis of a number of acyl imidazoles and demonstrated their reactivities. In subsequent publications[5] Staab and others described imidazole derivatives of phosphoric acids[6,7] and thionyl chloride,[7,8] as well as carbonyl diimidazole.[9]

On the basis of the preceding work, it was believed that the difunctional compound, diimidazol-1-ylphenylphosphine oxide, DIPPO (II), would be a useful intermediate for transamidative preparation of polymeric phenylphosphonamides.

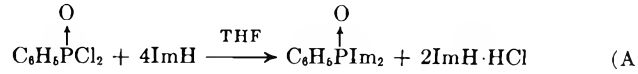


II

The displaced imidazole, unlike the hydrogen halide eliminated from the reaction of a phosphorus halide with an amine, would not react with the amine, thus permitting full utilization of the reactants and simplifying isolation of the main product.

DIPPO, not previously reported, was obtained in good yield by two methods (A and B, col. 2).

For most of our experiments, tetrahydrofuran (THF) solutions of DIPPO were utilized, and the compound was prepared by method A. When a very pure product was required, method B was applied.



(A)

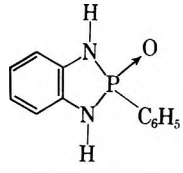
(B)

DIPPO was found to be thermally stable to *ca.* 360° when heated *in vacuo*. It was, however, quickly hydrolyzed by atmospheric moisture. The latter property necessitated the use of drybox and inert atmosphere techniques during its preparation and handling.

The reactivity of DIPPO toward representative monoamines, which would not yield polymeric products, was determined prior to using it as starting material in condensation polymerization reactions. Substitution of both imidazolyl groups was achieved with cyclohexylamine and aniline, yielding, respectively, N,N′-dicyclohexylphenylphosphonic diamide and N,N′-diphenylphenylphosphonic diamide. These compounds have been described by V. Gutmann, *et al.*,[10] and by Michaelis.[11]

Monosubstitution occurred ordinarily in model reactions between DIPPO and secondary aryl monoamines. Forcing conditions with N-methylaniline resulted in displacement of both imidazolyl groups, but this did not occur with diphenylamine. Failure of the monosubstituted derivative to undergo further substitution in this case is attributed to steric hindrance by the diphenylamino group, and the relatively poor nucleophilicity of aromatic amines. The reduced reactivity due to N-methylanilide substitution on phosphorus was shown further by the properties of diimidazol-1-yl-N-methyl-N-phenylphosphinic amide (III), $C_6H_5(CH_3)NP(O)(Im)_2$, which was synthesized. It has a relatively long half-life (about 4 hr.) in water at room temperature, and does not react readily with aniline in refluxing THF.

With *o*-phenylenediamine, DIPPO reacted to yield 1,3-dihydro-2-phenyl-2H-1,3,2-benzodiazaphosphole 2-oxide (IV) previously reported by another synthesis.[12]



IV

(1) Work reported in this publication was supported in part by the Air Force Materials Laboratory, Wright-Patterson Air Force Base, Ohio, under Contract AF 33(616)-7853.

(2) Central Research Department, Monsanto Chemical Company, St. Louis 66, Mo.

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(6) H. A. Staab, H. Schaller, and F. Cramer, *ibid.*, **73**, 736 (1959).

(7) L. Birkofer, W. Gilgenberg, and A. Ritter, *ibid.*, **73**, 143 (1961).

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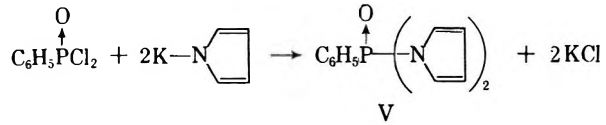
TABLE I

X-RAY POWDER DIFFRACTION DATA

Name and formula		Three strongest lines, d, Å.		
Diimidazol-1-ylphenylphosphine oxide, $C_6H_5P(O)(C_3H_3N_2)_2$		4.013 (100)	4.068 (91)	3.07 (78)
Imidazole hydrochloride, $C_3H_4N_2 \cdot HCl$		3.670 (100)	4.095 (83)	3.762 (81)
N,N′-Dicyclohexylphenylphosphonic diamide, $C_6H_5P(O)(NC_6H_{11})_2$		10.3 (100)	4.73 (40)	5.11 (7)
N,N′-Diphenylphenylphosphonic diamide, $C_6H_5P(O)(NHC_6H_5)_2$		9.07 (100)	4.541 (64)	4.201 (37)
1,3-Dihydro-2-phenyl-2H-1,3,2-benzodiazophosphole 2-oxide, $C_6H_5P(O)NC_6H_4NH$-2		8.63 (100)	4.439 (40)	5.44 (37)
Imidazol-1-ylsodium, $C_3H_3N_2Na$		4.022 (100)	5.025 (57)	2.793 (28)
Imidazol-1-yl-N-methyl-N-phenylphenylphosphinic amide, $C_6H_5P(O)(C_3H_3N_2)[N(CH_3)C_6H_5]$		3.995 (100)	8.0 (80)	7.2 (50)
N,N′-Dimethyl-N,N′-diphenylphenylphosphonic diamide, $C_6H_5P(O)[N(CH_3)C_6H_5]_2$		8.5 (100)	4.695 (35)	6.02 (27)
				5.95 (31)
Imidazol-1-yl-N,N-diphenylphenylphosphinic amide, $C_6H_5P(O)(C_3H_3N_2)[N(C_6H_5)_2]$	Form I	9.24 (100)	4.004 (90)	8.49 (75)
	Form II	8.76 (100)	3.909 (95)	5.22 (90)
Diimidazol-1-yl-N-methyl-N-phenylphosphinic amide, $C_6H_5(CH_3)NP(O)(C_3H_3N_2)_2$		6.03 (100)	3.715 (65)	3.453 (65)
Pyrrol-1-ylpotassium, C_4H_4NK		2.710 (100)	3.079 (17)	4.708 (12)
Dipyrrol-1-ylphenylphosphine oxide, $C_6H_5P(O)(NC_4H_4)_2$		7.53 (100)	4.390 (84)	3.826 (58)
5,5′-Bibenzimidazole, $C_{14}H_{10}N_4$		3.446 (100)	5.20 (53)	5.47 (40)
5,5′-Bibenzimidazole monohydrate, $C_{14}H_{10}N_4 \cdot H_2O$		13.7 (100)	5.053 (97)	6.84 (76)
5,5′-Bibenzimidazole monohydrochloride, $C_{14}H_{10}N_4 \cdot HCl$		3.363 (100)	6.01 (94)	5.081 (71)
5,5′-Bibenzimidazole dihydrochloride dihydrate, $C_{14}H_{10}N_4 \cdot 2HCl \cdot 2H_2O$		4.611 (100)	8.76 (87)	6.46 (57)
5,5′-Bibenzimidazole dihydrochloride monohydrate, $C_{14}H_{10}N_4 \cdot 2HCl \cdot H_2O$		3.215 (100)	6.56 (30)	4.646 (25)
3,3′-Diaminobenzidine, $(NH_2)_2C_6H_3C_6H_3(NH_2)_2$		4.783 (100)	5.31 (49)	9.4 (37)
3,3′-Diaminobenzidine tetrahydrochloride, $(NH_2)_2C_6H_3C_6H_3(NH_2)_2 \cdot 4HCl$		3.700 (100)	3.597 (78)	3.414 (53)

Polymers were prepared from DIPPO and difunctional amines by melt polymerization techniques. 1,6-Hexanediamine gave a polymer comparable to that obtained by interfacial methods from phenylphosphonic dichloride,[13,14] but having a higher softening temperature. With piperazine, DIPPO reacted to give a water-soluble polymer that would form a brittle film. 4,4′-Methylenedianiline yielded a polymer that could be cast into a flexible (though weak) film from dimethylformamide. Aryl diamines, including *p*-phenylenediamine and benzidine, gave polyphosphonamides with higher softening and decomposition temperatures than those made from aliphatic diamines. The secondary aryl diamine, N,N′-diphenyl-*p*-phenylenediamine, yielded no polymer. A low molecular weight polymer, perhaps more correctly called an oligomer, was obtained from DIPPO and 5,5′-bibenzimidazole. Thermogravimetric analysis indicated that this product began to decompose thermally at 360° in helium.

It is desirable in a condensation polymerization that the by-products formed be readily removable from reaction systems at temperatures at which the reactions are conducted. In an attempt to improve our synthesis of polymeric phosphorus amides by meeting this requirement, we synthesized dipyrrol-1-ylphenylphosphine oxide (V).



V

We determined its thermal stability and tested its reactivity toward representative amines. It was hoped that the greater volatility of pyrrole (b.p. 131°) compared with that of imidazole (b.p. 256°) would be advantageous.

The decomposition temperature of V, by the method of Blake and co-workers,[15] is 242°. Compound V proved to be unreactive toward cyclohexylamine and aniline at the respective reflux temperatures. Unlike DIPPO, it is practically inert toward water, with an extrapolated half-life in the order of weeks rather than seconds. This parallels the observation of Staab[5] on the rate of hydrolysis of N-acetylpyrrole and N-acetylimidazole.

In polymer synthesis, dipyrrol-1-ylphenylphosphine oxide was found to be a much less reactive intermediate than DIPPO. An oligomer of low molecular weight (degree of polymerization ~3) was obtained in a reaction with 5,5′-bibenzimidazole when the reaction was conducted at high temperature (*ca.* 300°). N,N′-Diphenyl-*p*-phenylenediamine did not react with V at 220°. Although pyrrole can be readily removed from the system, the low decomposition temperature and relatively low reactivity of V toward nucleophilic reagents greatly limit the usefulness of this reaction. The decreased reactivity of V, compared with DIPPO, is ascribed mainly to increased covalent nature of its P–N bond.

P^{31} nuclear magnetic resonance (n.m.r.) chemical shifts are reported for many of the compounds as an aid to identification. The relationship between the chemical shifts and the structure of these and other phosphorus–nitrogen compounds has been discussed elsewhere.[16]

Experimental[17]

Diimidazol-1-ylphenylphosphine Oxide (II) from Phenylphosphonic Dichloride and Imidazole. Method A.—To a stirred

(13) D. M. Harris, R. L. Jenkins, and M. L. Nielsen, *J. Polymer Sci.*, **35**, 540 (1959).

(14) M. S. Akutin, L. A. Rodivilova, K. P. Baibakov, and L. F. Nekrasova, Russian Patent 125,566 (April 13, 1959).

(15) E. S. Blake, *et al.*, *J. Chem. Eng. Data*, **6**, 87 (1961).

(16) M. L. Nielsen and J. V. Pustinger, Jr., *J. Phys. Chem.*, **68**, 152 (1964).

(17) All boiling points are uncorrected; all melting points are corrected. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., and by Schwarzkopf Laboratories, Woodside, N. Y. The P^{31} n.m.r. spectra were obtained with a Varian Model V-4300-2 high resolution n.m.r. spectrometer at a frequency of 16.192 Mc. and field intensity of approximately 9400 gauss. Chemical shifts are reported with reference to 85% H_3PO_4. H^1 n.m.r. spectra were recorded with a Varian Model A-60 spectrometer at a frequency of 60 Mc. and field intensity of about 14092 gauss. X-Ray diffraction data of analytically pure compounds were submitted for the A.S.T.M. X-Ray Powder Data File; the three strongest lines are shown in Table I. Infrared spectra were transmitted to the American Documentation Institute.

solution of 17.0 g. (0.25 mole) of imidazole in 400 ml. of THF (dried by distillation from lithium aluminum hydride and stored over sodium wire) was added a solution of 12.2 g. (0.0625 mole) of redistilled phenylphosphonic dichloride in 75 ml. of dry THF over a period of 15 min. under nitrogen. The reaction mixture was stirred at reflux for 3 hr. After cooling to room temperature, the imidazole hydrochloride was collected by filtration, and the product was obtained as its THF solution. Titration of a hydrolyzed aliquot with standard base showed that the reaction was essentially quantitative. Removal of the solvent by distillation left a white solid which, after drying under vacuum, melted at 99–104° and gave a single P^{31} n.m.r. peak at −6 p.p.m. Elemental analysis indicated that the product was somewhat impure.

Anal. Calcd. for $C_{12}H_{11}N_4OP$: C, 55.81; H, 4.29; N, 21.70; P, 12.00. Found: C, 52.67; H, 4.66; N, 18.20; P, 12.69.

As a modification of this method, toluene was used successfully in place of THF, the product being obtained as crystals.

Diimidazol-1-ylphenylphosphine Oxide (II) from Phenylphosphonic Dichloride and Imidazol-1-ylsodium. Method B.—Imidazol-1-ylsodium was prepared from imidazole and sodium in liquid ammonia at −40 to −33°,[18] with ferric nitrate as catalyst. Upon evaporation of ammonia there remained an occlusion compound of the composition $C_3H_3N_2Na{\cdot}0.5NH_3$. Ammonia was removed under vacuum at 70–194°. Yield of the very light tan product was 98.2%.

Anal. Calcd. for $C_3H_3N_2Na$: C, 40.01; H, 3.36; N, 31.11; Na, 25.53. Found: C, 40.26; H, 3.50; N, 31.10; Na, 25.33.

Imidazol-1-ylsodium (36.0 g., 0.40 mole) was partly dissolved in 400 ml. of dimethoxyethane (DME). Phenylphosphonic dichloride (39.0 g., 0.20 mole) was added over a period of 42 min. The reaction mixture was stirred at room temperature for 4 hr. and subsequently at reflux for 1.5 hr. Solids were removed by centrifuging, the solvent was evaporated under reduced pressure, and the crude product was recrystallized from hot toluene. There was obtained 23.8 g. (46%) of crystalline II, m.p. 115.5–117.0°, P^{31} n.m.r. shift in DME solution of −6 p.p.m.

Anal. Calcd. for $C_{12}H_{11}N_4OP$: C, 55.81; H, 4.29; N, 21.70; P, 12.00. Found: C, 55.78, 55.76; H, 4.26, 4.44; N, 21.71, 21.58; P, 11.99, 12.11.

N,N′-Dicyclohexylphenylphosphonic Diamide.—A solution of II in THF reacted at room temperature with excess cyclohexylamine substantially quantitatively to yield N,N′-dicyclohexylphenylphosphonic diamide, m.p. 166–167° (lit.[10] m.p. 167–168°).

N,N′-Diphenylphenylphosphonic Diamide.—A solution of 0.0305 mole of DIPPO in 225 ml. of THF reacted with 6.6 g. (0.071 mole) of aniline at reflux for 2 hr. under nitrogen to yield 17.2 g. (78%) of product, m.p. 211.5–213°, from ethanol (lit.[11] m.p. 211°). When the reaction was run at room temperature, a yield of 22% was obtained in 2 hr.

Imidazol-1-yl-N-methyl-N-phenylphenylphosphinic Amide (VI).—A mixture of 0.026 mole of DIPPO and 0.026 mole of N-methylaniline was heated stepwise to 235° over a 3-hr. period under nitrogen. Vacuum distillation yielded 0.021 mole of imidazole and 5.9 g. (77%) of product at a pot temperature of 205–215° (1 mm.), m.p. 132–139°, P^{31} n.m.r. chemical shift (in chloroform) of −16.6 p.p.m.

Anal. Calcd. for $C_{16}H_{16}N_3OP$: C, 64.64; H, 5.42; N, 14.13; P, 10.42. Found: C, 64.44; H, 5.62; N, 13.89; P, 10.36.

The material is sensitive to moisture; upon standing in air, it was degraded to a viscous brown tar having the odor of N-methylaniline.

N,N′-Dimethyl-N,N′-diphenylphenylphosphonic Diamide (VII).—A mixture of 0.0209 mole of DIPPO and 0.0418 mole of N-methylaniline was heated under nitrogen at 180° for 3 hr., then distilled under vacuum to remove excess N-methylaniline and imidazole (0.030 mole). The latter was collected on a cold-finger condenser. The reaction was continued with additional N-methylaniline (0.0274 mole) at 200° for 13 hr., after which the volatile products were distilled. The total amount of imidazole recovered was 0.0390 mole. The main product, b.p. 170–200° (1 mm.) pot temperature, consisted of 5.3 g. (76%) of $C_6H_5P(O)[N(CH_3)C_6H_5]_2$, m.p. 100–101° from heptane, identical by X-ray diffraction analysis with a sample prepared from the reaction of sodium N-methyl-N-phenylamide and phenylphosphonic dichloride.[19] A melting point of 92–93.5° has been reported by Gutmann, *et al.*[20]

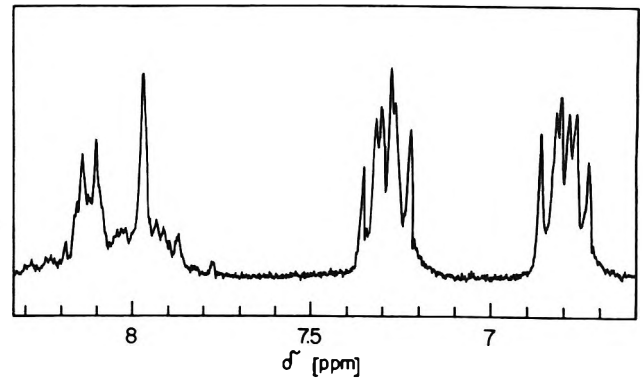


Fig. 1.—H^1 n.m.r. spectrum of dipyrrol-1-ylphenylphosphine oxide (14.8 wt. % solution in chloroform).

Imidazol-1-yl-N,N-diphenylphenylphosphinic Amide (VIII).—A mixture of 0.0189 mole of DIPPO and 0.0189 mole of diphenylamine was heated at 150° for 15 hr. under nitrogen. Vacuum distillation yielded two fractions: (1) b.p. 150–200° (1 mm.) pot temperature, 1.80 g., largely imidazole (calcd. 1.28 g.) together with diphenylamine; and (2) b.p. 200–250° (1 mm.), 4.90 g. (72%) of colorless crystalline product, m.p. 178–186° from chloroform–heptane, P^{31} n.m.r. chemical shift (in chloroform) of −12.7 p.p.m.

Compound VIII was soluble in chloroform, benzene, ethanol, acetone, or dioxane, slightly soluble in diethyl ether (better warm), and insoluble in heptane, cyclohexane, and water.

Anal. Calcd. for $C_{21}H_{18}N_3OP$: C, 70.19; H, 5.05; N, 11.69; P, 8.62. Found: C, 69.97; H, 5.05; N, 11.86; P, 8.44.

Compound VIII was surprisingly stable toward moisture and was recoverable from an ethanol–water solution on evaporation under vacuum.

Two crystalline forms were observed by X-ray diffraction, one from ether extraction or crystallization from chloroform–heptane, the other on melting (under nitrogen). The pattern of the first differed from that of the second in having split peaks (doublets) instead of many of the single peaks found in the second.

Diimidazol-1-yl-N-methyl-N-phenylphosphinic Amide (III).—To a stirred solution of 54.4 g. (0.8 mole) of imidazole in 600 ml. of dry benzene at 50–75° was added a solution of 44 g. (0.2 mole) of N-methyl-N-phenylphosphoramidic dichloride[21] in 75 ml. of benzene over a period of 10 min. The reaction mixture was heated at reflux under nitrogen for 2 hr. The solution was removed through a filter stick and cooled to yield 44 g. (92%) of crystals, m.p. 132–134°, P^{31} n.m.r. chemical shift (in dimethylformamide) of +7.6 p.p.m.

Anal. Calcd. for $C_{13}H_{14}N_5OP$: C, 54.35; H, 4.91; N, 23.38; P, 10.79. Found: C, 54.06; H, 4.97; N, 24.10; P, 10.50.

Compound III had a half-life in water of *ca.* 4 hr. at room temperature and failed to react with aniline in refluxing THF, or with N-methylaniline at 170°.

1,3-Dihydro-2-phenyl-2H-1,3,2-benzodiazaphosphole 2-Oxide (IV).—To 0.057 mole of II in 325 ml. of THF was added with stirring 6.2 g. (0.057 mole) of *o*-phenylenediamine in 110 ml. of THF over a period of 0.5 hr. A white precipitate formed immediately, which dissolved upon heating to reflux. After the solvent was distilled over 2 hr. with the pot temperature reaching 85°, a yellow solid remained. Washing with ether and filtration gave 16.1 g. of crude IV. Its X-ray diffraction pattern showed that the major component was identical with the material reported by Dannley and Wagner.[12]

Pyrrol-1-ylpotassium has previously been prepared under a variety of conditions.[22–26] We found it convenient to prepare

(18) H. H. Strain [*J. Am. Chem. Soc.*, **49**, 1995 (1927)] has referred to unpublished work by Wenzel in the course of which imidazolylsodium was prepared by this method.

(19) M. L. Nielsen, unpublished work.

(20) V. Gutmann, G. Moertl, and K. Utvary, *Monatsh.*, **92**, 1258 (1961).

(21) A. Michaelis, *Ann.*, **326**, 129 (1903).

(22) N. Ljubavrin, *Ber.*, **2**, 100 (1869).

(23) E. C. Franklin, *J. Phys. Chem.*, **24**, 85 (1919).

(24) J. E. Reynolds, *J. Chem. Soc.*, **95**, 505 (1909).

(25) G. R. Clemo and G. R. Ramage, *ibid.*, **49** (1931).

(26) A. Treibs and A. Dietl, *Ann.*, **619**, 80 (1958).

pyrrol-1-ylpotassium in the solvent that was to be used later in the synthesis of dipyrrol-1-ylphenylphosphine oxide. Also, we established the position of potassium substitution of the product spectroscopically. The preparation was conducted in an inert atmosphere. Potassium (15.6 g., 0.40 mole) was suspended in 300 ml. of DME in a 1-l. flask. The flask was equipped with a magnetic stirring bar and a pressure-equalizing dropping funnel which contained 29.5 g. (0.44 mole) of pyrrole dissolved in 100 ml. of DME. The pyrrole solution was added over a period of 2.5 hr. with the reaction temperature maintained at 26–32°. At lower temperatures, potassium became coated with the product and the rate of reaction was prohibitively slow. Finally, the mixture was heated slowly to 63° to complete the reaction and then was cooled and filtered. The colorless solid, pyrrolylpotassium, weighed 35.0 g. after vacuum drying. Solvent was removed from the filtrate under vacuum, leaving 5.4 g. of light tan product. The combined yield was 96%.

Anal. Calcd. for C_4H_4KN: C, 45.67; H, 3.83; N, 13.32; K, 37.17. Found: C, 45.35; H, 4.14; N, 12.95; K, 37.46.

The reaction, when repeated on a larger scale (1.2 moles), proceeded equally well when no external cooling was applied.

The infrared spectrum of solid pyrrol-1-ylpotassium conclusively indicates the absence of amino hydrogen. A very weak band at 3510 cm.$^{-1}$ is attributed to a rather small degree of hydrolysis. Exposure of the Nujol mull of pyrrol-1-ylpotassium to the atmosphere leads to hydrolysis, evidenced by strong infrared absorption at 1600–3600 cm.$^{-1}$. The infrared spectrum of the hydrolyzed sample is similar to that reported for pyrrol-1-ylpotassium by Treibs and Dietl.[26]

Dipyrrol-1-ylphenylphosphine Oxide (V).—To pyrrolylpotassium (21 g., 0.20 mole), partly dissolved in 400 ml. of DME, a solution of phenylphosphonic dichloride (19.5 g., 0.10 mole) in 100 ml. of DME was added over a period of 1 hr. under an inert atmosphere and with ice-bath cooling. External cooling was removed after the addition of phenylphosphonic dichloride had been completed. Although the reaction appeared to be complete, agitation was continued for 15 hr.

The solid was removed from the reaction mixture by centrifuging, and was washed with 400 ml. of DME. The combined DME solutions yielded 22.3 g. of slightly violet solid, m.p. 95–101°, upon removal of solvent by evacuation. Three recrystallizations from cyclohexane (300-ml. each) yielded a purified product, 7.8 g. (30% yield), m.p. 107–108°. The yield of V was later improved (59.5%) by using *n*-heptane as the solvent for recrystallization, P^{31} n.m.r. shift (in DME) solution) of −10.7 p.p.m.

Anal. Calcd. for $C_{14}H_{13}N_2OP$: C, 65.62; H, 5.11; N, 10.94; P, 12.09. Found: C, 65.60; H, 5.21; N, 10.82; P, 12.24.

The position of substitution on the pyrrole ring was determined spectroscopically. The infrared spectrum of the compound indicates lack of absorption at 3400 cm.$^{-1}$, the region where absorption attributable to N–H stretching in pyrrole occurs. Consequently, no rearrangement occurred in the reaction and the product was dipyrrol-1-ylphenylphosphine oxide. The proton n.m.r. spectrum of V (Fig. 1) was obtained in $CDCl_3$ solution, with tetramethylsilane as the internal standard. It is characterized by the following chemical shifts: 7.8–8.4 (phenyl group), 7.15–7.45 (pyrrolyl α-hydrogens), and 6.7–6.95 p.p.m. (pyrrolyl β-hydrogens). The integrated areas for these shifts have the ratio 5:4:4. The assignment of the n.m.r. shifts of dipyrrol-1-ylphenylphosphine oxide is based on published data[27] for pyrrole and its methylated derivatives.

The proton n.m.r. spectrum of V substantiates conclusions based upon its infrared spectrum. Additionally it reveals that the phosphorus atom decreases the shielding of ring protons of the pyrrole nucleus, especially in the α-positions. The spectral fine structure suggests nuclear spin coupling between the pyrrolyl hydrogen and the phosphorus atom.

Pure V is stable to atmospheric conditions for prolonged periods. We have found it advisable to recrystallize the compound in an inert atmosphere, since the material which has been recrystallized in air has discolored upon standing. Compound V did not react with cyclohexylamine or aniline at reflux, or with N,N′-diphenyl-*p*-phenylenediamine at 220° in a reasonable time.

Polymerizations.—In all experiments, except for the piperazine–DIPPO, 5,5′-bibenzimidazole–DIPPO, and 5,5′-bibenzimidazole–dipyrrol-1-ylphenylphosphine oxide polymerization, an aliquot of a THF solution of DIPPO was titrated to determine the concentration. Solvent was then removed by distillation under nitrogen and the solid residue was dried by evacuation. The amine was added to the solid DIPPO in a nitrogen-flushed drybox, and the polymerization reaction mixture was heated in an oil bath.

1,6-Hexanediamine with DIPPO.—A mixture of 0.0624 mole of DIPPO and 7.30 g. (0.0624 mole) of 1,6-hexanediamine was heated under nitrogen at 140–145° for 3 hr. The yellow product was washed with water, dissolved in methanol, and decolorized with charcoal. A small amount of a clear, insoluble, jelly-like material was separated and discarded. The polymer was precipitated with hexane as 5.5 g. (35%) of a white solid that softened at 80–85° and decomposed *in vacuo* at 250°, η_{inh} (1% in methanol) 0.08.

Anal. Calcd. for $C_{12}H_{19}N_2OP$: C, 60.49; H, 8.04; N, 11.76; P, 13.00. Found: C, 56.98; H, 7.85; N, 10.55; P, 12.67.

Piperazine with DIPPO.—To a solution of 0.054 mole of DIPPO in 300 ml. of THF was added a solution of 4.65 g. (0.054 mole) of piperazine (purified by sublimation from sodium hydroxide) under nitrogen. A white precipitate formed immediately. The solvent was removed by distillation under nitrogen over 2 hr. and the residue was heated at 230–240° (0.3 mm.) for 3.5 hr. The product was dissolved in methanol and decolorized with charcoal. The solvent was evaporated and the residue was dissolved in chloroform from which it was reprecipitated twice with hexane to give 5.7 g. of a hygroscopic, slightly water-soluble solid that softened at 185–190°, η_{inh} (1% in *m*-cresol) 0.09. The polymer melted with decomposition at 270° in air; *in vacuo* it decomposed at 310° without melting. The polymer gave a brittle film when cast from water solution.

4,4′-Methylenedianiline with DIPPO.—A mixture of 0.057 mole of DIPPO and 11.3 g. (0.057 mole) of recrystallized 4,4′-methylenedianiline was heated at 160° under nitrogen for 2 hr. Heating was continued at 160° (0.3 mm.) for an additional 0.5 hr., then at 190° (0.3 mm.) for 1.5 hr. The addition of methanol seemed to plasticize the product. Leaching successively with ethanol, then ether, afforded 10.5 g. of a fine, yellow powder that softened at 185–190° and decomposed *in vacuo* at 370°, η_{inh} (1% in dimethylformamide) 0.07.

Anal. Calcd. for $C_{19}H_{17}N_2OP$: C, 71.2; H, 5.31; N, 8.75; P, 9.69. Found: C, 65.94; H, 5.81; N, 8.39; P, 9.37.

***p*-Phenylenediamine with DIPPO.**—A mixture of 0.058 mole of DIPPO and 6.25 g. (0.058 mole) of recrystallized *p*-phenylenediamine was heated at 160–165° for 1.5 hr. under nitrogen, then at 160–165° (0.3 mm.) for 0.5 hr., and finally at 190° (0.3 mm.) for 2 hr. The methanol-insoluble portion of the product (7.6 g.) was the desired polymer, η_{inh} (1% in dimethyl sulfoxide) 0.05. The product did not melt *in vacuo* at 300°, but decomposed at 345°. It was oxidatively unstable at elevated temperatures. An additional 3.9 g. of solid was isolated from the methanol solution by precipitation with ether. This material softened at 195–200°.

Benzidine with DIPPO.—A mixture of 0.061 mole of DIPPO and 11.2 g. (0.061 mole) of recrystallized benzidine was heated at 160° for 1.5 hr. under nitrogen, at 160° (0.3 mm.) for an additional hour, followed by 1.5 hr. at 190° (0.3 mm.). Methanol was added and 11.8 g. of insoluble polymer was isolated. This material softened at 210–215° and decomposed *in vacuo* at 330°. No solvent could be found, hence viscosity was not determined.

Anal. Calcd. for $C_{18}N_{15}N_2OP$: C, 70.6; H, 5.9; N, 9.15; P, 10.1. Found: C, 67.66; H, 5.54; N, 9.71; P, 8.17.

Addition of ethanol to the concentrated methanol solution afforded an additional 2.5 g. of solid that softened at 190–195°.

1,1′-(5,5′-Bibenzimidazolyl)phenylphosphine Oxide Polymer, Prepared from DIPPO.—DIPPO (3.31 g., 0.013 mole) and 5,5′-bibenzimidazole (3.05 g., 0.013 mole, synthesis reported below) were mixed in the drybox and transferred into the polymerization vessel. This vessel, which was designed for quantitative condensation and recovery of imidazole and the polymer, consisted of a wide test tube fitted on top with a ₸ 29/42 male joint. The test tube was connected to a Z-shaped, externally cooled condenser. The system was under a dry nitrogen atmosphere at ambient pressure in the beginning of the experiment. Later, vacuum was applied slowly for removal of imidazole. The vessel was immersed in an oil bath maintained at 110°, and the bath temperature was raised at a slow rate. Melting was observed at 110°, and around 120° imidazole began to sublime from the reaction zone. Over a period of 3.5 hr. the temperature was raised to 225°, and the reaction mixture became homogeneous, setting up

(27) R. J. Abraham and H. J. Bernstein, *Can. J. Chem.*, **37**, 1056 (1959).

to a solid foam. The product was cooled, transferred into dry-box, and crushed mechanically. To force the reaction to completion, the material was again heated under vacuum at temperatures ranging from 217–245° for 2.5 hr. Imidazole continued to sublime from the system, and some sintering was observed at the highest temperature. The amount of imidazole obtained was 1.56 g. The weight of the brown polymer was 4.83 g. Based upon imidazole recovery, the average degree of polymerization (D.P.) was 4.19.

Anal. Calcd. (D.P. 4.19): C, 66.78; H, 3.78; N, 16.83; P, 8.31. Found: C, 64.47, 64.36; H, 4.05, 4.01; N, 16.70, 16.59; P, 8.32, 8.39.

The oligomer melts from 244–280°, it begins to decompose thermally at 360°. At room temperature the product is insoluble in toluene, dimethoxyethane, and methyl ethyl ketone; it is soluble in 2-benzoylpyridine.

The experiment was repeated, allowing the reaction to proceed for 5.5 hr. at 275–290°. Imidazole recovery and elemental analysis indicated an average degree of polymerization of 11.0. Again the product solidified at the reaction temperature.

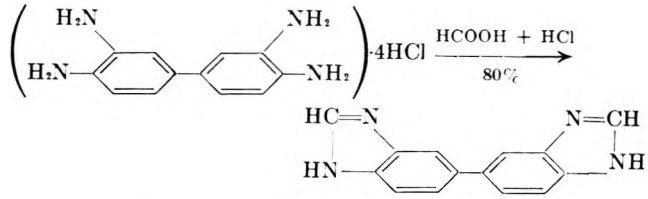
1,1′-(5,5′-Bibenzimidazolyl)phenylphosphine Oxide Oligomer, Prepared from Dipyrrol-1-ylphenylphosphine Oxide.—Compound V (5.12 g., 0.020 mole) and 5,5′-bibenzimidazole (4.68 g., 0.020 mole) were transferred into a 100-ml. flask in an inert atmosphere box. The flask was connected through a trap immersed in liquid nitrogen to a dry nitrogen by-pass line. Formation of liquid condensate was observed when the reaction temperature had been raised to 208°. The temperature was increased to 308° in order to melt the reactants and to obtain thorough mixing. Subsequently, the system was evacuated slowly to <1 mm., and heating was continued at 270–310° for 6 hr. The reaction mixture was converted to a dark brown solid product.

The liquid condensate, 2.08 g., was identified as pyrrole by its infrared spectrum. The infrared spectrum of the solid product (7.15 g.) is similar to that of poly[1,1′-(5,5′-bibenzimidazolyl)-phenylphosphine oxide] prepared from DIPPO. By elemental analysis of the solid product, the average degree of polymerization was 3.0 ± 0.3.

Anal. Calcd. (D.P. 3.0): C, 67.66; H, 3.90; N, 16.03; P, 8.18. Found: C, 66.41; H, 3.78; N, 15.49; P, 7.96.

Attempted Reaction of Dipyrrol-1-ylphenylphosphine Oxide with N,N′-Diphenyl-*p*-phenylenediamine.—Compound V (10.25 g., 0.04 mole) and pure N,N′-diphenyl-*p*-phenylenediamine (10.41 g., 0.04 mole) were heated in redistilled quinoline (40 ml.) solution at 220° for 15.5 hr. The system was evacuated at 80°. Gas chromatographic analysis of the collected quinoline indicated that it contained only 0.5% of the pyrrole expected from the desired polymerization. The nonvolatile solids were identical with starting materials by infrared spectra.

5,5′-Bibenzimidazole.—A mixture of 7.0 g. (0.021 mole) of 3,3′-diaminobenzidine tetrahydrochloride, 17.4 g. (0.378 mole) of formic acid, and 38 ml. of 5 *N* hydrochloric acid was heated at reflux for 0.5 hr. The reaction mixture was then poured into 55 ml. of concentrated ammonium hydroxide and 25 g. of ice. The brown solid was filtered off and dissolved in methanol. The solution, after filtration to clarify, was evaporated to dryness and the residue was washed with ether. The product weighed 4.0 g. (80%) and melted at 265–267°. Recrystallization from isopropyl alcohol yielded a 1:1 adduct which was decomposed at 190–200° to yield pure 5,5′-bibenzimidazole, melting at 292–293.5°. The X-ray diffraction pattern was unique.



Anal. Calcd. for $C_{14}H_{10}N_4$: C, 71.78; H, 4.30; N, 23.92. Found: C, 71.60; H, 4.18; N, 23.67.

5,5′-Bibenzimidazole is soluble in ethanol, formamide, ethylenediamine, dimethylformamide, pyridine, *m*-cresol, hot diglyme, and hot water. It is insoluble in acetone, ether, benzene, hexane, chloroform, dioxane, ethyl acetate, and tetrahydrofuran.

The neutralization equivalent, determined by titration with hydrochloric acid in glycol–isopropanol solution, was 119.6 (calcd. 117.1).

A sample that had been stirred in water and azeotroped with benzene to dry (m.p. 275–280°) gave a different X-ray diffraction pattern from the material above.

Anal. Calcd. for $C_{14}H_{10}N_4 \cdot H_2O$: C, 66.65; H, 4.79; N, 22.21. Found: C, 65.57; H, 4.28; N, 21.56.

This "monohydrate" was unchanged by recrystallization from methanol–benzene, according to the X-ray diffraction pattern. However, extraction with diethylamine converted it to the anhydrous bibenzimidazole as shown by X-ray diffraction.

As a means of identifying 5,5′-bibenzimidazole, the dihydrochloride was prepared for X-ray diffraction analysis. 5,5′-Bibenzimidazole was dissolved in dilute hydrochloric acid. On evaporating part of the water and adding acetone, a crystalline product was obtained, m.p. about 310°. Its X-ray diffraction pattern was unique.

Anal. Calcd. for $C_{14}H_{10}N_4 \cdot 2HCl \cdot 2H_2O$: Cl, 20.66; N, 16.32. Found: Cl, 20.57; N, 16.24.

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Phosphorus Compounds. V. Tautomerism in Phenylphosphinic Acid and Its Anion[1-3]

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Hydrogen isotope exchange in the P(O)H system in aqueous and deuterium oxide solutions of phenylphosphinic acid, its sodium salt, and the corresponding deuterated acid and salt, followed by infrared techniques, has shown the reaction to be both acid and base catalyzed. The almost total lack of exchange in buffered neutral solutions shows that a simultaneous attack by a nucleophile and an electrophile is not a significant factor in the exchange reaction. The proportion of "enol" in neutral phenylphosphinate solution probably does not exceed that found in aqueous acetone solutions.

A previous article[1] of this series reported both acid and base catalysis in the hydrogen isotope exchange reaction with dialkyl phosphonates. This finding is in marked contrast[4] to the same reaction with the parent acid, phosphorous acid, which is usually considered to have a structure somewhat similar to that

(1) Previous paper in this series: W. J. Bailey and R. B. Fox, *J. Org. Chem.*, **28**, 531 (1963).

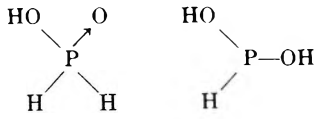
(2) Presented before the Division of Organic Chemistry at the 134th National Meeting of the American Chemical Society, Chicago, Ill., Sept., 1958.

(3) Abstracted from a thesis submitted to the Faculty of the Graduate School of the University of Maryland, in partial fulfillment of the requirements for the degree of Doctor of Philosophy, 1959.

(4) A. I. Brodskii and L. V. Sulima, *Dokl. Akad. Nauk SSSR*, **85**, 1277 (1952).

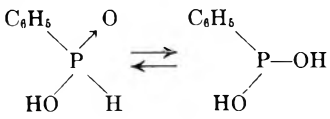
of its diesters. Although the parent acid undergoes exchange in acidic aqueous solution,[5,6] its anion has not been found to undergo hydrogen isotope exchange at the hydrogen atom bound to the phosphorus atom.[4,6] It has, therefore, been inferred that a prototropic equilibrium does not play a significant role in the reactions of the salts of this acid and that the possession of the P(O)H diadic system does not imply the existence of tautomers in a specific family of compounds.

Hypophosphorous acid, which also contains the P(O)H system, has often been designated as a tautomeric pair.



The reactions of the acid itself appear to substantiate the idea of a prototropic equilibrium preceding such reactions as hydrogen isotope exchange[4,5,7] and halogenation.[7] In neutral or basic solution, however, hydrogen isotope exchange in the anion is very slow[4,5,8,9] and, as in the case of phosphorous acid, tautomerism is not necessary to explain the observed reactions.

In view of these diverse results, it would be of interest to compare esters of hypophosphorous acid with those of phosphorous acid, but alkyl hypophosphites are, unfortunately, unknown. However, another family of compounds which may be related to hypophosphorous acid, is the phosphinic acids, and phenylphosphinic acid is readily available. This acid, as well as the parent acid, can be considered to exist as a tautomeric pair.



The phenyl group can, of course, be viewed as replacing an OH group on the phosphorus atom; in this sense phenylphosphinic acid might be thought of as a derivative of phosphorous acid. An investigation of prototropic equilibria in the P(O)H system of phenylphosphinic acid and its anion might be revealing in regard to the mechanism of the reactions of this derivative.

Experimental

Materials and Apparatus.—Stuart Oxygen Co. 99.8% deuterium oxide was employed in the exchange experiments. Phenylphosphinic acid, m.p. 84°, was a recrystallized commercial product. With the exception of the materials listed all other chemicals were C.P. reagent grade and used as received. The following compounds were prepared specifically for this work.

Phenylphosphinic acid-d_2, $C_6H_5P(O)D(OD)$, was obtained by the deuterolysis of phenylphosphonous dichloride with cold 99.8% deuterium oxide.

Sodium phenylphosphinate-d, $C_6H_5P(O)D(ONa)$, was prepared by the neuralization of the d_2-acid with a cold sodium deuteroxide solution. The salt also could be made by deuterolysis of phenylphosphonous dichloride with sodium deuteroxide solution, but the heat of reaction tended to produce disproportionation of the phosphine, and it was difficult to separate the phosphinate from sodium chloride. Both this deuterated salt and the corresponding undeuterated salt were readily separated from fairly concentrated aqueous solutions by precipitation with acetone or tetrahydrofuran.

Sodium phenylphosphinate, $C_6H_5P(O)H(ONa)$, was obtained by neutralization of the acid with sodium hydroxide, followed by precipitation with acetone. The salt prepared in this way invariably gave an aqueous solution which had a pH slightly below 7, although the break in the neutralization curve of the acid occurs slightly above pH 7.

In all infrared work, a Perkin-Elmer Model 21 spectrophotometer with sodium chloride optics was used. Solid samples were run as potassium bromide pellets.[10-13] Spectra of solutions were obtained with standard calcium fluoride absorption cells. The cell thicknesses, determined by measurement of interference fringes in the empty cells,[14] were 0.0982 and 0.109 mm.; the 0.0982-mm. cell was used for the compensating solution at all times. It was not felt necessary to make a correction for the difference in these path lengths, since the "blank" absorption in the reference cell was usually only a few per cent.

Hydrogen–Deuterium Exchange Experiments.—The infrared spectrum of phenylphosphinic acid[15] is generally unsuitable for following hydrogen–deuterium exchange in this molecule because of the greatly broadened bands and general absorption in the 2-6-μ range resulting from hydrogen bonding. In the sodium salt of phenylphosphinic acid, however, this broad absorption is absent. In Fig. 1, a comparison is made of the infrared spectra for the Na–H salt and its deuterated analog [$C_6H_5P(O)H(ONa)$ is designated the Na–H salt and $C_6H_5P(O)D(ONa)$ the Na–D salt]. Bands are very sharp, and although both the bands at the P–H stretching frequency (2280 cm.$^{-1}$) and the P–D stretching frequency (1650 cm.$^{-1}$) are fairly strong, there is some degree of interference in the 1650-cm.$^{-1}$ region which precludes the use of these bands in the quantitative analysis of this exchange. Fortunately, there is little absorption in either spectrum in the 3200–3600-cm.$^{-1}$ region where O–H stretching absorption would occur. This region has been used repeatedly in the analysis of water–heavy water mixtures.[16]

Preliminary Measurements on the P–H and P–D Bands.—Solutions of approximately 20% by weight of the Na–D salt in water were made acidic or basic by the addition of suitable amounts of hydrochloric acid or sodium hydroxide. At intervals, the solutions were neutralized and the salt precipitated by the addition of a large volume of tetrahydrofuran. No exchange was observed between tetrahydrofuran and the Na–D salt or deuterium oxide over a period of 24 hr. The precipitated salt was washed first with tetrahydrofuran and then with diethyl ether and dried by evacuation of the sample at 1-mm. pressure for 2 hr. at room temperature. The infrared spectrum was obtained with the sample in the form of a pressed potassium bromide pellet. Lack of significant absorption in the O–H stretching region was taken as evidence that the salt had been dried sufficiently. Transmittances (T) were measured for the absorption at 2280 (P–H), 1650 (P–D), and 1430 cm.$^{-1}$ (a phenyl ring-breathing absorption, assumed constant in both salts and, therefore, used as the reference band). Values of T were obtained by conventional base-line techniques.

Results

From the Beer–Lambert law, the absorbance from preliminary measurements on P–H and P–D bands is $\log 1/T = \alpha t x$, where α is the absorptivity (or extinction coefficient), t is the path length, and x is the mole fraction of the constituent responsible for the absorption. With the subscripts H, D, and R to refer to properties which are functions of the P–H, P–D, and reference portions of the molecules, one obtains the following ($x_R = 1$).

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(15) L. W. Daasch and D. C. Smith, *Anal. Chem.*, **23**, 853 (1951).
(16) J. Gaunt, *Spectrochim. Acta*, **8**, 57 (1956); *Analyst*, **79**, 580 (1954).

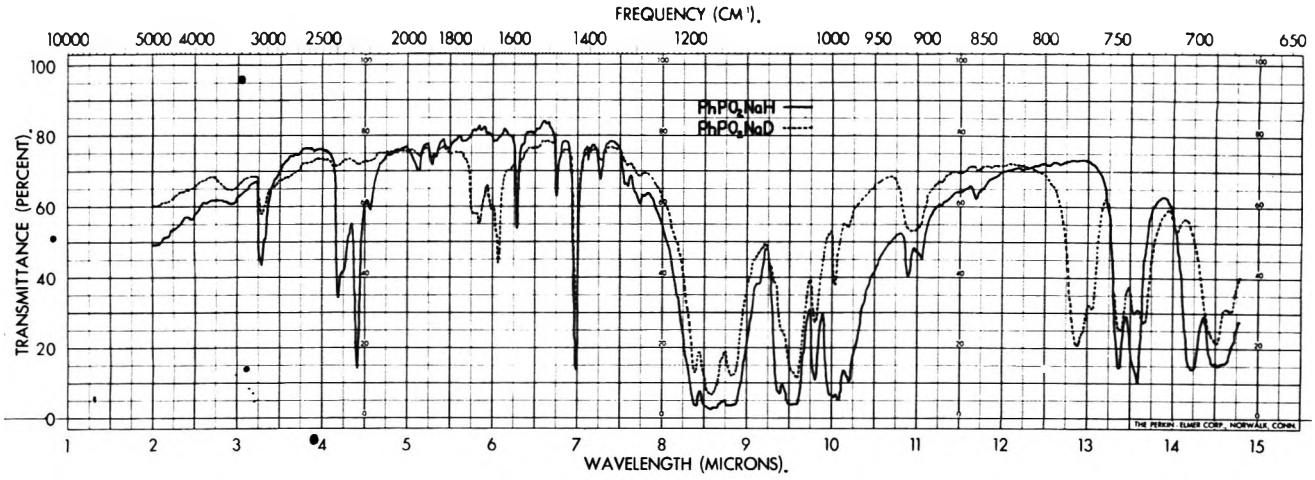


Fig. 1.—Infrared spectrum of the sodium–hydrogen and sodium–deuterium salts.

$$x_D = \frac{\alpha_R}{\alpha_D}\left(\frac{\log \frac{1}{T_D}}{\log \frac{1}{T_R}}\right)$$

The value of α_R/α_D is obtained from the spectrum of the pure Na–D salt, where $x_D = 1$; the best value was found to be 1.10. When a similar procedure was carried out to obtain x_H, α_R/α_H was found to be 1.02.

When these calculations were carried out with data such as that given in Table I, it was usually found that

TABLE I

INFRARED BANDS IN PRECIPITATED SODIUM SALT OF PHENYLPHOSPHINIC ACID-d_2

Solution	Time, min.	Transmission,[a] % T_D	T_H	T_R
pH 2 (HCl)	5	13.8	84.7	11.7
	60	35.9	86.0	30.5
	240	21.2	56.0	16.1
	1380	39.3	28.5	15.1
	2820	75.9	19.3	13.0
pH 4 (HCl)	5	13.3	87.5	12.6
	60	20.5	90.0	19.3
	240	21.7	89.2	18.4
	1380	37.9	94.1	33.2
	2820	48.1	94.5	38.8
pH 11.5 (NaOH)	1380	12.7	80.7	10.6
	6840	14.0	79.1	12.6
5% NaOH	120	27.3	85.0	23.7
	240	34.0	84.2	28.3
	1380	34.8	50.7	21.0

[a] T_D, T_H, and T_R are transmissions of the bands at 1650, 2280, and 1430 cm.$^{-1}$, respectively.

$x_H + x_D > 1$ (about 1.1 to 1.4). The reason for this is not known, but this discrepancy is possibly due to interference bands in the P–D region. A comparison of the spectra of the pure Na–H and Na–D salts in the 12–15-μ range (Fig. 1) shows changes in the position and intensities of the bands which indicate that some ring deuteration may have taken place during the preparation of salts. Since the degree to which this affects the intensity of the reference band is not known, a major source of error may reside in such changes. Therefore, for purposes of comparison, the figures were arbitrarily placed on a per cent basis by the following proportion.

$$\%D = 100\,\frac{x_D}{x_D + x_H}$$

In Table II the per cents of deuterium remaining in the Na–D salt under various conditions are given as calculated from the data in Table I. In neutral solution and in a phosphate buffer at pH 6.8, no exchange whatever was detected in this way.

At least at high concentrations, deuterium oxide has little effect on the rate of exchange (Table II). The rate of exchange does increase with increasing acid concentration for deuterium oxide solutions (Table II). Similarly, the rate is dependent on the concentration of base for the Na–H salt in deuterium oxide solutions containing sodium deuteroxide (Table II).

TABLE II

EXCHANGE RATES FOR PHENYLPHOSPHINIC ACID-d_2

Solution	Time, min.	Deuterium remaining in precipitated Na–D salt, %
pH 2 (HCl)	0	95
	5	93
	60	89
	240	74
	1380	45
	2820	13
pH 4 (HCl)	0	95
	5	94
	60	94
	240	94
	1380	95
	2820	93
pH 11.5 (NaOH)	0	95
	1380	92
	6840	90
5% NaOH	0	95
	120	90
	240	87
	1380	63

Several attempts also were made to measure the exchange taking place in neutral aqueous solutions of the Na–D salt. In these runs, the pellet technique was used over a period of 6 weeks. During this time, only negligible exchange was detected by the appearance of absorption in the region of 2280 cm.$^{-1}$ (the P–H stretching absorption frequency) under the following conditions: (a) 1 *M* Na–D salt in water, pH 6.3;

(b) 1 *M* Na–D salt in water, pH 6.3, vessel filled with glass helices to give increased surface; (c) 1 *M* Na–D salt in a citric acid–phosphate buffer, pH 6.3; (d) 1 *M* Na–D salt in a phosphate buffer, pH 6.8. In addition, pyridine did not appear to catalyze the exchange significantly.

Exchange Rates in Deuterium Oxide Solutions.—The applicability of the Beer–Lambert law to the absorption at 3350 cm.$^{-1}$ (the O–H stretching vibration) was shown over the range of concentration from 0.1 equiv./l. to 0.6 equiv./l., from which it is found that $C_H = 1.24 \log 1/T$. Solutions of known water content were prepared by transfer of suitable weighted amounts of a solution of 1.1188 g. of water in 19.1198 g. of tetrahydrofuran (162.8 mg. of this solution contains 1 mequiv. of O–H hydrogen; this is approximately the equivalent weight of the Na–D salt), followed by dilution to 5.00 ± 0.03 ml. with deuterium oxide.

The rate of exchange was followed by changes in the transmittance in the 3350-cm.$^{-1}$ region—that is, by the rate of formation of OH in solutions of the Na–H salt or the H acid under various conditions of acidity. The results are presented in Table III. In the next to last column is given the amount of exchange taking place per initial mole of P–H in the solution. Where significant, the time in which one-fourth the initial P–H hydrogen atoms were exchanged is given in the last column. Approximately 1 *M* Na–H salt solutions in deuterium oxide were used in the compensating cells in these runs. Over a period of 6 weeks, no appreciable exchange took place in the solutions used in the compensating cell. As a matter of comparison, it also was found that no appreciable exchange took place in a 1 *M* solution of pure acetone in deuterium oxide over the same period.

TABLE III

EXCHANGE OF PHENYLPHOSPHINIC ACID AND ITS SODIUM SALT WITH DEUTERIUM OXIDE

Time, hr.	Log $1/T$	C_{OH}, moles/l.	C_{OH}/C^0_{P-H}	$T_{0.25}$, hr.
$C_6H_5PO_2H_2$, 0.252 *M*; D_2O, 30.3 *M*; tetrahydrofuran, 406 mg./ml.				
0.15	0.156	0.193	0.77	2.1
0.40	0.174	0.216	0.86	
1.58	0.224	0.278	1.10	
3.82	0.280	0.347	1.38	
5.74	0.313	0.388	1.54	
23.9	0.393	0.487	1.93	
$C_6H_5PO_2H_2$, 0.253 *M*; D_2O, 40.6 *M*; tetrahydrofuran, 226 mg./ml.				
0.10	0.177	0.220	0.87	2.0
0.36	0.197	0.244	0.96	
1.67	0.252	0.312	1.23	
3.98	0.288	0.357	1.45	
5.90	0.318	0.394	1.56	
24.1	0.399	0.495	1.96	
$C_6H_5PO_2H_2$, 0.113 *M*; $C_6H_5PO_2HNa$, 0.97 *M*; D_2O, 49.9 *M*				
0.19	0.150	0.186	0.172	47
2.08	0.139	0.172	0.159	
4.57	0.139	0.172	0.159	
27.1	0.223	0.276	0.255	
51.7	0.337	0.418	0.386	
119.1	0.555	0.688	0.635	
$C_6H_5PO_2HNa$, 0.499 *M*; C_5H_5N, 5.85 *M*; D_2O, 30.2 *M*				
0.10	0.041	0.051	0.010	...
0.68	0.047	0.058	0.012	
18.5	0.064	0.079	0.016	
90.0	0.119	0.148	0.030	
138.0	0.137	0.170	0.034	
$C_6H_5PO_2HNa$, 0.975 *M*; OD^-, 0.022 *M*; D_2O solution				
2.80	0.018	0.022	0.023	190 (estd.)
19.7	0.051	0.063	0.065	
24.1	0.054	0.067	0.069	
93.6	0.119	0.147	0.151	
$C_6H_5PO_2HNa$, 0.929 *M*; OD^-, 0.105 *M*; D_2O solution				
0.16	0.044	0.055	0.059	67
2.35	0.061	0.077	0.083	
19.1	0.087	0.108	0.116	
23.6	0.094	0.117	0.126	
92.9	0.231	0.286	0.308	
$C_6H_5PO_2HNa$, 0.989 *M*; OD^-, 0.551 *M*; D_2O solution				
0.21	0.143	0.177	0.179	1
1.79	0.272	0.334	0.348	
18.6	0.367	0.455	0.450	
23.0	0.400	0.496	0.501	
92.3	0.796	0.997	1.008	

Discussion

Deuterium exchange reactions have played leading roles in the elucidation of prototropic mechanisms in both carbon and phosphorus systems. These reactions, which have been utilized in the present and earlier[1] studies, are generally considered to be representative of reactions involving electrophilic attacks in so far as acid catalysis is concerned. It is this kind of attack which is of interest since the less stable tautomer in these systems contains a free electron pair on the phosphorus atom. The interpretation of hydrogen–deuterium exchange in this work is based on the assumption that the rates of exchange of hydrogen atoms bound to phosphorus and oxygen are different by many orders of magnitude. Justification for this assumption is found in a comparison of the exchange rates in neutral phosphites and hypophosphites with the very high rates of exchange observed in aliphatic alcohols.[17,18] Acidic hydrogen atoms in P–OH groups undergo extremely rapid exchange.[4] An exhaustive study of the kinetics of these reactions would be necessary to elucidate completely the details of the mechanism of the prototropic changes taking place in these systems. Consequently, only a qualitative picture of the mechanism of these changes is presented in this paper.

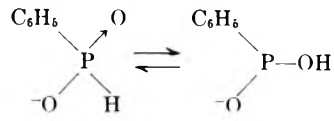
The extent of hydrogen–deuterium exchange can be followed by many methods: density measurements on the water removed from the reaction medium,[4] absorption at the P–D stretching frequency in the Raman spectra,[5,6] and, very recently, n.m.r. spectroscopy.[19,20] For accurate H/D ratios, mass spectrometry is often the method of choice. Less accurate, perhaps, but more informative in some respects, is infrared spectroscopy. This method not only allows one to measure the over-all extent of exchange through changes in band intensities, but also enables one to detect and, sometimes, to measure exchanges taking place simultaneously in various parts of the molecule. For example, phenylphosphinic acid contains at least three types of hydrogen atoms: O–H, P–H, and C–H. Each of these groups can be observed by means of the infrared

(17) J. Hine and C. H. Thomas, *J. Am. Chem. Soc.*, **75**, 739 (1953).
(18) H. Kwart, I. P. Kuhn, and E. L. Bannister, *ibid.*, **76**, 5998 (1954).
(19) Z. Luz and B. Silver, *ibid.*, **83**, 4518 (1961); **84**, 1095 (1962).
(20) P. R. Hammond, *J. Chem. Soc.*, 1365 (1962).

absorption bands at the appropriate frequencies. In this investigation, direct observation of the absorption at these P–H and P–D stretching frequencies in sodium phenylphosphinate was used as a qualitative measure of the exchange taking place in the phosphinic acid system. A more precise measure of the rate of exchange was obtained by following the increase in the intensity of the absorption at the O–H stretching frequency in deuterium oxide solutions containing the acid or its salt.

Since, in common with the majority of kinetic studies which have been made on hydrogen isotope exchange reactions, simultaneous exchange reactions can take place at points in the molecule which are not involved in the reaction of interest, the data are often at best interpreted on the basis of fractional exchange times, and only qualitative conclusions can be made regarding the mechanisms of the reactions involved.[21] This has been done in the present study. In place of more accurate assay methods, the use of the infrared spectrometer in this work not only has given information of sufficient accuracy but also has confirmed and, to a certain extent, identified the competing exchange reactions.

Aside from the interesting possibility of ring deuteration, several conclusions can be drawn from the results which are qualitatively in agreement with the previous work on the phosphonate.[1] There is the hint that perhaps the mechanisms suggested for the ester would also hold for the acid system. Two important points, however, are quite clear: (a) the exchange is catalyzed by both acids and bases, and (b) termolecular mechanisms involving both acids and bases are not important. The latter conclusion is established by the nearly complete absence of catalysis by the constituents of neutral buffers.[22] Since exchange is negligible over a period as long as 6 weeks in neutral or near-neutral aqueous solutions, it also may be concluded that the ionization constant for the P–H bond in this molecule must be exceedingly small. By the same token the postulation of an uncatalyzed equilibrium between the tautomers



does not appear to be well-founded. The findings that the amount of exchange in neutral solution is of the same order of magnitude as that found in acetone serves to place an upper limit on the rate of formation of enolic form in aqueous solutions of sodium phenylphosphinate. Schwarzenbach and Wittwer,[23] using a bromometric technique, found that a 10% aqueous solution of acetone contains about 10^{-4}% enol, but did not estimate a rate of formation.

Earlier work[4-6,8,9] showed that hydrogen isotope exchange took place rapidly with hypophosphorous acid, slowly with phosphorous acid, and was absent in the salts of these acids. It was assumed, but not proved, that exchange was preceded by an acid-catalyzed prototropic transformation to the enolic forms. The independence of the rate of exchange on the concentration of the attacking reagent was not established in any of these reports, and in the present work there is only an indication of such independence. It is of interest, however, that exchange in the phenylphosphinic acid system more closely resembles that of hypophosphorous acid than it does phosphorous acid, and, in fact, most closely resembles that of the dialkyl phosphonates reported previously.[1]

Acknowledgment.—Grateful acknowledgment is made to Dr. Ronald E. Kagarise, Dr. L. B. Lockhart, Jr., and Mr. L. W. Daasch of the Physical Chemistry Branch of the Naval Research Laboratory for many stimulating discussions regarding this problem.

(21) S. Z. Roginsky, "Theoretical Principles of Isotope Methods for Investigation of Chemical Reactions," AEC Translation 2873, Academy of Sciences U.S.S.R. Press, Moscow, 1956, p. 191.

(22) C. G. Swain, *J. Am. Chem. Soc.*, **72**, 4578 (1950).

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

Structure and Stereochemistry of Diels–Alder Adducts of Levopimaric Acid

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Levopimaric acid or rosin reacted with β-propiolactone and acrylic acid to form adducts, two of which have been isolated in pure form and are related to the adducts previously obtained with acrylonitrile. Structures of these substances and of the adducts formed with methyl acrylate and fumaric acid have been established.

Diene reactions of abietic-type resin acids with fumaric acid[6] and acrylonitrile[7] have been reported earlier from this laboratory, but structures of the products were left uncertain. In this paper we report the reaction of levopimaric acid or rosin with β-propiolactone, acrylic acid, and methyl acrylate. Structures of the major products as well as those of the adducts reported earlier[6,7] have been determined. In the special case of the adducts, levopimaric acid and acrylonitrile, our conclusions based on chemical evidence do not support the preference expressed by other workers on n.m.r. spectroscopic grounds.[8]

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(4) U. S. Public Health Postdoctoral Fellow, 1962–1964.

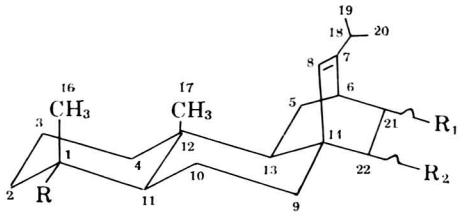
(5) U. S. Public Health Predoctoral Fellow, 1962–1964.

(6) N. J. Halbrook and R. V. Lawrence, *J. Am. Chem. Soc.*, **80**, 368 (1958).

(7) N. J. Halbrook, J. A. Wells, and R. V. Lawrence, *J. Org. Chem.*, **26**, 2641 (1961).

(8) W. L. Meyer and R. W. Huffman, *Tetrahedron Letters*, **16**, 691 (1962).

Reaction of levopimaric acid with 50% excess β-propiolactone at 225° for 4 hr. resulted in 7% of isomerized levopimaric acid and 93% of mixed adduct from which the major component I, $[\alpha]^{25}D$ +25.8°, was separated as a carbon tetrachloride solvate[9] in 57% yield. Partition chromatography of the soluble residue resulted in isolation of 17% of resin acids, 36% of a second adduct II, $[\alpha]^{25}D$ +68.2°, and 47% of a mixture III, $[\alpha]^{25}D$ 0°.



I, R = COOH; R_1 = H_2; R_2 = *endo*-COOH
II, R = COOH; R_1 = H_2; R_2 = *exo*-COOH
III, R = COOH; R_1 = mixed *endo,exo*-COOH; R_2 = H_2
VII, R = COOH; R_1 = H_2; R_2 = *endo*-$COOCH_3$
VIII, R = $COOCH_3$; R_1 = H_2; R_2 = *endo*-$COOCH_3$
IX, R = $COOCH_3$; R_1 = H_2; R_2 = *exo*-$COOCH_3$
X, R = COOH; R_1 = H_2; R_2 = *endo*-CN
XI, R = COOH; R_1 = H_2; R_2 = *exo*-CN
XII, R = $COOCH_3$; R_1 = H_2; R_2 = *endo*-CN
XIII, R = $COOCH_3$; R_1 = H_2; R_2 = *exo*-CN
XIV, R = COOH; R_1 = *endo*-CN; R_2 = H_2
XV, R = COOH; R_1 = *endo*-COOH; R_2 = *exo*-COOH
XVI, R = COOH; R_1 = *exo*-COOH; R_2 = *endo*-COOH
XVII, R = COOH; R_1 = *endo*-COOH; R_2 = *endo*-COOH
XX, R = CH_2OH; R_1 = H_2; R_2 = *endo*-CH_2OH
XXI, R = CH_2OH; R_1 = H_2; R_2 = *exo*-CH_2OH

Gum rosin on reaction with β-propiolactone gave yields of crude adducts equal to those expected on the basis of abietic-type resin acids present in the gum. Extraction with sodium bicarbonate solution and crystallization from carbon tetrachloride gave 30% of I. Crystallization of the residue from alcohol–water furnished 9.7% of II; the noncrystalline adducts III amounted to 18.3%. Reaction of rosin with acrylic acid afforded a mixture of approximately the same composition as that obtained with β-propiolactone.

Structures were assigned to these substances on the basis of the following evidence. I and II were partially interconvertible thermally, with I predominating and with no evidence of III, and are, therefore, epimers. Similarly, heating of the mixture III did not give any of isomer I. III is a mixture of two products differing from I and II and must, therefore, be a mixture of the epimers at C-21.

The possibility that a retrodiene reaction occurred during epimerization of I and II is disproved by the fact that no formation of III took place during the epimerization, and heating the mixture III did not give isomer I. The Diels–Alder reaction gave mixtures of I, II, and III, while a retrodiene reaction should have given the same mixtures. Further evidence against a reversal of the Diels–Alder reaction is provided by the results obtained on hydrolysis of XII and XIII; finally the heating of isomer I with fumaric acid, a more reactive dienophile, gave no detectable amount of fumaropimaric acid.

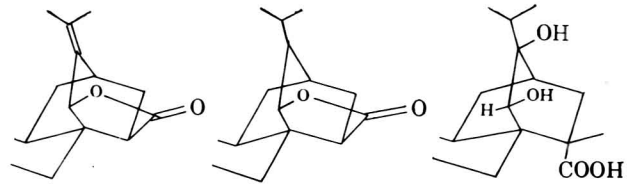
Lithium aluminum hydride reduction of I and II afforded different diols. Oxidation of I with dilute alkaline permanganate furnished a lactone IV (positive tetranitromethane test) whose infrared spectrum exhibited a strong band at 1770 $cm.^{-1}$ (γ-lactone), but no absorption at 890 $cm.^{-1}$, characteristic of an isopropenyl group. Treatment of I with formic acid–perchloric acid gave a saturated substance (V) which was also a γ-lactone (infrared band at 1770 $cm.^{-1}$)

Comparison of the n.m.r. spectra of I, II, IV, and V (Table I) with those of related compounds[13] demonstrates a shift of the H-8 signal of IV and V to higher field. This and its multiplicity (singlet in IV, doublet in V) indicate that the signal is associated with the lactone function which must, therefore, be closed to C-8. The downfield shift of the signals associated with the now vinylic C-19 and C-20 methyl groups required by formula IV are observed.

TABLE I
SELECTED N.M.R. PEAKS[a]

Compound	Assignments[b] C-17	C-16	H-8[c]	Isopropyl methyls[c]
I	0.67	1.36	5.54	1.09 d (7)
II	0.69	1.38	5.58	1.04 d (7)
IV	0.71	1.19	5.00	1.77, 1.72
V	0.97	1.20	4.59 d (6)	0.97 d (9)
VII	0.63	1.17	5.38	1.06 d (7)
VIII	0.62	1.15	5.38	1.06 d (7)

[a] In p.p.m. [b] See Experimental for details. [c] d = doublet; *J* values are in parentheses in c.p.s.



IV V VI

The facile formation of IV and V necessitates assignment of the *endo* configuration at C-22 to I. By contrast, II on alkaline permanganate oxidation furnished a dihydroxydicarboxylic acid VI which gave a negative tetranitromethane test. Since II is partially convertible to I, it represents the less stable C-22 *exo* isomer. We assume that approach of the oxidizing agent is less hindered from the α side of II, and that the two hydroxy groups of VI probably possess the configuration indicated in the formula.

The stereochemistry expressed in formula V is that expected from *trans*-diaxial lactone ring closure (although this would require double bond protonation from the more hindered side), as well as from thermodynamic considerations if a free carbonium ion were involved. A Drieding model of the C-7 epimer suggests the presence of large repulsive forces between the isopropyl and the C-17 methyl group. Support for this formulation is found in the H-8 coupling constant; the value, J = 6 c.p.s., is closer to that expected

(9) Maleopimaric acid[10] (both carboxyl groups *endo*[11]) also forms a carbon tetrachloride solvate as does the isomer of fumaropimaric acid, $[\alpha]$ +42.5°,[12] in which the C-22 carboxyl is *endo* (*vide infra*).

(10) R. V. Lawrence and O. S. Eckhardt, U. S. Patent 2,628,226 (Feb. 10, 1953).

(11) L. H. Zalkow, R. A. Ford, and J. P. Kutney, *J. Org. Chem.*, **27**, 3535 (1962).

(12) N. J. Halbrook, unpublished.

(13) W. A. Ayer, C. E. McDonald, and J. B. Stothers, *Can. J. Chem.*, **41**, 1113 (1963).

from V (dihedral angle about 15°) than from its C-7 epimer (approximate dihedral angle 100°).

The infrared spectrum of the noncrystalline adduct mixture III was not significantly different from that of I or II, although the rotation and the n.m.r. spectrum indicated the presence of different components. This was confirmed by gas chromatography of the dimethyl esters. III was separated into two components with retention times of 5.90 and 6.95 min., whereas the methyl esters of I and II had retention times of 5.95 and 4.90 min., respectively. This leads to the conclusion that III is a mixture of the two epimeric C-21 carboxylic acids, since it is possible to form only four isomers by an approach of the dienophile to the α face of levopimaric acid.[8]

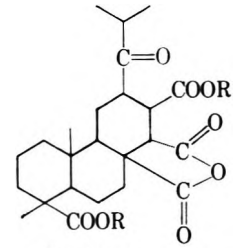
Condensation of levopimaric acid with methyl acrylate at 85° furnished in 90% yield[14] a crystalline isomer (VII) whose structure was established by conversion to the dimethyl ester of I (VIII), and hydrolysis with 10% sodium hydroxide solution to I.

The two acrylonitrile adducts X and XI reported earlier[7] furnished two different methyl esters (XII and XIII). A more convenient route to these compounds involved methylation of the crude mixture of adducts and separation by crystallization. Attempts to hydrolyze the nitrile function of either isomer with acid or with hydrogen peroxide were unsuccessful. Under the relatively drastic conditions required by base-catalyzed hydrolysis (potassium hydroxide in ethylene glycol at 170°), either isomer yielded a mixture of I and II. This demonstrated the point of attachment of the cyanide function as C-22, but does not permit assignment of *endo* or *exo* configuration to either isomer. Meyer and Huffman[8] suggested XI and XIV as the most likely formulas for the two acrylonitrile adducts.

Arbuzov and Khismatullina[15] reported the formation in low yield of an adduct from methyl acrylate and the crude resin acids of *Pinus maritima*. Saponification yielded material whose physical properties show it to be an isomer or isomer mixture differing from the substances reported in this paper.

Fumaropimaric acid,[6] the major Diels–Alder adduct of the abietic-type acids with fumaric acid, may be XV or XVI. Its thermal isomerization[6] to maleopimaric acid, recently shown to be XVII,[11,13,16] although tending to favor XV, might conceivably involve a retrodiene reaction. The following transformation conclusively establishes its structure as XV.

Ozonolysis of fumaropimaric acid in methyl alcohol solution at −70° followed by hypohalite decomposition of the ozonide[17] afforded in 70% yield the keto diacid anhydride XVIII. The dimethyl ester XIX had infrared bands at 1855 and 1790 (succinic anhydride), 1740 (double intensity, carbomethoxy groups), and 1715 cm.$^{-1}$ (ketone). Its n.m.r. spectrum exhibited methyl singlets at 1.11, 1.13 (angular methyls), 3.65, and 3.70 (carbomethoxy groups), and two superimposed methyl doublets at 1.01 p.p.m. (J = 7 c.p.s., isopropyl group), but no low-field protons. The formation of a succinic anhydride with these characteristics is only possible if fumaropimaric acid has structure XV.



XVIII, R = H
XIX, R = CH_3

Experimental[18a]

β-Propiolactone Adduct of Levopimaric Acid.—Levopimaric acid, $[\alpha]^{25}D$ −267.5°, was prepared according to the procedure of Harris and Sanderson.[19] A mixture of 30.2 g. (0.10 mole) of levopimaric acid and 10.8 g. (0.15 mole) of β-propiolactone was heated at 225° in an oil bath with stirring under nitrogen for 3 hr. The resinous mass was cooled, dissolved in ether, and filtered to remove any polymer formed by excess β-propiolactone. The ether solution was washed with water. Evaporation of the ether and drying at 0.5-mm. pressure for 3 hr. and 100° gave 37.4 g. (100%) of the crude product, neut. equiv. 193, $[\alpha]^{25}D$ +23.4°. The ultraviolet spectrum had λ_{max}^{EtOH} 242 mμ (α = 5.2)[18b] indicating the presence of some unchanged isomerized levopimaric acid.

Separation of Adduct I.—A 10.0-g. portion of the product was dissolved in ether, carbon tetrachloride was added, and the ether was removed by warming. The carbon tetrachloride adduct which formed was dried at 150° and 0.5 mm. for 4 hr., yielding 5.7 g. (57%) of crude product, $[\alpha]^{25}D$ +24.8°, neut. equiv. 187.0°. Two crystallizations from benzene and drying as above gave the analytical sample, $[\alpha]^{25}D$ +25.8°, m.p. 222–222.5°.

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15; neut. equiv., 187.3. Found: C, 73.53; H, 9.10; neut. equiv., 187.3.

Treatment of I with ethereal diazomethane gave the dimethyl ester VIII whose preparation and properties are described subsequently. On gas chromatography it gave a single peak, retention time 5.95 min.

Chromatographic Separation of the Products of the Carbon Tetrachloride Filtrate.—The carbon tetrachloride filtrate was evaporated and dried at 0.5 mm. and 100° to yield 4.20 g. of resin, neut. equiv. 203.0, $[\alpha]D$ +20.7. This resin was separated into three components by means of a partition chromatography column similar to that described by Ramsey.[20] The column was packed with 50 g. of silicic acid which had been mixed with 35 ml. of (80:20) methanol–water. The eluting solvents were prepared by saturating isooctane and 50:50 isooctane–toluene with the methanol–water mixture. The first and second peaks which were eluted at 50 and 80 ml. with the isooctane contained 11.4% and 38.3% of the acids based on titration with alkali. The third fraction was stripped from the column with toluene and contained 49.3% of the acids placed on the column. The acids of each peak were extracted from the isooctane as their sodium salts, acidified with 1 *N* hydrochloric acid, and taken in ether. The ether was washed, evaporated, and the samples were dried for 3 hr. at 0.5 mm.

(14) The high selectivity in this reaction may be a consequence of the relatively low temperature.

(15) B. A. Arbuzov and A. G. Khismatullina, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 2126 (1959).

(16) W. D. Lloyd and G. W. Hedrick, *J. Org. Chem.*, **26**, 2029 (1961).

(17) L. C. King and H. Farber, Abstracts, 136th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept., 1959, p. 89P; *J. Org. Chem.*, **26**, 326 (1961).

(18) (a) Rotations were determined on 2% solutions in 95% alcohol unless otherwise specified. Infrared spectra were run on Perkin-Elmer Model 21 and Infracord spectrophotometers. All gas chromatograms were obtained at 264° using a ⅛ in. × 5 ft. 5% SE-30 silicone rubber on 60–80-mesh Chromosorb W using helium as the carrier gas and a Wilkins Hi Fi flame ionization detector. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., or by Dr. F. Pascher, Bonn, Germany. Nuclear magnetic resonance spectra were run in deuteriochloroform or pyridine solutions on an A-60 spectrometer purchased with the aid of a grant from the National Science Foundation. The internal standard used was 3% tetramethylsilane. I and II were run in pyridine because of their insolubility in deuteriochloroform. Product names are used purely for information and do not constitute an endorsement of those named over any other. (b) α = absorptivity = ϵ/mol. wt.

(19) G. C. Harris and T. F. Sanderson, *J. Am. Chem. Soc.*, **70**, 334 (1948).

(20) L. L. Ramsey and W. J. Patterson, *J. Assoc. Offic. Agr. Chemists*, **31**, 139 (1948).

Rosin Acids.—The acids eluted in the first peak were recovered in 84% yield, calculated as rosin acids, and had neut. equiv. 295.0, $[\alpha]^{25}D$ −16.5°. The ultraviolet spectrum had λ_{max}^{EtOH} 242 mμ (α = 48.4) and 252 mμ (α = 55.2) characteristic of a mixture of abietic and neoabietic acids.

Adduct II.—The acids eluted in the second peak were recovered in 89.5% yield, calculated as the adduct, and had neut. equiv. 201.0, $[\alpha]^{25}D$ +51.9°. The adduct was recrystallized from methanol–water and dried at 0.5 mm. and 100°, to give a 78% yield based on the acids in the peak by titration, and had neut. equiv. 187.9, m.p. 268–269°, $[\alpha]^{25}D$ +68.1°.

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.68; H, 9.05.

The dimethyl ester IX was prepared by treatment of 0.5 g. of II with ethereal diazomethane. The product gradually crystallized on scratching. It was purified by chromatography over alumina (solvent and eluent, pentane) and recrystallized from methanol–water, yielding 0.475 g., m.p. 70–71° (depressed on admixture of VIII); $[\alpha]^{25}D$ +80.2°; infrared band at 1730 cm.$^{-1}$; n.m.r. signals at 5.47 (s, H-8)^D, 3.68 (s, 3p, $-OCH_3$), 3.65 (s, 3p, $-OCH_3$), 1.13 (s, 3p, C–16 methyl), 1.01 (doublet, J = 7 c.p.s., 6p, C–19 and C–20 methyls), and 0.06 p.p.m. (s, 3p, C–17 methyl). The dimethyl ester gave a single peak on the gas chromatography with retention time of 4.90 min.

Anal. Calcd. for $C_{25}H_{38}O_4$: C, 74.59; H, 9.52. Found: C, 74.62; H, 9.68.

Adduct III.—The acids stripped from the column were recovered in 94% yield, calculated as the adduct from titration data, and had neut. equiv. 201.5, $[\alpha]^{25}D$ 0°, m.p. 134–138°. The material was converted to the cyclohexylamine salt in acetone. Removal of the solvent and drying at room temperature *in vacuo* over sodium sulfate furnished glassy material which was suspended in ether and washed with 1 *N* hydrochloric acid. The ether solution was washed with water, dried over sodium sulfate, and evaporated to dryness. The residue was dried at 100° (0.5 mm.), 57.0% yield, $[\alpha]^{25}D$ 0°, m.p. 136–140°.

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15; neut. equiv., 187.3. Found: C, 73.70; H, 9.37; neut. equiv., 188.5.

Treatment of III with ethereal diazomethane gave a mixture of dimethyl esters which was noncrystalline and had a double gas chromatogram peak at 5.90 and 6.95 min. Because of its noncrystalline nature, this material was not separated into the two components.

β-Propiolactone Adduct of Gum Rosin.—WW gum rosin, wt. 2225 g. containing approximately 1305 g. (4.35 moles) of abietic-type acids, was heated at 225° with slow stirring, and 482 g. (6.80 mole) of practical grade β-propiolactone was added during 1 hr. Heating at 225° was continued for 4 hr. A 1.6% loss occurred. The product was grade WW on the rosin scale, and had neut. equiv. 240, m.p. 128–134°. The modified rosin (100 g.) was dissolved in 500 ml. of ether, from which the adduct acids were extracted with 5% sodium bicarbonate. The sodium bicarbonate solution was acidified to pH 3 with dilute hydrochloric acid and extracted with ether. The ether solution was washed with water, dried over sodium sulfate, and evaporated. The residue was dried at 100° (0.5 mm.) for 3 hr. and weighed 60.0 g., neut. equiv. 194.2, $[\alpha]^{25}D$ +19.3°.

The crude adduct was refluxed in carbon tetrachloride. The carbon tetrachloride adduct which formed on cooling was dried at 100° (0.5 mm.) for 3 hr to give 30.0 g. of acid I, neut. equiv. 191.3, $[\alpha]^{25}D$ +24.1. Recrystallization from benzene gave the analytical sample, neut. equiv. 188.0, m.p. 218–222.5°, $[\alpha]^{25}D$ +25.8°. Admixture with I gave no depression in the melting point.

The carbon tetrachloride liquors were diluted with isooctane to incipient cloudiness and filtered to remove oxidized material. Cooling of the filtrate furnished crystals which were recrystallized from alcohol–water and dried at 100° (0.5 mm.) for 3 hr., yielding 9.67 g., m.p. 264–265°, $[\alpha]^{25}D$ +68.2°. Admixture with II gave no melting point depression.

The mother liquors were evaporated and the residue was dried at 100° (0.5 mm.) for 3 hr. to give 18.3 g. of adduct, m.p. 130–134°, neut. equiv. 192.1, $[\alpha]^{25}D$ +8.43°. There was no appreciable difference between the infrared spectrum of this noncrystalline β-propiolactone adduct of rosin acids and adduct I. The noncrystalline solid was not further examined.

Adduct of Rosin and Acrylic Acid.—An adduct was prepared as described in the procedure for rosin and β-propiolactone. A 50.0-g. sample of this modification was subjected to the recovery and drying procedures as described above for recovery of adducts I and II. Adducts I and II were obtained in approximately the same yield. No attempt was made to recover the noncrystalline adducts.

Oxidation of I and II with Alkaline Permanganate. Preparation of IV and VI.—Adduct I, 3.78 g. (0.02 equiv.), was dissolved in 25 ml. of water containing 0.80 g. of sodium hydroxide. The solution was cooled to 20° and added to a cold solution of 1.58 g. (3 equiv. of oxidizing agent) of potassium permanganate in 75 ml. of water. The reactants were stored in a refrigerator overnight. The precipitated manganese dioxide was removed, and the filtrate was acidified (pH 3) with dilute hydrochloric acid. The precipitated lactone was collected by filtration and dissolved in 15 ml. of ether. The ether was washed with water and dried over sodium sulfate. Carbon tetrachloride was added and the ether was removed by warming. The unchanged acid crystallized from the carbon tetrachloride. The carbon tetrachloride liquors were concentrated, and the residue was dried under vacuum. Crystallization from acetonitrile gave 3.10 g., 82% yield, of lactone IV, $[\alpha]^{25}D$ −92.3°, m.p. 257–258°. Recrystallization from acetone–water and drying at 0.5 mm. and 100° gave the analytical sample, m.p. 257–258°, $[\alpha]^{25}D$ −92.4°, positive tetranitromethane test, ν_{max}^{mull} 1770 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66; neut. equiv., 374.5. Found: C, 73.95; H, 8.92; neut. equiv., 374.5.

Adduct II was oxidized as described above for the oxidation of I. A 1.88-g. (0.005 mole) sample was used. Evaporation of the ether solution gave a white powder which was recrystallized from 50:50 toluene–isooctane; the yield of VI was 81.5%, $[\alpha]^{25}D$ +74.0°, neut. equiv. 198.6. Recrystallization from toluene gave the analytical sample, m.p. 180–184° dec., $[\alpha]^{25}D$ +78.0, negative tetranitromethane test.

Anal. Calcd. for $C_{23}H_{36}O_6$: C, 67.62; H, 8.87; neut. equiv., 204.2. Found: C, 67.86; H, 8.69; neut. equiv., 203.8.

The noncrystalline dimethyl ester was prepared using diazomethane, $\nu_{max}^{CCl_4}$ 3492 (O–H) cm.$^{-1}$.

Lactonization of Adduct I.—A suspension of 1.0 g. of diacid I in 10 ml. of formic acid containing 1 ml. of perchloric acid was refluxed for 24 hr. On cooling there precipitated 0.54 g. of lactone V, m.p. 240–248°. Dilution of the filtrate with water resulted in the recovery of 0.43 g. of I. Chromatography of crude V over silicic acid furnished 0.47 g. of V in the benzene–ether fractions. Crystallization from ether–petroleum ether (b.p. 30–60°) gave white needles, m.p. 271–273°, $[\alpha]^{25}D$ +33.5°, infrared bands at 1770 (γ-lactone) and 1700 cm.$^{-1}$ (carboxyl).

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15; O, 17.09. Found: C, 73.98; H, 9.24; O, 16.50.

Reduction of I and II with Lithium Aluminum Hydride. Preparation of XX and XXI.—A solution of 1.25 g. (0.003 mole) of I in 50 ml. of ether was added to an ether solution containing 3.40 g. (0.92 mole) of lithium aluminum hydride. After refluxing for 4 hr., the excess lithium aluminum hydride was destroyed with water and 20% sodium hydroxide. The ether layer was separated and the precipitate was washed with ether. The ether solution was washed, dried over sodium sulfate, and concentrated to give 1.10 g. (96%) of XX as needles, m.p. 163–165°. Recrystallization from acetone and drying at 100° (0.5 mm.) for 3 hr. gave the analytical sample, m.p. 166–167°, $[\alpha]^{25}D$ 0°, positive tetranitromethane test, ν_{max}^{mull} 3290 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{38}O_2$: C, 79.71; H, 11.05. Found: C, 79.62; H, 10.91.

Adduct II was reduced in the same manner. A 0.75-g. (0.002 mole) sample was used. The alcohol was obtained on evaporation of the ether as a powder, and had a 0.651-g. (94%) yield of XXI, m.p. 122–124°, $[\alpha]^{25}D$ +84.5°. Recrystallization from hexane and drying at 180° (0.5 mm.) for 3 hr. gave the analytical sample, m.p. 125–126.5°, $[\alpha]^{25}D$ +86.0°, positive tetranitromethane test, ν_{max}^{mull} 3290 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{38}O_2$: C, 79.71; H, 11.05. Found: C, 79.75; H, 11.11.

Isomerization of I and II.—Adduct I (2.22 g.) was heated at 250° for 2 hr., and the product was dissolved in ether. Carbon tetrachloride was added and the ether was removed by warming. The unchanged isomer was recovered as the carbon tetrachloride adduct in a 1.27-g. yield. The carbon tetrachloride liquors were extracted with 5% sodium bicarbonate solution. The bicarbonate solution was acidified and extracted with ether. The ether was washed with water, dried over sodium sulfate, evaporated, and dried at 100° (0.5 mm.) for 3 hr., yielding 0.325 g. of the diastereoisomer, $[\alpha]^{25}D$ + 50.1°. Recrystallization from alcohol–

water gave adduct II, $[\alpha]^{25}D$ +68.2°, m.p. 268–269°, neut. equiv. 188.0. Admixture with II gave no melting point depression.

Adduct II (0.55 g.) was heated for 2 hr. at 250°, and the products were recovered as above. A 57% yield of I was obtained, neut. equiv. 187.8, m.p. 218–218.5. Admixture with I gave no melting point depression. Adduct II was recovered in 22% yield from the carbon tetrachloride liquors. Adduct mixture III was heated at 225–230° for 4 hr. and dissolved in 5 ml. of carbon tetrachloride. The insoluble carbon tetrachloride addition product of I was not obtained.

Attempted Dienophile Exchange.—A mixture of 3.74 g. (0.01 mole) of I was heated under nitrogen with 2.32 g. (0.02 mole) of fumaric acid at 250° for 1 hr. The mixture was dissolved in ether, and unchanged fumaric acid was removed by filtration and washing. No fumaropimaric acid could be detected in the reaction mixture.

Methyl Acrylate Adduct of Levopimaric Acid.—A solution of 10.0 g. of levopimaric acid in 20 ml. of methyl acrylate was refluxed for 8 hr. and allowed to stand at ambient temperature overnight. Excess methyl acrylate was removed by steam distillation. The residue, 12.8 g., m.p. 107–134°, was recrystallized from methanol, yielding 9.8 g. of VII, m.p. 161–162°, $[\alpha]^{25}D$ +19.5°, infrared bands at 1725 (ester) and 1690 cm.$^{-1}$ (carboxyl). A second crop, 1.7 g., m.p. 154–158°, was obtained from the mother liquors; the total yield was 90%.

Anal. Calcd. for $C_{23}H_{36}O_4$: C, 74.19; H, 9.34; O, 16.47. Found: C, 74.47; H, 9.52; O, 16.26.

The dimethyl ester VIII was prepared by treatment of 1 g. of VII with ethereal diazomethane. Evaporation of the solvent furnished a colorless oil which was taken up in hot methanol, treated with decolorizing charcoal, and diluted with water to incipient cloudiness. Upon cooling, an oil separated which crystallized on scratching, yielding 0.95 g., m.p. 68–69°, $[\alpha]^{25}D$ +17.5°, infrared band at 1725 cm.$^{-1}$ (ester). The substance was homogeneous on a thin layer chromatogram and also was prepared by esterification of I.

Anal. Calcd. for $C_{25}H_{38}O_4$: C, 74.59; H, 9.52; O, 15.90. Found: C, 74.43; H, 9.48; O, 16.35

Hydrolysis of 10 g. of VII by refluxing with 100 ml. of 10% sodium hydroxide solution for 24 hr. followed by acidification and recrystallization from benzene furnished 8.9 g. of I, m.p. 223–225°, $[\alpha]^{25}D$ +27.5°. The infrared and n.m.r. spectra were superimposable with the levopimaric acid β-propiolactone adduct and reesterification furnished VIII.

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15; O, 17.09. Found: C, 73.43; H, 9.24; O, 17.17.

Acrylonitrile Adducts of Levopimaric Acid.—The crude adduct mixture prepared by the method of Halbrook, Wells, and Lawrence[7] was esterified with ethereal diazomethane. One gram of the mixture was chromatographed over 50 g. of alumina (Alcoa F-20). Benzene–petroleum ether (b.p. 30–60°, 1:1) eluted 0.39 g. of an oil which was dissolved in methanol. Water was added to incipient cloudiness whereupon one ester nitrile (XII or XIII) separated. Recrystallization furnished material, m.p. 120–121°; $[\alpha]^{25}D$ +84°; infrared bands at 2230 (–CN) and 1725 cm.$^{-1}$ (ester); n.m.r. signals at 5.42 (H–8), 3.68 (methoxyl), 1.16 (C–16 methyl), 1.03 (doublets, J = 7 c.p.s., isopropyl methyls), and 0.61 p.p.m. (C–17 methyl). This ester also was prepared by direct methylation of the acrylonitrile adduct, m.p. 191°, $[\alpha]^{25}D$ +88°.[7]

Anal. Calcd. for $C_{24}H_{35}NO_2$: C, 78.00; H, 9.55; N, 3.79; O, 8.66. Found: C, 78.10; H, 9.57; N, 3.95; O, 8.87.

Benzene–petroleum ether (3:1) eluted 0.47 g. of solid, m.p. 132–149°, which was recrystallized from methanol, m.p. 174–176°; $[\alpha]^{25}D$ 0°; infrared bands at 2230 (–CN) and 1720 cm.$^{-1}$ (ester); n.m.r. signals at 5.52 (H–8), 3.67 (methoxyl), 1.17 (C–16 methyl), 1.06 (doublet, J = 7, c.p.s., isopropyl methyls), and 0.62 p.p.m. (C–17 methyl). This substance could be obtained also from the acrylonitrile adduct, m.p. 182°, $[\alpha]^{25}D$ 0°.[7]

Anal. Calcd. for $C_{24}H_{35}NO_2$: C, 78.00; H, 9.55; O, 8.66. Found: C, 78.14; H, 9.44; O, 9.04.

For separation of larger quantities of the two ester nitriles, fractional crystallization was more convenient. Five grams of the ester nitrile mixture was dissolved in a minimum of boiling ether. Chilling produced 1.96 g. of the higher melting isomer, m.p. 174–176°. Concentration of the mother liquor furnished 0.67 g. of additional material. Evaporation of the mother liquor gave 2.28 g. of a somewhat impure lower melting isomer; several recrystallizations from methanol were required to raise the melting point to 120–121°.

Hydrolysis of XII and XIII.—A mixture of 1.5 g. of the isomer, m.p. 120–121°, and 3 g. of potassium hydroxide in 25 ml. of ethylene glycol was refluxed in a copper flask. Evolution of ammonia continued for 70 hr. The mixture was poured into ice–hydrochloric acid, yielding 1.46 g., m.p. 164–203°. Purification as described for the β-propiolactone adducts provided 0.72 g. of cubes, m.p. 222–224°, and 0.64 g. of needles, m.p. 267–269°, which were identical with adducts I and II.

Hydrolysis of 3 g. of the isomer, m.p. 174–176°, in the same manner furnished 3.12 g. of crude diacids, m.p. 171–196°, which were separated into 1.73 g. of adduct I and 1.25 g. of adduct II.

Ozonolysis of Fumaropimaric Acid.—A solution of 6 g. of fumaropimaric acid, m.p. 293–295° (sinters at 180°),[6] in 100 ml. of methanol was ozonized at −70° until the blue color of excess ozone was present. It was then added rapidly, with stirring, to an ice-cold solution prepared from 70 ml. of Clorox, 300 ml. of water, 100 ml. of methanol, and 200 g. of ice to which concentrated hydrochloric acid had been added until the green color of free chlorine appeared. Reaction was almost instantaneous, product XVIII separating as a white precipitate which was filtered after a few minutes and dried, yielding 4.5 g. (70%), m.p. 254–259° dec. Purification was difficult owing to limited solubility; the analytical sample, m.p. 267–269° dec., was prepared by allowing a saturated ethyl acetate solution to evaporate slowly.

Anal. Calcd. for $C_{24}H_{32}O_8$: C, 64.27; H, 7.19; O, 28.54. Found: C, 64.02; H, 7.27; O, 29.05.

The dimethyl ester XIX was prepared from 4 g. of XVIII with excess diazomethane in ether. After 15 min. excess diazomethane was destroyed with acetic acid; the solution was washed with dilute sodium bicarbonate solution, dried, and evaporated; and the residue was recrystallized from ethanol to yield 2.69 g., m.p. 222–224°; infrared bands at 1855, 1790, 1740, and 1715 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{36}O_8$: C, 65.53; H, 7.61; O, 26.86. Found: C, 65.39; H, 7.73; O, 27.11.

Constituents of *Iva* Species. II. The Structures of Asperilin and Ivasperin, Two New Sesquiterpene Lactones[1]

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The structures of asperilin and ivasperin, two new sesquiterpene lactones from *Iva asperifolia* Less., are shown to be II and X. Asperilin and ivasperin also have been isolated from *Iva texensis* Jackson.

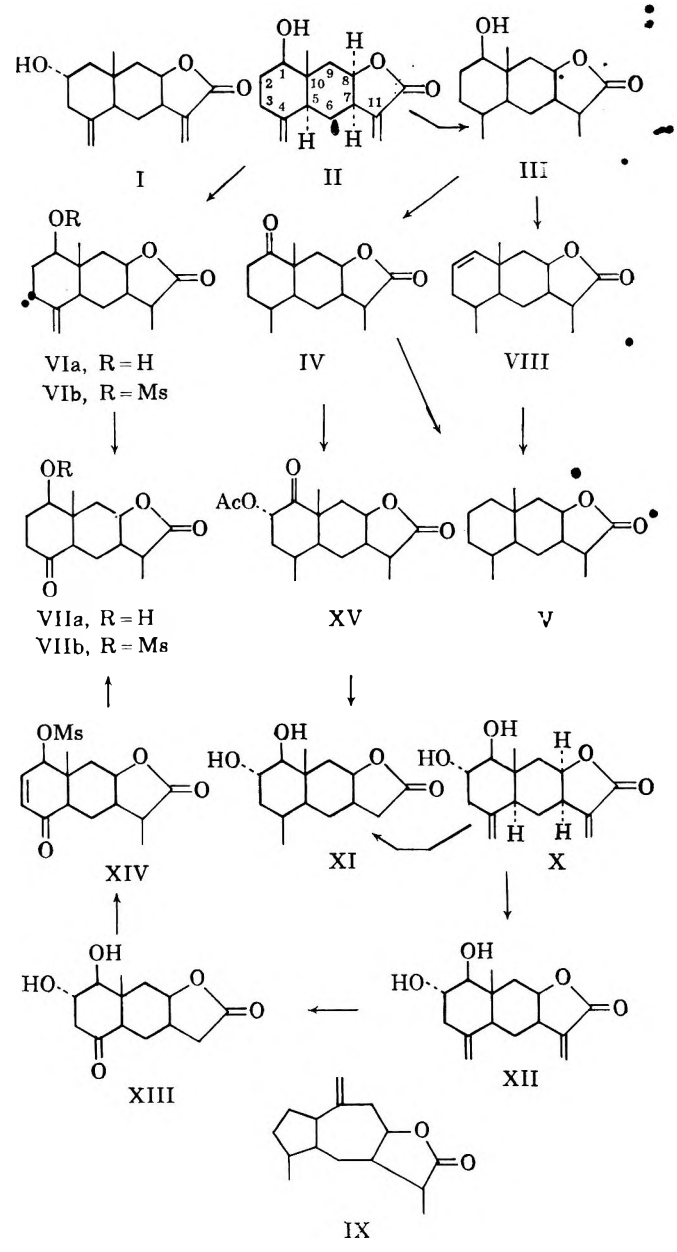
In order to delineate more clearly possible connections between genera related to *Ambrosia* and *Parthenium* suggested by our earlier work,[2,3] we have initiated a systematic phytochemical survey of the genus *Iva*.[4] In the first paper[5] we discussed the structure of ivalin (I), the main sesquiterpene lactone constituent of *I. microcephala* Nutt., and *I. imbricata* Walt. We now report the isolation and structure determination of asperilin and ivasperin, constituents of *I. asperifolia* Less. and *I. texensis* Jackson. Work on other *Iva* species is in progress.

Iva asperifolia is a Mexican species (state of Veracruz) whose distribution in the United States is limited to a small area near the old port of St. Marks, Florida.[4] Material from this source, which may represent an introduction from Mexico, furnished two new sesquiterpene lactones in 0.16 and 0.029% yields, respectively, which we have named asperilin and ivasperin.

Asperilin (II), the less polar material, m.p. 151–152°, $[\alpha]^{23}D$ +149.6°, had the formula $C_{15}H_{20}O_3$ and contained a hydroxyl group (infrared bands at 3700 and 3500 cm.$^{-1}$; formation of an acetate) and two double bonds (infrared bands at 1655 and 1645 cm.$^{-1}$). One of the double bonds was conjugated with a γ-lactone function (ν_{max} 1755 cm.$^{-1}$) as evidenced by the ultraviolet maximum at 211 mμ (ε 8730) and the formation of a pyrazoline from asperilin acetate. Hence asperilin is dicarbocyclic.

Catalytic hydrogenation of asperilin in acetic acid using platinum oxide gave tetrahydroasperilin (III) by saturation of both double bonds. Chromic acid oxidation of III gave a ketone (IV) whose infrared spectrum (ν_{max} 1704 cm.$^{-1}$) showed that the carbonyl group was in a six- or higher-membered ring. Hence the hydroxyl group in asperilin is secondary. Desulfurization of the ethylenethioketal of dehydrotetrahydroasperilin (IV) afforded tetrahydroalantolactone[6] (V), identical in all respects with an authentic sample. This establishes the carbon skeleton of asperilin and the stereochemistry at positions 5, 7, 8, and 10.

The nature of the double bonds was indicated by selective reduction of II to dihydroasperilin (VIa), which possessed no ultraviolet maximum. Ozonolysis of its mesylate gave the norketone VIIb. This indicates that asperilin contains one isolated exocyclic methylene group and another methylene group conjugated with a γ-lactone.



The n.m.r. spectra[8] of II, III, VIa, and the acetates of II and III confirmed these conclusions. II had two low-field doublets (6.01 and 5.48 p.p.m., $J \sim 1$ c.p.s.), each representing one proton, characteristic of a methylene group conjugated with a lactone.[2,3,5] These were absent in III and VIa. A doublet at 4.85 p.p.m. ($J \sim 1.5$) represented one proton of the unconjugated exocyclic methylene group, and a multiplet centered

(1) Supported in part by grants from the U. S. Public Health Service (RG-5814) and the National Science Foundation (NSF-G-14396).

(2) W. Herz and G. Högenauer, *J. Org. Chem.*, **26**, 5011 (1961).

(3) W. Herz, H. Watanabe, M. Miyazaki, and Y. Kishida, *J. Am. Chem. Soc.*, **84**, 2601 (1962).

(4) The most recent revision is that of R. C. Jackson, *Univ. Kansas Sci. Bull.*, **41**, 793 (1960).

(5) W. Herz and G. Högenauer, *J. Org. Chem.*, **27**, 905 (1962).

(6) The C-11 methyl group of tetrahydroalantolactone recently has been shown to be β-oriented.[7]

(7) W. Cocker and M. A. Nisbet, *J. Chem. Soc.*, 534 (1963).

(8) N.m.r. spectra were run on an A-60 instrument in deuteriochloroform solution with tetramethylsilane serving as internal reference.

at 4.50 p.p.m., corresponding to two protons, was due to the superposition of the other methylene proton on the signal of the lactonic hydrogen on C-8. A three-proton singlet at 0.80 p.p.m. was due to a tertiary methyl group. A complex set of bands (two doublets centered at 3.4 p.p.m., J_{AX} = 9.5, J_{AY} = 6 c.p.s.) had to be ascribed to the hydrogen on carbon carrying the hydroxyl group since it moved downfield to near 4.5 p.p.m. on acetylation and disappeared on oxidation.

III had no olefinic protons but exhibited, in addition to the methyl singlet at 0.965 p.p.m., two methyl doublets at 1.19 and 1.31 p.p.m. (J = 7 c.p.s.). VIa had two narrowly split doublets centered at 4.84 and 4.55 due to the unconjugated methylene protons,[9] one methyl singlet of 0.79, and one methyl doublet at 1.22 p.p.m. (J = 6 c.p.s.).

The close similarity between asperilin and ivalin (I)[5] suggested that the two compounds differed only in the position of the hydroxyl group on the ring skeleton. That IV contained a $-CO-CH_2-$ system was shown by its positive Zimmermann test and the formation of a monopiperonylidene derivative. Positions 2 and 3, however, were untenable as the locus of the hydroxyl group in asperilin, since IV was different from dehydrotetrahydroivalin (2-ketotetrahydroalantolactone)[5] and dehydrotetrahydroisotelekin (3-ketotetrahydroalantolactone).[10] By elimination, dehydrotetrahydroasperilin (IV) had to be 1-ketotetrahydroalantolactone, and the position of the hydroxyl group in asperilin was hence uniquely fixed as in II. The optical rotatory dispersion of IV supported this conclusion since it exhibited a positive Cotton effect and was very similar to that of 9-methyl-*trans*-1-decalones.[11]

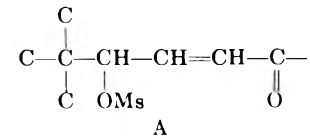
The configuration of this C-1 hydroxyl group remained to be settled. Reduction of IV with sodium borohydride, sodium–ethanol, or hydrogenation with platinum oxide in acetic acid all gave tetrahydroasperilin as the only isolable product. Reduction to the equatorial alcohol is favored on steric grounds as well as on considerations of thermodynamic stability. The hydroxyl group of asperilin must, therefore, be β-oriented.

It is interesting to note that the (noncrystallizable) mesylate of tetrahydroasperilin on treatment with collidine at 200–210° gave VIII in 20% yield, and not IX as was expected in analogy with earlier work[12,13] which would have afforded an entry into the guaianolide series. The structure of VIII was made evident by its reduction to V and by its n.m.r. spectrum (p.p.m.): singlet at 5.5 corresponding to two olefinic protons,[14] two methyl doublets at 0.94 and 1.27, (J = 7 c.p.s.), one methyl singlet at 1.08, and an H-8 multiplet at 4.5. Since much decomposition accompanied the reaction, the formation of IX cannot be completely excluded and further efforts to effect this conversion are contemplated, pending availability of material.

The minor and more polar constituent, ivasperin (X), was $C_{15}H_{20}O_4$, m.p. 150–151°, $[\alpha]^{23}D$ +140.5°. Its ultraviolet [λ_{max} 210.5 mμ (ϵ 7750)] and infrared spectra (bands at 3650, 3450, 1760, 1660, and 1650 cm.$^{-1}$) were very similar to those of asperilin. Compound X had two double bonds as shown by hydrogenation with platinum oxide to tetrahydroivasperin (XI). Hydrogenation with palladium–calcium carbonate catalyst gave dihydroivasperin (XII) by reduction of the double bond conjugated with the lactone carbonyl. Ivasperin also contained two hydroxyl groups as shown by the formation of a diacetate. That these were vicinal was indicated by the positive periodic acid test shown by ivasperin and its reduction products.

The n.m.r. spectrum (p.p.m.) of ivasperin had two pairs of doublets at 6.24 and 5.59 (J = 1 c.p.s., $=CH_2$ conjugated with γ-lactone), a doublet at 4.90 (J = 1.5 c.p.s., one of the protons of the unconjugated exocyclic methylene groups), a multiplet centered at 4.59 (two protons, superposition of the other olefinic proton on the lactonic hydrogen at C-8), a poorly defined series of bands near 3.5 (two protons, presumably H on carbon carrying hydroxyl groups), and a methyl singlet at 0.81. Ivasperin diacetate exhibited doublets at 6.06 and 5.54 (conjugated methylene), a complex multiplet centered at 4.86 (three protons, two due to H on carbon carrying acetates and one belonging to the unconjugated methylene), a doublet at 4.63 (J = 1.5 c.p.s., second proton of $=CH_2$), a multiplet at 4.44 (H-8), two acetate singlets at 2.06 and 1.97, and a methyl singlet at 0.91 p.p.m. On the other hand, tetrahydroivasperin (XI) had no peaks in the vinyl proton region, but exhibited two methyl doublets at 1.18 (J = 8 c.p.s.) and 0.945 (J = 6 c.p.s.), and the usual methyl singlet at 1 p.p.m., in addition to the lactone hydrogen multiplet at 4.54, and the two-proton signal centered at 3.5 p.p.m.

Dihydroivasperin (XII) on ozonolysis furnished a norketone (XIII) which exhibited a positive Zimmermann test. The dimesylate of XIII when heated with pyridine afforded an anhydro ketone (XIV) which retained one mesylate function and whose ultraviolet [λ_{max} 222.5 mμ, (ϵ 8150)] and infrared spectra (bands at 1680 and 1630 cm.$^{-1}$) showed that it was an α,β-unsaturated ketone. The n.m.r. spectrum (set of twelve ABX type signals: A at 6.80, B at 6.12, X at 5.42 p.p.m., J_{AB} = 10, J_{AX} = 1.5, J_{BX} = 2.5 c.p.s., lactone hydrogen at 4.5, mesylate at 3.16, methyl doublet at 1.24 p.p.m., J = 7 c.p.s., and methyl singlet at 1.0 p.p.m.) established the presence of partial structure A and confirmed that the two hydroxyl groups of ivasperin were secondary.



A

Catalytic reduction of XIV with palladium on charcoal furnished the ketomesylate VIIb identical in all respects with a mesylate obtained by ozonolysis of dihydroasperilin mesylate. This established the gross

(9) The second of these was again superimposed on the signal of H-8.

(10) V. Benešová, V. Herout, and F. Šorm, *Collection Czech. Chem. Commun.*, **26**, 1350 (1961).

(11) C. Djerassi and W. Klyne, *J. Chem. Soc.*, 4029 (1962). We are indebted to Dr. Ulrich Weiss, Laboratory of Physical Biology, National Institute of Arthritis and Metabolic Diseases, for carrying out this measurement.

(12) R. Hirschmann, C. S. Snoddy, C. F. Hiskey, and N. L. Wendler, *J. Am. Chem. Soc.*, **76**, 4013 (1954).

(13) D. H. R. Barton, O. C. Böckman, and P. de Mayo, *J. Chem. Soc.*, 2263 (1960).

(14) Apparently H-1 and H-2 exhibit the same chemical shift and H-2 is split only slightly by the two adjacent protons at C-3.

structure of ivasperin as well as its stereochemistry, excepting the configuration of the hydroxyl at C-2.

This was clarified as follows. Lead tetraacetate oxidation of dehydrotetrahydroasperilin (IV) under conditions which favor the equatorial isomer[15] gave the 2-α-acetoxy ketone XV. The acetoxy group in this must be equatorial since it is unchanged on prolonged refluxing in acetic acid. Sodium borohydride reduction of XV resulted in simultaneous hydrolysis of the acetoxy group to yield the diol XI identical with tetrahydroivasperin. The hydroxyls of ivasperin must, therefore, be both equatorial which leads to the stereochemistry depicted in X.

Iva texensis Jackson, a newly distinguished species[4] which is very closely related morphologically to *I. asperifolia*, was investigated subsequently and furnished asperilin and ivasperin in 0.22 and 0.18% yield.

Experimental[16]

Extraction of *I. asperifolia* Less.—Ground whole plant, 12 lb., collected in St. Marks, Florida (in September, 1962), was extracted with hot chloroform for 3 days. The chloroform was removed and the residue was dissolved in 1.2 l. of ethanol, warmed to about 50°, and heated with a hot solution of 56 g. of lead acetate and 20 ml. of acetic acid in 1.3 l. of water. The mixture was allowed to stand overnight; the supernatant liquid was filtered, concentrated to about 1.5 l. *in vacuo*, and extracted thoroughly with chloroform; and the chloroform extract was washed, dried, and evaporated. The residual gum, 160 g., was chromatographed over 2 lb. of Alcoa F-20 alumina in benzene solution. The material eluted with benzene was rechromatographed in 3:2 petroleum ether (b.p. 35–60°)–benzene to give 8.5 g. of asperilin, needles from acetone–ether–petroleum ether, m.p. 151–152°. The more polar material in the first chromatogram, eluted with benzene–chloroform and chloroform, gave a slowly solidifying gum, sparingly soluble in benzene and chloroform and very soluble in methanol. Repeated crystallization from ethyl acetate gave prisms of ivasperin, 1.61-g. yield, m.p. 150–151°. The homogeneity of asperilin and ivasperin was checked by thin layer chromatography using silica as adsorbent; R_f values in ether were: asperilin, 0.43; ivasperin, 0.10; in acetone–methanol (97:3): asperilin, 0.98; ivasperin, 0.70.

Asperilin had λ_{max} 211 mμ (ϵ 8730); ν_{max} 3700, 3500, 1755, 1655, and 1645 cm.$^{-1}$; $[\alpha]^{23}D$ +149.6° (*c* 1.35).

Anal. Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12; O, 19.33. Found: C, 72.86; H, 8.16; O, 19.25.

Ivasperin had λ_{max} 210 mμ (ϵ 7750); ν_{max} 3650, 3450, 1760, 1660, and 1650 cm.$^{-1}$; $[\alpha]^{23}D$ +140.5° (*c* 2, methanol).

Anal. Calcd. for $C_{15}H_{20}O_4$: C, 68.19; H, 7.58; O, 24.24. Found: C, 67.90; H, 7.56; O, 24.45.

Acetylasperilin.—A mixture of 0.2 g. of asperilin, 2 ml. of acetic anhydride, and 1 ml. of pyridine was allowed to stand for 12 hr. The usual work-up resulted in 0.18 g. of the acetate, m.p. 176–178°, prisms from ethyl acetate–petroleum ether, having ν_{max} 1765 (γ-lactone), 1740 (acetate), 1655, and 1645 cm.$^{-1}$ (double bonds); n.m.r. signals (p.p.m.) at 6.12 and 5.59 (narrowly split doublets, J = 1 c.p.s., conjugated methylene), 4.83 and 4.55 (narrowly split doublets, unconjugated methylene) superimposed on multiplets of H-1 centered at 4.7, and H-8 centered at 4.55, 2.06 (acetate), and 0.89 (C-10 methyl).

Anal. Calcd. for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64; O, 22.04. Found: C, 70.70; H, 7.59; O, 21.94.

The pyrazoline was prepared by allowing 0.12 g. of the acetate in 10 ml. of ether to stand with 20 ml. of ethereal diazomethane for 3 days at ice-box temperature. Evaporation followed by several crystallizations from acetone–petroleum ether furnished the derivative, m.p. 170° dec.

Anal. Calcd. for $C_{18}H_{24}N_2O_4$: C, 65.04; H, 7.28. Found: C, 65.48; H, 6.96.

Tetrahydroasperilin (III).—A solution of 1 g. of II in 50 ml. of acetic acid was hydrogenated with 0.2 g. of platinum oxide at 30 lb./in.^{2} for 2 hr. The catalyst was filtered, the solvent was evaporated, and the residue was crystallized twice from ethyl acetate–petroleum ether, yielding 0.71 g., m.p. 150–151°; $[\alpha]^{23}D$ +16.6° (c, 3.3); ν_{max} 3700, 3500 (–OH), and 1770 cm.$^{-1}$ (γ-lactone).

Anal. Calcd. for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59; O, 19.02. Found: C, 71.46; H, 9.56; O, 18.85.

The acetate was prepared in the usual manner and was crystallized from ethyl acetate–petroleum ether, m.p. 104–105°. The n.m.r. spectrum (p.p.m.) had signals at 4.52 (two protons, complex multiplet, superposition of H-1 and H-8), 2.02 (acetate), 1.18 and 0.90 (two doublets, C-4 and C-11 methyls), and 1.02 (singlet, C-10 methyl).

Anal. Calcd. for $C_{17}H_{26}O_4$: C, 69.39; H, 8.85; O, 21.77. Found: C, 69.37; H, 9.15; O, 21.53.

Dehydrotetrahydroasperilin (IV).—A solution of 1 g. of III in 15 ml. of acetic acid was treated dropwise with a solution of 0.75 g. of chromic acid in 15 ml. of acetic acid and 2 ml. of water. The resulting mixture was allowed to stand overnight at room temperature, concentrated at reduced pressure, diluted with water, and extracted with chloroform. The extract was washed, dried, and evaporated. The residue on crystallization from ether–petroleum ether gave 0.76 g. of IV, m.p. 131–132°; $[\alpha]^{23}D$ +64.85° (*c*, 2.39); infrared bands at 1770 (γ-lactone) and 1704 cm.$^{-1}$ (ketone); positive Zimmermann test; optical rotatory dispersion curve in methanol (c 0.081): $[\alpha]_{589}$ +64.8°, $[\alpha]_{405}$ +821°, $[\alpha]_{275}$ −117°. The n.m.r. spectrum (p.p.m.) exhibited signals at 4.5 (multiplet, H-8), 1.25 (singlet, C-10 methyl), and 1.20 and 1.15 (doublets, J = 7 c.p.s., C-4 and C-11 methyls).

Anal. Calcd. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.55; H, 8.66.

The piperonylidene derivative was prepared by allowing a solution of 0.135 g. of IV and 0.22 g. of piperonal in 5 ml. of ethanol to stand overnight with 5 ml. of ethanol saturated with hydrogen chloride. The solution was diluted with ice–water and extracted with methylene chloride. The extract was washed, dried, and concentrated, and the residue was taken up in benzene and chromatographed over acid-washed alumina. Benzene–chloroform (4:1) eluted the material which was crystallized from acetone–petroleum ether. The silky needles melted at 204–205°.

Anal. Calcd. for $C_{23}H_{26}O_5$: C, 72.24; H, 6.81; O, 20.94. Found: C, 71.93; H, 6.81; O, 21.62.

Tetrahydroalantolactone (V).—A suspension of 0.22 g. of IV in 0.45 ml. of ethanedithiol was cooled, mixed with 1.1 ml. of boron trifluoride etherate, left overnight at room temperature, diluted with water, and extracted thoroughly with ether. The ether extract was washed, dried, and evaporated, and the residue was crystallized from benzene–petroleum ether, yielding 0.19 g. of thioketal, m.p. 214–215°.

Anal. Calcd. for $C_{17}H_{26}O_2S_2$: C, 62.56; H, 8.03; S, 19.61. Found: C, 62.01; H, 8.00; S, 20.12.

A solution of 0.32 g. of the thioketal in 25 ml. of absolute ethanol was refluxed for 24 hr. with 2 teaspoonfuls of Raney nickel. Evaporation of the filtrate and crystallization of the residue from ethanol afforded 0.13 g. of tetrahydroalantolactone, m.p. 143–144°, undepressed on admixture of an authentic sample. The infrared spectra and the rotations of the two samples were identical.

Reductions of Dehydrotetrahydroasperilin. A. Sodium Borohydride.—A solution of 0.32 g. of IV in 25 ml. of methanol was left overnight with 0.15 g. of sodium borohydride. Excess reagent was decomposed with a few drops of acetic acid, the solution was concentrated *in vacuo*, and the residue was diluted with water and extracted with chloroform. The extract was washed, dried, and evaporated; crystallization of the residue afforded 0.25 g. (78%) of tetrahydroasperilin, m.p. and m.m.p. (with an authentic sample) 149–150°. The infrared spectra and rotations of the two samples were identical.

B. Catalytic Reduction.—A solution of 0.1 g. of IV in 15 ml. of acetic acid was shaken with 0.03 g. of platinum oxide at a hydrogen pressure of 35 lb./in.^{2}. The solution was filtered and concentrated, and the residue was recrystallized from ethyl acetate–petroleum ether, yielding 0.075 g. (74%) of tetrahydroasperilin, m.p. and m.m.p. 150°.

C. Sodium–Ethanol.—A solution of 0.15 g. of IV in 40 ml. of ethanol was warmed on a water bath and treated, during 20 min., with 2.2 g. of sodium. After 45 min. at reflux, the solution was concentrated, acidified to congo red, and extracted with chloro-

(15) K. Yamakawa, *J. Org. Chem.*, **24**, 897 (1959).

(16) Melting points are uncorrected; analyses are by Dr. F. Pascher, Bonn Germany. Infrared spectra and rotations were run in chloroform solution unless otherwise specified, ultraviolet spectra in 95% ethanol.

form; the extract was washed and dried. Chromatography over acid-washed alumina and recrystallization afforded 0.065 g. (43%) of tetrahydroasperilin, m.p. and m.m.p. 150°. No other fraction was isolated.

Dihydroasperilin (VIa).—A solution of 0.6 g. of II in 30 ml. of ethanol was hydrogenated at atmospheric pressure with 0.09 g. of 5% palladium on calcium carbonate. The reduction was stopped when 60 ml. of hydrogen (at NTP) had been absorbed. The catalyst was filtered, the solution was evaporated, and the solid residue was recrystallized twice from ethyl acetate–petroleum ether, yielding 0.375 g. of needles, m.p. 184–185°. The product had infrared bands at 3700 and 3450 (—OH), 1770 (γ-lactone), and 1650 cm.$^{-1}$ (double bond); no ultraviolet maximum; and n.m.r. signals at 4.84 d and 4.55 d (2, exocyclic methylene), 4.55 m (H-8), 1.22 d (C-11 methyl), and 0.79 p.p.m. (C-10 methyl).

Anal. Calcd. for $C_{14}H_{22}O_4$: C, 71.97; H, 8.86; O, 19.17. Found: C, 72.14; H, 8.76; O, 19.11.

Ozonolysis of Dihydroasperilin.—A solution of 0.4 g. of VIa in 15 ml. of methanol was ozonized at −70°. The resulting solution was shaken with hydrogen at 20 lb./in.^{2} for 0.5 hr. in the presence of 0.05 g. of 5% palladium on charcoal, filtered, and evaporated. The residue was recrystallized from ethyl acetate, yielding 0.15 g. of VIIa, m.p. 202–203°, infrared bands at 1780 (γ-lactone) and 1718 cm.$^{-1}$ (ketone).

Anal. Calcd. for $C_{14}H_{20}O_4$: C, 66.64; H, 7.99; O, 25.37. Found: C, 66.85; H, 7.72; O, 25.61.

Ozonolysis of VIb.—The mesylate of VIa (VIb) melted at 128° dec. after recrystallization from ethyl acetate–petroleum ether.

Anal. Calcd. for $C_{16}H_{24}O_5S$: C, 58.41; H, 7.37; S, 9.77. Found: C, 57.65; H, 7.18; S, 10.19.

A solution of 0.2 g. of the mesylate in 20 ml. of methanol was ozonized at −70° for 1 hr. The solution was shaken with 0.06 g. of 5% palladium-on-charcoal catalyst at a hydrogen pressure of 20 lb./in.^{2} for 0.5 hr., filtered, and evaporated. The residue was taken up in chloroform and filtered by passage through a short column of acid-washed alumina. Elution with chloroform and crystallization of the product from chloroform–petroleum ether gave 0.085 g. of the ketomesylate VIIb, m.p. 158–159°; infrared bands at 1775 (γ-lactone), 1720 (ketone), 1360, and 1170 cm.$^{-1}$ (mesylate group).

Anal. Calcd. for $C_{15}H_{22}O_6S$: C, 54.54; H, 6.71. Found: C, 54.30; H, 6.97.

Anhydrotetrahydroasperilin (VIII).—A solution of 0.33 g. of III in 3 ml. of pyridine was treated at 5° with 0.4 ml. of mesyl chloride and left overnight at 5°. The solution was diluted with water and extracted with ether. The ether extract was washed, dried, and evaporated to yield the mesylate as an uncrystallizable gum. The mesylate was heated in a sealed tube at 200–210° with 7 ml. of collidine for 15 hr., the base was removed at reduced pressure, and the residue was poured on ice–hydrochloric acid. Extraction with chloroform gave a gum which was chromatographed over acid-washed alumina, with benzene–petroleum ether (2:1) as solvent and eluent. The solid material was recrystallized from ether–petroleum ether, yielding 0.045 g. of VIII, m.p. 140–142°, infrared bands at 1770 (γ-lactone) and 1645 cm.$^{-1}$ (weak, double bond).

Anal. Calcd. for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46; O, 13.66. Found: C, 76.82; H, 9.37; O, 13.79.

A solution of 0.06 g. of VIII in 10 ml. of ethanol was hydrogenated catalytically with platinum oxide. After removal of solvent and crystallization from ethanol there was obtained 0.04 g. of tetrahydroalantolactone, m.p. and m.m.p. 142–143°.

Diacetylivasperin.—A mixture of 0.18 g. of ivasperin, 2 ml. of acetic anhydride, and 1 ml. of pyridine was warmed, left overnight at room temperature, poured on water, and filtered. The solid was recrystallized from benzene–petroleum ether, yielding 0.15 g., m.p. 170–172°; infrared bands at 1770 (γ-lactone), 1745 (double strength, acetates), 1665, and 1655 cm.$^{-1}$ (double bonds).

Anal. Calcd. for $C_{19}H_{24}O_6$: C, 65.51; H, 6.90; O, 27.58. Found: C, 65.64; H, 6.87; O, 27.14.

Tetrahydroivasperin (XI).—A solution of 0.31 g. of X in 5 ml. of acetic acid was added to 0.07 g. of prereduced platinum oxide in 25 ml. of acetic acid and shaken at atmospheric pressure until hydrogen absorption ceased. The catalyst was filtered, the solution was concentrated, and the residual solid was recrystallized from ethyl acetate–petroleum ether, yielding 0.24 g. of prisms, m.p. 163–165°, $[\alpha]^{22}D$ +30° (c 2, methanol), infrared bands at 3700 and 3500 (—OH) and 1770 cm.$^{-1}$ (γ-lactone).

Anal. Calcd. for $C_{15}H_{24}O_4$: C, 67.17; H, 8.96; O, 23.89. Found: C, 66.88; H, 8.73; O, 24.03.

The diacetate was prepared using pyridine–acetic anhydride and recrystallized from ethyl acetate–petroleum ether, m.p. 186–187°, infrared bands at 1760 (γ-lactone) and 1740 cm.$^{-1}$ (double strength, acetates).

Anal. Calcd. for $C_{19}H_{28}O_6$: C, 64.75; H, 8.01; O, 27.24. Found: C, 64.80; H, 8.14; O, 27.39.

Dihydroivasperin (XII).—A solution of 0.7 g. of X in 15 ml. of ethanol was hydrogenated at atmospheric pressure with 0.14 g. of 5% palladium-on-calcium carbonate catalyst. The solution was evaporated and the residue was recrystallized from ethyl acetate; yielding 0.58 g., m.p. 180–181°, no ultraviolet maximum.

Anal. Calcd. for $C_{15}H_{22}O_4 \cdot H_2O$: C, 63.36; H, 8.51; O, 28.14. Found: C, 63.48; H, 8.71; O, 27.88.

Ozonolysis of Dihydroivasperin.—A solution of 0.2 g. of XII in 15 ml. of methanol was ozonized at −70° for 1 hr. and worked up reductively as described for previous ozonolyses. Recrystallization of the solid residue from methanol–ether furnished 0.11 g. of the norketone XIII, m.p. 194–195°; infrared bands at 3700 and 3500 (—OH), 1770 (γ-lactone), and 1725 cm.$^{-1}$ (ketone); positive Zimmermann test.

Anal. Calcd. for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51; O, 29.82. Found: C, 62.34; H, 7.64; O, 30.27.

A solution of 0.09 g. of XIII in 2 ml. of pyridine was mixed with 1 ml. of methanesulfonyl chloride at 5° and allowed to stand at 10–15° overnight. The solution was poured on ice and extracted with chloroform. The extract on washing, drying, and evaporating furnished a gummy residue which was a mixture of dimesylate and anhydromonomesylate XIV (infrared and n.m.r. spectrum). To complete the conversion, it was heated on the steam bath with 3 ml. of pyridine for 3 hr., poured on ice–hydrochloric acid, and extracted with chloroform. The product XIV was crystallized from chloroform–petroleum ether as needles, m.p. 124°, in 0.05-g. yield; infrared bands at 1775 (γ-lactone), 1680 (conjugated ketone), 1630 (weak, double bond), 1365, and 1170 cm.$^{-1}$ (mesylate); λ_{max} 222.5 mμ (ε 8150). Since the material decomposed fairly rapidly on standing, it was not analyzed.

A solution of 0.09 g. of XIV in 15 ml. of methanol was hydrogenated at 20 lb./in.^{2} with 0.03 g. of 5% palladium on charcoal. The solution was filtered and evaporated, the residue was taken up in chloroform and chromatographed over acid-alumina. Chloroform eluted material which was recrystallized from chloroform–petroleum ether had m.p. 157–158°, undepressed on admixture of the mesylate VIIb. Infrared spectra of the samples were identical.

2-α-Acetoxy-1-ketotetrahydroalantolactone (XV).—A solution of 0.5 g. of IV in 100 ml. of acetic acid was refluxed for 5 hr. with 1 g. of lead tetraacetate. The solvent was removed *in vacuo*, and the residue was heated with aqueous sodium bicarbonate solution and extracted with chloroform. The chloroform extract was washed, dried, and concentrated. Repeated crystallization of the residue from ethyl acetate–petroleum ether gave 0.14 g. of needles, m.p. 203–204°; infrared bands at 1775 (γ-lactone), 1745 (acetate), and 1725 cm.$^{-1}$ (ketone). The n.m.r. spectrum (p.p.m.) exhibited signals at 5.72 (quadruplet, X of ABX spectrum, J_{AX} = 12, J_{BX} = 7 c.p.s., H-2), 4.55 (multiplet, H-8), 2.78 (quadruplet, J = 7 c.p.s., H-11), 2.10 (acetate), 1.36 (C-10 methyl), and 1.26 and 1.24 (two doublets, J = 7 c.p.s., C-4 and C-11 methyls).

Anal. Calcd. for $C_{17}H_{28}O_5$: C, 65.80; H, 8.40; O, 25.80. Found: C, 65.60; H, 8.19; O, 26.47.

Reduction of 0.1 g. of XV in 5 ml. of methanol with 0.1 g. of sodium borohydride for 1 hr. at reflux and overnight at room temperature, dilution with water, and extraction with chloroform gave, after recrystallization from ethyl acetate–petroleum ether, 0.035 g. of needles, m.p. 163–164°, undepressed on admixture of an authentic sample of tetrahydroivasperin (XI). The infrared spectra of the two samples were identical.

Extraction of *I. texensis* Jackson.—Extraction of 17.5 lb. of *I. texensis* (above-ground part), collected by Dr. N. C. Henderson on the north end of Galveston Island, Texas, on September 29, 1962, in the usual manner, furnished a gum, approximately 200 g., which was chromatographed over 3 lb. of Alcoa alumina F-20. Elution with benzene, benzene–chloroform, and chloroform gave oils and gums. Elution with chloroform–methanol (19:1) gave solid material which was crystallized from ethyl acetate–petroleum ether, 7.4 g., m.p. 150–151°, identified as ivasperin by mixture melting point and comparison of the n.m.r. and infrared spectra. The identity was confirmed by conversion to diacetylivasperin, m.p. 170–172°, undepressed on admixture with an authentic sample.

A 40-g. aliquot of the less polar gummy fractions (total wt. 240 g. from 35 lb. of plant) was dissolved in benzene–petroleum ether (1:2) and rechromatographed over 600 g. of alumina. Benzene–petroleum ether and benzene eluted oils. Benzene–chloroform (3:1, 2:1, 1:2) eluted semisolid material which was triturated with ether–petroleum ether, filtered, and recrystallized from ether–petroleum ether–acetone, yielding 4.0 g. of asperilin, m.p. 150–151°, undepressed on admixture with an authentic sample, infrared spectra superimposable. Chloroform eluted a noncrystallizable gum and chloroform–methanol (19:1) eluted an additional 1.3 g. of ivasperin. Altogether, 35 g. (0.22%) of asperilin and 29 g. (0.18%) of ivasperin were obtained from 35 lb. of plant material.

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Configurational Studies with 2,3-Dihydroxyoctadecanoic Acids

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The configurations of 2,3-dihydroxyoctadecanoic acids have been proved unambiguously by conversion to 2,3-octadecanediols. The properties of the intermediate cyclic ketals as well as of some other derivatives are compared and discussed. An attempt is made to explain the unusual melting points of long-chain 2,3-dihydroxyalkanoic acids in terms of unusual preferred conformations.

The interrelationship between 2,3-dihydroxyoctadecanoic acids was studied by Myers[1] and was based on Swern's previous work with 9,10-dihydroxyoctadecanoic acids.[2] Using stereospecific methods, Myers could transform the higher melting acid to the lower melting one, but their unusual melting points were probably the reason why he was unable to ascertain which of them had the *erythro* and which the *threo* configuration. In a recent review,[3] it was stated again that the unusual melting points are due to the proximity of the carboxyl group, but no explanation of this effect was given. The problem was, therefore, to determine unambiguously the configurations of 2,3-dihydroxyoctadecanoic acids, and, in addition, to explain some "anomalous" physical properties on the basis of preferred conformations.

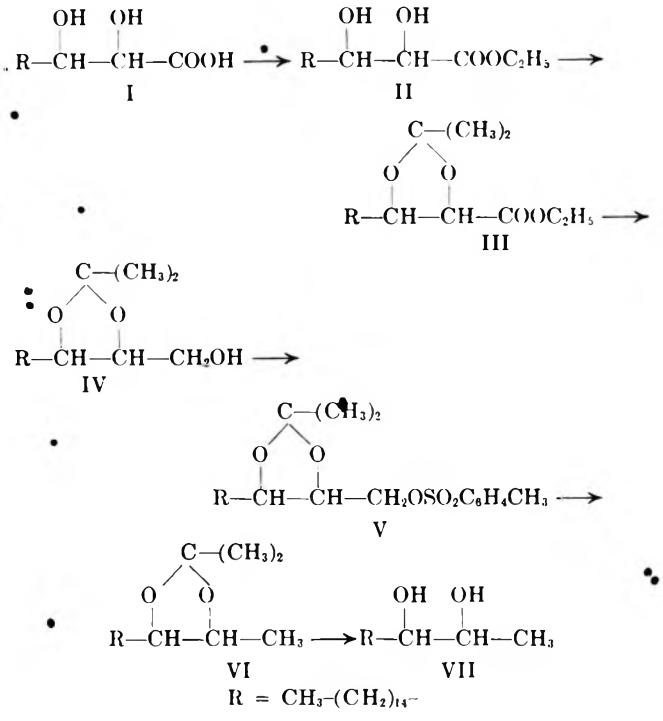
The first question was settled by elimination of the bulky carboxyl group which could influence the configuration of the adjacent carbon atom.[4] This was done even though it is known[5] that the attack of a positively charged agent in hydroxylation reactions occurs preferentially on the adjacent carbon atom which is the most electronegative site of the double bond, and that it is preferentially the C-3 atom, the configuration of which might be influenced, and which is electron deficient. In spite of this evidence it seemed desirable to introduce at the end of the molecule a group which by itself would be unable to disturb the normal hydroxylation reaction. For preliminary studies, *trans*-2-octadecenol, prepared by the method of Grob and Jenny,[6] was subjected to the Woodward *cis* hydroxylation method. The product was 1,2,3-octadecanetriol (m.p. 91–94°) identical in all respects with the triol obtained by lithium aluminum hydride reduction of the 2,3-dihydroxyoctadecanoic acid, melting at 127°.[7] Thus it was confirmed that the *trans* double bond is hydroxylated in the same manner when vicinal to a primary hydroxyl or to a carboxyl group.

The most rigorous proof for the *threo* and *erythro* configurations of 2,3-dihydroxyoctadecanoic acids (I),[8] melting at 127 and 108°, respectively, was based on Swern's theoretical considerations for 9,10-dihydroxyoctadecanoic acids[9] and consisted in comparing steric relationships between hydroxyl groups of the two isomeric 2,3-octadecanediols (VII). The configurations of such vicinal diols are known with certainty as a result of lead tetraacetate cleavage experiments made by Criegee, *et al.*[10] Each acid (I) was esterified separately, and the free hydroxyl groups of these esters (II) were protected in the form of cyclic ketals. The ketal esters (III) were then reduced by lithium aluminum hydride to give ketal alcohols (IV), treated with *p*-toluenesulfonyl chloride, and the resulting tosyl esters (V) reduced with lithium aluminum hydride to VI from which the diols (VII) were obtained by acid hydrolysis. (See Scheme I.)

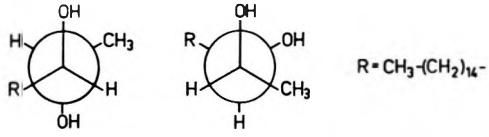
In the most favorable staggered conformation of *erythro*-2,3-octadecanediol (VIII) the hydroxyl substituents are on opposite sides of the axis between the C-2 and C-3 atoms and are, therefore, almost or wholly incapable of intramolecular hydrogen bonding, while *threo*-2,3-octadecanediol (IX), because of the proximity of hydroxyl substituents, allows a higher degree of intramolecular hydrogen bonding in the crystal lattice. Even in very dilute solutions *threo* diols show a greater tendency to form intramolecular hydrogen bonds than *erythro* diols,[11] and the anti-*trans* conformation is less abundant in the *threo* than in the *erythro* derivatives.[12] The diol having the lower melting point (70°) was de-

(1) G. S. Myers, *J. Am. Chem. Soc.*, **73**, 2100 (1951); **74**, 1390 (1952).
(2) D. Swern, *ibid.*, **70**, 1235 (1948).
(3) H. J. Harwood, *Chem. Rev.*, **62**, 99 (1962).
(4) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 382; W. Lwowski, *Angew. Chem.*, **70**, 490 (1958).
(5) B. M. Lynch and K. H. Pausacker, *J. Chem. Soc.*, 1525 (1955); F. D. Gunstone and L. J. Morris, *ibid.*, 487 (1957); R. B. Woodward and F. V. Brutcher, Jr., *J. Am. Chem. Soc.*, **80**, 209 (1958).
(6) C. A. Grob and E. F. Jenny, *Helv. Chim. Acta*, **36**, 1936 (1953).
(7) B. Palameta and M. Prostenik, *Tetrahedron*, in press.
(8) Each formula shown is considered to represent both enantiomers of the *erythro* (*cis*) series. The same reaction sequence applies to the *threo* (*trans*) series.
(9) D. Swern, L. P. Witnauer, and H. B. Knight, *J. Am. Chem. Soc.*, **74**, 1655 (1952).
(10) R. Criegee, E. Höger, G. Huber, P. Kruck, F. Marktscheffel, and H. Schellenberger, *Ann.*, **599**, 81 (1956).
(11) L. P. Kuhn, *J. Am. Chem. Soc.*, **80**, 5950 (1958).
(12) G. Chiudoglu, R. de Groote, W. Masschelein, and M. H. van Risseghem, *Bull. soc. chim. Belges*, **70**, 342 (1961); *Chem. Abstr.*, **56**, 8185 (1962).

SCHEME I



rived from the higher melting *threo*-2,3-dihydroxyoctadecanoic acid. Therefore, all compounds in this series would have the *threo* configuration. By analogous considerations, the higher melting diol (m.p. 80–81°), derived from the lower melting 2,3-dihydroxyoctadecanoic acid, must belong to the *erythro* series, and its hydroxyls are not sterically hindered but are internally associated as in 1,2-octadecanediol (m.p. 79–80°). The infrared spectra of the 2,3-octadecanediols are shown in Fig. 1.



The second question was to explain some experimental facts in terms of the established configurations of 2,3-dihydroxyoctadecanoic acids and to suggest preferred conformations in the crystal state.

In our opinion, the "reversed" melting points of 2,3-dihydroxyoctadecanoic acids, as compared with 9,10-dihydroxy acids, might have their explanation in reversed conformations; namely, the influence of the adjacent carboxyl groups might be such as to drive the hydroxyl substituents into particular positions (X for the *erythro*, XI for the *threo* acid). This would have a profound effect on physical properties of the acids. This would be in accordance with the observation that the *threo* acid undergoes cyclization with acetone at a slower rate than the *erythro* acid owing to the unfavorable conformation in the initial state. The same would apply to the formation of a cyclic sulfite, although in this case the attack of thionyl chloride on carboxyl group probably precedes the attack on hydroxyl groups. The different conformations also might explain why the *threo* acid affords the diacetoxy derivative

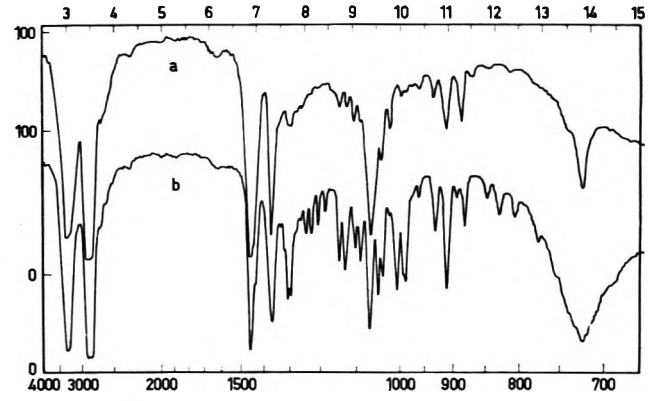
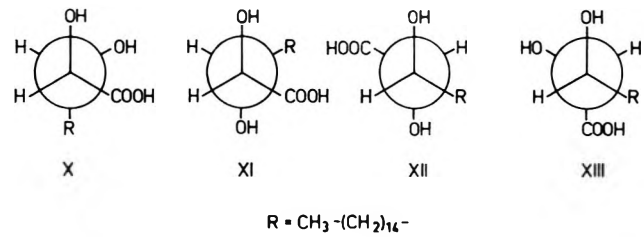


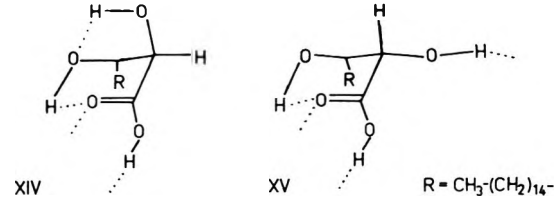
Fig. 1.—Infrared spectra in Nujol: (a) *erythro*-2,3-octadecanediol and (b) *threo*-2,3-octadecanediol.

even under strenuous conditions, while with the *erythro* acid intermolecular condensation probably takes place.

However, several facts cannot be reconciled with the proposed conformations. Why should these acids find their energy minimum in more crowded dispositions of functional groups (X and XI) and not in others (*e.g.*, XII and XIII) where the approach of substituents capable of hydrogen bonding simultaneously relieves the steric repulsions between the other two groups? Obviously, the tendency to form hydrogen bonds overcomes the steric hindrance in eclipsed conformations of these dihydroxy acids.



Therefore, if we accept the above-mentioned conformations (X and XI) as most favorable and if we show the hydrogen-bonded oxygen functions of the Newman projection formulas in the form of a distorted six-membered ring, it can be seen that the *erythro* acid dimer (XIV) forms preferentially intramolecular hydrogen bonds, whereas the C-2 hydroxyl group of the *threo* acid dimer (XV), unsuitably located towards both carboxyl and C-3 hydroxyl functions, also forms intermolecular hydrogen bonds. This is reflected in the lower melting point, powdery appearance, and higher solubility in organic solvents of the *erythro* acid, as compared with the *threo* acid which has higher melting point, lower solubility, and scaly appearance.

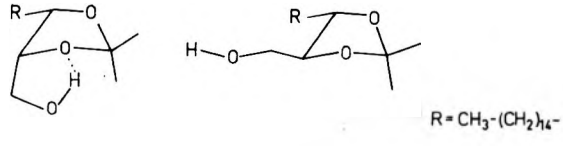


These assumptions are, of course, not without criticism. The identity of hydrogen bonds between the carboxyl and the C-3 hydroxyl groups in both proposed conformations does not explain the differences in the wave lengths of infrared carbonyl absorptions

(the band of the *erythro* acid at 1695 cm.$^{-1}$, of the *threo* acid at 1745 cm.$^{-1}$). Jones and Sandorfy[13] ascribe these differences in 2- and 3-hydroxyoctadecanoic acids to exo- and endocyclic carbonyl functions in five- and six-membered hydrogen-bonded rings. In our case, this has not been attempted. The situation seems to be more complicated; in amides of 2,3-dihydroxyoctadecanoic acids it is just the *erythro* diastereoisomer for which the carbonyl band occurs at higher wave length, and in the esters both compounds have the carbonyl band at 1725 cm.$^{-1}$.

The *cis* and *trans* cyclic ketal esters (III) were prepared in boiling anhydrous acetone using anhydrous cupric sulfate as dehydrating agent, a shorter reflux time being necessary for the *erythro* dihydroxy ester than for the *threo* ester. In their experiments with 9,10,12-trihydroxyoctadecanoic acids, using anhydrous hydrogen chloride as condensing agent, Esafov and Torgashina[14] came to the opposite conclusion and were able to obtain quantitative cyclization of the *threo* acid, while the *erythro* acid remained completely unaffected under the same conditions.

The most striking and unexplainable feature of these compounds is the difference of 30° between the melting points of the *cis* and *trans* tosyl esters of ketals (V). In going from the diastereoisomeric dimeric cyclic ketal acids with similar melting points, to the cyclic ketal alcohols one observes the expected melting point decrease which is greater for the presumably intramolecularly hydrogen-bonded *cis* ketal alcohol (XVI) than for the presumably intermolecularly hydrogen-bonded *trans* ketal alcohol (XVII). The melting point of the *trans* cyclic tosyl ester remains practically constant, the loss of intermolecular hydrogen bonds being compensated by the enlargement of the molecule. However, the melting point of the *cis* compound is too high compared with the *trans* isomer, so that, in our opinion, other unknown factors may operate in this case. This is even more surprising in light of Haresnape's calculations[15] for the 1,2-dimethylcyclopentanes where the *cis* compound has higher internal energy content than the *trans* isomer.



XVI XVII

The infrared absorption bands in the 1300–800-cm.$^{-1}$ region of diastereoisomeric cyclic ketals are shown in Table I.[16] Their wave lengths are quite similar, and on the basis of these bands alone it is not possible to distinguish the *cis* from the *trans* cyclic compounds. Partial assignments of frequencies can be made by analogy with the results on substituted dioxolanes[17]: the bands at 1260–1240 and 1230–1190 cm.$^{-1}$ can be attributed to *gem*-methyl symmetrical and antisymmetrical rocking vibrations, bands at 1050–1030 and 1190–1170 cm.$^{-1}$ to symmetrical and antisymmetrical ring-stretching vibrations, and bands at 1115–1090 cm.$^{-1}$ to a skeletal stretch.

The reported data concerning long-chain 2,3-alkanediols are very scarce and lacking adequate configurational interpretation. One 2,3-dodecanediol (m.p. 68–69°) has been prepared by Lüttringhaus, *et al.*,[18] in the perbenzoic acid hydroxylation of the mixture of 1- and 2-dodecenes. From a similar starting material 2,3-alkanediols have been prepared by Asahara and Ito[19] and were readily distinguishable from the 1,2-diols by their higher melting points. We could not prove this statement, but, in comparison with the *erythro* and *threo*-9,10-octadecanediols,[20] it is significant that moving of the two vicinal hydroxyl substituents to the middle of the hydrocarbon chain raises considerably the melting point of the *erythro* compound (2,3-diol 80–81°, 9,10-diol 130°) and has only minor effect on the *threo* diols (2,3-diol 70°, 9,10-diol 77–78°).

Of the other derivatives, cyclic sulfites have been prepared from the dihydroxy acids (I) and thionyl chloride. Their infrared spectra reveal the presence of S=O stretching frequencies near 1220 cm.$^{-1}$,[21] although the derivative of the *threo* acid could not be purified to give the correct elemental analysis. Both dihydroxy acids can be recovered from these cyclic sulfites with unchanged original configurations by acid hydrolysis. The formation of cyclic sulfites also can probably explain the apparent unreactivity of hydroxyl groups of 9,10-dihydroxyoctadecanoic acids during the reaction with thionyl chloride.[22] The dihydroxy acids (I) also have been treated with acetic anhydride in pyridine. From the *threo* acid only the normal diacetyl derivative could be isolated, and with the *erythro* acid at 80° intermolecular dehydration probably took place giving predominantly a product melting at 95–96°. The normal diacetylated acid remains impure in the residual oil which is the sole product if the acetylation is carried out at 20°.

Experimental[23]

2,3-Dihydroxyoctadecanoic Acids (I).—*erythro* and *threo*-2,3-dihydroxyoctadecanoic acids were prepared from *trans*-2-octadecenoic acid by peracid *trans* hydroxylation and Woodward *cis* hydroxylation methods in 33 and 38% yields, respectively, and, after purification *via* copper chelate, melted at 108 and 127°, respectively.[7]

Ethyl 2,3-Dihydroxyoctadecanoates (II). ***erythro* Isomer.**—*erythro*-2,3-Dihydroxyoctadecanoic acid (10.8 g.) was esterified by refluxing for 5 hr. with 65 ml. of anhydrous ethanol and 1.5 ml. of concentrated sulfuric acid. The bulk of the solvent was evaporated; the residue was extracted with ether, washed with water, with sodium hydrogen carbonate solution, and again with

(13) R. N. Jones and C. Sandorfy, "Chemical Applications of Spectroscopy," A. Weissberger, Ed., Interscience, New York, N. Y., 1956, p. 491.

(14) V. I. Esafov and Z. I. Torgashina, *J. Gen. Chem. USSR*, **8**, 1594 (1938); *Chem. Abstr.*, **33**, 4583 (1939); *cf.* also P. A. Artamonov, *Zh. Obshch. Khim.*, **27**, 2726 (1957).

(15) J. N. Haresnape, *Chem. Ind.* (London), 1091 (1953).

(16) The infrared data were obtained with a Perkin-Elmer Infracord 137 double beam spectrophotometer with sodium chloride prism. Measurements were carried out in Nujol mull or in liquid films.

(17) S. A. Barker, E. J. Bourne R. M. Pinkard, and D. H. Whiffen, *J. Chem. Soc.*, 807 (1959).

(18) A. Lüttringhaus, G. Wagner-Sääf, E. Sucker, and G. Borth, *Ann.*, **577**, 51 (1947).

(19) T. Asahara and T. Ito, *J. Soc. Org. Syn. Chem.* (Japan), **9**, No. 7, 19 (1951); *Chem. Abstr.*, **47**, 6855 (1953).

(20) A. N. Wrigley, F. D. Smith, and A. J. Stirton, *J. Org. Chem.*, **24**, 1793 (1959).

(21) H. H. Szmant and W. Emerson, *J. Am. Chem. Soc.*, **78**, 454 (1956); P. B. D. de la Mare, D. J. Millen, J. G. Pritchard, and D. Watson, *J. Chem. Soc.*, 1813 (1956); D. Ben-Ishay, *J. Org. Chem.*, **23**, 2013 (1958).

(22) J. A. Lamberton, *Australian J. Chem.*, **9**, 528 (1956).

(23) All melting points were determined on "Culatti" apparatus and are uncorrected. Chromatographic separations were carried out on Fluka alumina, Type 507c, neutral, activity stage 1, according to Brockmann. The petroleum ether refers to the fraction boiling at 45–60°. Microanalyses were carried out by Mrs. J. Zake and Mrs. E. Galogaža.

TABLE I

INFRARED ABSORPTION BANDS OF CYCLIC KETALS

a	b	c	d	e	f	g	h	i	k	l
1260 (s)[m]	1260 (s)		1270 (vs)		1270 (m)					
1250 (s)		1240 (vs)		1240 (vs)	1255 (s)	1250 (s)	1250 (vs)	1250 (s)	1250 (m)	1250 (s)	1240 (vs)
		1230 (vs)			1235 (vs)			1230 (s)			1230 (s)
1220 (s)			1220 (vs)		1220 (vs)	1220 (vs)	1220 (vs)		1220 (m)	1220 (vs)	
	1210 (vs)			1215 (vs)	1210 (vs)						
1190 (vs)	1190 (vs)							1190 (vs)	1195 (vs)		
		1175 (m)	1175 (s)	1170 (s)	1175 (m)	1175 (m)	1170 (s)	1180 (vs)	1185 (vs)		
			1140 (m)	1130 (w)	1140 (w)			1130 (m)			
		1110 (s)		1115 (vs)				1115 (s)			
1100 (vs)	1100 (vs)	1090 (vs)	1090 (vs)	1090 (vs)	1105 (vs)	1100 (m)	1100 (vs)	1105 (s)	1105 (s)	1090 (vs)	1100 (vs)
		1055 (m)	1045 (w)	1045 (m)		1050 (vs)	1050 (vs)	1045 (vs)			
1040 (m)	1035 (m)	1030 (m)	1020 (w)	1030 (s)				1020 (m)	1020 (w)		
		1010 (w)	1005 (m)	1010 (m)	1000 (w)		1000 (m)				1010 (m)
990 (w)			995 (w)	980 (w)	990 (w)			990 (vs)	990 (vs)		
			955 (w)	955 (w)	950 (w)			950 (w)		945 (w)	
			930 (w)		930 (w)	925 (w)	925 (m)	925 (w)	930 (w)		935 (m)
				915 (s)	920 (w)		905 (m)	905 (w)			
		885 (m)	895 (m)	885 (s)	890 (m)	880 (m)	880 (m)	890 (m)			
875 (m)		870 (w)	875 (m)		870 (s)						
	860 (m)		850 (w)			850 (m)	860 (s)	865 (s)	860 (w)	865 (m)	865 (m)
				840 (w)	845 (m)		845 (m)	845 (vs)	835 (s)		
	810 (m)	810 (m)	820 (m)	815 (w)	815 (m)		815 (w)	820 (vs)	820 (s)		

[a] Ethyl *cis*-2,2-dimethyl-5-*n*-pentadecyl-1,3-dioxolane-4-carboxylate. [b] Ethyl *trans*-2,2-dimethyl-5-*n*-pentadecyl-1,3-dioxolane-4-carboxylate. [c] Amide of *cis*-2,2-dimethyl-5-*n*-pentadecyl-1,3-dioxolane-4-carboxylic acid. [d] Amide of *trans*-2,2-dimethyl-5-*n*-pentadecyl-1,3-dioxolane-4-carboxylic acid. [e] *cis*-2,2-Dimethyl-5-*n*-pentadecyl-1,3-dioxolane-4-carboxylic acid. [f] *trans*-2,2-Dimethyl-5-*n*-pentadecyl-1,3-dioxolane-4-carboxylic acid. [g] *cis*-2,2-Dimethyl-4-hydroxymethyl-5-*n*-pentadecyl-1,3-dioxolane. [h] *trans*-2,2-Dimethyl-4-hydroxymethyl-5-*n*-pentadecyl-1,3-dioxolane. [i] *cis*-2,2-Dimethyl-4-hydroxymethyl-5-*n*-pentadecyl-1,3-dioxolane *p*-toluenesulfonate. [j] *trans*-2,2-Dimethyl-4-hydroxymethyl-5-*n*-pentadecyl-1,3-dioxolane *p*-toluenesulfonate. [k] *cis*-5-*n*-Pentadecyl-2,2,4-trimethyl-1,3-dioxolane. [l] *trans*-5-*n*-Pentadecyl-2,2,4-trimethyl-1,3-dioxolane. [m] vs = very strong, s = strong, m = medium, w = weak.

water, and dried over anhydrous sodium sulfate. The solvent was evaporated, and the residue was crystallized from petroleum ether to give 10.4 g. (89%) of colorless product melting at 68–69°. Recrystallization from petroleum ether raised the melting point to 69°; main infrared absorption bands at 3430, 3270, 1725, 1240, 1220, 1205, 1130, 1080, 1050, 1035, 1020, and 960 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{40}O_4$ (344.52): C, 69.72; H, 11.70. Found: C, 69.47; H, 11.39.

threo **Isomer.**—The *threo* ester was prepared by the same procedure from 10.5 g. of *threo*-2,3-dihydroxyoctadecanoic acid. The yield was 10.1 g. (88%) of the crude product which, after two crystallizations from acetonitrile, melted at 71–72°. Infrared spectrum shows absorptions at 3360, 1725, 1310, 1290, 1275, 1255, 1235, 1215, 1135, 1115, 1090, 1080, 1030, and 870 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{40}O_4$ (344.52): C, 69.72; H, 11.70. Found: C, 70.03; H, 11.45.

Ethyl 2,2-Dimethyl-5-*n*-pentadecyl-1,3-dioxolane-4-carboxylates (III). ***cis* Isomer.**—The crude ethyl *erythro*-2,3-dihydroxyoctadecanoate (2.4 g.) was dissolved in 25 ml. of anhydrous acetone (dried over calcium sulfate), and 4 g. of anhydrous cupric sulfate was added. After refluxing for 6 hr., the acetone solution was filtered off, and acetone was evaporated under reduced pressure. The slightly colored oily residue was dissolved in petroleum ether and chromatographed over alumina. Elution with benzene gave 1.5 g. (56%) of colorless oil.

trans **Isomer.**—Under exactly the same conditions as above, 2.4 g. of ethyl *threo*-2,3-dihydroxyoctadecanoate afforded, after chromatography over alumina, 0.8 g. (30%) of the pure product.

Better yields (*cis* ester 91%, *trans* ester 80%) were obtained by prolonging the refluxing time to 10 hr. for the *erythro*, and to 20 hr. for the *threo* ester.

2,2-Dimethyl-5-*n*-pentadecyl-1,3-dioxolane-4-carboxylic Acids. ***cis* Isomer.**—Ethyl *cis*-2,2-dimethyl-5-*n*-pentadecyl-1,3-dioxolane-4-carboxylate (3.7 g.) was refluxed for 3 hr. with a solution of 5.6 g. of potassium hydroxide in 100 ml. of ethanol. The bulk of solvent was removed under reduced pressure; the residue was poured into dilute hydrochloric acid and extracted with ether. The organic layer was washed with water and dried over anhydrous sodium sulfate; ether was evaporated. The residue was dissolved in petroleum ether, cooled, filtered from traces of 2,3-dihydroxyoctadecanoic acid, and evaporated to dryness leaving 3.2 g. (94%) of the product melting at 54.5–56°. Recrystallization from acetonitrile yielded a colorless product melting at 56–58°.

Anal. Calcd. for $C_{21}H_{40}O_4$ (356.53): C, 70.74; H, 11.31. Found: C, 70.40; H, 11.25.

trans **Isomer.**—The same procedure was repeated with 7.2 g. of ethyl *trans*-2,2-dimethyl-5-*n*-pentadecyl-1,3-dioxolane-4-carboxylate giving 90% of the crude product, m.p. 48–50°. Two recrystallizations from acetonitrile yielded the product melting at 53–54°.

Anal. Calcd. for $C_{21}H_{40}O_4$ (356.53): C, 70.74; H, 11.31. Found: C, 70.98; H, 11.11.

From both *cis* and *trans* acids the original 2,3-dihydroxyoctadecanoic acids have been obtained by acid hydrolysis, as seen by comparing their melting points and infrared spectra with authentic samples.

2,2-Dimethyl-4-hydroxymethyl-5-*n*-pentadecyl-1,3-dioxolanes (IV). ***cis* Isomer.**—A solution of 9.3 g. of ethyl *cis*-2,2-dimethyl-5-*n*-pentadecyl-1,3-dioxolane-4-carboxylate in 50 ml. of anhydrous ether was added dropwise to a suspension of 1.5 g. of lithium aluminum hydride in 50 ml. of anhydrous ether, and the whole refluxed for 30 min. Water was added cautiously and was followed by 10% aqueous potassium hydroxide until two layers were formed. The ethereal layer was filtered off and evaporated under reduced pressure leaving 7.2 g. (87%) of an oily residue. Further purification was effected by dissolving the oil in acetonitrile and keeping in a refrigerator overnight. The colorless crystals melted at 30°.

Anal. Calcd. for $C_{21}H_{42}O_3$ (342.55): C, 73.63; H, 12.36. Found: C, 74.08; H, 12.14.

trans **Isomer.**—The reduction of ethyl *trans*-2,2-dimethyl-5-*n*-pentadecyl-1,3-dioxolane-4-carboxylate (4.0 g.) was carried out in the same manner as described for the *cis* cyclic ester yielding 2.85 g. (80%) of the crude product, m.p. 37–40°. Several recrystallizations from acetonitrile raised the melting point to 44–45°.

Anal. Calcd. for $C_{21}H_{42}O_3$ (342.55): C, 73.63; H, 12.36. Found: C, 74.01; H, 12.57.

2,2-Dimethyl-4-hydroxymethyl-5-*n*-pentadecyl-1,3-dioxolane *p*-Toluenesulfonates (V).[24] ***cis* Isomer.**—To a solution of 7.2 g. of *cis*-2,2-dimethyl-4-hydroxymethyl-5-*n*-pentadecyl-1,3-dioxolane in 20 ml. of anhydrous pyridine was added 8 g. of *p*-toluenesulfonyl chloride in several portions with stirring and keeping the temperature below 10°. Stirring was continued for additional 3 hr., while the temperature was not allowed to raise above 20°. The thick paste was poured into ice-cooled dilute hydrochloric acid. The precipitate was collected, thoroughly washed with water, dissolved in ether, and again washed with water. Evaporation under reduced pressure left 8.6 g. of the crude product which was crystallized from petroleum ether giving 7.25 g. (69%) of colorless powder melting at 63–65.5°. A sample was recrystallized from petroleum ether and melted at 66°.

Anal. Calcd. for $C_{28}H_{48}O_5S$ (496.76): C, 67.70; H, 9.74. Found: C, 67.31; H, 9.47.

trans **Isomer.**—The preparation of *trans* cyclic *p*-toluenesulfonate was performed in the same manner as for the corresponding *cis* derivative. The crude product from 2.8 g. of *trans*-2,2-dimethyl-4-hydroxymethyl-5-*n*-pentadecyl-1,3-dioxolane was crystallized from ethanol to yield 2.7 g. (66%) of colorless powder melting near 35°. Recrystallizations from acetonitrile and then from ethanol raised the melting point to 36–37°.

Anal. Calcd. for $C_{28}H_{48}O_5S$ (496.76): C, 67.70; H, 9.74. Found: C, 68.09; H, 9.43.

5-*n*-Pentadecyl-2,2,4-trimethyl-1,3-dioxolanes (VI). ***cis* Isomer.**—A solution of 2.0 g. of *cis*-2,2-dimethyl-4-hydroxymethyl-5-*n*-pentadecyl-1,3-dioxolane *p*-toluenesulfonate in 30 ml. of anhydrous ether was added dropwise with stirring and cooling to the suspension of 1.0 g. of lithium aluminum hydride in 30 ml. of anhydrous ether. Well protected from moisture, the suspension was refluxed with stirring for 10 hr. Water was added cautiously to the reaction mixture and was followed by 10% aqueous potassium hydroxide. The organic layer was washed with water, dried over anhydrous sodium sulfate, and evaporated under reduced pressure. There was obtained 1.2 g. (92%) of colorless oil without *p*-toluenesulfonyl absorption bands in the infrared spectrum.

trans **Isomer.**—The above reduction was repeated with 2.3 g. of *trans*-2,2-dimethyl-4-hydroxymethyl-5-*n*-pentadecyl-1,3-dioxolane *p*-toluenesulfonate, but the reaction mixture was refluxed for 12 hr. The crude oil had no *p*-toluenesulfonyl absorption bands in the infrared spectrum.

2,3-Octadecanediols (VII). ***erythro* Isomer.**—The crude *cis*-5-*n*-pentadecyl-2,2,4-trimethyl-1,3-dioxolane (1.0 g.) was refluxed for 8 hr. with 40 ml. of 10% aqueous sulfuric acid in 60 ml. of dioxane. The cooled reaction mixture was poured into water and taken up with ether. The ethereal layer was thoroughly washed with water, dried over anhydrous sodium sulfate, and evaporated under reduced pressure to dryness. The yield of once crystallized product (from acetonitrile) was 0.5 g. (56%), m.p. 79–79.5°. The recrystallized product melted at 80–81°.

Anal. Calcd. for $C_{18}H_{38}O_2$ (286.48): C, 75.46; H, 13.37. Found: C, 75.73; H, 13.27.

threo **Isomer.**—The same procedure was applied to 1.0 g. of *trans*-5-*n*-pentadecyl-2,2,4-trimethyl-1,3-dioxolane. The crude product was crystallized from petroleum ether to give 0.65 g. (74%) of colorless leaflets melting at 69°. Recrystallization from the same solvent yielded the pure product, m.p. 70°.

Anal. Calcd. for $C_{18}H_{38}O_2$ (286.48): C, 75.46; H, 13.37. Found: C, 75.59; H, 13.11.

2,3-Diacetoxyoctadecanoic Acids. ***threo* Isomer.**—The solution of 10 g. of *threo*-2,3-dihydroxyoctadecanoic acid in 10 ml. of acetic anhydride and 25 ml. of anhydrous pyridine was maintained at 80° for 5 hr. The cooled mixture was poured into cold dilute hydrochloric acid and extracted with ether. The ethereal layer was washed with water, dried over anhydrous sodium sulfate, and evaporated under reduced pressure. The oily residue was treated with petroleum ether and left in the refrigerator overnight. There was obtained 6.9 g. (54%) of colorless powder melting at 65–68°. Several recrystallizations from petroleum ether raised the melting point to 71–72°; main infrared absorption bands at 1770–1740 (C=O ester and acid), 1260, 1210 (acetate), 1165, 1120, 1090, 1075, 1045, 1030, 1010, 980, 935, 910, 865, and 705 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{40}O_6$ (400.54); C, 65.97; H, 10.07. Found: C, 66.44; H, 9.97.

(24) C. S. Marvel and V. C. Sekera, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 366.

erythro **Isomer.**—Under exactly the same conditions, 25.3 g. of *erythro*-2,3-dihydroxyoctadecanoic acid yielded 15.3 g. of crude product. Repeated crystallizations from petroleum ether and acetonitrile gave a sample melting at 95–96°; main infrared absorption bands at 1780, 1720, 1670, 1290, 1210, 1165, 1090, 1010, 940–915, 885, and 760 cm.$^{-1}$.

Anal. Found: C, 70.73; H, 10.31.

One gram of this compound, refluxed for 2 hr. with 1 g. of potassium hydroxide in 10 ml. of water and 10 ml. of ethanol, gave, after the usual treatment, a solid product melting at 75–76°. After several recrystallizations from acetonitrile the melting point remained constant at 76°; infrared absorption bands at 1720, 1290, 1270, 1080, 1050, 1020, and 900 cm.$^{-1}$.

Anal. Found: C, 73.15; H, 11.40.

A solution of 3 g. of *erythro*-2,3-dihydroxyoctadecanoic acid in 3 ml. of acetic anhydride and 7.5 ml. of anhydrous pyridine was kept overnight at 20°. After the treatment as above, a slightly colored oil was obtained which was completely soluble in ice-cold petroleum ether and had infrared absorption bands at 1760 (C=O), 1220 (acetate), 1120, 1075, 1030 (C–O), and 960 (COOH) cm.$^{-1}$, but no satisfactory analysis could be obtained. It has not been possible to induce crystallization of this oil. Alkaline hydrolysis gave high yield of the original *erythro*-2,3-dihydroxyoctadecanoic acid, proved by its melting point and infrared spectrum.

Cyclic Sulfites of 2,3-Dihydroxyoctadecanoic Acids. *cis* **Isomer.**—*erythro*-2,3-Dihydroxyoctadecanoic acid (1 g.) was refluxed for 3 hr. with 10 ml. of thionyl chloride. The excess of thionyl chloride was carefully removed under reduced pressure. The residual dark brown oil was hydrolyzed by shaking with a great excess of cold water. The precipitate was extracted with ether, washed, and dried. The residue, after evaporation of ether, was crystallized from petroleum ether yielding 0.45 g. (39%) of colorless product melting at 96–97°. Recrystallization from petroleum ether containing several drops of ether did not change the melting point. The infrared spectrum showed bands at 1720, 1250, 1220, 1010, 940, 835, 815, and 790 cm.$^{-1}$ and had no absorption bands in the 3600–3400-cm.$^{-1}$ region.

Anal. Calcd. for $C_{18}H_{34}O_5S$ (362.52): C, 59.64; H, 9.46; S, 8.84. Found: C, 59.81; H, 9.44; S, 8.6.

trans **Isomer.**—*threo*-2,3-Dihydroxyoctadecanoic acid was treated with thionyl chloride as above, but after evaporation of ether there remained a semisolid mass from which only dark brown powder, melting at 62–67°, could be separated by acetonitrile. The infrared spectrum showed strong bands at 1770, 1230, and 1040 cm.$^{-1}$, and medium bands at 950, 870, 835, 820, and 790 cm.$^{-1}$.

Alkaline hydrolysis of *cis* and *trans* cyclic sulfites afforded *erythro*- and *threo*-2,3-dihydroxyoctadecanoic acids, respectively, identical in all respects with the original acids.

Amides of 2,3-Dihydroxyoctadecanoic Acids.—Ethyl *erythro*- and *threo*-2,3-dihydroxyoctadecanoates (about 2 g.) were separately dissolved in 10 ml. of anhydrous methanol and mixed with 30 ml. of saturated solution of ammonia in anhydrous methanol. The solutions were maintained at room temperature until the precipitation was complete (1 or 2 days). The precipitates were filtered, washed with ice-cold methanol, and dried. The yield was almost quantitative. The crude *erythro* amide melted at 133–135°, and after crystallization from methanol had m.p. 135–136°.

Anal. Calcd. for $C_{18}H_{37}NO_3$ (315.48): C, 68.52; H, 11.82; N, 4.44. Found: C, 68.78; H, 11.60; N, 4.45.

The crude *threo* amide, m.p. 150–154°, was crystallized from methanol. The analytical sample had m.p. 154°.

Anal. Calcd. for $C_{18}H_{37}NO_3$ (315.48): C, 68.52; H, 11.82; N, 4.44. Found: C, 68.96; H, 11.57; N, 4.35.

Amides of 2,2-Dimethyl-5-*n*-pentadecyl-1,3-dioxolane-4-carboxylic Acids.—These amides have been prepared essentially like amides of 2,3-dihydroxyoctadecanoic acids.

After standing for 4 days in saturated methanolic ammonia, ethyl *trans*-2,2-dimethyl-5-*n*-pentadecyl-1,3-dioxolane-4-carboxylate gave an almost quantitative yield of the *trans* amide, which was recrystallized from ether and melted at 70°.

Anal. Calcd. for $C_{21}H_{41}NO_3$ (355.55): C, 70.94; H, 11.62; N, 3.94. Found: C, 70.94; H, 11.30; N, 4.26.

From ethyl *cis*-2,2-dimethyl-5-*n*-pentadecyl-1,3-dioxolane-4-carboxylate (2 g.) only 1.2 g. (65%) of the product, m.p. 76–77°, was isolated after standing for 5 days at 20°, owing to its higher solubility in methanolic ammonia. A sample for analysis was twice recrystallized from petroleum ether yielding a colorless powder, m.p. 81–82°. Another crop of crystals (0.4 g.) was obtained by saturating the filtrate with ammonia.

Anal. Calcd. for $C_{21}H_{41}NO_3$ (355.55): C, 70.94; H, 11.62. N, 3.94. Found: C, 71.06; H, 11.23; N, 4.01.

Hydroxylation of *trans*-2-Octadecenol.—A mixture of 2.6 g. of crude *trans*-2-octadecenol,[6] 3.7 g. of dry silver acetate, and 2.5 g. of iodine in 65 ml. of glacial acetic acid was mechanically shaken for 1 hr. at 20°. Water (0.2 ml.) and 10 ml. of glacial acetic acid were added, and all were refluxed on an oil bath (130–140°) for 3 hr. The cooled suspension was filtered; the filtrate was evaporated under reduced pressure to remove acetic acid, poured into dilute hydrochloric acid, and extracted with ether. The filtered ethereal solution was evaporated, and the residue was hydrolyzed with 4.2 g. of potassium hydroxide in 25 ml. of 1:1 ethanol–water mixture. The cooled solution was neutralized with dilute hydrochloric acid and extracted with ether. By cooling the organic layer to 0°, 0.6 g. (21%) of a colorless powder was obtained, m.p. 91–94°, identical with an authentic sample of *threo*-1,2,3-octadecanetriol, m.p. 94°.

Stereospecific Syntheses of Long-Chain 1,2,3,4-Alkanetetrols

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The four possible stereochemically pure isomers of long-chain DL-1,2,3,4-alkanetetrols have been synthesized in reactions involving stereospecific additions to the double bond, chain lengthening by one carbon atom, and stereospecific lithium aluminum hydride reductions. Cyclic and dipolar transition state models for lithium aluminum hydride reduction of α-hydroxy ketones are discussed. The postulated configurations of tetrols are correlated and explained with the aid of infrared spectra.

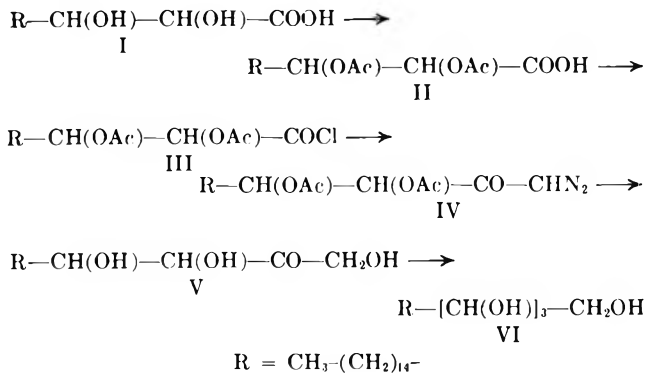
Phytosphingosine is 2-amino-1,3,4-octadecanetriol of D-*ribo* configuration.[1] In an approach to the synthesis of this molecule we have prepared the four possible long-chain DL-1,2,3,4-alkanetetrols. Two of them have been synthesized from *erythro*- and *threo*-2,3-dihydroxyoctadecanoic acids in a reaction of chain lengthening by one carbon atom, while the remaining two have been obtained from 4-hydroxy-*trans*-2-octadecenoic acid.

erythro- and *threo*-2,3-dihydroxyoctadecanoic acids (I) were separately acetylated in order to protect the hydroxyl groups. The difficulties with the *erythro* acid have been avoided by keeping the temperature at 20°.[2] Diacetoxy acids (II) were treated with thionyl chloride, and the resulting acid chlorides (III) with diazomethane gave diazo ketones (IV) having one car-

(1) H. E. Carter, W. C. Celmer, W. E. M. Lands, K. L. Mueller, and H. H. Tomizawa, *J. Biol Chem.*, **206**, 613 (1954); H. E. Carter and H. S. Hendrickson, *Biochemistry*, **2**, 389 (1963).

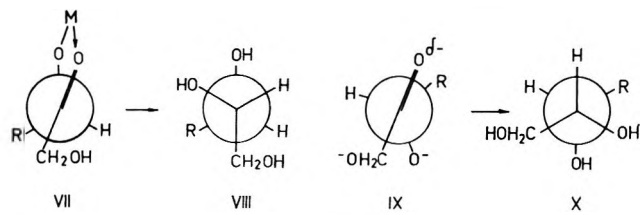
(2) B. Palameta and N. Zambeli, *J. Org. Chem.*, **29**, 1026 (1964).

bon atom more in the straight chain. The decomposition of the diazo ketones was unsuccessfully attempted with glacial acetic acid and copper powder,[3] since it was not possible to use the resulting dark brown oil in the subsequent step. The trihydroxy ketones (V), probably in a mixture with partially acetylated products, were obtained by refluxing the diazo ketones (IV) with dilute sulfuric acid in dioxane.[4] Reduction with lithium aluminum hydride afforded 1,2,3,4-nonadecanetetrols (VI).



The configurational relationships between the hydroxyl substituents on carbon atoms C-3 and C-4 of the products remained unchanged with respect to the original 2,3-dihydroxy acids. However, it was necessary to establish whether the hydroxyl substituent on the newly formed asymmetric center had the *erythro* or *threo* configuration or if there was a mixture of both diastereoisomers in the reaction product. The whole reaction sequence was, therefore, repeated with 2-hydroxyoctadecanoic acid using both copper powder in glacial acetic acid and dilute sulfuric acid to obtain the hydroxy ketone, on which the stereospecificity of lithium aluminum hydride reduction had to be examined. In both cases only *threo*-1,2,3-nonadecanetriol was isolated as seen by comparing the product with 1,2,3-octadecanetriols of known configurations.[5]

This result may seem a little confusing, since a cyclic model (VII) of the transition state[6] is expected to control the stereochemical course of this reaction, because the hydroxyl substituent on the adjacent carbon atom forms a system which is capable of complexing with organometallic reagents.[7] The main product of this reaction should then be *erythro*-1,2,3-nonadecanetriol (VIII). However, if dipolar (IX) or open-chain models are used to depict the stereochemistry of lithium aluminum hydride reduction, *threo*-1,2,3-nonadecanetriol (X) is expected to predominate in the product.

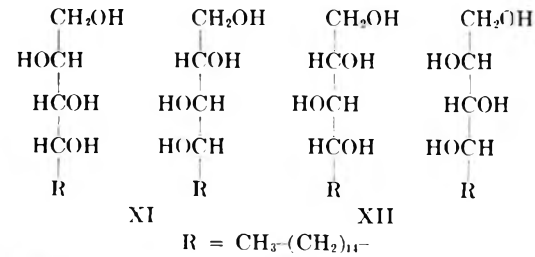


R = CH_3–$(CH_2)_{15}$–

Here it is necessary to point out several differences between the systems usually employed as models for 1,2-asymmetric induction and ours. It is found that both open-chain and cyclic models predict the same stereochemical outcome only if the hydroxyl group on the adjacent carbon atom is the medium-sized group phenyl being the largest group.[7] In our case, although methyl has been shown elsewhere to have larger effective bulk than hydroxyl,[8] it is by no means certain that the hydroxyl should flank one side of the carbonyl group. The reagents commonly used in stereochemical studies have been alkyl- and aryllithium compounds and magnesium halides, and in complexing with hydroxyl substituents they do not necessarily have the same steric requirements as lithium aluminum hydride. Even with the assumption that an alkyl group does occupy more space than a hydroxyl, the difference in size is not so great as that between phenyl and hydroxyl and could be overcome, for instance, by repulsions between the two electronegative charges, on carbonyl and secondary hydroxyl groups. By analogy with α-chloro ketones,[9] these repulsions lead finally to anti-*trans* conformation of dipoles in the transition state (IX) allowing a full polarization of the carbonyl group and thus enhancing its reactivity toward nucleophilic agents which approach from the least hindered side, that is, through the C-3 hydrogen atom.[10] *threo*-1,2,3-Nonadecanetriol (X) would, therefore, predominate in the product as predicted by the dipolar model. This may be the explanation of the unusual results on the basis of a cyclic transition state model, which are not surprising if we know that there are disagreements with this model in much less complicated examples.[11]

The same reasoning applies to the fraction in the product which has resisted acid hydrolysis and has retained its acetoxy group (as proved by the infrared spectrum), which, being reduced first by lithium aluminum hydride, becomes an oxygen–metal complex and behaves as described above.

From these considerations it is concluded that DL-*arabino*-[12] (XI) and DL-*xylo*- (XII) 1,2,3,4-nonadecanetetrols have been obtained from *erythro*- and *threo*-2,3-dihydroxyoctadecanoic acids, respectively. Their infrared spectra are shown in Fig. 1. Yields are unspecified in the Experimental section, since only the first crystallized fraction of the product has been isolated and further analyzed in order to avoid possible contamination with another diastereoisomeric pair.

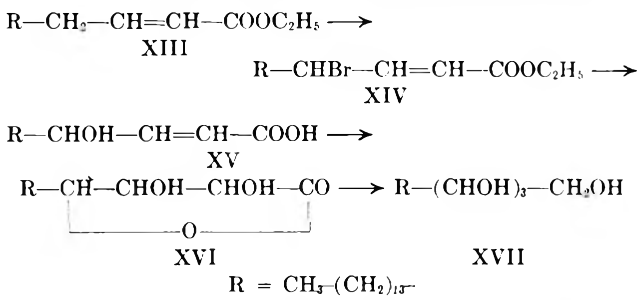


R = CH_3–$(CH_2)_{14}$–

(3) F. Weygand and R. Schmiechen, *Chem. Ber.*, **92**, 535 (1959).
(4) L. Long, Jr., and A. Burger, *J. Org. Chem.*, **6**, 852 (1941); J. H. Burckhalter and J. Sam, *J. Am. Chem. Soc.*, **74**, 187 (1952).
(5) B. Palameta and M. Prošenik, *Tetrahedron*, in press.
(6) D. J. Cram and D. R. Wilson, *J. Am. Chem. Soc.*, **85**, 1245 (1963).
(7) D. J. Cram and K. R. Kopecky, *ibid.*, **81**, 2748 (1959).
(8) S. Winstein and N. J. Holness, *ibid.*, **77**, 5562 (1955).
(9) J. W. Cornforth, R. H. Cornforth, and K. K. Mathews, *J. Chem. Soc.*, 112 (1959).
(10) D. J. Cram and F. A. A. Elhafez, *J. Am. Chem. Soc.*, **74**, 5828 (1952).
(11) J. H. Stocker, P. Sidisunthorn, B. M. Benjamin, and C. J. Collins, *ibid.*, **82**, 3913 (1960).
(12) For nomenclature see *J. Org. Chem.*, **28**, 281 (1963).

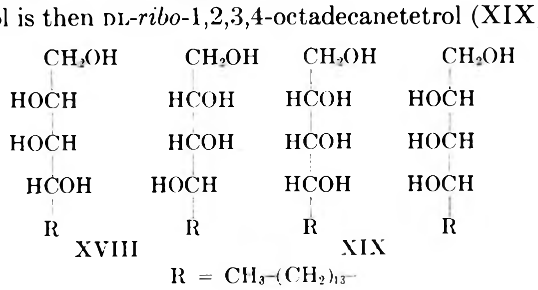
The other two tetrols, DL-*lyxo*- and DL-*ribo*-octadecanetetrols, were synthesized from 4-hydroxy-*trans*-2-octadecenoic acid (XV) which was obtained from ethyl *trans*-2-octadecenoate (XIII) by allylic bromination and subsequent hydrolysis of the bromo ester (XIV). Peracid hydroxylation of the unsaturated hydroxy acid (XV), in which lactonization was not possible owing to the *trans* double bond, afforded a mixture of two isomeric lactones (XVI), from which the tetrols (XVII) were obtained by lithium aluminum hydride reduction.

The steric course of this reaction is not influenced by 1,2-asymmetric induction of the C-4 hydroxyl group, since the primary attack of the hydroxylating agent occurs on the C-2 carbon atom of the double bond, the inductive effect of the carboxyl group outweighing the attraction by C-4 hydroxyl substituent. The addition to the double bond is completed by a simultaneous attack on the C-3 carbon atom followed by inversion of configuration, but, since the system is not rigid with regard to the C-4 hydroxyl, the entering agent is allowed



to approach from both sides, so that both diastereoisomeric pairs are to be expected in the product. They were actually separated by crystallization giving two fractions melting at 98–101 and 120°, respectively, and having essentially dissimilar infrared spectra. It follows, of course, from the preparative method that both isomers have the *erythro* configuration of hydroxyl groups on carbon atoms C-2 and C-3.

The configurations of these two tetrols have been assigned on the basis of their melting points and infrared spectra. It is expected that a certain degree of similarity should exist between the spectrum of the DL-*arabino* tetrol (with *threo–erythro* relationship between the hydroxyl groups) and the DL-*lyxo* isomer (with *erythro–threo* relationship).[13] The examination of infrared spectra (Fig. 1) reveals striking similarities between the bands of the DL-*arabino* isomer and the tetrol melting at 120°, to which, therefore, the DL-*lyxo* configuration can be ascribed (XVIII). The remaining tetrol is then DL-*ribo*-1,2,3,4-octadecanetetrol (XIX).



By correlating the melting points of the four tetrols, it can be seen that the *xylo* isomer with hydroxyl groups in the *threo* configurations melts at 133°, the *arabino*

(13) B. Palameta and M. Proštenik, *Tetrahedron*, in press.

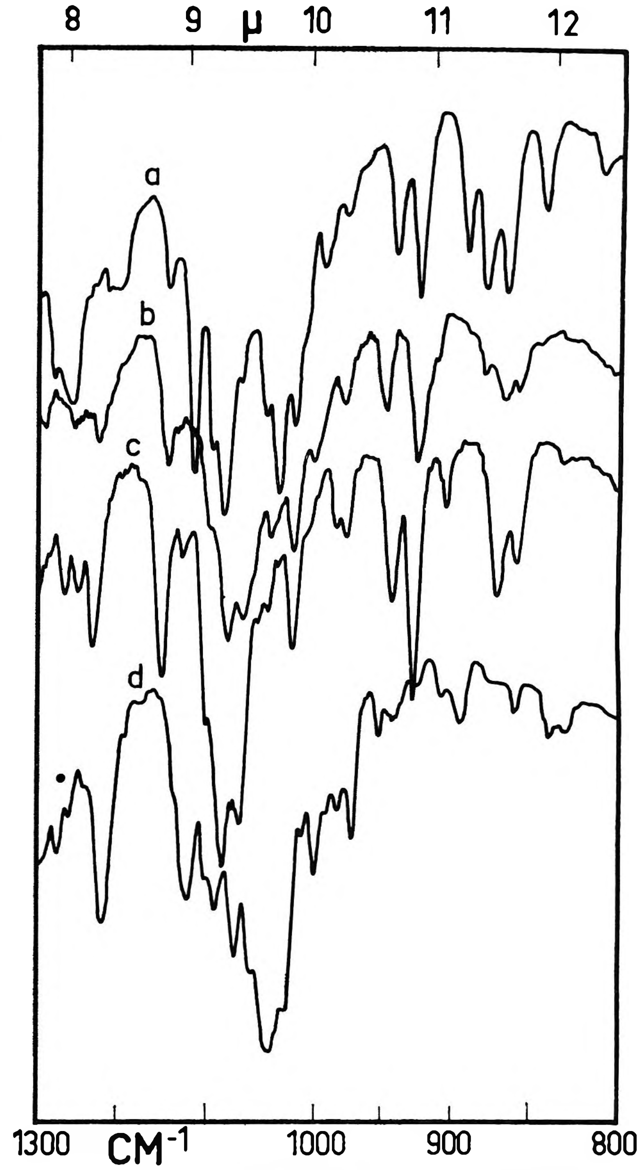


Fig. 1.—Infrared spectra in Nujol: (a) DL-*xylo*-1,2,3,4-nonadecanetetrol; (b) DL-*arabino*-1,2,3,4-nonadecanetetrol; (c) DL-*lyxo*-1,2,3,4-octadecanetetrol; and (d) DL-*ribo*-1,2,3,4-octadecanetetrol.

and *lyxo* isomers with one *threo* and one *erythro* relationship melt at 120 and 110–114°, respectively, whereas the *ribo* isomer with both hydroxyls *erythro* related melts at 98–101°. This is, without doubt, the consequence of their packing in crystal lattices, which, in turn, depends on the nature of hydrogen bonds between their hydroxyl groups. There is one recent report concerned with hydrogen bonding in a series of monomethyl ethers of 1,2,4-butanetriol,[14] but in long-chain 1,2,3,4-alkanetetrols this should be even more complicated and awaits further studies.

Experimental[15]

2-Acetoxyoctadecanoic Acid.—2-Hydroxyoctadecanoic acid was obtained as a by-product in the preparation of *trans*-2-octade-

(14) A. B. Foster, A. H. Haines, and M. Stacey, *ibid.*, **16**, 177 (1961).

(15) The melting points were determined on "Culatti" electrically heated apparatus and are uncorrected. Chromatographic separations were carried out on Fluka alumina, Type 507c, neutral, activity stage 1, according to Brockmann. The petroleum ether refers to the fraction boiling at 45–60°. Microanalyses were carried out by Mrs. J. Zake and Mrs. E. Galogaža.

cenoic acid from 2-bromooctadecanoic acid[16] and, after purification *via* copper chelate,[7] melted at 91°. A solution of 50.5 g. of 2-hydroxyoctadecanoic acid in 140 ml. of anhydrous pyridine and 75 ml. of acetic anhydride was kept at 80° for 3 hr. and was left overnight at 20°. The brown solution was poured into dilute hydrochloric acid, extracted with ether, washed, and dried. The solvent was evaporated, and the residue was crystallized from petroleum ether yielding 56 g. (87%) of colorless product, m.p. 70.5–71.5° (lit.[17] m.p. 70.1–70.3°). From the filtrate, there was obtained 5.8 g. of additional product, m.p. 67–68°.

3-Acetoxy-1-diazo-2-nonadecanone.—2-Acetoxyoctadecanoic acid (56 g.) was refluxed for 4 hr. with 48 ml. of freshly distilled thionyl chloride. After standing overnight at 20°, the solution was refluxed for an additional 4 hr. The excess thionyl chloride was evaporated under reduced pressure, and the remaining traces were removed by repeated evaporations with anhydrous benzene leaving 56.6 g. (96%) of brown oil which solidified and melted at 34–35°. The infrared spectrum showed bands at 1810 (C=O, acid chloride), at 1770 (C=O, acetate), and at 1230 cm.$^{-1}$ (acetate).

The solution of 51.8 g. of 2-acetoxyoctadecanoyl chloride in 120 ml. of anhydrous ether was added dropwise to a stirred and cooled (−20°) solution of diazomethane (prepared from 70 g. of N-nitrosomethylurea) in 700 ml. of ether. The whole reaction mixture was stirred for an additional 30 min. at −20°. The crystals which separated were collected yielding 44 g. (84%) of product, m.p. 73–75°. A portion was crystallized from ethyl acetate for analysis; pale yellow powder, m.p. 76°; infrared absorption bands at 3100, 2120 (N≡N), 1750 (C=O, acetate), 1640 (C=O, conj.), 1340, 1260, 1230 (acetate), 1050 and 1040 (C–O) cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{38}N_2O_3$ (366.53): C, 68.81; H, 10.45; N, 7.64. Found: C, 68.62; H, 10.11; N, 7.84.

Reactions of 3-Acetoxy-1-diazo-2-nonadecanone. (A) With Glacial Acetic Acid and Copper Powder.—The solution of 7 g. of 3-acetoxy-1-diazo-2-nonadecanone in 50 ml. of glacial acetic acid, containing 0.3 g. of copper powder, was cautiously heated on an oil bath. Vigorous evolution of nitrogen began at 90°. The reaction mixture was kept at 100° for an additional 1 hr. and was evaporated to dryness under reduced pressure. The solid residue was crystallized from 100 ml. of 80% ethanol giving 6.8 g. (89%) of pale yellow powder, m.p. 47–48°. After several recrystallizations and after chromatography over alumina (elution with benzene), the product melted at 48–49°, but it was not possible to obtain the correct elemental analysis. The infrared spectrum shows absorption bands at 1770–1750 (C=O, ketone and ester), 1230 (acetate), 1090, 1050, and 1030 cm.$^{-1}$ (C–O).

This 1,3-diacetoxy-2-nonadecanone (1 g.) was reduced with lithium aluminum hydride in the usual manner. Crystallization from ether gave 0.5 g. (63%) of pure *threo*-1,2,3-nonadecanetriol, m.p. 93°. Recrystallization from ethanol gave an analytical sample; infrared absorption bands at 3400, 1150, 1135, 1090, 1060, 1040, 1030, 1020, 910, and 895 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{40}O_3$ (316.51): C, 72.10; H, 12.74. Found: C, 72.49; H, 12.77.

The residual material was examined for *erythro*-1,2,3-nonadecanetriol, but the solid was completely soluble in cold petroleum ether and had a quite different infrared spectrum.

(B) With Aqueous Sulfuric Acid in Dioxane.—The diazo ketone (1.0 g.) was dissolved in 30 ml. of dioxane, and 10 ml. of 10% aqueous sulfuric acid was added. The slightly turbid solution was kept at 70–80° until the gas evolution ceased, and then at 90° for 30 min. The clear solution was poured into water and extracted with ether. The ethereal layer was washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue (m.p. 80–84°) was dissolved in anhydrous ether and reduced with lithium aluminum hydride. Only *threo*-1,2,3-nonadecanetriol could be isolated from the reaction mixture.

It was not possible to obtain *erythro*-1,2,3-nonadecanetriol using sodium and ethanol instead of lithium aluminum hydride.

DL-*xylo*-1,2,3,4-Nonadecanetetrol (XII).—*threo*-2,3-Diacetoxyoctadecanoic acid[2] (II, 6.9 g.) was refluxed for 2 hr. with 25 ml. of thionyl chloride. The excess thionyl chloride was evaporated under reduced pressure, and the last traces were removed azeotropically with anhydrous benzene.

The crude acid chloride (III) was dissolved in 50 ml. of anhydrous ether and was added with stirring during 30 min. to the ethereal solution of diazomethane (from 15 g. of N-nitrosomethylurea) maintained at −15°. The reaction mixture was stirred for additional 30 min. and was kept overnight at 0°, well-protected from moisture. Since no precipitation occurred, the solution was evaporated to dryness leaving 7.0 g. (96%) of crude diazo ketone. Crystallized once from acetonitrile it melted at 62–67°. The infrared spectrum shows bands at 3180, 2120 (N≡N), 1750 (C=O, acetate), 1640 (C=O, conj.), 1340, 1230 (acetate), 1150, 1080, and 1040 cm.$^{-1}$.

The diazo ketone (IV, 3.0 g.) was dissolved in 40 ml. of dioxane, and 10 ml. of 10% aqueous sulfuric acid was added. The mixture was warmed at 90° (oil bath) until the evolution of nitrogen ceased. The dark yellow solution was poured into water, taken up with ether, washed with water, aqueous sodium hydrogen carbonate solution, and again with water, and dried. The solid residue (about 2 g.) was reduced with 1 g. of lithium aluminum hydride in the usual manner. The excess reagent was carefully decomposed with water, and excess 10% aqueous sulfuric acid was added. The aqueous layer was discarded, and, since the product was insoluble in ether, the remaining ethereal suspension was evaporated to dryness and crystallized from ethanol. The tetrol (0.6 g.) melted at 120–125°. Several recrystallizations from ethanol raised the melting point to 133°.

Anal. Calcd. for $C_{19}H_{40}O_4$ (332.51): C, 68.63; H, 12.13. Found: C, 68.22; H, 11.76.

DL-*arabino*-1,2,3,4-Nonadecanetetrol (XI).—This isomer was obtained essentially like DL-*xylo*-1,2,3,4-nonadecanetetrol, from 5.3 g. of crude oily *erythro*-2,3-diacetoxyoctadecanoic acid.[2] The crude tetrol was crystallized many times from acetonitrile. It had constant m.p. 95° but incorrect elemental analysis. Several recrystallizations from ethanol–water raised the melting point to 110–114° (with sintering at 105°).

Anal. Calcd. for $C_{19}H_{40}O_4$ (332.51): C, 68.63; H, 12.13. Found: C, 68.43; H, 11.60.

Ethyl *trans*-2-Octadecenoate (XIII).—*trans*-2-Octadecenoic acid[15] (25.5 g.) was esterified with 100 ml. of anhydrous ethanol containing 2 ml. of concentrated sulfuric acid. After refluxing for 5 hr., the bulk of the ethanol was evaporated under reduced pressure, and the residue was poured into water. The organic layer was washed with aqueous sodium hydrogen carbonate solution and with water. Evaporation of ether left a dark brown oil which was distilled yielding 27.3 g. (97%) of colorless oil, b.p. 224° (10 mm.); infrared absorption bands at 1740 (C=O), 1670 (C=C), 1320, 1270, 1190, 1140, 1110, 1050, 990 (*trans* C=C), and 865 cm.$^{-1}$.

4-Hydroxy-*trans*-2-octadecenoic Acid (XV).—Ethyl *trans*-2-octadecenoate (31 g.) in 200 ml. of carbon tetrachloride (dried over P_2O_5) was refluxed for 3 hr. with 21.4 g. of N-bromosuccinimide. The cooled reaction mixture was poured into water and taken up with ether. The ethereal layer was washed with water and dried. The solvents were evaporated leaving 39 g. of crude ethyl 4-bromo-*trans*-2-octadecenoate, which was chromatographed over alumina. Elution with petroleum ether yielded 29 g. of colorless oil which showed infrared absorption bands at 1740 (C=O), 1670 (C=C), 1310, 1270, 1210, 1180, 1110, 1050, 985 (*trans* C=C), and 870 cm.$^{-1}$.

The bromo ester (XIV) was hydrolyzed by refluxing for 4 hr. with 20 g. of potassium hydroxide in 300 ml. of 1:1 ethanol–water mixture. The bulk of ethanol was evaporated, and the cooled residue was poured into dilute hydrochloric acid, extracted with ether, washed, and dried. The ether was evaporated, and petroleum ether was added. After standing at 0° overnight, 12.3 g. (41%) of yellowish powder was filtered off, m.p. *ca.* 65°. Several recrystallizations from petroleum ether yielded the pure colorless product, m.p. 74.5–76°. The infrared spectrum shows bands at 3550, 1750, 1690, 1640, 1300, 1240, 1210, 1140, 1105, 1080, 1060, 1050, 980, 970, 930, 890 cm.$^{-1}$.

Anal. Calcd. for $C_{18}H_{34}O_3$ (298.45): C, 72.43; H, 11.48. Found: C, 72.32; H, 11.47.

2,3,4-Trihydroxyoctadecanoic Acid and γ-Lactone (XVI).—To the solution of 10 g. of 4-hydroxy-*trans*-2-octadecenoic acid in 25 ml. of glacial acetic acid and 0.3 ml. of concentrated sulfuric acid, there was added 10 ml. of 90% hydrogen peroxide in 0.5-ml. portions during 5 hr. with stirring and at an oil-bath temperature of 90°. The reaction mixture was stirred and heated for an additional 3 hr. and was left overnight at 20°. The mixture was diluted with water, taken up with ether, washed, and evaporated

(16) G. S. Myers, *J. Am. Chem. Soc.*, **73**, 2100 (1951).

(17) A. C. Chibnall, S. H. Piper, and E. F. Williams, *Biochem. J.*, **30**, 100 (1936).

under reduced pressure. The residue was refluxed for 2 hr. with 25 g. of potassium hydroxide in 150 ml. of 1:1 ethanol–water mixture. The bulk of the ethanol was evaporated; the remaining solution was poured into dilute hydrochloric acid and extracted with ether. By filtering off the ethereal suspension, a colorless powder (1.2 g.), m.p. 129°, was isolated showing only infrared absorption bands of a trihydroxy acid: O–H stretching vibrations at 3650, 3450, and 3350 cm.$^{-1}$, COOH vibrations at 1710 and 920 cm.$^{-1}$, other distinctive bands at 1280, 1140, 1090, 1055, and 950 cm.$^{-1}$. The free acid, m.p. 129°, could not be recrystallized unchanged from ethanol but yielded a product, m.p. 113°, which was a mixture of trihydroxy acid and its γ-lactone, as evidenced by a new strong infrared spectral band at 1780 cm.$^{-1}$.

The preparation of copper chelate with cupric acetate in methanol acidified with glacial acetic acid[6] was attempted. The greenish blue powder remained suspended in the ethereal layer.

Anal. Calcd. for $C_{36}H_{70}CuO_{10}$ (726.49): C, 59.52; H, 9.71; Cu, 8.75. Found: C, 58.99; H, 9.24; Cu, 8.65.

DL-*lyxo*- and DL-*ribo*-1,2,3,4-Octadecanetetrols (XVIII and XIX).—A mixture of 2,3,4-trihydroxyoctadecanoic acid and its γ-lactone (1.0 g.) was reduced with lithium aluminum hydride in anhydrous ether in the usual manner. The first crop of crystals (0.2 g.) has been obtained from the ethereal suspension at 20°. One crystallization from ethanol yielded the pure colorless powder, m.p. 120°, to which the DL-*lyxo* configuration was assigned on the basis of its infrared spectrum.

Anal. Calcd. for $C_{18}H_{38}O_4$ (318.48): C, 67.88; H, 12.03. Found: C, 68.01; H, 11.90.

The second isomer (0.3 g.) was isolated from the ethereal filtrate cooled to 0°. Several crystallizations from ethanol gave the colorless DL-*ribo* tetrol, m.p. 98–101° (with sintering at 91°).

Anal. Calcd. for $C_{18}H_{38}O_4$ (318.48): C, 67.88; H, 12.03. Found: C, 67.83; H, 11.80.

Acknowledgment.—With regard to this and the preceding paper, the authors are indebted to Professor M. Prošťenik for his interest.

Condensation of Acetals with Cyanoacetic Acid

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Acetals of benzaldehydes containing +M substituents in the ring condense with cyanoacetic acid more slowly than the free aldehydes, whereas *p*-anisaldehyde acetal condenses at a higher rate than the aldehyde. Cyanoacetic acid condenses more rapidly with acetals than ethyl cyanoacetate, but, in the presence of bases, the ester is more reactive. Addition of strong acid lowers the rate of condensation.

Acetals of aromatic aldehydes condense with malonic acid and ethyl hydrogen malonate in the Knoevenagel–Doebner reaction to give the unsaturated acids or esters, respectively. *p*-Tolualdehyde diethyl acetal and cinnamaldehyde diethyl acetal can also be condensed in benzene with ethyl hydrogen malonate in the presence or absence of added catalyst to give the monoethyl esters of the corresponding unsaturated dicarboxylic acids; the aldehyde is not an intermediate in these reactions, since it does not condense under the same conditions.[2]

Further experiments have now shown that in benzene solution benzaldehyde diethyl acetal does not condense with ethyl hydrogen malonate. In the hope that this lack of reactivity of the acetal could be compensated by a greater reactivity of the active methylene compound employed, the reaction of a series of aromatic acetals with cyanoacetic acid has been studied.

The condensations were carried out in tetrahydrofuran or in benzene–dioxane (cyanoacetic acid being only slightly soluble in benzene alone) and in the presence or absence of acidic and basic catalysts.

The influence of substituents in the phenyl ring on the course of the reaction was also studied, the condensations being performed under similar conditions so that the yield could be considered to reflect the reactivity of the acetals (the acetal which did not condense was recovered after the reaction either unchanged or in the form of the corresponding aldehyde). Yields were determined by the isolation of the products. Quantitative estimation of the course of the reaction by physical methods was difficult since competitive reactions were taking place, *e.g.*, esterification of the acids with formation of the aldehydes from the acetals. The results obtained in the absence of catalyst are summarized in Table I.

TABLE I

CONDENSATION OF ACETALS WITH CYANOACETIC ACID

Diethyl acetal of	Yield[a] of acid, % T[b]	B[b]	M.p. of acid, °C.
Benzaldehyde	18	15	185[c]
p-Tolualdehyde	26	20	211[d]
p-Anisaldehyde	35	65	237[d]
m-Nitrobenzaldehyde	10		165
p-Nitrobenzaldehyde	2		209[d]
Cinnamaldehyde	60	40	212[e]
3,4-Dimethoxybenzaldehyde	47	93	204[f]
p-Chlorobenzaldehyde		60	203[g]

[a] After 6-hr. reflux. [b] Solvent used: T, tetrahydrofuran; B, benzene + 10% dioxane. [c] E. Fiquet, *Ann. chim.*, [6]**29**, 472 (1893). [d] E. J. Corey and C. Fraenkel, *J. Am. Chem. Soc.*, **75**, 1168 (1953). [e] G. Wittig, R. Kethur, A. Klein, and R. Wietbrock, *Ber.*, **B69**, 2078 (1936). [f] See footnote *d* and A. Lapworth and J. A. McRae, *J. Chem. Soc.*, **121**, 1699 (1922). [g] R. von Walther and W. Raetze, *J. prakt. Chem.*, [2]**65**, 258 (1902).

It appears that electron-donating groups raise the yield of the α-cyanocinnamic acids formed, whereas electron-attracting groups, like the nitro group, but not the chlorine atom, lower the yield. The results support the view that a dissociation process (1) with formation of a positive charge on the carbon α to the phenyl ring

$$RCH(OEt)_2 + CH_2(CN)COOH \longrightarrow R\overset{+}{C}HOEt + CH_2(CN)COO^- + EtOH \quad (1)$$

determines the rate of the reaction. The formed ion pair condenses, or gives the free aldehyde which may also undergo the condensation.

(1) Taken in part from the M.S. thesis of A. Y. M., The Hebrew University, 1960. A preliminary communication was published: *Bull. Res. Council Israel, Sect. A*, **9**, 62 (1960).

(2) J. Klein and E. D. Bergmann, *J. Am. Chem. Soc.*, **79**, 3452 (1957).

TABLE II

Aldehyde or acetal	Moles	Moles of EC[a]	Moles of C[b]	Solvent	Catalyst, mole	Duration of reaction, hr. (70°)	Yield of condensation products, %
Benzaldehyde	0.05	0.05		T[c]	0.05 P[d]	8	30 E[e]
Benzaldehyde acetal[f]	0.05	0.05		T	0.05 P	2	8 E
Benzaldehyde	0.05		0.05	T	...	8	18 A[g]
p-Tolualdehyde	0.05	0.05	0.05	T	...	8	7 E, 15 A
p-Tolualdehyde acetal	0.05	0.05	0.05	T	...	8	7 E, 17 A
p-Tolualdehyde	0.05		0.05	T	...	8	30 A
	0.05		0.05	T	0.03 Pi[h]	8	82 A
	0.05	0.05	0.05	T	0.03 Pi	8	44 E, 23 A
	0.05	0.05	0.05	T	0.02 F	8	2 A
p-Tolualdehyde acetal	0.05	0.05	0.05	T	0.03 Pi	8	56 E, 28 A
	0.05	0.05	0.05	T	0.02 F[i]	8	8 A
	0.05	0.05	0.05	B[j]		8	25 A
m-Nitrobenzaldehyde	0.03		0.03	T		8	85 A
	0.02		0.05	T		8	98 A
p-Nitrobenzaldehyde	0.03		0.03	T		8	83 A
	0.02		0.05	T		8	95 A
m-Nitrobenzaldehyde acetal	0.025	0.03	0.03	T		8	15 A
	0.025	0.03	0.03	B	0.05 Pi	8	...
	0.025	0.03	0.03	B	0.01 F	8	...
p-Anisaldehyde	0.05	0.05	0.05	B		2	8 A
	0.05	0.05	0.05	B	0.02 F	2	1 A
	0.05	0.05	0.05	B		8	20 A
	0.05	0.05	0.05	T		8	25 A
	0.05	0.05	0.05	B	0.02 F 0.06 Pi	2	50 E, 40 A
	0.05	0.05	0.05	B	0.08 Pi	2	56 E, 40 A
	0.05	0.05	0.05	EtOH	0.08 Pi	2	40 E, 40 A
	0.05	0.05	0.05	EtOH	NaOH 0.05	2	66 E, 13 A
p-Anisaldehyde acetal	0.05	0.05	0.05	B		8	63 A
	0.05	0.05	0.05	T		8	20 A
	0.05	0.05	0.05	B	0.02 F	8	23 A
	0.05	0.05	0.05	B	0.01 F	2	42 A
	0.05	0.05	0.05	T	0.01 F	2	22 A
	0.05	0.05	0.05	B		2	55 A, 8 E
	0.05	0.05	0.05	B	0.02 F 0.02 Pi	2	50 E, 50 A
	0.05	0.05	0.05	B	0.02 Pi	2	50 E, 50 A
	0.05	0.05	0.05	B	0.07 Pi	2	50 E, 20 A
	0.05	0.05	0.05	T		2	8 E, 20 A
3,4-Dimethoxybenzaldehyde	0.05	...	0.05	B		8	26 A

[a] Ethyl cyanoacetate. [b] Cyanoacetic acid. [c] Tetrahydrofuran. [d] *p*-Nitrobenzoic acid. [e] Unsaturated α-cyano ester. [f] All acetals are diethyl acetals. [g] Unsaturated α-cyano acid. [h] Piperidine. [i] Trifluoroacetic acid. [j] Benzene + 10% dioxane.

The acetal of benzaldehyde yielded only about 6% of ethyl α-cyanocinnamate when condensed in tetrahydrofuran with ethyl cyanoacetate in the presence of *p*-nitrobenzoic acid. The free aldehyde, however, gave under the same conditions a yield of 53%. These results are different from those obtained in the case of ethyl hydrogen malonate. We, therefore, studied the reactivity of the aldehydes under the same conditions as their acetals, as well as the influence of added basic and acidic catalysts.

Competitive reactions between aldehydes or their acetals and equimolar mixtures of cyanoacetic acid and ethyl cyanoacetate were also carried out. The results are summarized in Table II. The yields recorded for the esters are less accurate than those of the acids, particularly in the low-yield cases, since the isolation of esters was carried out by fractional distillation, whereas the acids were isolated by alkaline extraction and acidification. Table II indicates that almost no reaction takes place between the acetals and cyanoacetic acid or its ester in the case of nitrobenzaldehydes; the nitro group would indeed destabilize a positive charge on the carbon atom next to the aromatic ring. The corresponding aldehydes, however, are very reactive. Acetals of benzaldehyde and *p*-tolualdehyde did undergo only limited condensation, much less than the free aldehydes, and it is probable that the reaction of these acetals with cyanoacetic acid proceeds through the intermediary of the aldehydes. This assumption is supported by the rise in yield upon the addition of piperidine and the drop in yield upon addition of trifluoroacetic acid in the condensation of both the aldehyde and the acetal. With *p*-anisaldehyde, however, the acetal gave higher yields than the aldehyde. It may, therefore, be assumed that from the acetal in the first step of the reaction a carbonium ion is formed, which condenses with cyanoacetic acid before it can decompose to the free aldehyde.

The ratio of acid–ester in the product of the competitive reaction with cyanoacetic acid and its ester was

much larger than unity in the absence of catalysts; it was reduced to one or even less when piperidine was added. This result may be attributed to the higher reactivity of enolates as compared to that of enols, and to the slower rate of formation or lower stationary concentration of the enolate of the cyanoacetate anion $(NCCH{=}CO_2)^{-2}$ which has to accommodate two negative charges, and not only one, as in the enolate of ethyl cyanoacetate. In the absence of base, however, the enol of cyanoacetic acid or of its anion reacts faster than the enol of ethyl cyanoacetate. The reason for this is, perhaps, that an ion pair of the enol of cyanoacetate anion and the carbonium ion is formed in the first step of the reaction.

The possibility of thermodynamic and not kinetic product control in the competitive reaction is ruled out, since no exchange[3] is observed when α-cyano-*p*-methoxycinnamic acid or its ester is heated with equimolar amounts of ethyl cyanoacetate and cyanoacetic acid under the conditions of the condensation reaction.

The observed influence of the solvent on the course of the condensation reaction is of interest. Whereas reactions in tetrahydrofuran, which would be expected to assist ionization more effectively than benzene, give, in fact, higher yields of condensation products than in benzene for the less reactive acetals, lower yields were obtained in tetrahydrofuran in the case of the acetal of *p*-anisaldehyde. A possible explanation of this effect is the preferential conversion in more polar solvents of the carbonium ion formed in the first step of the reaction into the less reactive aldehyde.

Addition of trifluoroacetic acid lowered the yields of condensation products. It may be that the strong acid alone is not a good catalyst for the enolization of cyanoacetic acid and that an additional weak base is necessary. Swain[4] has found that acid-catalyzed enolization of ketones proceeds through a reversible, fast protonation of the ketone and that the rate-determining step is the action of a weak base on the protonated species. In our case, when aprotic solvents were used, the concentration of an appropriate base may have a greater influence than the concentration of the acid.[5]

Experimental

Melting and boiling points are uncorrected. Benzene and tetrahydrofuran were dried on sodium and distilled. Dioxane was purified by the method of Fieser.[8]

Preparation of Diethyl Acetals.—The acetals were prepared by method I of ref. 1 yielding ***p*-chlorobenzaldehyde diethyl acetal,** b.p. 108° (3 mm.) (*Anal.* Calcd. for $C_{11}H_{15}ClO_2$: C, 61.5; H, 7.04. Found: C, 61.26; H, 7.15.), ***m*-nitrobenzaldehyde diethyl acetal,** b.p. 181° (23 mm.),[9] and ***p*-nitrobenzaldehyde diethyl acetal,** b.p. 179° (23 mm.).[10]

Condensation in Benzene.—To a solution of 0.05 mole of the acetal in 50 ml. of benzene, a solution of 0.05 mole of cyanoacetic acid in 5 ml. of dioxane was added. The reaction mixture was heated under reflux or kept at the desired temperature for a given time and cooled. The benzene solution was washed with a 10% aqueous sodium carbonate solution and then with water and distilled. The aqueous layer was acidified and the product collected.

Condensation in Tetrahydrofuran.—The working procedure was similar to that in benzene, but dioxane was omitted and tetrahydrofuran was substituted for benzene. Tetrahydrofuran was removed *in vacuo* at the end of the reaction, benzene was added, and the work-up was similar to that after the condensation in benzene. The **α-cyano-*m*-nitrocinnamic acid,** thus formed, had m.p. 265°.

Anal. Calcd. for $C_{10}H_6N_2O_4$: C, 55.0; H, 2.75; N, 12.8. Found: C, 55.3; H, 2.83; N, 12.49.

This acid forms a sparingly soluble sodium salt, and a precipitate appears on treatment of the reaction mixture with aqueous sodium carbonate. This salt can be collected, suspended in water, and acidified to give the acid.

Experiments to Test the Exchange of the Active Methylene Compounds.—A mixture of 5.8 g. of ethyl α-cyano-*p*-methoxycinnamate,[11] 2.8 g. of ethyl cyanoacetate, 3.2 g. of cyanoacetic acid, and 1 ml. of piperidine in 5 ml. of dioxane and 25 ml. of benzene was heated under reflux for 5 hr. The solution was cooled and washed with aqueous sodium carbonate. Distillation gave 5.6 g. of the unsaturated ester, b.p. 150° (0.5 mm.), m.p. 78° (lit.[11] m.p. 85°).

In a similar exchange experiment between α-cyano-*p*-methoxycinnamic acid and ethyl cyanoacetate, all of the starting acid was recovered.

(3) S. Patai and Z. Rappoport, *J. Chem. Soc.*, 377 (1962).

(4) C. G. Swain, A. J. DiMilo, and J. P. Cordner, *J. Am. Chem. Soc.*, **80**, 5985 (1958); C. G. Swain, E. C. Stivers, J. F. Reuver, Jr., and L. J. Schead, *ibid.*, **80**, 5885 (1958).

(5) A referee suggested that the obtained results, particularly the influence of added acid, can be explained better by assuming that the cyanoacetate anion is the reacting species in the condensation reaction. It is known, however, that bromination of cyanoacetic acid and ethyl cyanoacetate in aqueous solution is much faster than that of sodium cyanoacetate.[6] The assumption that cyanoacetate ion is the reacting species cannot be accommodated with the influence of added base on the acid–ester ratio in the products. The importance of the presence of some weak basic species in the enolization of cyanoacetic acid can be illustrated by the fact that 0.1 *M* solutions of this acid or its ethyl ester did not absorb bromine in dry acetonitrile at 0° during 2 days,[7] whereas in aqueous solution[6] the reaction was too fast to be measured.

(6) H. M. Dawson, R. Sugden, and A. Taylor, *J. Chem. Soc.*, **107**, 1030 (1915).

(7) Our unpublished results.

(8) L. F. Fieser, "Experiments in Organic Chemistry," 3rd Ed., D. C. Heath and Co., Boston, Mass., 1957, p. 284.

(9) L. Claisen, *Ber.*, **31**, 1010 (1898).

(10) A. C. J. Opfermann, *Chem. Abstr.*, **49**, 9038 (1955).

(11) C. Bechert, *J. prakt. Chem.*, [2]**50**, 10 (1894).

The Decarboxylation of α-Cyano- and α-Carboxycinnamic Acids

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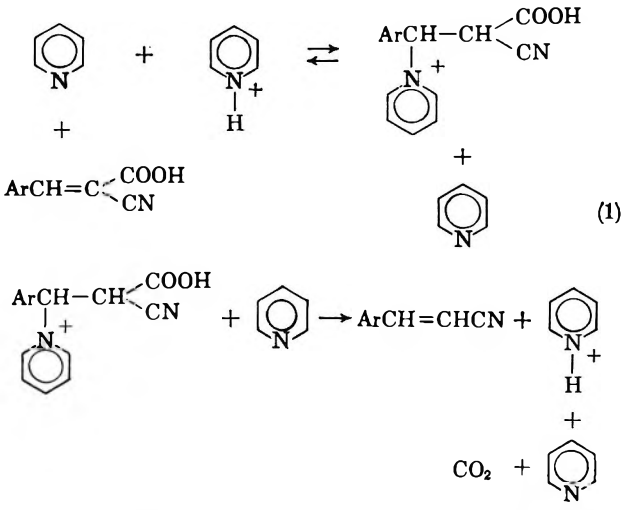
Received May 20, 1963

The steric course of the decarboxylation of benzylidenecyanoacetic and cinnamylidenemalonic acids depends on the solvent used and on other reaction conditions. Different mechanisms for the decarboxylations in pyridine and quinoline solutions are discussed.

Recently,[2] we have prepared a series of α-cyanocinnamic acids by condensation of acetals of aromatic aldehydes with cyanoacetic acid, and thought it of interest to study the stereochemistry of their decarboxylation in view of the fact that Liebermann[3] isolated *trans–cis*-styrylacrylic acid from the product of decarboxylation of cinnamylidenemalonic acid in quinoline, whereas Doebner[4] obtained the *trans* isomer by decarboxylation of this acid in pyridine.

The decarboxylation of α-cyanocinnamic acid in pyridine has already been studied by Corey.[5] The reaction was found to depend on the concentration of the unsaturated acid and the pyridinium ion, and an addition–elimination mechanism (1) was proposed.[5]

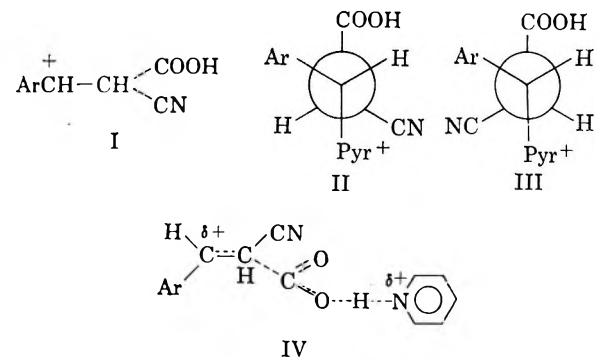


(1)

The two processes were assumed to proceed in *trans* fashion and should have given one cinnamonitrile. The product of the decarboxylation, however, contained the equilibrium mixture of 35% *cis*- and 65% *trans*-cinnamonitrile, and equilibration of the nitrile formed under the reaction conditions was assumed.[5]

Our experiments confirmed the results of Corey as to the composition of the product of decarboxylation of α-cyanocinnamic acid in pyridine. However, the decarboxylation of this acid in quinoline has given, in different experiments, between 50 and 98% of the *cis* isomer, as determined by optical refraction measurements.[6]

Harfenist and Phillips[7] have reported that the copper-catalyzed decarboxylation of *o*-chlorocyanocinnamic acid yielded a product containing 52% of *cis*-*o*-chlorocinnamonitrile. We have found 65% of *cis*-cinnamonitrile in the cuprous chloride-catalyzed decarboxylation of α-cyanocinnamic acid and 46 to 60% of this isomer in the noncatalyzed, solventless decarboxylation of the same acid, depending on the conditions of the reaction. The high proportion of the less stable cinnamonitrile observed in the decarboxylation in quinoline at 130–150° makes improbable the assumption that the primary product has equilibrated when the decarboxylation was carried out in pyridine at 110°. Indeed, when cinnamonitrile with a high *cis* content was subjected to conditions of decarboxylation in pyridine in the absence or in the presence of α-cyanocinnamic acid, isomerization took place only to a small extent. This shows that the product of decarboxylation is kinetically controlled, and the identity of its composition with that of the equilibrium mixture of the isomers is probably connected with the similarity between the transition state in pyridine and the product of reaction. The addition of a proton to the double bond, therefore, takes place before the decarboxylation step, as assumed by Corey,[5] but either the addition of the proton is not *trans* and simultaneous with the addition of pyridine to the other end of the double bond, or the elimination of CO_2 and pyridinium ion in the decarboxylation step is not concerted. It seems more probable that the first step is not concerted and a carbonium ion (I) solvated by pyridine molecules is obtained, which collapses to a mixture of isomers II and III, where II predominates because it would be more stable. An even more probable hypothesis would be that I undergoes direct decarboxylation as in IV and that the breaking of the bond between the carboxyl and carbon is advanced in the transition state, so that the composition of the product will be similar to the equilibrium mixture of the stereoisomers. In both mechanisms, the positive charge formed in the molecule by addition of a proton or of a pyridinium ion favors the decarboxylation because of its electron-attracting character.



The results of decarboxylation in quinoline show that in this solvent a mechanism different from that in pyridine is operative. Since more of the less stable isomer is obtained, it has to be assumed that the addition of

(1) Taken in part from the M.S. thesis of A. Y. M., The Hebrew University, 1960. A preliminary communication was published: *Bull. Res. Council Israel, Sect. A*, **9**, 62 (1960).

(2) J. Klein and A. Y. Meyer, *J. Org. Chem.*, **29**, 1035 (1964).

(3) C. Liebermann, *Ber.*, **28**, 1438 (1895).

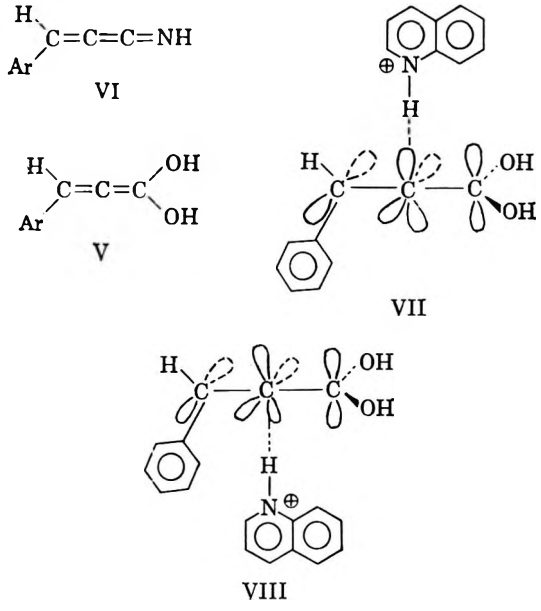
(4) O. Doebner, *ibid.*, **35**, 2129 (1902).

(5) E. J. Corey and G. Fraenkel, *J. Am. Chem. Soc.*, **75**, 1168 (1953).

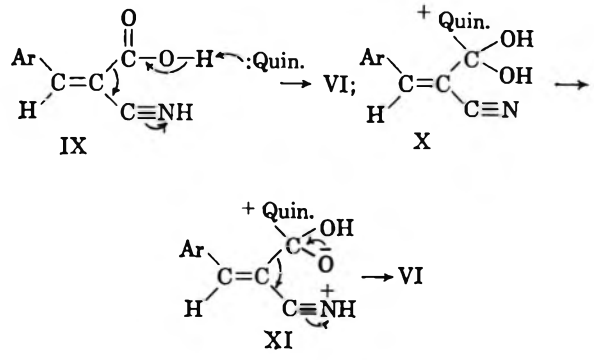
(6) G. B. Kistiakowsky and W. R. Smith, *ibid.*, **58**, 2438 (1936).

(7) M. Harfenist and A. P. Phillips, *ibid.*, **80**, 6261 (1958).

hydrogen takes place in a fast reaction and is not subject to thermodynamic control. Such addition is known in the case of ketonization of various enols and also during the decarboxylation of 1,1-cyclohexanedicarboxylic acid. This last reaction proceeds also through the intermediary of an enol[8] which is then protonated from the sterically more accessible side of the cyclohexane system. Decarboxylation of an unsaturated dicarboxylic acid[9] without previous addition of a proton or of a quinolinium ion to the double bond will give an enol or enolate which has the character of an allene with two cumulative bonds, V, or an enol-like intermediate VI in the case of α-cyano acids. The protonation of this enol will be easier from the side remote from the aryl substituent, since the proton-bearing acid has to approach the molecule in the same plane in which the aryl is located, as in VII, which gives the *cis* product, or, as in VIII, which yields the *trans* isomer. The approach of the acid depicted in VII is more favorable than that in VIII, and the *cis* product will be formed predominantly.



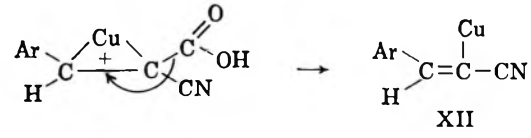
The reason for the difference in the mechanism of decarboxylation in quinoline and in pyridine is not entirely clear. One reason could be the greater bulk of quinoline which would not favor the addition to the double bond or the stabilization of the tertiary carbonium ion by solvation. It could be that 1,4-addition of quinoline takes place,[11] but more probably the quinolinium ion protonates the second carboxyl or cyano group instead of the double bond, and decarboxylation of this ion gives the enol as in IX. Another possibility is that a preliminary 1,2-addition of quinolinium ion or quinoline to the carboxyl takes place followed by intramolecular proton transfer and finally by decarboxylation; *i.e.*, X → XI. Although decarboxylation in quinoline occurs at a higher temperature than in pyridine, it proceeds, nevertheless, at a much lower temperature than solvent-



less decarboxylation. This indicates participation of quinoline in the reaction.

The erratic results of the decarboxylation in quinoline (50 to 98% *cis* isomer in the product) could be traced to the source of the quinoline. In the synthetic quinoline the reaction is slowest and the *cis* isomer content in the product highest (98%); with pure commercial quinoline from coal tar the rate is higher and the amount of *cis* isomer lower. It seems, therefore, that coal tar quinoline contains a catalyst, which permits the reaction to proceed partly *via* a double bond addition mechanism. Corey[5] has already found a large acceleration of the decarboxylation in pyridine by addition of a sulfur compound.

The results of the cuprous chloride-catalyzed decarboxylation can be correlated with those in quinoline. Cuprous ions are known to coordinate with double bonds,[12] and the positive center formed by this coor-



dination lowers the activation energy of decarboxylation and yields a cuprous enolate XII which is protonated to give predominantly the *cis* product.[13]

(8) H. E. Zimmerman and T. Cutshall, *J. Am. Chem. Soc.*, **80**, 2893 (1958).

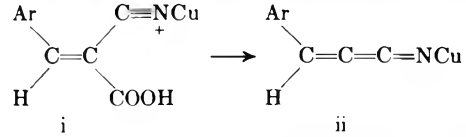
(9) This discussion is pertinent only in the case of conjugated acids, where isomerization by migration of the double bond is impossible. The acids which can isomerize to β,γ-unsaturated compounds have been shown by Corey[10] to decarboxylate through the intermediary of the latter.

(10) E. J. Corey, *J. Am. Chem. Soc.*, **74**, 5897, 4952 (1952); **75**, 1163 (1953).

(11) We are grateful to Professor E. J. Corey for this suggestion.

(12) G. N. Schrauzer, *Ber.*, **95**, 260 (1962).

(13) The copper in the enolate also may be located on the nitrogen, and the reaction proceeds perhaps *via* a nitrogen-complexed compound i → ii. A different form of coordination with chelate formation (iii) is also possible.



The reaction then proceeds iii → iv. This form of chelate corresponds to a cyclic proton transfer in the noncatalyzed decarboxylation (v). Similar chelates would be formed less readily in α-cyano acids but are possible.

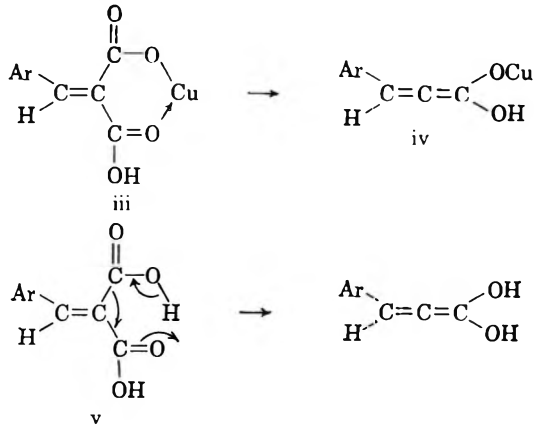


TABLE I

DECARBOXYLATION OF α-CYANOCINNAMIC ACID[a]

Starting acid, g.	Solvent, ml.	Temp., °C.	Time, hr.	Yield,[b] %	n_D[b]	% cis[c]	% acid[c]
8	Pyridine, 50	110°	8.5	72	1.5965	35	..
10	Quinoline,[d] 20	140°	5	40	1.5946	45	25
8	Quinoline,[e] 20	155°	2	13	1.5852	96	75
10	Quinoline,[f] 100	140°	5	45	1.5939	50	22
10	Collidine, 50	150°	4	35	1.5964	36	..
10	Collidine, 50	150°	1	28	1.5930	56	17

[a] All the experiments were performed at least twice. The numbers are average values. [b] Cinnamonitrile. [c] Recovered starting materials. [d] B. D. H. reagent. [e] Eastman Kodak synthetic. [f] Practical grade.

Noncatalyzed decarboxylation requires higher temperatures than the copper-catalyzed reaction or the reaction in quinoline. In spite of the high amount of *trans* isomer in the product, we favor the enol mechanism in this case. The different composition of the reaction product in different runs may well indicate that two reactions take place in these difficultly controllable conditions, one of decarboxylation, another of isomerization. The direct product of noncatalyzed decarboxylation probably contains more of the *trans* isomer than the copper-catalyzed product, since the stereospecificity of the reaction will be lower at higher temperatures. The formation of a highly reactive allenic enol in the solventless catalyzed decarboxylation is reflected in the formation of tars during this reaction. The amount of tar formed is higher in the noncatalyzed reaction.

We have also reinvestigated quantitatively the decarboxylation of cinnamylidenemalonic acid in pyridine[4] and quinoline.[3] The ratio of the stereoisomers formed was determined by infrared analysis. The product obtained in pyridine contained 80 ± 5% of the *trans* isomer, that in quinoline 80 ± 5% of the *cis* isomer. The analysis of the ultraviolet spectra of the products gave somewhat different figures: 93% *cis* form in the quinoline and 22% in the pyridine product.

We have also carried out the decarboxylation of α-cyanocinnamic and cinnamylidenemalonic acids in 2,4,6-collidine to see if in this hindered pyridine derivative the results of decarboxylation are similar to those in quinoline. In fact, cinnamylidenemalonic acid yielded a product containing 90% of the *cis* isomer, and α-cyanocinnamic acid gave a *cis* isomer content of 56%.

These results seem to support the view that steric hindrance plays an important role in the geometrical course of the decarboxylation reaction.

Experimental

α-Cyanocinnamic acid was prepared from benzaldehyde diethyl acetal[2] or by the following method. A solution of 105 g. of cyanoacetic acid in 150 ml. of water was neutralized by 30% aqueous sodium hydroxide, and 106 g. of freshly distilled benzaldehyde dissolved in 250 ml. of ethanol was added.

The solution was acidified after 24 hr., and 162 g. (93%) of the acid, m.p. 185°, was collected.

Cinnamylidenemalonic Acid.—A 56-g. portion of piperidine was added to a cooled solution of 70 g. of malonic acid and 88 g. of freshly distilled cinnamaldehyde in 350 ml. of ethanol. The solution was kept for 24 hr. at room temperature and acidified, and 133 g. (91%) of the acid, m.p. 212°, was collected.[3]

***trans trans*-Styrylacrylic Acid.**—A 30-g. sample of benzylidenemalonic acid and 100 ml. of pyridine were heated at 110° for 6 hr. The solution was cooled and poured onto ice and concentrated hydrochloric acid. The precipitate which formed was collected, washed with dilute hydrochloric acid, and dissolved in 10% aqueous sodium carbonate. The solution obtained was neutralized slowly with hydrochloric acid but not acidified completely. This procedure precipitates the monocarboxylic acid, but leaves the residual dicarboxylic acid in solution. The precipitate was collected, washed with water, and crystallized from ethanol. Thus 7 g. of the *trans* acid, m.p. 164–166°,[4] was obtained.

***trans*-*cis*-Styrylacrylic Acid.**—A 10-g. sample of benzylidenemalonic acid and 80 ml. of redistilled quinoline were heated for 1.5 hr. at 140°, then for 15 min. at 160°. The cooled solution was poured onto ice and concentrated hydrochloric acid, and the precipitate which formed was collected. There was obtained 8.5 g. of a product, m.p. 128–133°. Crystallization from benzene gave 5.5 g. of the acid melting at 141–142°.[3]

Decarboxylation of α-Cyanocinnamic Acid in Solution.—The acid was dissolved in five times its weight of an aromatic base and heated (duration of heating and temperature of bath are recorded in Table I). The solution was then cooled, poured onto ice and hydrochloric acid, and the product was extracted with benzene. The benzene solution was washed twice with dilute hydrochloric acid, then with 10% aqueous sodium carbonate, and finally with water. The benzene solution was distilled and the isomer composition of the obtained nitrile determined by its refractive index.[6] The alkaline solution was acidified and the recovered acid collected.

Isomerization of Cinnamonitrile. A.—A 10-g. sample of cinnamonitrile, containing 27% of the *trans* isomer, was heated for 8.5 hr. at reflux with 150 ml. of pyridine and 5.5 g. of *p*-nitrobenzoic acid. The solution was worked up as above, and 9 g. (90%) of the nitrile was isolated by distillation at 135° (20 mm.), $n^{22}D$ 1.5931 (47% *trans*).

B.—A 2.9-g. sample of cinnamonitrile containing 25% of the *trans* isomer and 3.9 g. of α-cyanocinnamic acid was heated for 8.5 hr. at reflux in 50 ml. of pyridine. After the usual work-up, there was isolated 3.5 g. of the nitrile (60%), $n^{23}D$ 1.5939, containing 50% of the *trans* isomer. Assuming the usual yield of 72% in the decarboxylation and proportional losses during the isolation of the product in the original nitrile and in the one formed by decarboxylation, an isomerization from 25 to 40% *trans* content can be found.

Decarboxylation of cinnamylidenemalonic acid was carried out similarly to that of α-cyanocinnamic acid. The results are summarized in Table II.

TABLE II

DECARBOXYLATION OF CINNAMYLIDENEMALONIC ACID[a]

Solvent[b]	Time, hr.	Temp., °C.	Yield,[c] %	% cis
Pyridine	10.5	110	94	20
Quinoline	1.5	140	75	90
Collidine	1.5	150	81	90

[a] Two grams of the acid was decarboxylated in each run. [b] Amount, 10 ml. [c] Styrylacrylic acid.

Solventless Decarboxylation of α-Cyanocinnamic Acid.—A Claisen flask containing 20 g. of the acid was immersed in an oil bath at 180°. The temperature of the bath was raised slowly.

A slow evolution of gas started at 205° (internal temperature). The melt was heated for 30 min. at 210–220°, at which temperature the decarboxylation proceeded fast. Distillation gave then 3.8 g. (26%) of the nitrile, boiling at 135° (25 mm.), $n^{23}D$ 1.5955 (60% of *trans*).

The decarboxylation of the acid was repeated in the presence of 0.2 g. of cuprous chloride. The decarboxylation started at 190° (internal temperature) and was finished after 10 min. at 210°. Distillation then gave 10.3 g. (69%) of the nitrile boiling at 135° (20 mm.), $n^{23}D$ 1.5919 (35% *trans*-nitrile).

The Rates of Acid Hydrolysis of the Phenyl β-D-Glucopyranosiduronic Acids and Phenyl β-D-Glucopyranosides of Phenol, *p*-Cresol, and *p*-Chlorophenol

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The effects of the electron affinity of the aglycon group on the rates of acid hydrolysis of phenyl β-D-glucopyranosiduronic acids and phenyl β-D-glucopyranosides were studied. The aglycon groups were *p*-cresyl, phenyl, and *p*-chlorophenyl, and the rates were determined at 50–60° in 2.00–20.0 wt. % sulfuric acid. Linear correlations between the logarithms of the first-order rate constants and the Hammett acidity function were found for both series. The large positive entropies of activation were essentially the same for both series (+10 cal. per °K. per mole) so that the greater free energies of activation of the phenyl β-D-glucopyranosiduronic acids (2.0 kcal. per mole greater) were due to greater enthalpies of activation. The Hammett ρ-values for the phenyl β-D-glucopyranosides and β-D-glucopyranosiduronic acids were −0.48 ± 0.04 and −0.09 ± 0.05, respectively. These results are most consistent with the interpretation that the two series hydrolyzed *via* the rapid protonation of the glycosidic oxygen followed by slow heterolysis of the glycosyl oxygen bond. The stabilizing effect of the C-5 carboxyl group compared to the hydroxymethyl group was due to a greater inductive effect of the latter. The nature of the inductive effect is discussed.

Of recent interest has been the stabilizing effect produced when a C-5 hydroxymethyl group of a glycopyranoside is replaced by a carboxyl group (carboxyl stabilizing effect).[2-8] While the carboxyl stabilizing effect seems well-established, the nature of the effect is not well-understood. Two explanations have been offered. The first of these is the inductive effect hypothesis which proposes that the hydrolysis takes place *via* a cyclic mechanism [A-1 (A) mechanism], and that the carboxyl stabilizing effect is due to the greater inductive effect of the carboxyl group.[3-9] The proposed cyclic mechanism of acid-catalyzed glycoside hydrolysis[10-12] is shown in Fig. 1.

More recently, a second explanation has been offered based on work on the acid hydrolysis of methyl uronosides.[2,7] It was suggested that replacement of the C-5 hydroxymethyl group with a carboxyl group causes an undefined change in the reaction mechanism.

For the most part, kinetic studies of the carboxyl stabilizing effect have been confined to the effect of temperature on the acid hydrolysis rates of the uronosides and their corresponding C-5 hydroxymethyl glycosides at a given acid concentration.[2,6,7] In some cases, these rates were determined only at a single temperature and acid concentration.[3,8] A better understanding of the carboxyl stabilizing effect would be gained through an investigation of the effect of the electron affinity of the aglycon group as well as the effects of temperature and acid concentration. The β-D-glucopyranosiduronic acids (β-D-glucuronides) and β-D-glucopyranosides (β-D-glucosides) of phenol, *p*-chlorophenol, and *p*-cresol were chosen for this purpose.

Results

Figure 2 shows plots of the first-order rate constants of phenyl β-D-glucuronide *vs.* the hydronium ion concentration. The hydronium ion concentrations were calculated from the ionization of aqueous sulfuric

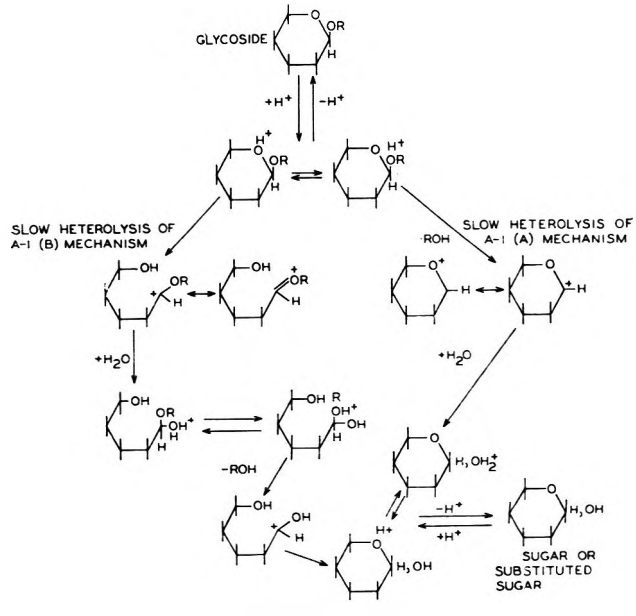

Fig. 1.—Proposed mechanisms of acid-catalyzed glycoside hydrolysis.

(1) A portion of a thesis submitted in partial fulfillment of the requirements of The Institute of Paper Chemistry for the degree of Doctor of Philosophy from Lawrence College, Appleton, Wis., June, 1963.

(2) S. Morell and K. P. Link, *J. Biol. Chem.*, **104**, 183 (1934).

(3) R. L. Whistler and G. N. Richards, *J. Am. Chem. Soc.*, **80**, 4888 (1958).

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(5) J. K. Hamilton and N. S. Thompson, *Pulp Paper Mag. Can.*, **61**, 263 (1960).

(6) J. Nakano and B. G. Rånby, *Svensk Papperstid.*, **65**, 29 (1962).

(7) D. B. Easty, *J. Org. Chem.*, **27**, 2102 (1962).

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TABLE I

COEFFICIENTS FOR THE RATE-CONSTANT ISOTHERMS OF PHENYL β-D-GLUCURONIDES AND PHENYL β-D-GLUCOSIDES

Glycoside	Temp., ±0.05°C.	Isotherm coefficients[a] B	D	F
Phenyl β-D-glucuronide	50.45	13.34	0.9341	0.06984
	55.15	28.36	0.7967	0.3168
	59.90	56.97	3.805	0.3275
p-Chlorophenyl β-D-glucuronide	50.45	12.14	0.6564	0.06738
	55.15	25.21	0.3303	0.2712
	59.90	51.78	2.663	0.3792
p-Cresyl β-D-glucuronide	50.45	12.49	1.136	0.02422
	55.15	25.82	1.924	0.1393
	59.90	53.50	4.617	0.1653
Phenyl β-D-glucoside	50.10	279.4	82.37	−4.670
	55.00	571.3	151.3	−6.746
	59.95	1182.	250.2	4.544
p-Chlorophenyl β-D-glucoside	50.10	203.1	63.33	−3.466
	55.00	410.1	113.7	−5.358
	59.95	803.0	334.7	−36.43
p-Cresyl β-D-glucoside	50.10	301.4	111.6	−10.58
	55.00	655.4	202.8	−17.83
	59.95	1266	494.9	−60.40

[a] $k' = B[H_3O^+] + D[H_3O^+]^3 + F[H_3O^+]^5$ where k' is the first-order rate constant (min.$^{-1}$ × 10^6), $[H_3O^+]$ is the hydronium ion concentration (moles per liter), and B, D, F are isotherm coefficients.

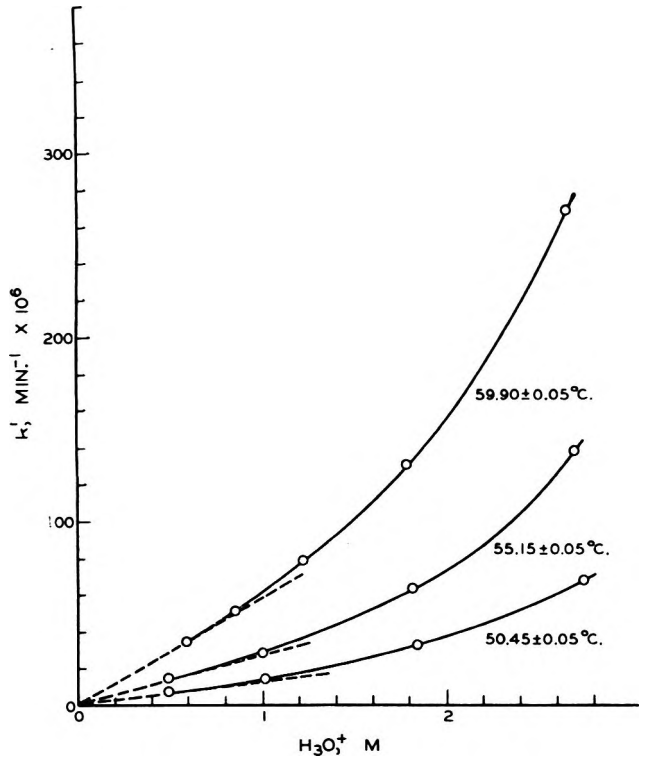

Fig. 2.—Effect of hydronium ion concentration on the hydrolysis rate of phenyl β-D-glucuronide.

acid[13] (1.20, 1.18, and 1.17 times the molarity of sulfuric acid at the 50, 55, and 60° levels, respectively). The rate constants are nearly proportional to the hydronium ion concentration at low concentrations but increase faster above approximately 0.75 *M*. The dotted lines are straight lines through the origin and the first data point. The other phenyl β-D-glucuronides as well as the phenyl β-D-glucosides gave similar rate-constant isotherms. Each isotherm can be represented by the equation $k' = B[H_3O^+] + D[H_3O^+]^3 + F[H_3O^+]^5$. The coefficients B, D, and F in Table I can then be used to calculate the rate constant at any hydronium ion concentration, and were so used in the application of Arrhenius and Hammett equations to the data.

The activation energies and their estimated standard deviations were calculated from the least-squares, straight-line fits of Arrhenius plots. There were no significant differences in activation energies between various levels of hydronium ion concentration nor did the various phenyl substituents produce a measurable change. The activation energies of the phenyl β-D-glucuronides and phenyl β-D-glucosides are 33.0 ± 0.2 and 30.8 ± 0.3 kcal. per mole, respectively. The activation energy of phenyl β-D-glucoside is 30.6 ± 0.2 kcal. per mole as compared to literature values of 32.30 ± 0.43[14] and 31.0 ± 1.2 kcal. per mole.[15]

Shown in Fig. 3 and 4 are plots of the logarithms of the rate constants at various hydronium ion concentrations of the phenyl β-D-glucuronides and the phenyl β-D-glucosides near 60° *vs.* the Hammett substituent constant, σ.[16] Since the activation energies in each series were found to be essentially independent of the substituent, plots of the logarithms of the rate constants in the 50–60° range *vs.* σ determined at 25° will have the same slopes (Hammett reaction series constant,[16] ρ) as if the logarithms at 25° were plotted. The values of ρ were calculated by least-squares, straight-line fits and found to be essentially independent of the hydronium ion concentration. The phenyl β-D-glucuronides showed little sensitivity to polar aglycon group effects ($\rho = -0.09 \pm 0.05$), while the hydrolysis rates of the phenyl β-D-glucosides were reduced by lowering the glycosyl group electron density ($\rho = -0.48 \pm 0.04$). Similar results were obtained at the other temperature levels. For a more extensive series of phenyl β-D-glucosides, Nath and Rydon[17] obtained a ρ of −0.66.

(13) T. F. Young, L. F. Maranville, and H. M. Smith, "The Structure of Electrolytic Solutions," W. J. Hamer, Ed., John Wiley and Sons, Inc., New York, N. Y., 1959, p. 48.

(14) L. J. Heidt and C. B. Purves, *J. Am. Chem. Soc.*, **66**, 1385 (1944).

(15) W. G. Overend, C. W. Rees, and J. S. Sequeira, *J. Chem. Soc.*, 3429 (1962).

(16) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940.

(17) R. L. Nath and H. N. Rydon, *Biochem. J.*, **57**, 1 (1954).

Table II lists the carboxyl stabilizing effect, as determined by the ratio of the rate constants of the C-5 hydroxymethyl and C-5 carboxyl glycopyranosides, for several glycosides at 95° in similar acid media. The carboxyl stabilizing effect of the phenyl glycosides was dependent on the phenyl substituent, since the susceptibility of the phenyl β-D-glucosides to polar aglycon effects was greater than the susceptibility of the phenyl β-D-glucuronides. This stabilizing effect was large and about the same magnitude as that for the reduced and unreduced aldobiouronic acid. These results are in sharp contrast to relatively small carboxyl stabilizing effects of the methyl glycosides.

TABLE II

CARBOXYL STABILIZING EFFECT FOR VARIOUS GLYCOSIDES AT 95°

Glycoside pair	Acid catalyst	Carboxyl stabilizing effect[a]	Ref.
Methyl α-D-glucopyranoside/methyl α-D-glucopyranosiduronic acid	1 *N* sulfuric	2.3[b]	8
Methyl β-D-glucopyranoside/potassium (methyl β-D-glucopyranosid)uronate	0.94 *N* sulfuric	2.6[b]	7
Methyl α-D-galactopyranoside/methyl α-D-galactopyranosiduronic acid	1*N* hydrochloric	2.3[b]	3
2-*O*-(4-*O*-Methyl-α-D-glucopyranosyl)-D-xylitol/2-*O*-(4-*O*-methyl-α-D-glucopyranosyluronic acid)-D-xylose	1.07 *N* sulfuric	18	4
4-*O*-(α-D-Glucopyranosyl)-D-glucose/2-*O*-(4-*O*-methyl-α-D-glucopyranosyluronic acid)-D-xylose	1.07 *N* sulfuric	19	4
p-Cresyl β-D-glucoside/*p*-cresyl β-D-glucuronide	0.855 *N* sulfuric	19[b]	This work
Phenyl β-D-glucoside/phenyl β-D-glucuronide	0.855 *N* sulfuric	16[b]	This work
p-Chlorophenyl β-D-glucoside/*p*-chlorophenyl β-D-glucuronide	0.855 *N* sulfuric	13[b]	This work

[a] Defined as the ratio of the rate constants of the C-5 hydroxymethyl and C-5 carboxy glucopyranosides at 95°. [b] Estimated from data at other temperatures by means of the Arrhenius equation.

According to Hammett,[16] an acid-catalyzed reaction whose transition state behaves like the conjugate acid of the uncharged reactant will show a linear correlation of the unit slope between the logarithm of the rate constant, log k', and the negative of the Hammett acidity function,[18] $-H_0$. Since the activation energies were found to be independent of the hydronium ion concentration, unit slope should still be found when log k' in the 50–60° range is plotted against the Hammett acidity function at the same hydronium ion concentration at 25°. Figure 5 shows such plots for phenyl β-D-glucuronide. The slopes determined by the least-squares, straight-line fits were 0.82–0.85 ± 0.01, which are slightly lower than the predicted value of unity. Similar linear relationships were found for the other phenyl β-D-glucuronides. McIntyre and Long[19] considered deviations of this magnitude in detail and concluded that they were probably due to small deviations

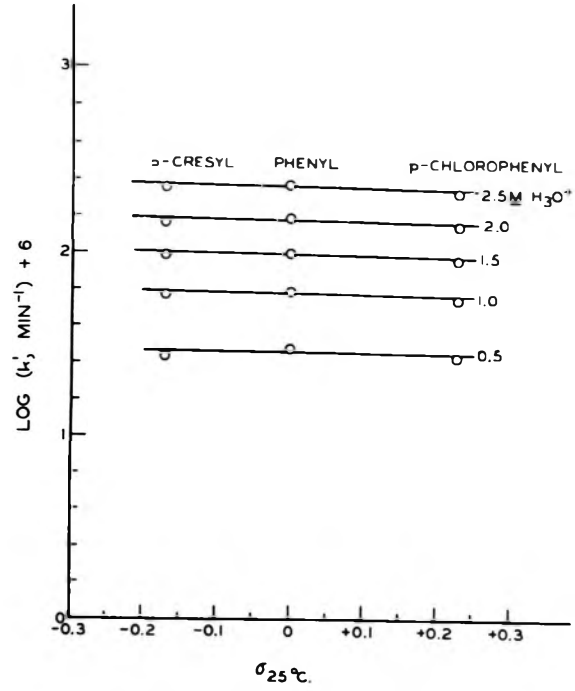

Fig. 3.—Effect of the electron-attracting tendency of the aglycon group (as measured by the Hammett substituent constant of the *para* substituent[15]) on the rates of acid hydrolysis of phenyl β-D-glucuronides at 59.90 ± 0.05°.

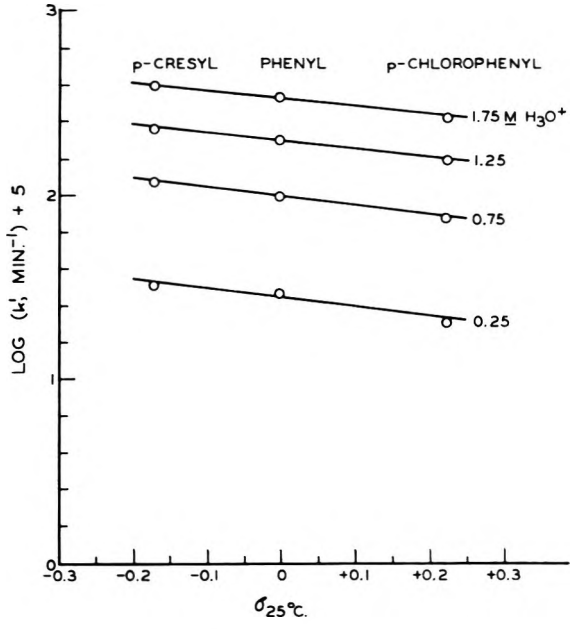

Fig. 4.—Effect of the electron-attracting tendency of the aglycon group (as measured by the Hammett substituent constant of the *para* substituent[15]) on the rates of acid hydrolysis of phenyl β-D-glucosides at 59.95 ± 0.05°.

of the uncharged base activity coefficient from those of the bases used to establish the Hammett acidity scale. All of the slopes for the phenyl β-D-glucosides were the predicted value of unity (1.00–1.03 ± 0.01). Bunton and co-workers[20] found a slope of 0.94 for phenyl β-D-glucoside at 72.9° in perchloric acid.

Calculations of the thermodynamic activation functions of the two glycoside series were made based on

(18) M. A. Paul and F. A. Long, *Chem. Rev.*, **57**, 1 (1957).
(19) D. McIntyre and F. A. Long, *J. Am. Chem. Soc.*, **76**, 3240 (1954).
(20) C. Armour, C. A. Bunton, S. Patai, L. H. Selman, and C. A. Vernon, *J. Chem. Soc.*, 412 (1961).

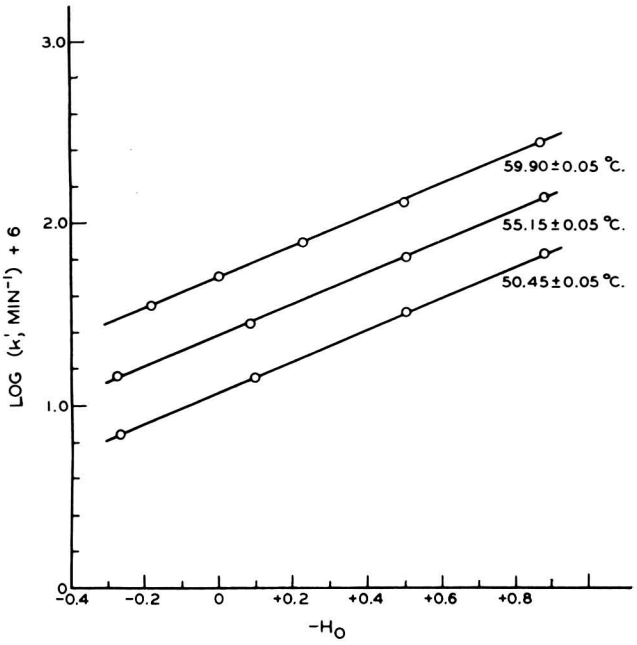

Fig. 5.—Relationship between the Hammett acidity function and the acid hydrolysis rate of phenyl β-D-glucuronide.

the theory of absolute reaction rates.[21] The specific rates employed in determining the free energies of activation were calculated from the slopes of the rate-constant isotherms as the acid concentration approached zero. The activation energies used to calculate the enthalpies of activation were average values taken over the range of hydronium ion concentration investigated. The calculated activation functions are listed in Table III. The activation functions within each series were not significantly different. Since the entropies of activation for the two series were essentially the same, the differences in free energy of activation of the two series were reflected primarily in the enthalpy function. This difference was about 2.0 kcal. per mole.

TABLE III

ESTIMATED THERMODYNAMIC ACTIVATION FUNCTIONS FOR THE ACID HYDROLYSIS OF PHENYL β-D-GLUCURONIDES AND PHENYL β-D-GLUCOSIDES

Glycoside	ΔF^*, kcal. per mole[c]	ΔH^*, kcal. per mole	ΔS^*, cal. per °K. per mole
p-Cresyl β-D-glucuronide[a]	28.8 ± 0.1	32.3 ± 0.2	+10 ± 1
Phenyl β-D-glucuronide[a]	28.7 ± 0.1	32.2 ± 0.2	+10 ± 1
p-Chlorophenyl β-D-glucuronide[a]	28.8 ± 0.1	32.4 ± 0.6	+11 ± 2
p-Cresyl β-D-glucoside[b]	26.7 ± 0.1	30.3 ± 0.3	+11 ± 1
Phenyl β-D-glucoside[b]	26.7 ± 0.1	29.9 ± 0.2	+10 ± 1
p-Chlorophenyl β-D-glucoside[b]	27.0 ± 0.1	30.1 ± 0.6	+ 9 ± 2

[a] Calculated at 59.90 ± 0.05°. [b] Calculated at 59.95 ± 0.05°. [c] The standard deviation of ΔF^* was estimated from the standard deviation of the first-order rate constants at the lowest acid concentrations rather than from the standard deviations of the slopes of the rate-constant isotherms as the acid concentration approached zero.

(21) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt, New York, N. Y., 1960.

Discussion

There is now a considerable amount of data indicating that the hydrolysis of glycosides usually proceeds with glycosyl-oxygen fission[10,20] and that protonation of glycosides is rapid.[15,20] Furthermore, studies[10,15,20] have consistently indicated that the slow heterolysis step is unimolecular. Two possible unimolecular mechanisms have been proposed and these are shown schematically in Fig. 1. The fact that the effect of acid concentration on the hydrolysis rates of phenyl β-D-glucuronides and phenyl β-D-glucosides indicates that the transition states behave like the conjugate acids, agrees with either of the proposed unimolecular mechanisms. Furthermore, the large positive entropies of activation, +9 to +11 cal. per °K. per mole, are characteristic of the acid-catalyzed cleavage of carbon–oxygen bonds where the slow heterolysis step is unimolecular.[21] Hence, the results of this investigation are consistent with either the A-1 (A) or A-1 (B) mechanism.

The work of Banks and co-workers[22] on the acid hydrolysis of methyl α-D-glucoside indicates that the A-1 (A) mechanism predominates. Also, their studies of the acid-catalyzed methanolysis of phenyl α- and β-D-glucoside suggest the A-1 (A) mechanism. Some indication of the generality of this to glycosides is gained from the fact that the entropies of activation of the glycosides studied by Banks and co-workers[22] are about the same as most other glycosides (+10 to +20 cal. per °K. per mole[15]) including the phenyl β-D-glucosides and phenyl β-D-glucuronides. Therefore, a reasonable assumption would be that the phenyl β-D-glucosides and phenyl β-D-glucuronides hydrolyzed *via* the A-1 (A) mechanism.

As to the origin of the C-5 carboxyl group stabilization of the glycosidic linkage, Whistler and Richards[3] considered the increased conformational resistance to the formation of the A-1 (A) carbonium ion and concluded that this effect was too small to account for large carboxyl stabilizing effects. The molecular models show that when the phenyl β-D-glucuronides are in the Cl conformation the oxygens of the carboxyl group are in good position to hydrogen bond with the C-4 hydroxyl. Since this tendency would be even greater in the A-1 (A) transition state, one would expect less conformational resistance[23] and an activating rather than a stabilizing effect. A large ponderal effect[24] would be surprising since the maximum difference in the mass between any of the glycoside pairs studied was only about 5%. Thus, none of these effects appear to be an adequate explanation for the carboxyl stabilization.

According to the inductive effect hypothesis,[3] the greater inductive effect of the carboxyl group compared to the hydroxymethyl group decreases the rate of the heterolysis step by opposing the migration of the electron pair of the glycosyl-oxygen bond to the glycosidic oxygen.[4] In addition, the induction of a smaller partial negative charge on the glycosidic oxygen would diminish the ease of protonation and decrease the con-

(22) B. E. Banks, Y. Meinwald, A. J. Rhind-Tutt, I. Sheft, and C. A. Vernon, *J. Chem. Soc.*, 3240 (1961).

(23) J. T. Edward, *Chem. Ind.* (London), 1102 (1955).

(24) P. B. D. De la Mare, L. Fowden, E. D. Hughes, C. K. Ingold, and J. D. H. Mackie, *J. Chem. Soc.*, 3200 (1955).

centration of conjugate acid.[5] Finally, since the ring oxygen stabilizes the carbonium ion by a drift of electron density toward C-1 giving the ion some oxonium ion character, the induction of the electron cloud of the ring oxygen toward C-5 would hinder this drift. Stabilization of the carbonium ion would thus be more difficult, making the hydrolysis rate lower. Considering the fact that the ring oxygen is α to the carboxyl group, this latter factor may be the dominant aspect of the inductive effect. Thus, even if the inductive effect of a C-5 substituent extended only to the ring oxygen, a stabilizing effect would result.

In studying the relationships between the electronic theories of reactivity, the influence of substituents, and the activation energies, Hinshelwood, Laidler, and Timm[25] concluded that changes in reactivity which result from inductive effects are reflected primarily in the activation energies. The difference in reactivity of the phenyl β-D-glucosides and phenyl β-D-glucuronides is almost entirely associated with changes in the enthalpies of activation. Since the enthalpy of activation nearly equals the energy of activation,[21] these results are consistent with the view that the carboxyl group stabilizes the glycosidic linkage by an inductive effect.

A greater electron affinity of the aglycon group decreases the ease of protonation of the glycosidic oxygen but increases the rate of glycosyl-oxygen bond heterolysis[15]; thus, the negative ρ-values of the two series indicate that the effect on protonation predominates. If the hypothesis of the carboxyl inductive effect is valid, the carboxyl group would tend to lower the effective electron density on the atoms of the reaction center (O–C-1–O) reducing its polarizability. According to Smith and Eyring,[26] the inductive effect of a substituent is dependent on the electron density at the reaction center. Therefore, the polar aglycon group effects should be less for the phenyl β-D-glucuronide series than for the phenyl β-D-glucoside series. Thus, the low Hammett constants, ρ, of the former as compared to the latter support the inductive effect hypothesis.

The inductive effect of *n*-alkyl carboxylic acids are well-known,[27] and it is recognized that this inductive effect may be transmitted not only through the atoms attached to these groups but also to some extent through the surrounding solvent molecules. However, the ionization constants of *meta*- and *para*-substituted phenyl carboxylic acids are measurably affected by phenyl substituents even when a methyleneoxy[28] or two methylene[16] groups have been interposed between the carboxyl and phenyl groups. Hence, the polar effects of phenyl substituents could extend to the ring oxygen. Therefore, the inductive effects of the phenyl substituents and the C-5 substituent could interact. Such an interaction could cause the phenyl β-D-glucuronides to be less susceptible to polar aglycon effects since the C-5 carboxyl would be expected to reduce the polarizability of the reaction center.

It might be argued that the large negative ρ-values of the phenyl β-D-glucosides compared to the phenyl β-D-glucuronides indicate a change from the A-1 (A) mechanism for the former to the A-1 (B) mechanism for the latter. However, although the A-1 (A) and A-1 (B) mechanisms are similar, it would be surprising to find nearly identical entropies of activation as was observed.

In contrast to this, the activation entropies of methyl α-D-glucuronide[7] and of methyl α-D-galacturonide[2] were significantly different from their corresponding glucosides, suggesting that these glycopyranosiduronic acids hydrolyzed *via* a different mechanism than most glycopyranosides. Indeed, it might be expected that replacing the hydroxymethyl group of methyl α-D-glucoside or methyl α-D-galactoside with a carboxyl group would cause a change in mechanism, since they are among the least susceptible of the glycosides to acid hydrolysis, and further stabilization by a C-5 carboxyl group may place them in a region of reactivity where some other mechanism predominates. Easty[7] calculated the free energy of activation for the acid hydrolysis of methyl α-D-glucoside to be 28.2 kcal. per mole at 80°. Assuming that replacement of the C-5 hydroxymethyl group with a carboxyl group increases the enthalpy of activation by the observed 2.0 kcal. per mole, the free energy of activation of methyl α-D-glucuronide would be 30.2 kcal. per mole for the A-1 (A) transition state. Easty calculated 28.6 kcal. per mole for the free energy of activation of methyl α-D-glucuronide at 80°. An alternate mechanism is thus feasible for these methyl glycopyranosiduronic acids.

It appears, therefore, that the A-1 (A) mechanism is applicable to the acid hydrolysis of most glycopyranosides, and that the carboxyl stabilizing effect is due to the greater inductive effect of the C-5 carboxyl group compared to the hydroxymethyl group. In cases of relatively acid-resistant C-5 hydroxymethyl methyl glycopyranosides, the introduction of the C-5 carboxyl group may cause some other mechanism to predominate.

Experimental

Preparation of Phenyl β-D-Glucuronides.—Methyl tetra-*O*-acetyl-β-D-glucopyranuronate was prepared by the methanolysis of D-glucuronolactone in alkaline methanol followed by the pyridine-catalyzed acetylation of the methyl ester with acetic anhydride as described by Bollenbeck and co-workers.[29] The product was isolated in 29% yield, m.p. 176–177.5°, $[\alpha]^{29}D$ +6.7° (*c* 2.2, chloroform) (lit. m.p. 176.5–178°,[29] 178°[30]), and $[\alpha]^{23}D$ +7.4° (*c* 2, chloroform),[31] +8.7° (*c* 1, chloroform).[32]

The methyl (phenyl tri-*O*-acetyl-β-D-glucopyranosid)uronates were prepared by fusing methyl tetra-*O*-acetyl-β-D-glucopyranuronate with *p*-cresol, phenol, or *p*-chlorophenol under vacuum at 110° with *p*-toluenesulfonic acid as catalyst, as described by Bollenbeck and co-workers.[26] The yields were about 30% in all instances. Methyl (*p*-chlorophenyl tri-*O*-acetyl-β-D-glucopyranosid)uronate had m.p. 151–152° (lit. m.p. 152–153°[29] and 151–152°[32]); methyl (*p*-cresyl tri-*O*-acetyl-β-D-glucopyranosid)uronate, m.p. 137.5–139° (lit. m.p. 137–138°[29] and 140°[32]); methyl (phenyl tri-*O*-acetyl-β-D-glucopyranosid)uronate, m.p. 118–119° (lit. m.p. 126–27.5°[29] and 116°[33]).

(25) C. N. Hinshelwood, K. J. Laidler, and E. W. Timm, *J. Chem. Soc.*, 848 (1938).

(26) R. P. Smith and H. Eyring, *J. Am. Chem. Soc.*, **75**, 5183 (1953).

(27) N. A. Lange and G. M. Forkner, "Handbook of Chemistry," Handbook Publishers, Inc., Sandusky, Ohio, p. 1198.

(28) N. V. Hayes and G. E. K. Branch, *J. Am. Chem. Soc.*, **65**, 1555 (1943).

(29) G. N. Bollenbeck, J. W. Long, D. G. Benjamin, and J. A. Lindquist, *ibid.*, **77**, 3310 (1955).

(30) B. Helferich and H. Scheiber, *Z. Physiol. Chem.*, **226**, 272 (1934).

(31) W. F. Goebel and F. H. Babers, *J. Biol. Chem.*, **106**, 63 (1934).

(32) I. A. Kamil, J. N. Smith, and R. T. Williams, *Biochem. J.*, **50**, 235 (1952).

(33) J. W. Porteus and R. T. Williams, *ibid.*, **44**, 46 (1949).

TABLE IV

PROPERTIES OF PHENYL, *p*-CHLOROPHENYL, AND *p*-CRESYL β-D-GLUCURONIDES

	Aglycon group of β-D-glucuronide		
	Phenyl	*p*-Cresyl	*p*-Chlorophenyl
Melting point, °C.			
Found	162.5–163.5	147.5–148.5	154–155
Literature	161–162[a]	147 dec.[b]	151[c]
	163–164[d]		
Equivalent weight[e]			
Found	272	284	307
Theoretical	270	284	305
Specific rotation, $[\alpha]_D$			
Found	−90.7° (*c* 1.02, water, 27°)	−87.9° (*c* 1.38, water, 28°)	−87.2° (*c* 1.32, water, 27°)
Literature	−90.0° (*c* 1, water, 25°)[d]	−76.4° (*c* 0.4, water, 22°)[b]	−87° (*c* 0.5, water, 19°)[c]
	−87.5° (*c* 2.10, water, 29°)[f]		

[a] See ref. 33. [b] H. G. Bray, W. V. Thorpe, and K. White, *Biochem. J.*, **46**, 275 (1950). [c] See ref. 29. [c] B. Spencer and R. T. Williams, *Biochem. J.*, **47**, 279 (1950). [d] See ref. 29. [e] Titrated with 0.1 *N* sodium hydroxide. [f] K. Tsou and A. M. Seligman, *J. Am. Chem. Soc.*, **75**, 1042 (1953).

TABLE V

PROPERTIES OF PHENYL, *p*-CHLOROPHENYL, AND *p*-CRESYL β-D-GLUCOSIDES

	Aglycon group of β-D-glucoside		
	Phenyl	*p*-Cresyl	*p*-Chlorophenyl
Melting point, °C.			
Found	174–176.5	178–179	174.5–176.5
Literature	171–172[a]	175–177[b]	173–175[a]
	175–176[c]	178–179.5[d]	173–174[e]
	174–175[f]		
Specific rotation, $[\alpha]_D$			
Found	−72.0° (*c* 1.52, water, 29°)	−68.1° (*c* 1.36, water, 25°)	−71.6° (*c* 1.49, water, 28°)
Literature	−71.9° (*c* 2.0, water, 20°)[c]	−67.7° (*c* 2, water, 20°)[d]	−82.0° (*c* 1.13, water, 19°)[a]
	−71.0° (*c* 3.91, water, 20°)[f]		−69.5° (*c* 1.0, water, 20°)[e]

[a] See ref. 17. [b] See ref. 34. [c] E. Fischer and L. Mechel, *Ber.*, **49**, 2813 (1916). [d] See ref. 30. [e] A. Dyfverman and B. Lindberg, *Acta Chem. Scand.*, **4**, 878 (1950). [f] E. Fischer and E. F. Armstrong, *Ber.*, **34**, 2885 (1901).

Deacetylation was accomplished by allowing 6.0 mequiv. of methanolic sodium methoxide to react with 0.025 mole of the methyl (phenyl tri-*O*-acetyl-β-D-glucopyranosid)uronates in 200 ml. of dry methanol for 30 min. The solutions were evaporated to dryness at 35° in a rotary evaporator. Sufficient 1 *N* sodium hydroxide was added to the residues to saponify the remaining methyl ester groups. After deionization with Amberlite IR 120H resin and decolorizing with charcoal, the filtrates were evaporated to 60 ml. and stored at 4.5°. The crystalline products which formed overnight were dried over phosphorus pentoxide. The yields in all instances were about 50% and the properties of the three phenyl β-D-glucuronides are given in Table IV.

Preparation of Phenyl β-D-Glucosides.—A sample of phenyl β-D-glucoside was crystallized from water at 4.5° in 64% yield. The melting point and specific optical rotation are listed in Table V.

The *p*-chlorophenyl and *p*-cresyl tetra-*O*-acetyl-β-D-glucosides were prepared by fusing β-D-glucopyranose pentaacetate with *p*-cresol or *p*-chlorophenol under vacuum at 110° with *p*-toluenesulfonic acid as a catalyst as described by Bollenbeck and coworkers[29] for the preparation of the methyl (phenyl tri-*O*-acetyl-β-D-glucopyranosid)uronates. The yields were about 35%. *p*-Chlorophenyl tetra-*O*-acetyl-β-D-glucoside had m.p. 123.5–124.5° (lit. m.p. 123–124°[31]); *p*-cresyltetra-*O*-acetyl-β-D-glucoside, m.p. 119–120° (lit. m.p. 119–120°[34] and 116–118°[30]).

Deacetylation was accomplished by treating 2.0 mequiv. of methanolic sodium methoxide with 0.025 mole of the phenyl β-D-glucosidtetraacetates in 200 ml. of anhydrous methanol for 1 hr. The solutions of the glycosides were evaporated to dryness at 35° in a rotary evaporator. The residues were slurried in 50 ml. of water, neutralized with acetic acid, heated to effect complete solution, and allowed to crystallize overnight at 4.5°. A commercial sample of phenyl β-D-glucoside was crystallized from water under similar circumstances. The yields of all three glycosides were about 63%, and their properties are given in Table V.

Hydrolysis Procedure.—Solutions were prepared containing 0.0200–0.0400 *M* glycoside and 2.00–20.0 wt. % sulfuric acid. Four to six aliquots (*ca.* 1.9 ml.) were placed in glass ampoules with a syringe whose delivered volume was reproducible within ±0.1%. The ampoules were sealed and then simultaneously plunged into an ethylene glycol bath maintained at constant temperatures ±0.05° in the region 50–60°. Each ampoule was removed at a predetermined time and plunged into an ice–water bath. After 3 min., the ampoule contents were transferred to a 10-ml. volumetric flask and neutralized with sodium hydroxide solution. A maximum of 2–3% hydrolysis was allowed.

Analysis of Hydrolysates.—The reducing power of the samples was determined by the method of Hoffman.[35] An AutoAnalyzer (Technicon Controls, Inc., Chauncey, N. Y.) was employed to measure automatically the change in intensity at 420 mμ due to unreduced potassium ferricyanide. A flow cuvette with a 6-mm. light path was employed. It was found that essentially all of the reducing power of the hydrolysates was associated with the hydrolysis products. Hence, the reducing power of the hydrolysates was calibrated to measure the concentrations of products from which the hydrolysis rates could be calculated. Each hydrolysate was analyzed four times and the results averaged. The concentrations of products were of the order of 5×10^{-5} *M* and analyses in this range could be reproduced within ±0.75%.

(34) J. Ryan, *J. Chem. Soc.*, **75**, 1054 (1899).

(35) W. S. Hoffman, *J. Biol. Chem.*, **120**, 51 (1937).

The AutoAnalyzer was calibrated with equal molar solutions of D-glucose or sodium D-glucuronate monohydrate and the appropriate phenol. The calibration for the instrument was established with three to four analyses at four to six concentration levels.

Calculation of Rate Constants.—From a knowledge of the concentration of the products and the initial glycoside concentration, the fraction of the glycoside unreacted was calculated. It was assumed that each mole of glycoside hydrolyzed produced 1 mole of D-glucuronic acid or D-glucose. Plots of the natural logarithm of the fraction of glycoside unreacted *vs.* time were made. The first-order rate constants were calculated by least-squares, straight-line fits with estimated standard deviations about ±1–2%. Duplicate rate-constant determinations agreed within ±2.0%.

Acknowledgment.—Sincere appreciation is expressed to Dr. J. W. Green for a sample of phenyl β-D-glucoside, and to E. E. Dickey for his many suggestions.

Synthetic Nucleosides. LVIII.[1,2] Studies on the Synthesis of *cis*-2,3-Diamino Sugars. I. The Nitroguanidine Neighboring Group

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1-(2-Mesyloxyethyl)-3-nitroguanidine (XIV) rapidly cyclized in pyridine at 40° to the imidazoline (XV), a precursor to the ethylenediamine system formed by a neighboring group reaction. In contrast, the sugar pyranoside, methyl 4,6-*O*-benzylidene-3-deoxy-2-*O*-mesyl-3-(3-nitroguanidino)-α,D-altropyranoside (XXII), failed to cyclize even in boiling pyridine. Anionic cyclization of XXII with a strong base led to the thermodynamically unstable tricyclic imino sugar derivative (XXIV) rather than the expected and more stable tricyclic imidazoline (XXI). Even methyl 3-acetamido-4,6-*O*-benzylidene-3-deoxy-2-*O*-mesyl-α,D-altropyranoside (XXVI), when treated with a strong base, was converted to the imino sugar (XXV) *via* an anion; this result contrasts to the cyclization of XXVI to an oxazoline (VI) in the presence of sodium acetate.

The antibiotic, puromycin (I), was the first example of an inhibitor derived from a nucleoside by replacement of a hydroxyl group by an amino function.[3,4] The corresponding aminonucleoside (II) also had interesting biological properties.[4,5] Among the analogs of puromycin synthesized for biological evaluation was the adenine analog (III),[6] which was subsequently

I, B = 6-dimethylamino-9-purinyl
R = *p*-methoxy-L-phenylalanyl
II, B = 6-dimethylamino-9-purinyl
R = H
III, B = 6-amino-9-purinyl
R = H

IV

isolated from *Helminthosporium* sp., and *Cordyceps militaris*.[7] The corresponding 2,3-diamino-2,3-dideoxy-D-ribonucleosides (IV) represented a logical extension of structural modification of II that would be worthy of biological evaluation if these could be synthesized; in addition, no synthesis of a *cis*-2,3-diamino sugar had been reported,[8] and the projected synthetic schemes represented an unexplored area of neighboring group reactions.

The use of a neighboring group reaction for inversion of the configuration of an amino sugar from a *trans* system (V) to *cis* (VI) was introduced into the carbohydrate field by Baker and Schaub[9,10] and fruitfully has been extended by Jeanloz, *et al.*,[11] and others (Scheme I). That the same principle[12] could be used for the introduction of an amino function (VIII)[13] or a sulfur function (X)[14,15] into the pyranose ring of a glycoside subsequently was shown. A logical extension for synthesis of the *cis*-diamino system (XII) would be the use of the appropriate nitrogen derivative of amino sugar XI. In this paper is presented our investigations with the nitroguanidine neighboring group; in the accompanying papers are presented studies with the urea, guanidine, and thiourea neighboring groups.

(1) This work was generously supported by Grant CY-5845 of the National Cancer Institute, U. S. Public Health Service.

(2) For the previous paper of this series, see B. R. Baker and H. S. Sachdev, *J. Org. Chem.*, **28**, 2135 (1963).

(3) For a review of the studies leading to the synthesis of puromycin and some of its analogs, see B. R. Baker, "The Chemistry and Biology of Purines," G. E. W. Wolstenholme and C. M. O'Conner, Ed., J. and A. Churchill Ltd., London, 1957, pp. 120–133.

(4) For a review of the biological properties of puromycin and its analogs, see B. H. Hutchings, *ibid.*, pp. 177–191; M. B. Yarmolinsky and G. L. de la Haba, *Proc. Natl. Acad. Sci. U. S.*, **45**, 1721 (1959), have shown that puromycin can inhibit protein synthesis at the s-RNA level.

(5) B. R. Baker, J. P. Joseph, and J. H. Williams, *J. Am. Chem. Soc.*, **76**, 2838 (1954); **77**, 1 (1955).

(6) B. R. Baker, R. E. Schaub, and H. M. Kissman, *ibid.*, **77**, 5911 (1955); E. J. Reist and B. R. Baker, *J. Org. Chem.*, **23**, 1083 (1958).

(7) (a) N. N. Gerber and H. L. Lechevalier, *ibid.*, **27**, 1731 (1962); (b) A. J. Guarino and N. M. Kredich, *Biochem. Biophys. Acta*, **68**, 317 (1963).

(8) R. D. Guthrie and D. Murphy, *Chem. Ind.* (*London*), 1473 (1962), recently have synthesized methyl 2,3-diamino-2,3-dideoxy-α,D-mannopyranoside by treatment of methyl 2-azido-4,6-*O*-benzylidene-2-deoxy-3-*O*-tosyl-α,D-altropyranoside with sodium azide, followed by reduction. The synthesis of the corresponding alloside from a 3-azido-2-tosyl-D-altropyranoside was unsuccessful (private communication from Dr. Guthrie).

(9) B. R. Baker and R. E. Schaub, *J. Org. Chem.*, **20**, 646 (1954); *J. Am. Chem. Soc.*, **75**, 3864 (1953).

(10) This reaction was based on a similar study in the cyclohexane area by G. E. MacCasland, R. K. Clark, Jr., and H. E. Carter, *ibid.*, **71**, 637 (1949).

(11) R. W. Jeanloz *ibid.*, **79**, 2591 (1957), and related papers by Jeanloz and co-workers.

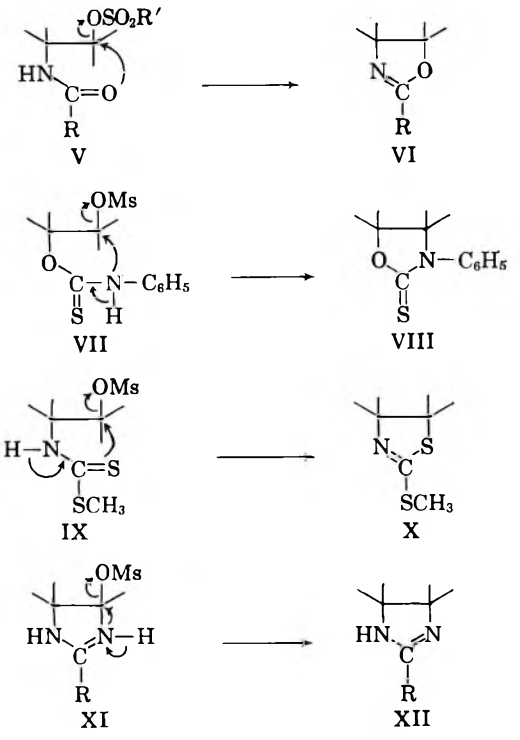
(12) S. Winstein and R. Boschan, *ibid.*, **72**, 4669 (1950), have discussed the probable generality of neighboring group reactions for introduction of other hetero atoms into a chain or ring, but did not carry the study past that reported by MacCasland, *et al.*[10] Later F. L. Scott, R. E. Glick, and S. Winstein, *Experientia*, **13**, 183 (1957), reported results with urea and urethane neighboring groups.

(13) B. R. Baker, K. Hewson, L. Goodman, and A. Benitez, *J. Am. Chem. Soc.*, **80**, 6577 (1958).

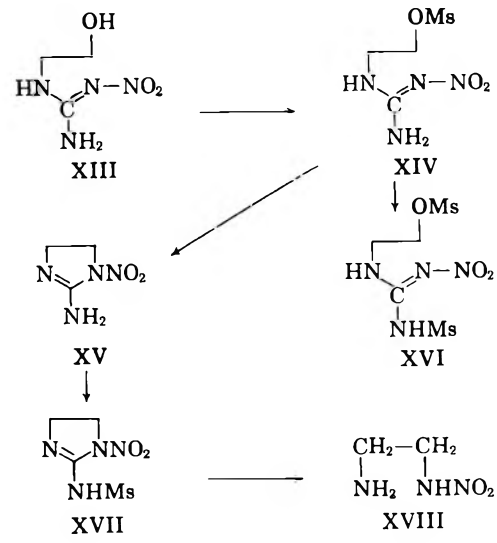
(14) L. Goodman and J. E. Christenson, *ibid.*, **83**, 3823 (1961); **82**, 4738 (1960).

(15) W. M. zu Reckendorf and W. A. Bonner, *Chem. Ind.* (London), 429 (1961).

SCHEME I



SCHEME II



In a study of 1-substituted 3-nitro-1-nitrosoguanidines as antileukemic agents, Baker, *et al.*,[16] noted that mesylation[17] of 1-(β-hydroxyethyl)-3-nitroguanidine (XIII) led not to the expected *O*-mesyl derivative (XIV), but cyclization and further mesylation, or *vice versa*, to the imidazoline (XVII) occurred[18] (Scheme II). Since the ease of cyclization suggested that the nitroguanidine neighboring group might be of use for synthesis of *cis* diamines in the carbohydrate area, the details of the conversion of XIII to XVII were investigated.

Mesylation of XIII with two equivalents of mesyl chloride in pyridine at 0° gave the mono-*O*-mesyl derivative (XIV) in 65% yield and none of XVI or XVII could be isolated; however, if no precautions were taken to avoid localized heating during the acid chloride addition, then XVII could be isolated in poor yield.[16] When XIV was warmed to 40° in pyridine for 5 min. and then allowed to stand at ambient temperature, cyclization to the methanesulfonate salt of XV occurred in 86% yield. The free base (XV) could be obtained by addition of cold aqueous ammonia to an aqueous solution of the salt; XV was identical with an authentic sample,[18,19] and the authentic sample could be converted to the same methanesulfonate salt by adding methanesulfonic acid to a methanol solution of XV. Treatment of XV, its hydrochloride, or its methanesulfonate salt with methanesulfonyl chloride in pyridine at 0° gave XVII in about 75% yield. Thus, the original formation[16] of XVII from XIII must have proceeded *via* XIV and a salt of XV and not XVI as previously proposed.[16] From the studies of McKay,[20] it could be anticipated that XV or XVII could be converted to ethylenediamine by hydrolysis and reductive cleavage; aqueous potassium hydroxide readily cleaved XVII to potassium methanesulfonate (isolated) and 2-aminoethylnitramine (XVIII). The presence of XVIII was determined by paper chromatography in 1-butanol–acetic acid–water (5:3:2) as an ultraviolet absorbing spot (R_f 0.62) that gave a purple ninhydrin color.

Condensation of 1-methyl-3-nitro-1-nitrosoguanidine[20] with the aminoaltroside (XIX)[21] in 70% ethanol at 50° gave the nitroguanidine derivative (XX) in 70% yield. In a pilot run, a lower melting dimorph, m.p. 220°, was isolated; in all subsequent runs, a higher melting dimorph, m.p. 270°, was obtained. The infrared spectrum of the higher melting dimorph in the 6.0–6.8-μ region was similar to that of the model compound, XIII, whereas the lower melting form was quite different in this region; the lower melting form could be converted to the higher melting form on recrystallization from alcohol. The gross difference in the infrared spectra in the 6.0–6.8-μ region indicates that these two compounds may be double bond tautomers. That the nitroguanidyl residue could be split to an amine was shown by basic hydrolysis of XX back to XIX.

Mesylation of XX with either one or two equivalents of mesyl chloride in pyridine at 0 or 25° gave the monomesyl derivative (XXII) in 92% yield as an analytically pure, solid gum suitable for further transformations (Scheme III). Crystallization led to about 40% loss and was considered uneconomical. That cyclization to the methanesulfonate salt of XXI or an isomer (XXIV) had not occurred was demonstrated by the fact that the mesyl group was covalently bound. When refluxed for several hours in pyridine with or without triethylamine, the *O*-mesyl derivative (XXII) was recovered unchanged, whereas long boiling caused decomposition and XXI was not formed; this result

(16) W. A. Skinner, H. F. Gram, M. O. Greene, J. Greenberg, and B. R. Baker, *J. Med. Pharm. Chem.*, **2**, 299 (1960).

(17) The following structural abbreviations are used: Ms, methanesulfonyl; Ac, acetyl; Me, methyl.

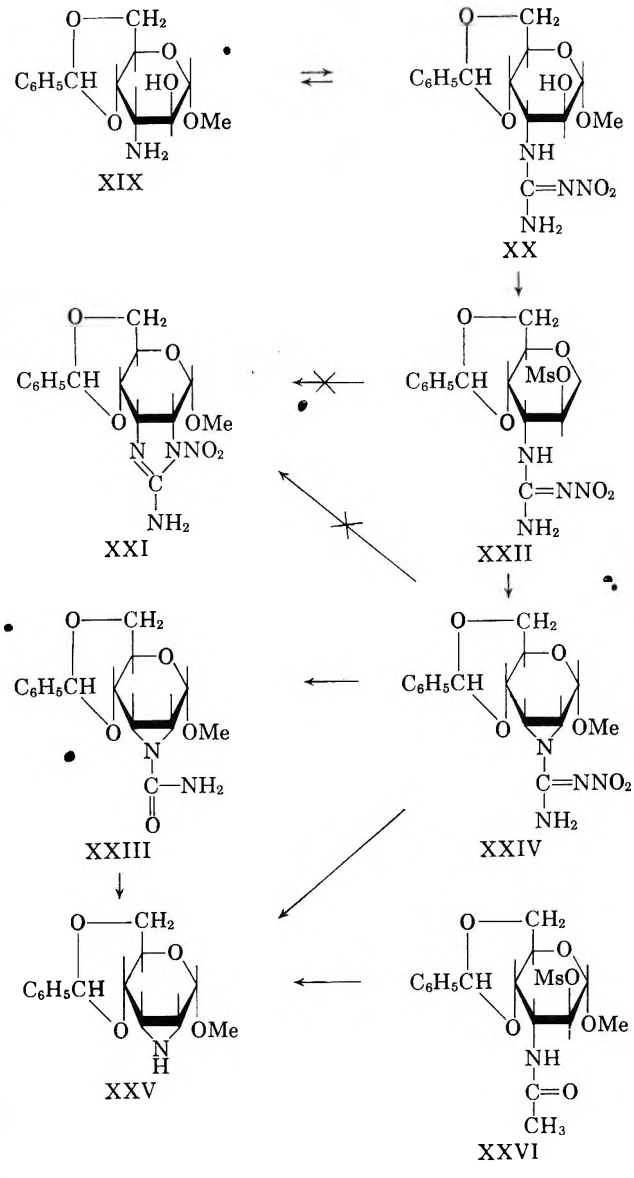
(18) The ready cyclization of 1-(β-chloroethyl)-3-nitroguanidine to the imidazoline (XV) had been observed previously by A. F. McKay and J. E. Milks [*J. Am. Chem. Soc.*, **72**, 1618 (1950)].

(19) If concentrated aqueous ammonia were used for neutralization, ring cleavage occurred to give a mixture of 1-(β-nitraminoethyl)urea and the corresponding guanidine.

(20) A. F. McKay, *Chem. Rev.*, **51**, 301 (1952).

(21) Prepared by the method of W. H. Myers and G. J. Robertson, *J. Am. Chem. Soc.*, **65**, 8 (1943), as modified by B. R. Baker and R. E. Schaub.[9]

SCHEME III

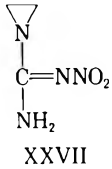


contrasts with the ease of ring closure of the open-chain mesylate (XIV) to XV.

When the mesylate (XXII) was treated with cold ethanolic sodium ethoxide, sodium methanesulfonate rapidly separated. Processing of the reaction mixture afforded 76% yield of a cyclic nitramino derivative, subsequently shown to have the ethylenimine structure XXIV rather than the imidazoline structure XXI. The nitramino group of XXIV was readily hydrolyzed with dilute aqueous base to form XXIII which could be extracted with chloroform. Strong alkaline hydrolysis of XXIV did not give a diamine, as would be expected from XXI, but gave the imino sugar (XXV), identical in properties previously described for XXV prepared by a different route[14]; in fact, treatment of the *O*-mesyl derivative (XXII) with aqueous base gave directly the imino sugar (XXV) in 61% yield, presumably *via* XXIV and XXIII. The ease of formation of an ethylenimino derivative (XXIV) from the mesylate (XXII) is certainly surprising since XXIV has a highly strained tricyclic system which is thermodynamically less stable than the tricyclic imidazoline XXI; however, formation of an imino sugar by anionic attack has been observed previously,[14] and additional examples can be found in the accompanying papers. In fact, even the prototype compound XXVI, first used in a neighboring group reaction on a glycoside to form an oxazoline (VI) with sodium acetate, formed XXV in 75 and 90% yield when treated with methanolic or aqueous base, respectively. A similar observation has recently been noted with the neighboring benzamido group, except that the more stable *N*-benzoyl derivative of XXV was obtained.[22]

Attempts to rearrange the nitro imine (XXIV) to a thermodynamically more stable imidazoline such as XXI or an isomer gave unchanged XXIV below temperatures and times causing decomposition; the more nucleophilic *N*-dithiocarbomethoxy derivatives of XXV have been rearranged to thiazolines.[14]

Since an aziridine was not observed in the model series when XIV was prepared or treated, the aziridine (XXVII) was synthesized from ethylenimine and 1-methyl-3-nitro-1-nitrosoguanidine in 80% yield when the components were reacted at 0° in ethanol.[23] When refluxed in ethanol, this crystalline material was highly unstable and polymerized with or without an equivalent of methanesulfonic acid; XXVII even polymerized on standing open to the air, perhaps catalyzed by



carbon dioxide. Evans, *et al.*,[23] have shown recently that XXVII could be ring expanded with *p*-toluenesulfonic acid in ethanol in poor yield, or with cyanogen bromide in benzene. It is, therefore, unlikely that XXVII is an intermediate when XIV is cyclized to the imidazoline (XV), although Evans, *et al.*, did not study ring expansion under basic conditions.

Experimental[24]

1-(2-Mesyloxyethyl)-3-nitroguanidine (XIV).—To a stirred suspension of 6.6 g. (0.045 mole) of XIII[16,20] in 25 ml. of reagent pyridine cooled to 0° was added dropwise a chilled solution of 11 g. (0.096 mole) of methanesulfonyl chloride in 12 ml. of reagent pyridine. Solution was complete in a few minutes. After standing at 0° for 2 hr. protected from moisture, the mixture was poured into 200 ml. of ice-water. The product gradually separated at 0° to yield 6.5 g. (65%) of product with m.p. 130° (resolidifies and remelts about 170° dec.); λ_{max} 2.80, 2.90, 2.98, 3.12 (NH), 6.07 (C=N), 6.18, 6.45 (NH, NO_2), 7.45, and 8.55 μ (sulfonate).

Anal. Calcd. for $C_4H_{10}N_4O_5S$: C, 21.2; H, 4.47; N, 24.8; S, 14.1. Found: C, 21.5; H, 4.46; N, 24.8; S, 14.1.

2-Amino-3-nitro-1-imidazoline (XV) Methanesulfonate. A.—A mixture of 7.3 g. of XIV and 100 ml. of reagent pyridine was warmed to 40° then left overnight at ambient temperature. A white crystalline solid separated (4.5 g.) and was collected and washed with 50 ml. of petroleum ether (b.p. 30–60°). By work-up of the filtrate, an additional 2.3 g. was obtained. Recrystal-

(22) R. D. Guthrie, D. Murphy, D. H. Buss, L. Hough, and A. C. Richardson, *Proc. Chem. Soc.*, 84 (1963).

(23) While this manuscript was in preparation, J. U. Lowe, Jr., T. A. Oda, and R. Evans, *J. Org. Chem.*, **28**, 1496 (1963), reported the preparation of XXVII from ethylenimine and 2-methyl-1-nitro-2-thiopseudourea in 80% yield.

(24) Melting points were taken in capillary tubes in a Mel-Temp block; those below 230° are corrected. Infrared spectra were determined in Nujol mull with a Perkin-Elmer 137B recording spectrophotometer. Rotations were determined in a 1-dm. microtube in *N,N*-dimethylformamide unless otherwise indicated; concentrations are indicated in g./100 ml. as %.

lization from methanol yielded 6.3 g. (86%) of product as needles, m.p. 177–178°; λ_{max} 2.88 (NH), 5.83 (C=NH$^+$), 6.43 (NH, NO_2), 7.45, and 8.61 μ (sulfonate).

Anal. Calcd. for $C_7H_{19}N_4O_5S$: C, 21.2; H, 4.47; N, 24.8; S, 14.1. Found: C, 21.2; H, 4.48; N, 24.8; S, 14.2.

To a solution of 1.00 g. of the methanesulfonate salt in 2 ml. of water was added 2.2 ml. of 3 *N* aqueous ammonia. After 5 min. at 0°, the product was collected and yielded 0.55 g. (70%); it had m.p. 128° that was identical with a sample prepared from 1-(2-chloroethyl)-3-nitroguanidine.[18]

B.—To a solution of 0.55 g. of XV, prepared from 1-(2-chloroethyl)-3-nitroguanidine,[18] in 2.5 ml. of methanol was added 0.3 ml. of methanesulfonic acid. Chilling gave 0.77 g. (81%) of the salt, m.p. 176–177°, that was identical with preparation A.

2-Methanesulfonamido-3-nitro-1-imidazoline (XVII).—To a solution of 400 mg. of 2-amino-3-nitro-1-imidazoline (XV)[8] in 3 ml. of reagent pyridine was added 0.3 ml. of methanesulfonyl chloride dropwise with stirring and ice cooling. After an additional 2 hr. at 0°, the mixture was added to 10 g. of ice, and the product was collected on a filter, yielding 480 mg. (75%) with m.p. 166–167°; a melting point of 167–171° has been recorded[6] for this compound and the reported infrared peaks agreed.

Similarly, 750 mg. of the methanesulfonate salt of XV gave 425 mg. (73%) of XVII, m.p. 167–168°.

When 400 mg. of XVII was refluxed for 10 min. with a solution of 0.35 g. of potassium hydroxide in 10 ml. of water, 100 mg. of pure potassium methanesulfonate was isolated by crystallization from aqueous ethanol. Chromatography of the filtrate on paper with butanol–acetic acid–water (5:3:2) showed an ultraviolet absorbing spot at R_f 0.62 that gave a purple color with ninhydrin; these properties correspond to those expected for XVIII.

1-(Nitroamidino)aziridine (XXVII).—To a magnetically stirred solution of 2 g. of ethylenimine in 5 ml. of ethanol cooled in an ice bath was added 2 g. of 1-methyl-3-nitro-1-nitrosoguanidine in small portions over a period of 1 hr. After standing overnight at 0°, the mixture was filtered and the product was washed with cold ethanol to yield 1.4 g. (80%) with m.p. 115°; λ_{max} 2.91, 3.02 (NH), 6.28 (C=N), and 6.61 μ (NO_2).

The compound gradually polymerized on standing in the solid state or on short heating in ethanol.

Anal. Calcd. for $C_3H_6N_4O_2$: C, 27.7; H, 4.65; N, 43.1. Found: C, 27.9; H, 4.79; N, 43.1.

Methyl 4,6-*O*-Benzylidene-3-deoxy-3-(3-nitroguanidino)-α,D-altropyranoside (XX).—To a swirled suspension of 6.6 g. of XIX[2] in 10 ml. of water and 25 ml. of 95% ethanol at 40–50° was added portionwise 2.9 g. of 1-methyl-3-nitro-1-nitrosoguanidine. The mixture was held at this temperature for an additional hour, then chilled overnight at 0°. The product was collected on a filter and washed with 20 ml. of water to yield 6.0 g. (70%) with m.p. 269–270°; λ_{max} 2.88, 2.99, 3.10 (OH, NH), 6.20, 6.40 (NH, C=N), 6.68 (NO_2), 13.2, and 14.3 μ (C_6H_5—); $[\alpha]^{22}D$ 89 ± 1° (0.64%).

Anal. Calcd. for $C_{15}H_{20}N_4O_7$: C, 49.0; H, 5.45; N, 15.2. Found: C, 49.0; H, 5.65; N, 15.0.

In a pilot run, the yield was 600 mg. (70%) of product, m.p. 219–220°, that had a different infrared spectrum from the higher melting dimorph.

Anal. Found: C, 48.7; H, 5.71; N, 14.9.

Refluxing a suspension of the low melting dimorph in ethanol gave the high melting dimorph.

The nitramidine group of XX could be removed when 250 mg. was refluxed with 25 ml. of 0.2 *N* sodium hydroxide for 1 hr. On spin evaporation *in vacuo* to about 10 ml., 153 mg. of crude XIX separated. Recrystallization from methanol gave white crystals, m.p. 183–184°, that were identical with authentic XIX.

Methyl 4,6-*O*-Benzylidene-3-deoxy-2-*O*-mesyl-3-(3-nitroguanidino)-α,D-altropyranoside (XXII).—To a stirred suspension of 4 g. of XX in 30 ml. of pyridine cooled below 5° in an ice bath was added dropwise 2.6 ml. of mesyl chloride over a period of about 10 min. After being stirred an additional 30 min. in the ice bath, the mixture was allowed to stand about 18 hr. at 3–5° protected from moisture. The mixture was poured into 150 ml. of ice-water and the gummy product was extracted with three 100-ml. portions of chloroform. The combined extracts, washed with three 100-ml. portions of water and dried with magnesium sulfate, were spin evaporated to residue *in vacuo* to yield 4.5 g. (92%) of a glass suitable for further transformations. Crystallization from ethanol required several days and about 60% was recovered as nearly white crystals, m.p. 183–184°; λ_{max} 2.90, 2.95, 3.05 (NH), 6.05 (C=N), 6.34 (NH), 6.47 (NO_2), 7.35, 8.40 (sulfonate), 13.2, and 14.3 μ (C_6H_5—); $[\alpha]_D$ +36 ± 1° (0.49%).

Anal. Calcd. for $C_{16}H_{22}N_4O_9S$: C, 43.1; H, 4.94; N, 12.5; S, 7.17. Found for crude product: C, 43.3; H, 4.88; N, 10.8; S, 6.80. Found for recrystallized material: C, 43.1; H, 4.93; N, 12.7; S, 7.11.

Methyl 4,6-Benzylidene-2,3-dideoxy-N-(nitramidino)-2,3-imino-α-D-allopyranoside (XXIV).—To a solution of 500 mg. of XXII in 10 ml. of absolute ethanol at ambient temperature was added 1.5 ml. of 1 *N* methanolic sodium methoxide. After standing for about 18 hr. in a closed flask, the solution was neutralized with solid carbon dioxide, then spin evaporated *in vacuo;* the residue was extracted with two 20-ml. portions of chloroform. The combined extracts, washed with two 20-ml. portions of water and dried with magnesium sulfate, were spin evaporated *in vacuo*. Crystallization from ethanol gave 300 mg. (76%) of product as white needles, m.p. 232–233°; λ_{max} 2.90, 3.00 (NH), 6.28 (C=N), 6.73 (NO_2), 13.4, and 14.4 μ (C_6H_5—); $[\alpha]^{22}D$ +108 ± 1° (0.97%).

Anal. Calcd. for $C_{15}H_{18}N_4O_9$: C, 51.5; H, 5.20; N, 15.9; S, 0.0. Found: C, 51.7; H, 5.36; N, 15.7; S, 0.0.

If the reaction mixture were processed without carbon dioxide neutralization, some hydrolysis to the corresponding carbonyl derivative (XXIII) occurred, as shown by carbonyl absorption at 5.90 μ.

Methyl-4,6-Benzylidene-2,3-dideoxy-2,3-imino-α,D-allopyranoside (XXV). A.—A solution of 70 mg. of XXIV in 5 ml. of 0.2 *N* aqueous sodium hydroxide was refluxed for 1 hr., then extracted with three 10-ml. portions of chloroform. The combined extracts, washed with two 10-ml. portions of water and dried with magnesium sulfate, were evaporated *in vacuo*. Recrystallization from ethyl acetate–petroleum ether gave 51 mg. (95%) of white crystals, m.p. 144–145°; λ_{max} 3.05 (NH), 13.3, and 14.3 μ (monosubstituted phenyl), no bands in the 6–7-μ region; $[\alpha]^{22}D$ 145.5 ± 0.8° (0.99%).

Anal. Calcd. for $C_{14}H_{17}NO_4$: C, 63.8; H, 6.52; N, 5.32; mol. wt., 263. Found: C, 63.7; H, 6.59; N, 5.55; mol. wt., 275.

A melting point of 143–145°, but no optical rotation or molecular weight, has been recorded for this compound prepared by a different route.[14]

B.—A solution of 500 mg. of XXII in 25 ml. of 0.2 *N* aqueous sodium hydroxide was refluxed for 1 hr., then processed as in method A to yield 180 mg. (61%). An additional 50 mg. (total, 78%) was obtained by extracting the basic solution 2 days later. Both fractions had melting points and infrared spectra identical with preparation A.

C.—A solution of 50 mg. of XXVI in 5 ml. of methanol and 0.5 ml. of 1 *N* methanolic sodium methoxide was heated to reflux, then cooled, and neutralized with solid carbon dioxide. Methanol was evaporated *in vacuo* and 10 ml. of water was added to the residue. The solution was extracted with three 15-ml. portions of chloroform, then processed as in A to yield 25 mg. (75%) of product, m.p. 143–144°, that gave an infrared spectrum identical with preparation A.

D.—When water was substituted for methanol in preparation C, 30 mg. (90%) of product, m.p. 143–144°, was obtained that gave an infrared spectrum identical with A.

E.—The *N*-acetyl derivative of XXV gave 85 and 96% yields of XXV, respectively, by methods C and D.

Methyl *N*-Acetyl-4,6-benzylidene-2,3-dideoxy-2,3-imino-α-D-allopyranoside.—To a stirred solution of 320 mg. of XXV in 3 ml. of reagent pyridine cooled in an ice bath was added 2 ml. of acetic anhydride. After standing for about 18 hr. in a stoppered flask at room temperature, the solution was diluted with 15 ml. of water and the product was collected on a filter. Recrystallization from ethanol gave white crystals with m.p. 183–184°; λ_{max} 5.95 (amide C=O), 13.3, and 14.4 μ (monosubstituted phenyl), no NH near 3 μ; $[\alpha]^{22}D$ 155 ± 2°.

Anal. Calcd. for $C_{16}H_{19}NO_5$: C, 63.0; H, 6.28; N, 4.59. Found: C, 63.1; H, 6.39; N, 4.56.

Acknowledgment.—The authors thank the Cancer Chemotherapy National Service Center, National Cancer Institute, and Starks Associates, Inc., for large scale preparation of certain intermediates, mediated by Contract No. SA-43-ph-4346.

Synthetic Nucleosides. LIX.[1,2] Studies on the Synthesis of *cis*-2,3-Diamino Sugars. II. The Thiourea Neighboring Group

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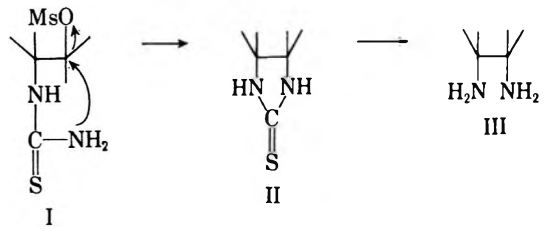
September 25, 1963

Neighboring group ring closure of the *N*-thiocarbamyl derivative (IX) of methyl 3-amino-4,6-*O*-benzylidene-3-deoxy-2-*O*-mesyl-α,D-altropyranoside under acid acceptor conditions gave a thiazolino sugar (VIII). When the anion of IX was cyclized, an *N*-thiocarbamyl imine derivative (X) was obtained rather than the expected imidazoline (XIII). That the ring closure of IX to the imine (X) could not be attributed to the fixed *trans*-diaxial conformations of attacking and leaving groups was shown by the anionic ring closure of the same *N*-thiocarbamyl altroside without the *trans*-fused benzylidene blocking group (XV); since the participating groups in the anionic ring closure of XV can assume either *trans*-diaxial or *trans*-diequatorial conformations with little energy difference, the formation of the *N*-thiocarbamyl imine (XVIII) rather than an imidazoline (XVI) must be attributed to factors apparently more important than the conformational factors. The *N*-thiocarbamyl derivative (XXX) of methyl 2-amino-4,6-*O*-benzylidene-2-deoxy-3-*O*-mesyl-β,D-glucopyranoside, which has *trans*-diequatorial participating groups, ring closed to a thiazoline (XXXII) under acid acceptor conditions. In contrast to IX, anionic ring closure of XXX did not lead to nitrogen attack to form either an imine or an imidazoline; sulfur attack took place to give the same thiazoline (XXXII) obtained under acid acceptor conditions.

In the previous paper of this series,[2] the rationale for synthesis of nucleosides derived from 2,3-diamino-2,3-dideoxy-D-ribofuranose was presented, and general methods for their synthesis by neighboring group reactions were discussed. Among the "complex neighboring groups" that might be suitable for synthesis of the necessary 2,3-diamino system (III) would be the thiourea group (I) *via* the imidazolidine (II). The



I II III

investigation of the thiocarbamyl derivatives of methyl 3-amino-3-deoxy-α,D-altropyranoside and methyl 2-amino-2-deoxy-β,D-glucopyranoside is the subject of this paper.

When methyl 3-amino-4,6-*O*-benzylidene-3-deoxy-α,D-altropyranoside (IV) in dilute alcohol was treated with potassium thiocyanate with or without the presence of one equivalent of acetic acid, mixtures were obtained from which the desired thiourea (VI) could not be isolated. In contrast, IV reacted smoothly with potassium cyanate and an equivalent of acetic acid in dilute alcohol to give the crystalline urea derivative (V) in 82% yield. Treatment of V with 3 moles of mesyl chloride in pyridine not only formed the 2-mesylate derivative, but, as could be predicted,[3] dehydrated the urea group to a cyanamide (VII) in 82% yield. When the cyanamide (VII) was treated with hydrogen sulfide in pyridine at ambient temperature, addition across the triple bond occurred with formation of the desired thiourea[4] (IX) in 73% yield (Scheme I).

Cyclization of IX in boiling pyridine gave a 70% yield of crystalline product that appeared to be the thiazoline (VIII), since it showed C=N absorption at 6.10 μ, whereas the imidazolidine (XIII) would not be expected to have absorption in this region. The structure, VIII, was confirmed by basic hydrolysis to the amino thiol (XI) which gave a noncrystalline, though pure *N*,*S*-diacetyl derivative (XII). The intermediate thiol (XI) could not be crystallized, but XI gradually formed a crystalline disulfide[5] by air oxidation.

Cyclization of the thiourea (IX) by conversion to the anion with methanolic sodium methoxide gave a crystalline product in 85% yield that was isomeric to the thiazoline (VIII) and had infrared spectral properties agreeing with either the aziridine structure, X, or the imidazolidine structure, XIII. That the former structure was correct was shown by basic hydrolysis to the imino sugar (XIV).[2,6] The anionic cyclization of IX to the thermodynamically labile aziridine (X), rather than the thermodynamically stable imidazoline, is indeed surprising; similar results were observed previously with the nitroguanidine[2] and dithiocarbomethoxy[6] neighboring groups.

Jeanloz, *et al.*,[7] have shown that the 4,6-*O*-benzylidene blocking group in the α,D-galactopyranoside system could negate a neighboring group reaction, whereas the same system without the benzylidene group would undergo neighboring group reaction. Therefore, an investigation of ring closure of a thiourea derivative without the benzylidene group (XV) was undertaken to determine whether or not the benzylidene group was controlling the ring closure to the thermodynamically unstable aziridine (X). Treatment of IX with Dowex 50W-X 8 (H^+) resin in boiling 80% methanol for 4 hr. gave the debenzylidenated glycol (XV) in

(1) This work was generously supported by Grant CY-5845 of the National Cancer Institute, U. S. Public Health Service.

(2) For the previous paper of this series, see B. R. Baker and T. Neilson, *J. Org. Chem.*, **29**, 1047 (1964).

(3) Primary amides can be converted to nitriles with sulfonyl chlorides in pyridine, presumably *via* the imino-*O*-sulfonate. Secondary amides have been converted to thioamides by formation of imino-*O*-sulfonates with a sulfonyl chloride in pyridine followed by treatment with hydrogen sulfide. *Cf.* P. Oxley, D. A. Peak, and W. F. Short, *J. Chem. Soc.*, 1618 (1948); J. Witte and R. Huisgen, *Chem. Ber.*, **91**, 1129 (1958).

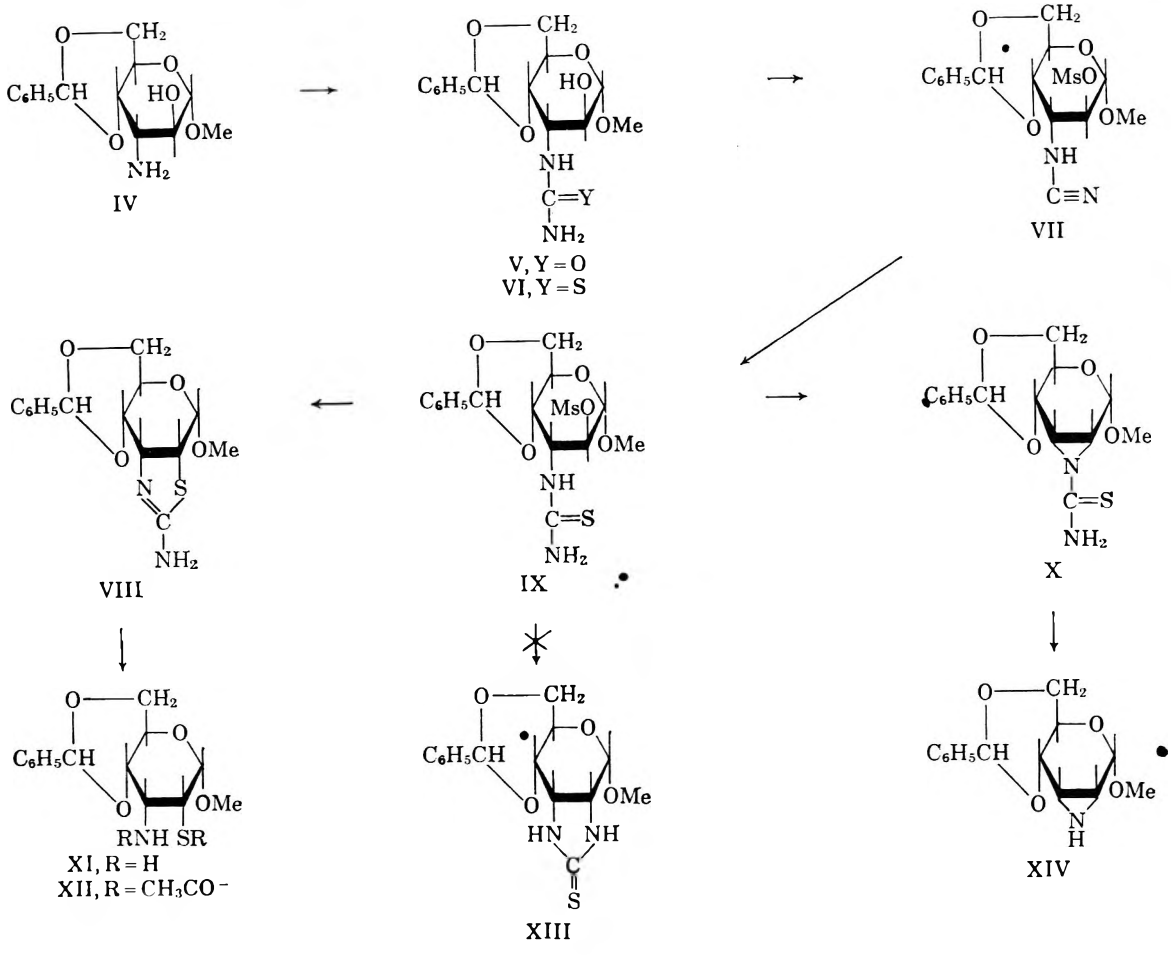
(4) The preparation of thioureas by addition of hydrogen sulfide to nitriles has been described by A. E. S. Fairfull, J. L. Lowe, and D. A. Peak, *J. Chem. Soc.*, 742 (1952); see also O. Wallach, *Ber.*, **32**, 1872 (1899), and *Org. Syn.*, **36**, 23 (1956).

(5) Ring closure of IX in pyridine to the thiazoline (VIII) could be expected in view of the similar cyclization of the corresponding dithiocarbomethoxy derivative (XXIV) to a thiazoline.[6] The melting point of the disulfide of XI is about 100° lower than that recorded,[6] probably because our sample crystallized as a solvate, whereas the disulfide has been reported[6] as solvent free.

(6) L. Goodman and J. E. Christenson, *J. Am. Chem. Soc.*, **83**, 3823 (1961); **82**, 4738 (1960).

(7) Z. Jarasiejska and R. W. Jeanloz, *ibid.*, **79**, 4215 (1957).

SCHEME I



95% yield as a glass; the ion-exchange resin[8] was found to give a cleaner product than methanolic hydrochloric acid or dilute sulfuric acid in aqueous acetic acid. Treatment of XV with ethanolic sodium ethoxide gave rapid formation of sodium methanesulfonate; the resultant cyclized product (XVI or XVIII) was a glass that gave a crystalline diacetate of structure XVII or XIX in 75% yield for the three steps (Scheme II). That this cyclization still had formed the aziridine XVIII was shown by chemical structure proof, as well as by infrared and n.m.r. studies.

Treatment of the benzylidene aziridine (X) with Dowex 50W-X8 (H^+) to give crude XVIII followed by acetylation with acetic anhydride and pyridine gave crystalline XIX in 46% over-all yield, which was identical with the cyclization product (XIX) from XV *via* XVIII. Basic hydrolysis of XIX gave XXI as a glass that was acetylated to pure XX, obtained as an oil: the lack of NH absorption in the infrared and combustion analyses confirmed the structure as the aziridine XX, rather than a di-*O*-acetyl-di-*N*-acetyl derivate of an alloside derived from XVII.

That XX was an aziridine was further confirmed by comparison of the n.m.r. spectra of XXII, XXIII,[2] XX, and XIV shown in Table I. The mean signal assigned to the protons of the epoxide ring of the anhydromannoside (XXII) was 196 c.p.s. in agreement with 190 c.p.s. usually attributed to the corresponding protons of an epoxide ring fused in a bicyclic structure. By use of the empirical rule that substitution of nitrogen for oxygen causes a shift of 50 c.p.s. upfield toward tetramethylsilane, it is reasonable to expect that XIV should give a signal near 146 c.p.s.; a signal at 158 c.p.s. was actually observed.

TABLE I

NUCLEAR MAGNETIC RESONANCE COMPARISONS

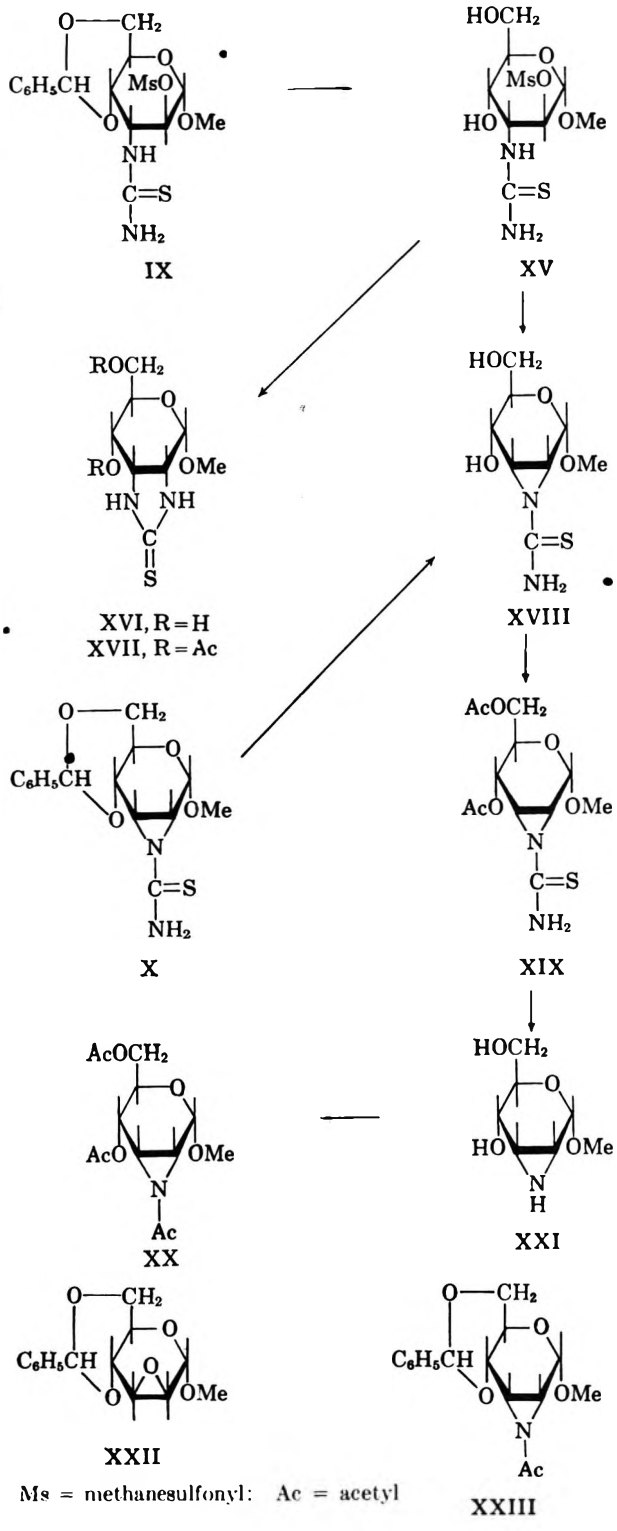
Compounds	Bands in c.p.s.	Half width in c.p.s.	Integration
XXII	187, 191, 201, 205	2 each	2H
XIV	158	10	2H
XXIII	185	8	2H
XX	192	5	2H

The vicinal proton for an amide, as demonstrated by the comparison of pyrrolidine with 2-pyrrolidone, shows a shift downfield. Hence the *N*-acetyl derivatives (XXIII and XX) could be expected to have aziridine ring proton signal near 196 − 50 + 40 = 186 c.p.s., in good agreement with the observed signals at 185 and 192 c.p.s., respectively.

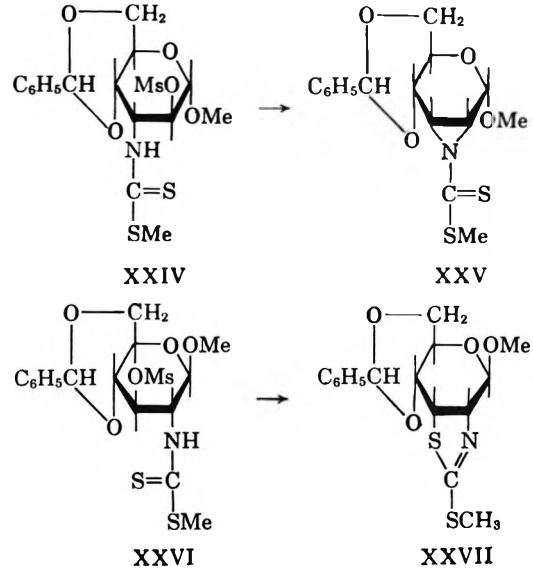
The anionic ring closure of IX and XV to the aziridines (X and XVIII), respectively, parallels the reported anionic ring closure of the dithiocarbomethoxy derivative (XXIV) to the aziridine derivative (XXV)[6] (Scheme III). However, it could not necessarily be anticipated that ionic ring closure of the thiourea neighboring group would follow a similar course; IX and XV have an additional possible mode of anionic

(8) See B. R. Baker, K. Hewson, L. Goodman, and A. Benitez, *J. Am. Chem. Soc.*, **80**, 6577 (1958), for removal of a 4,6-*O*-benzylidene group with a sulfonic type ion-exchange resin.

SCHEME II



SCHEME III



ring closure to the imidazolidines (VIII and XVI), respectively, not possible with XXIV. In contrast, Bonner, *et al.*,[9] have observed recently that the isomeric dithiocarbomethoxy derivative of 2-amino-D-glucopyranoside (XXVI) underwent anionic ring closure to the thiazoline (XXVII) rather than to the β anomer of XXV; the same ring closure occurred in aqueous pyridine. Bonner attributed this difference to the fact that the participating groups in XXVI are *trans*-diequatorial, whereas those of XXIV are *trans*-diaxial. Therefore, the mode of ring closure of the 2-thiourea derivative D-glucose configuration (XXX) was investigated.

Methyl 2-amino-4,6-*O*-benzylidene-2-deoxy-β,D-glucopyranoside (XXVIII) was synthesized from D-glucosamine essentially according to Bonner, *et al.*[10] The subsequent conversion of XXVIII to XXX paralleled the similar conversion of the 3-amino-D-altroside (IV) to IX. Reaction of XXVIII with potassium cyanate in dilute alcohol containing one equivalent of acetic acid gave the crystalline urea derivative (XXIX) in 90% yield. Treatment of XXIX with three equivalents of mesyl chloride in pyridine gave the mesylated cyanamide (XXXI) in 82% yield as a glass that had poor crystallizing properties. When crude XXXI was reacted with hydrogen sulfide in pyridine, the crystalline thiourea (XXX) was obtained in 42% yield (Scheme IV).

Surprisingly, either anionic ring closure of XXX or ring closure in the presence of an acid acceptor, pyridine, gave the same product in 71 and 66% yields, respectively, which was shown to have the thiazoline structure (XXXII). It is notable that the thiazoline (XXXII) and the isomeric thiazoline (VIII) had radically different infrared spectra in the 6.0–6.8-μ region, indicating that one of the compounds was a 2-aminothiazoline and the other a 2-iminothiazolidine. Since XXXII had a C=N band at 6.03 μ and VIII a C=N band at 6.10 μ, it is likely that XXXII is a 2-iminothiazolidine; an exocyclic C=N of a five-membered ring should show absorption at a lower wave length than an endocyclic C=N.

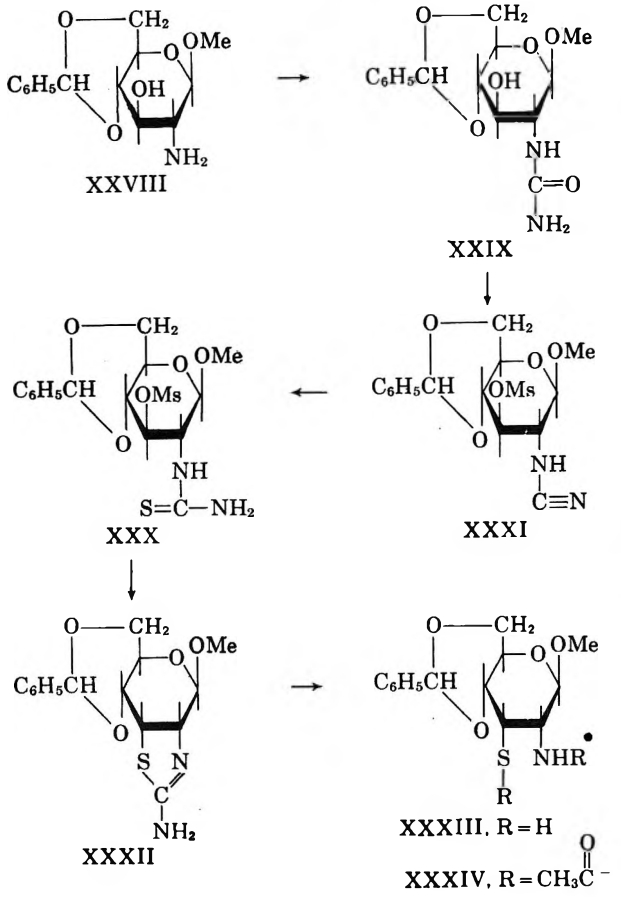
Hydrolysis of the thiazoline (XXXII) with 20% sodium hydroxide to XXXIII followed by acetylation gave the crystalline *N*,*S*-diacetate (XXXIV) in 62% yield that had physical properties agreeing with this same compound prepared previously from the methylthiothiazoline (XXVII) by Bonner.[10b]

Conformational aspects alone appear to be insufficient to explain the observed neighboring reactions in the anionic conversion of IX to X, XVa to XVIII,

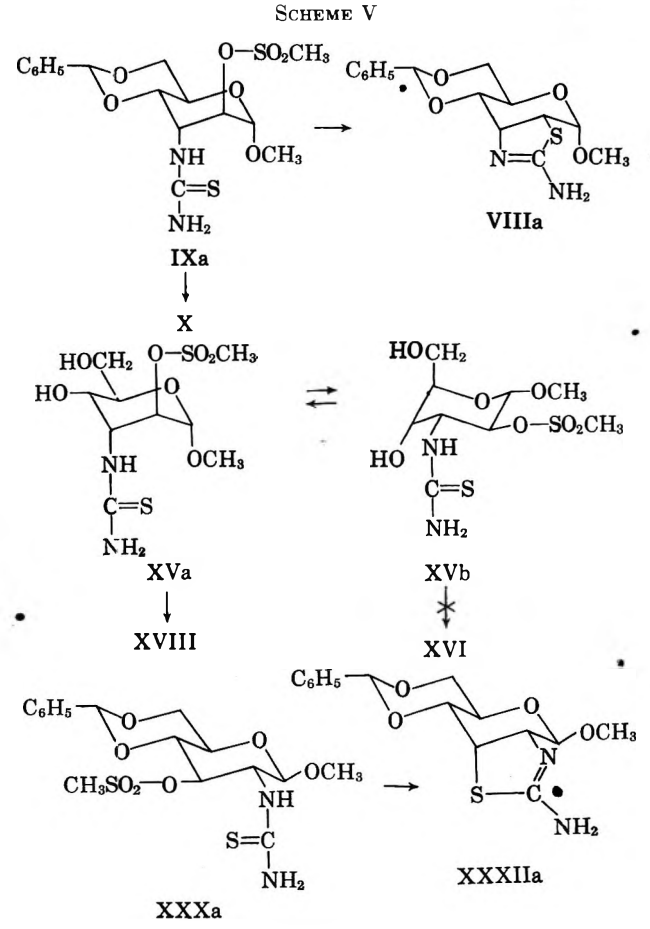
(9) (a) W. M. Reckendorf and W. A. Bonner, *Chem. Ind.* (London), 429 (1961); (b) *Tetrahedron*, **19**, 1711, 1721 (1963). We wish to thank Professor Bonner for sending us the latter manuscript prior to publication.

(10) W. M. Reckendorf and W. A. Bonner, *Chem. Ber.*, **94**, 3293 (1961).

SCHEME IV



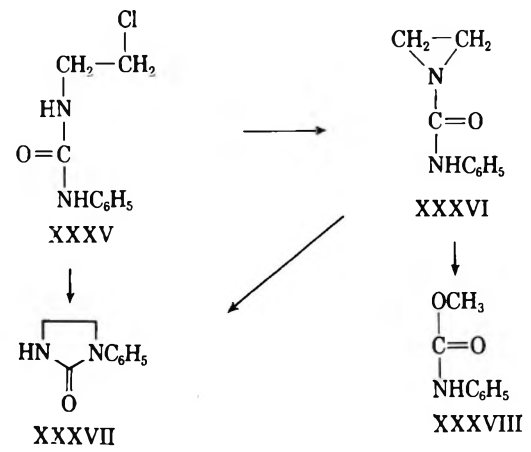
SCHEME V



and XXXa to XXXIIa. The 1-C and C-1 conformations of XVa and XVb appear about energetically equal; XVb has two axial groups and three equatorial groups, although the bulkiest group—the hydroxymethyl—being in an unfavorable axial position probably counterbalances the gain in more equatorial groups than axial groups. In contrast, XVa with three axial groups and two equatorial groups has the bulky hydroxymethyl group in a favorable equatorial conformation. With the assumption that XVa and XVb are readily interconvertible, then treatment of XV with methanolic sodium methoxide should have given the more thermodynamically stable imidazoline (XVI) or thiazoline (VIII) rather than the strained imine (XVIII) (Scheme V).

One possible explanation follows. If there were an equal conformational probability for formation of an imine (XVIII) or an imidazoline (XVI), the imine could be formed preferably, owing simply to a faster rate factor even though the imine was thermodynamically less stable than the imidazoline. If such were the case, then neighboring group reactions on an ethane system such as XXXV also should give an imine; this imine could be an intermediate in the known formation of a five-membered ring, but the sluggishly reacting pyranose system would stop at the imine stage. 1-(2-Chloroethyl)-3-phenylurea (XXXV) has been reported to form the imidazolone (XXXVII) when treated with ethanolic sodium hydroxide,[11] as did the corresponding bromide when treated with ethanolic sodium ethoxide.[12] If this reaction proceeded through

SCHEME VI



an imine (XXXVI) as the rate-limiting step, then XXXVI should be convertible to the imidazolone (XXXVII) when treated with an alkoxide. That this reaction did *not* proceed through the imine (XXXVI) was shown by treatment of XXXVI with methanolic sodium methoxide; the product was methyl-*N*-phenylurethane (XXXVIII), formed by methanolysis due to the imine activation of the carbonyl group[13] (Scheme VI).

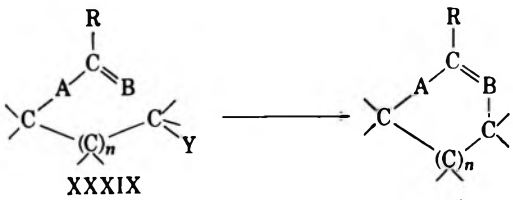
Further investigation will certainly be required to find an explanation for the differences in products in the anionic neighboring group reactions with IXa, XVa and b, and XXXa. Even the anionic attack by

(11) S. Gabriel and R. Stelzner, *Ber.*, **28**, 2929 (1895).

(12) F. L. Scott, R. E. Glick, and S. Winstein, *Experientia*, **13**, 183 (1957).

(13) The higher reactivity of the carbonyl group in an acylaziridine compared to an ordinary *t*-amide has been reported previously; see H. C. Brown and A. Tsukamoto, *J. Am. Chem. Soc.*, **83**, 4549 (1961), and H. W. Heine, M. A. Fetter, and E. M. Nicholson, *ibid.*, **81**, 2202 (1959).

sulfur in the ring closure of XXXa to XXXIIa, contrasted to anionic attack by nitrogen in ring of IXa and XVa, resists suitable explanation with the currently available information. One precaution certainly can emerge from the above reactions with the thiourea neighboring group; one should hesitate at the present time to write a general mechanism, such as XXXIX to XL proposed by Winstein and Boschan,[14] since any one of the groups A, B, or R (if R is nucleophilic) may participate in a ring closure *the mode of which can be dependent on the carrier* $(>C)_{n+2}$ *for the participating groups.*



XXXIX XL

Experimental[15]

Methyl 4,6-*O*-Benzylicene-3-deoxy-3-ureido-α,D-altropyranoside (V).—To a hot solution of 18 g. of IV in 100 ml. of ethanol was added a solution of 7.5 g. of potassium cyanate in 100 ml. of water followed by 4.8 ml. of glacial acetic acid. After being heated on a steam bath for 15 min., the hot solution was filtered, then cooled. The product was collected on a filter and washed with 50 ml. of water to yield 15.9 g. (77%) with m.p. 229–230°; $[\alpha]_D$ + 111 ± 1°; λ_{max} 2.85, 2.98, 3.12 (NH), 5.98 (C=O), 6.25, 6.54 (amide II), and 12.93, 14.11 μ (C_6H_5—).

Anal. Calcd. for $C_{15}H_{20}N_2O_6$: C, 55.5; H, 6.24; N, 8.64. Found: C, 55.5; H, 6.46; N, 8.69.

An additional 1.0 g. (total 82%) was isolated by concentration of the mother liquor.

Methyl 4,6-*O*-Benzylidene-3-cyanamido-3-deoxy-2-*O*-mesyl-α,D-altropyranoside (VII).—To a magnetically stirred suspension of 4.4 g. of V in 20 ml. of reagent pyridine cooled in an ice bath was added 3.5 ml. of methanesulfonyl chloride over a period of 30 min. with strict temperature control in the range of 0–5°. After being stirred an additional 15 min., the mixture was allowed to stand at 0–5° for about 18 hr. protected from moisture, then poured onto about 100 g. of ice. The mixture was extracted with two 100-ml. portions of chloroform; the combined extracts, washed with two 100-ml. portions of water and dried with magnesium sulfate, were spin evaporated to residue *in vacuo*. Traces of pyridine were removed from the residue by spin evaporation of toluene (two 25-ml. portions) *in vacuo*. Recrystallization from ethanol gave 4.2 g. (82%) of white needles, m.p. 154–155°; $[\alpha]^{22}_D$ + 61 ± 1° (1.13%); λ_{max} 3.13 (NH), 4.48 (C≡N), 7.30, 8.55 (sulfonate), and 13.3, 14.3 μ (C_6H_5—).

Anal. Calcd. for $C_{16}H_{20}N_2O_7S$: C, 50.0; H, 5.50; N, 7.29; S, 8.44. Found: C, 49.9; H, 5.45; N, 7.46; S, 8.57.

Methyl 4,6-*O*-Benzylidene-3-deoxy-2-*O*-mesyl-3-thioureido-α,D-altropyranoside (IX).—Through a solution of 1.00 g. of VII in 10 ml. of reagent pyridine was bubbled slowly hydrogen sulfide for 15 min. After standing about 18 hr., the solution was spin evaporated to residue *in vacuo;* traces of pyridine were removed from the residue by spin evaporation of toluene (two 5-ml. portions). Crystallization from ethyl acetate–petroleum ether gave 0.80 g. (73%) of white prisms, m.p. 160–161°; $[\alpha]^{22}_D$ + 60.5 ± 0.7° (1.02%); λ_{max} 2.85, 3.00, 3.15 (NH), 6.26, 6.45 (amide II), 7.30 (C=S), 7.45, 8.56 (sulfonate), 13.4, 14.3 (C_6H_5), and no C≡N near 4.5 μ.

Anal. Calcd. for $C_{16}H_{22}N_2O_7S_2$: C, 45.9; H, 5.30; N, 6.70; S, 15.3. Found: C, 46.2; H, 5.35; N, 6.72; S, 15.2.

2-Amino-4′,6′-*O*-benzylidene-1′-*O*-methyl-α,D-allopyrano[3′,2′:4,5]-2-thiazoline (VIII).—A solution of 250 mg. of IX in 8 ml. of reagent pyridine was refluxed for 1 hr., then poured into 20 ml. of water, and extracted with two 20-ml. portions of chloroform. The combined extracts, washed with two 20-ml. portions of water and dried with magnesium sulfate, were spin evaporated *in vacuo*. Traces of pyridine were removed from the residue by spin evaporation with toluene (two 10-ml. portions) *in vacuo*. Crystallization from ethyl acetate–petroleum ether gave white prisms, m.p. 195–196°; $[\alpha]^{22}_D$ + 196 ± 2° (0.64%); λ_{max} 2.91 (NH), 6.10, 6.30 (NH, C=N), 13.35, 14.35 (C_6H_5—), and no C=S or sulfonate absorption near 7.4 μ.

Anal. Calcd. for $C_{15}H_{18}N_2O_4S$: C, 55.9; H, 5.64; N, 8.70; S, 9.96. Found: C, 56.1; H, 5.70; N, 8.79; S, 10.1.

Anal. Calcd. for $C_{15}H_{18}N_2O_4S$: C, 55.9; H, 5.64; N, 8.70; S, 9.96. Found: C, 56.1; H, 5.70; N, 8.79; S, 10.1.

Methyl 3-Acetamido-2-acetylthio-4,6-*O*-benzylidene-2,3-dideoxy-α,D-allopyranoside (XII).—A mixture of 1.00 g. of VIII and 25 ml. of 20% sodium hydroxide was refluxed for about 18 hr. The cooled solution was neutralized to pH 8–9 with glacial acetic acid, then immediately stirred with 2 ml. of acetic anhydride for 1 hr. The solution was extracted with three 30-ml. portions of chloroform; the combined extracts, washed with three 20-ml. portions of water and dried with magnesium sulfate, were spin evaporated *in vacuo* to yield 0.91 g. (77%) of a glass that could not be crystallized, but was nearly pure. The sample showed $[\alpha]^{22}_D$ + 13.5 ± 1.7° (0.28%); λ^{film}_{max} 2.97, 3.03 (NH), 6.0 (broad) (ester and amide C=O), 6.65 (amide II), and 13.3, 14.4 μ (C_6H_5—).

Anal. Calcd. for $C_{18}H_{23}NSO_6$: C, 56.7; H, 6.08; N, 3.67; S, 8.36. Found: C, 56.1; H, 6.09; N, 3.66; S, 8.06.

Disulfide of Methyl 3-amino-4,6-*O*-benzylidene-2,3-dideoxy-2-mercapto-α,D-allopyranoside (XI).—Treatment of 1.00 g. of VIII as in the previous experiment, except that the acetic anhydride was omitted, gave XI as a glass that showed SH absorption at 3.89 μ. When XI was allowed to stand in ethanol, the disulfide slowly crystallized as an ethanol solvate to yield 420 mg. (43%), m.p. 123–124° (gas); $[\alpha]^{22}_D$ + 47 ± 3° (0.17%); λ_{max} 2.85, 2.99, 6.31, 6.35 (NH_2), and 13.2, 14.4 μ (C_6H_5—).

Anal. Calcd. for $C_{14}H_{17}NO_4S \cdot {}^2/_3C_2H_5OH$: C, 56.3; H, 6.78; N, 4.28; S, 9.78; mol. wt., 654. Found: C, 55.9; H, 6.85; N, 4.31; S, 9.88; mol. wt., 690.

The n.m.r. spectrum ($DCCl_3$) showed a CH_3 peak of ethanol at 70 c.p.s., the intensity of which was $^2/_3$ mole compared to the phenyl ring. The compound gave a negative nitroprusside test.

Goodman and Christensen[6] obtained this compound free of solvate by a different route; they recorded m.p. 228–236°, but did not record an optical rotation.

Methyl 4,6-*O*-Benzylidene-2,3-dideoxy-2,3-imino-*N*-thiocarbamyl-α-D-allopyranoside (X).—To a warm solution of 2.00 g. of IX in 25 ml. of absolute ethanol was added 8.0 ml. of 1 *N* methanolic sodium methoxide. After being refluxed 10 min., during which time solid separated, the mixture was allowed to stand overnight at ambient temperature. The solids were collected on a filter and recrystallized from aqueous ethanol to give 1.30 g. (85%) of product as white needles, m.p. 177–178°; $[\alpha]_D$ + 132.4 ± 0.8° ± 0.8° (1.22%); λ_{max} 2.90, 3.04, 3.15, 6.15, 6.22 (NH), 7.35 (C=S), and 13.4 μ (C_6H_5—).

Anal. Calcd. for $C_{15}H_{18}N_2O_4S$: C, 55.9; H, 5.64; N, 8.70; S, 9.96. Found: C, 55.7; H, 5.89; N, 8.53; S, 9.66.

A solution of 300 mg. of X in 25 ml. of 0.2 *N* sodium hydroxide was refluxed for 2 hr. As previously described,[2] XIV was isolated in 85% yield (210 mg.) with m.p. 144–145°, that was identical with the earlier sample.[2]

Methyl 3-deoxy-2-*O*-mesyl-3-thioureido-α,D-altropyranoside (XV).—A magnetically stirred solution of 2.00 g. of IX in 200 ml. of 80% aqueous methanol was refluxed with 5 g. of sulfonic acid resin [Dowex 50W-X8 (H^+)] for 4 hr. The filtered solution was spin evaporated *in vacuo* leaving the product as a glass; yield 1.60 g. (95%); λ_{max} 2.92, 3.01, 3.13 (NH, OH), 6.25, 6.50 (amide NH), 7.40, 8.56 μ (sulfonate), and no C_6H_5– absorption in the 13–14.5-μ region.

Anal. Calcd. for $C_9H_{18}N_2O_7S_2$: C, 32.7; H, 5.47; N, 8.48; S, 19.4. Found: C, 32.6; H, 5.27; N, 8.30; S, 19.2.

Similarly, hydrolysis of X gave a quantitative yield of **methyl 2,3-dideoxy-2,3-imino-*N*-thiocarbamyl-α,D-allopyranoside (XVIII)** that was suitable for further transformation to XIX. Crystallization from ethanol gave only a 14% recovery of white crystals with m.p. 223–224°; $[\alpha]^{24}_D$ + 150 ± 1° (0.41%);

(14) S. Winstein and R. Boschan, *J. Am. Chem. Soc.*, **72**, 4669 (1950).

(15) Melting points were taken in capillary tubes in a Mel-Temp block and those below 230° are corrected. Infrared spectra were determined in Nujol mull with a Perkin-Elmer Model 137B spectrophotometer. Nuclear magnetic resonance spectra were determined in $DCCl_3$ with a Varian A-60 spectrometer using tetramethylsilane as the internal standard. Optical rotations were determined in a 1-dm. microtube in *N,N*-dimethylformamide unless otherwise indicated. Petroleum ether was a fraction boiling at 30–60°.

λ_{max} 2.92, 3.01, 3.15 (NH, OH), 6.25, 6.32 μ (NH), and no C_6H_5– peak in the 14-μ region.

Anal. Calcd. for $C_8H_{14}N_2O_4S$: C, 41.0; H, 6.02; N, 12.0; S, 13.7. Found: C, 41.0; H, 6.15; N, 11.8; S, 13.5.

Methyl 4,6-Di-*O*-acetyl-2,3-dideoxy-2,3-imino-*N*-thiocarbamyl α,D-allopyranoside (XIX). A.—To a solution of 400 mg. of XV in 10 ml. of absolute ethanol was added 2.0 ml. of 1 *N* methanolic sodium methoxide. The mixture was warmed to 40°, then allowed to cool to room temperature; sodium methanesulfonate separated. The mixture was spin evaporated to dryness *in vacuo*. To the residue of crude XVIII was added 5 ml. of acetic anhydride. After standing for about 18 hr., 10 ml. of ethanol was added; 1 hr. later, the mixture was spin evaporated *in vacuo*, then diluted with 20 ml. of water, and extracted with three 20-ml. partions of chloroform. The combined chloroform extracts, washed with two 20-ml. portions of water and dried with magnesium sulfate, were spin evaporated *in vacuo*. Crystallization from ethyl acetate–petroleum ether (30–60°) gave 290 mg. (75%) of white crystals, m.p. 139–140°; $[\alpha]^{24}D$ + 208 ± 3° (0.14%); λ_{max} 2.92, 3.02, 3.12 (NH), 5.78 (ester C=O), 6.22 (NH), 8.0–8.4 (ester C—O—C), and no sulfonate near 8.6 μ.

Anal. Calcd. for $C_{12}H_{18}N_2O_6S$: C, 45.3; H, 5.71; N, 8.80; S, 10.1. Found: C, 45.6; H, 5.92; N, 8.81; S, 10.2.

B.—To a solution of 500 mg. of crude XVIII, prepared *via* X, in 10 ml. of reagent pyridine was added 0.5 ml. of acetic anhydride. After 2 hr. at room temperature, the solution was diluted with 20 ml. of water and processed as in method A. Traces of pyridine in the crude product were removed by spin evaporation with toluene (two 10-ml. portions). Crystallization from ethyl acetate–petroleum ether gave 305 mg. (46%) of white needles, m.p. 139–140°, that were identical with preparation A.

Methyl *N*-Acetyl-4,6-O-acetyl-2,3-dideoxy-2,3-imino-α,D-allopyranoside (XX). A.—The crude XVIII, prepared from XV by method A, was hydrolyzed with boiling 0.2 *N* aqueous sodium hydroxide for 2 hr. Spin evaporation *in vacuo*, followed by acetylation as described for XIX, gave 282 mg. (77%) of the product as an oil; $[\alpha]^{24}D$ + 162 ± 1° (1.02%); λ_{max} 5.77 (ester C=O), 5.90 (amide C=O), 8.0–8.4 (ester C—O—C), and no NH near 3 or 6 μ.

Anal. Calcd. for $C_{16}H_{19}NO_5$: C, 63.0; H, 6.28; N, 4.59. Found: C, 63.1; H, 6.39; N, 4.56.

B.—Hydrolysis of 250 mg. of crystalline XIX with 0.2 *N* aqueous sodium hydroxide, followed by acetylation as in method A, gave 156 mg. (66%) of product as an oil that was identical with preparation A.

Methyl 4,6-*O*-benzylidene-2-deoxy-2-ureido-β,D-glucopyranoside (XXIX).—Methyl 2-amino-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranoside was prepared essentially according to the method of Reckendorf and Bonner[10] with the following notation. (1) In the formylation of D-glucosamine, sodium chloride was not removed by filtration prior to addition of methyl formate, since, in some runs, D-glucosamine base rapidly crystallized from the methanol and was rejected with the salt; the salt did not interfere with the benzylidenation step. The over-all yield, m.p. 236–237°, for the two steps was 26%; however, the first step did not work consistently unless the D-glucosamine hydrochloride was finely ground. (2) The insoluble material remaining prior to adding dimethyl sulfate to a basic solution of *N*-formyl-4,6-*o*-benzylidene-D-glucosamine was unchanged material and could be used again; thus, the yield of β anomer was 57%, m.p. 260–261°.

To a solution of 1.8 g. of crude XXVIII (free base)[10] in 15 ml. of warm ethanol was added a solution of 0.75 g. of potassium cyanate in 10 ml. of water followed by 0.48 ml. of glacial acetic acid. After being heated to about 80°, the mixture was allowed to cool to room temperature and the product was collected. A second crop was obtained by concentration of the mother liquor *in vacuo*. Recrystallization of the combined crops from ethanol gave 1.8 g. (90%) of product, m.p. 321–323°; $[\alpha]^{24}D$ −73 ± 3° (0.084%); λ_{max} 2.90, 2.95, 3.05 (OH, NH), 6.05 (amide C=O), 6.28, 6.40 (amide II), and 13.2, 14.4 μ (C_6H_5—).

Anal. Calcd. for $C_{15}H_{20}N_2O_6$: C, 55.5; H, 6.24; N, 8.64. Found: C, 55.4; H, 6.22; N, 8.43.

Methyl 4,6-*O*-Benzylidene-2-thioureido-2-deoxy-3-*O*-mesyl-β,D-glucopyranoside (XXX).—XXX was prepared from 1.50 g. of crude XXXI as described for V → VII → IX. Crystallization from ethanol gave 0.71 g. (43%) of white needles, m.p. 223–224°; $[\alpha]^{24}D$ + 103 ± 1° (0.36%); λ_{max} 3.05, 3.19, 5.99, 6.21 (NH), 7.27, 8.62 (sulfonate), 8.43 (C=S), and 13.2, 14.3 (C_6H_5—).

Anal. Calcd. for $C_{16}H_{22}N_2O_7S_2$: C, 45.9; H, 5.30; N, 6.70; S, 15.3. Found: C, 46.1; H, 5.40; N, 6.54; S, 15.5.

2-Amino-4′,6′-*O*-benzylidene-1′-*O*-methyl-α,D-allopyrano-[2′,3′:4,5]-2-thiazoline (XXXII). A.—To a solution of 1.0 g. of XXX in 20 ml. of methanol was added 5 ml. of 1 *N* methanolic sodium methoxide. The mixture was warmed to 50° during which time sodium mesylate separated. The mixture was spin evaporated *in vacuo*, then diluted with 20 ml. of water, and extracted with three 25-ml. portions of chloroform. The combined chloroform extracts, washed with two 20-ml. portions of water and dried with magnesium sulfate, were spin evaporated *in vacuo*. Crystallization from ethanol gave 550 mg. (71%) of white needles, m.p. 235–237°; $[\alpha]D$ +54 ± 1° (0.30%); λ_{max} 2.91, 3.00 (NH), 6.03, 6.15, 6.30, 6.41 (C=N, NH), and 13.2, 14.4 μ (C_6H_5—).

Anal. Calcd. for $C_{15}N_{18}N_2O_4S$: C, 55.9; H, 5.64; N, 8.70; S, 9.96. Found: C, 56.1; H, 5.71; N, 8.66; S, 9.70.

B.—A solution of 300 mg. of XXX in 10 ml. of reagent pyridine was refluxed for 2 hr., then processed as described for VIII. Crystallization from ethanol gave 153 mg. (66%) of product, m.p. 235–236°, that was identical with preparation A.

Methyl 2-Acetamido-3-acetylthio-4,6-*O*-benzylidene-2,3-dideoxy-β,D-allopyranoside (XXXIV).—Hydrolysis of 500 mg. of XXXII with 20% sodium hydroxide, then acetylation of the intermediate aminothiol (XXXIII), as described for the preparation of XII, gave, after recrystallization from ethanol, 370 mg. (62%) of white needles, m.p. 233–234°; $[\alpha]^{24}D$ −118 ± 3° (0.20% in chloroform); λ_{max} 3.05 (NH), 5.92 (thiol C=O), 6.08 (amide C=O), 6.58 (amide NH), and 13.2, 14.4 μ (C_6H_5—).

Anal. Calcd. for $C_{18}H_{23}NSO_6$: C, 56.7; H, 6.08; N, 3.67; S, 8.36. Found: C, 56.9; H, 6.31; N, 3.77; S, 8.13.

Reckendorf and Bonner[9b] have recorded m.p. 231–232° (uncor.) and $[\alpha]^{23}D$ −122° (1.06% in chloroform).

Acknowledgment.—We wish to thank Professor Alan J. Solo of this department for the experimental design of the n.m.r. studies and their interpreattion. We also wish to thank the Cancer Chemotherapy National Service Center, National Cancer Institute, and Starks Associates, Inc., for large scale preparation of certain-intermediates, mediated by Contract No. SA-43-ph-4346.

Synthetic Nucleosides. LX.[1,2] Studies on the Synthesis of *cis*-2,3-Diamino Sugars. III. The Urea Neighboring Group

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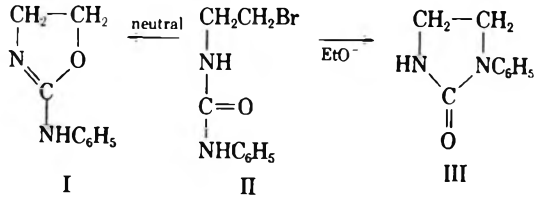
September 25, 1963

Anionic cyclization of methyl 4,6-*O*-benzylidene-3-deoxy-2-*O*-mesyl-3-ureido-α,D-altropyranoside (VII) occurred by nitrogen attack to form an *N*-carbamyl imino alloside (VIII), rather than the desired imidazolidone. Cyclization of VII under acid acceptor conditions proceeded by oxygen attack with formation of an imino-oxazoline (XVII). In order to block imine formation, the addition of water or methanol to the C≡N of methyl 3-benzylamino-4,6-*O*-benzylidene-*N*-cyano-3-deoxy-2-*O*-mesyl-α,D-altropyranoside (XXVI) with concurrent cyclization was investigated. Treatment of XXVI with sodium hydroxide in boiling 2-methoxyethanol gave only 3% yield of the expected imidazolone (XXVII) formed by anionic nitrogen attack; most of the intermediate urea derivative cyclized by oxygen attack to give an oxazolidone (XXVIII). However, when XXVI was treated with methanolic ammonia at 130–150° under pressure, the desired imidazolone (XXVII) was formed in 73% yield. Vigorous basic hydrolysis at 150–170°, followed by acetylation, gave 82% of a crystalline derivative of a *cis*-2,3-diamino sugar, namely methyl 2-acetamido-3-benzylamino-4,6-*O*-benzylidene-2,3-dideoxy-α,D-altropyranoside (XXX).

Among the neighboring groups that have the potential[3] for introduction of nitrogen on a vicinal carbon is the urea group. The phenylurea neighboring group has been investigated previously by Winstein, *et al.*, in an acylic system.[4] Under neutral conditions, the bromide of II was eliminated by oxygen attack to give



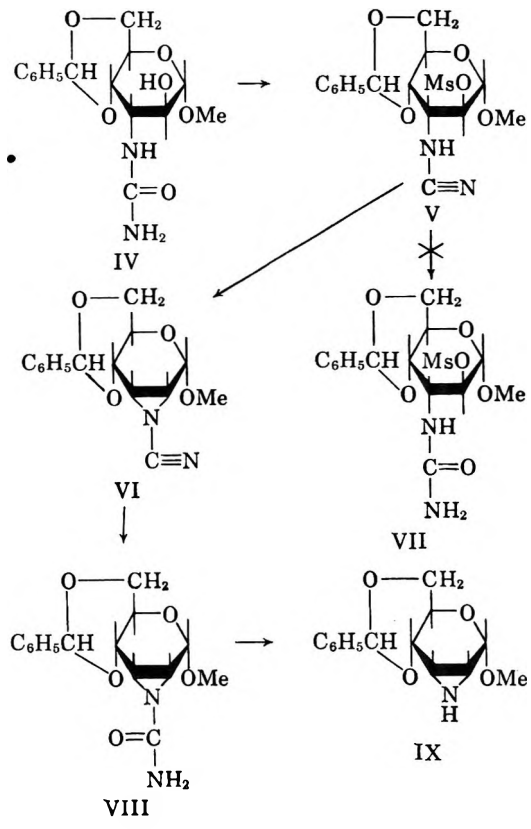
I II III

the 2-anilino-2-oxazoline (I); in contrast, when II was treated with ethanolic sodium ethoxide, nitrogen attack—presumably as an anion—took place to give the cyclic urea (III). Although they did not investigate the simple ureido neighboring group without a phenyl, it might be anticipated that similar results would be obtained.

As previously described,[2] mesylation of the urea (IV) did not give the urea mesylate (VII), but further elimination of the elements of water with formation of a cyanamide group (V) occurred; such a dehydration would be expected under these conditions.[2] The availability of the cyanamido mesylate (V) suggested that attempts be made to hydrate the cyanamido group in order to regenerate a ureido mesylate (VII). Since acidic conditions can remove the benzylidene group, it would be necessary to do such a hydration under neutral or basic conditions.

In boiling water, the benzylidene group of V underwent cleavage. When V was refluxed with 0.2 *N* aqueous sodium hydroxide solution for 2 hr., the desired ureido mesylate (VII) was not obtained; instead the aziridino sugar (IX)[2,3,5] was obtained in 90% yield

SCHEME I



(Scheme I). That the aziridine (IX) was formed by the sequence V → VI → VIII → IX was shown as follows.

Treatment of an ethanolic solution of the cyanamide (V) with methanolic sodium methoxide at room temperature caused almost instantaneous ring closure to the cyano imine (VI) in 88% yield. Further treatment of VI with 0.25 *N* alcoholic sodium hydroxide at 60–70° led to hydration of the cyanamido group and the carbamyl imine (VIII) was obtained in 74% yield. Finally, hydrolysis of VIII with boiling 0.2 *N* sodium hydroxide for 2 hr.—the conditions used for the conversion of V to IX—gave IX in 91% yield. The failure of this approach for the preparation of the ureido mesylate (VII) from the cyanamide (V) clearly can be

(1) This work was generously supported by Grant CY-5845 from the National Cancer Institute, U. S. Public Health Service.

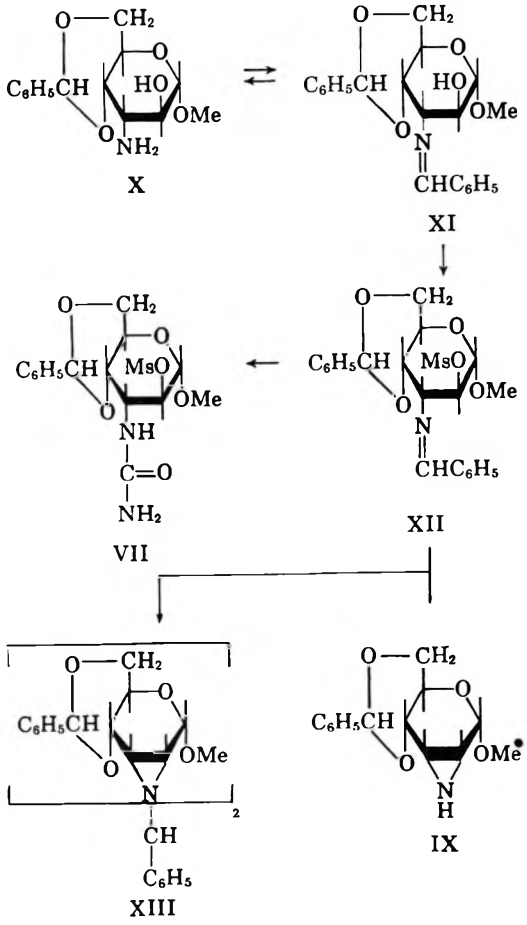
(2) For the previous paper of this series, see B. R. Baker and T. Neilson, *J. Org. Chem.*, **29**, 1051 (1964).

(3) B. R. Baker and T. Neilson, *ibid.*, **29**, 1047 (1964), paper LVIII of this series.

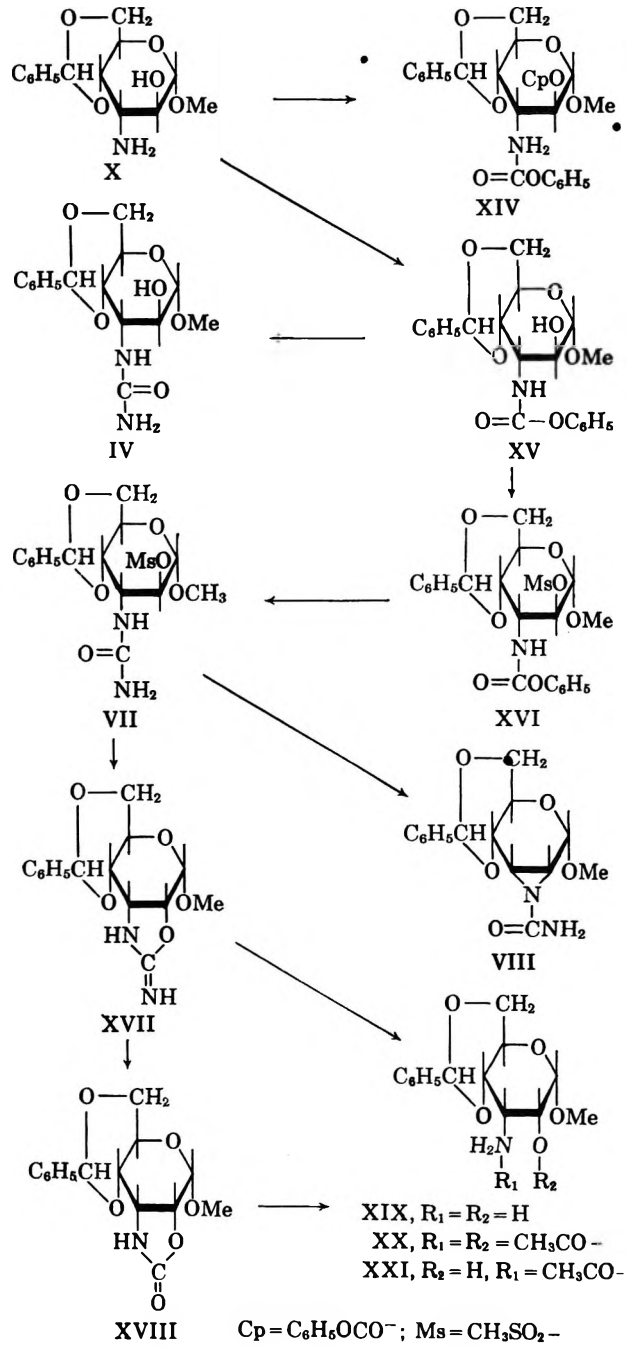
(4) (a) F. L. Scott, R. E. Glick, and S. Winstein, *Experientia*, **13**, 183 (1957); (b) S. Gabriel and R. Stelzner, *Ber.*, **28**, 2929 (1895).

(5) L. Goodman and J. E. Christenson, *J. Am. Chem. Soc.*, **82**, 4738 (1960); **83**, 3823 (1961).

SCHEME II



SCHEME III



attributed to the faster rate of ring closure of V → VI, than the hydration of the triple bond of V → VII (compare VI → VIII).

Since substituted cyanamides such as V are more acidic than ureas such as VII, it could be anticipated that V would ring close more rapidly to an aziridine (VI) than VII would cyclize to VIII under basic conditions. Therefore, alternate routes for the preparation of the ureido mesylate (VII) were sought. The amino altroside (X) smoothly reacted with benzaldehyde to give the crystalline *N*-benzylidene derivative (XI) in 87% yield (Scheme II); that this protecting group for the amine was readily removed under mild conditions was shown by the hydrolysis of XI back to X in 89% yield when heated in aqueous alcohol for 2 hr. Mesylation of XI with methanesulfonyl chloride in pyridine at 0° gave a quantitative yield of XII as a glass that could not be crystallized, but had the proper infrared spectrum; its structure was verified by treatment with 0.2 *N* sodium hydroxide, when 20% of the aziridine IX and 32% of benzylidene diaziridine (XIII) were formed. When XII was treated with potassium cyanate in 50% alcohol containing acetic acid, the benzylidene group was removed and the resultant amine reacted with cyanic acid to give the urea VII as a glass; under these conditions the intermediate amino mesylate reacts more rapidly with cyanic acid than it ring closes to IX.

Earlier, an alternate route to the ureido mesylate (VII) utilizing a latent ureido group was investigated. *O*-Phenylurethanes have been found to be excellent intermediates for synthesis of mixed ureas[6,7] and usually are prepared by the reaction of an amine with phenyl chloroformate. Carefully controlled conditions—that is, addition of the amine to the acid chloride or total immediate mixing—must be used to avoid formation of the symmetrical urea.[7] Unfortunately, in addition to formation of the desired *N*-carbophenoxy derivative (XV), these conditions led to formation of considerable *N*,*O*-dicarbophenoxy derivative (XIV), probably due the insolubility of X and the solubility of XV in the reaction medium. The *N*-carbophenoxy derivative (XV) was best prepared by fusion of the amino altroside (X) with excess diphenyl carbonate; XV was obtained as a glass in 96% yield that was characterized by conversion to the crystalline urea (IV)[2] in 65%

(6) D. G. Crosby and C. Niemann, *J. Am. Chem. Soc.*, **76**, 4458 (1954).
(7) B. R. Baker and R. P. Patel, *J. Pharm. Sci.*, **52**, 927 (1963).

yield with ammonia in aqueous alcohol. Mesylation of XV in pyridine gave a 92% yield of XVI, which could not be crystallized but contained the proper infrared absorption bands. Further reaction of XVI with ammonia in dilute alcohol at room temperature afforded the desired VII as a glass in 92% yield; this compound could not be crystallized but was estimated to be at least 80% pure by combustion analyses.

When the ureido mesylate (VII) was heated with ethanolic sodium ethoxide, the desired imidazolidone was not obtained, but again cyclization to an aziridine (VIII)[2,3] took place in good yield; VIII was further characterized by basic hydrolysis to the imino alloside (IX). Cyclization of the ureido mesylate in boiling 2-methoxyethanol in the presence of sodium acetate as an acid acceptor gave 92% of a glass that had the spectral properties for a mixture of a cyclic iminourethane (XVII), formed by neighboring oxygen attack, and the cyclic urethane (XVIII), formed by hydrolysis of the imino group of XVII. Basic hydrolysis of XVIII gave the crystalline 3-amino alloside (XIX), further characterized by conversion to the authentic acetyl derivatives XX and XXI[8] (Scheme III).

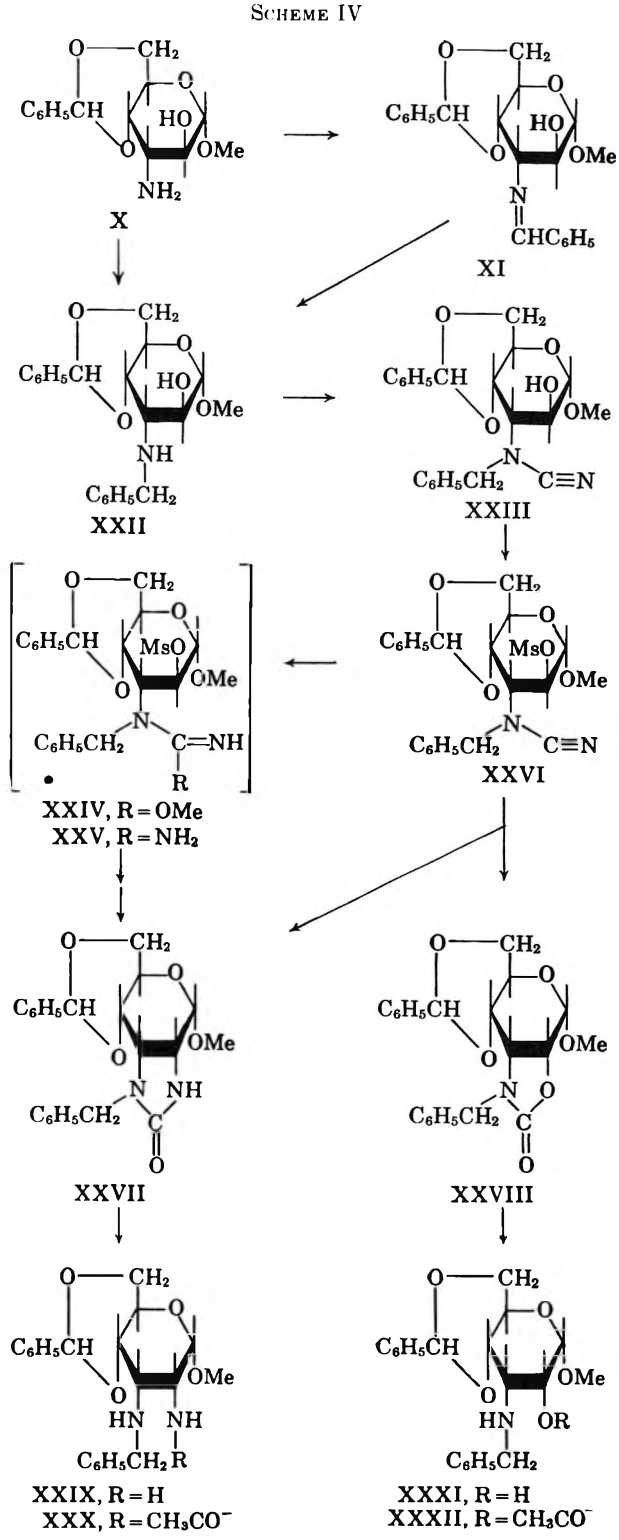
Similarly, when VII was refluxed in pyridine, oxygen attack to an iminocarbonate (XVII) took place in 84% yield; XVII also was characterized by conversion to XIX, XX and XXI.

Thus, the urea neighboring group of VII behaved in participation reactions exactly the same as the corresponding thiourea neighboring group[2]; reaction in the presence of an acid acceptor led to oxygen or sulfur attack, respectively, whereas conversion to an anion resulted in attack by the secondary amide group to give aziridine derivatives in both cases. It was concluded that the secondary amide NH would have to be blocked in order that the slower reacting primary amide group could attack to give a five-membered imidazolidone ring; the blocking group should be stable to the ring-closure conditions, yet should be removable at the proper time. The *N*-benzyl blocking group was selected for this purpose.

Sodium borohydride reduction of the anil (XI) gave the 3-benzylamino altroside (XXII) in 82% yield, 71% over-all for the two steps from the amino altroside (X). Direct reaction of 2 moles of X with 1 mole of benzyl bromide in ethanol gave a 91% yield of the benzylamino altroside (XXII), and most of the second mole of X used as an acid acceptor could be recovered. Treatment of XXII with cyanogen bromide in alcohol gave XXIII in 94% yield. Mesylation of XXIII in pyridine gave the cyanamido mesylate (XXVI) in 91% yield as a glass that could not be crystallized, but was analytically pure. Repetition of the sequence X → XXII → XXIII with *p*-nitrobenzyl bromide also failed to give crystalline compounds.

The *N*-benzylcyanamide (XXVI) was considerably less reactive towards hydroxide ion and hydrogen sulfide than were the corresponding nonbenzylated cyanamides (V and VI); XXIII was recovered unchanged under conditions where the nitrile group of V and VI underwent addition reactions. When the *N*-benzylcyanamide (XXVI) was refluxed with 0.4 *N* sodium hydroxide in 2-methoxyethanol for 3 days, the C≡N absorption finally disappeared. The product was mainly the cyclic urethane (XXVIII); a small amount (3%) of cyclic urea (XXVII) could be isolated after the crude XXVIII was hydrolyzed further with boiling 0.2 *N* sodium hydroxide for 2 hr. (Scheme IV). Neither the resultant benzylamino alloside (XXXI) nor its *O*-acetyl derivative (XXXII) could be crystallized. Although the evidence is good that the mesylate was ejected by neighboring group reaction to give an alloside *via* the oxazoline (XXVIII), it is also possible that some alloside was formed by direct SN2 displacement of the mesylate and that some altroside also could be present by cleavage of the O–S

SCHEME IV



(8) B. R. Baker and R. E. Schaub, *J. Org. Chem.*, **19**, 646 (1954).

group of the mesylate.[9] In view of the relatively good yield of the imidazolone (XXVII) obtained under the conditions described later and the apparent oxygen participation in ring closure to XXVIII under basic conditions, this sequence was not investigated further. However, it is notable that under these basic conditions oxygen attack rather than the expected nitrogen attack took place. Since it has been shown[4] that nitrogen attack would be preferred over oxygen attack when the urea neighboring group is converted to sufficient quantity of anion, it is probable that the disubstituted urea is so weakly acidic that insufficient anion is formed to complete with oxygen attack. In contrast, the ureido group of VII must be ionized sufficiently in aqueous sodium hydroxide to allow N^- attack to give VIII. In fact, the much more acidic cyanamido mesylate (V) is converted to the anion in dilute ammonia, thus causing rapid nitrogen attack with formation of the cyanoimine (VI).[10]

When the *N*-benzylcyanamide (XXVI) was heated in a steel bomb at 130–150° with saturated methanolic ammonia, slow reaction took place. After 7 days, 42% of the crystalline imidazolone (XXVII) had separated and 40% of the starting mesylate (XXVI) could be recovered unchanged. Since the imidazolone (XXVII) was isolated, rather than the corresponding aminoimidazoline, several steps must be involved in this transformation. The rate-limiting step must be the first step since only starting material and imidazolone (XXVII) are obtained. Thus, the first step could be the addition of methanol or ammonia to give the *O*-methylurea (XXIV) or the amidine (XXV) which could cyclize to a 2-methoxy or 2-aminoimidazoline, respectively; the 2-methoxy or 2-amino group could then be displaced by traces of water in the reaction or, less likely, the 2-methoxyimidazoline could react further with ammonia to give XXVII and methylamine. The odor of methylamine was noticeable when the bomb was opened. Although at first glance this might seem to be evidence for the conversion of a methoxyimidazoline to methylamine and XXVII, it also could be evidence for the first mechanism, since ammonia and methyl alcohol could give small amounts of methylamine and water under these conditions. Further evidence for the addition of methanol to a cyanamido group in the presence of ammonia is presented in the following paper.[10]

The imidazolone (XXVII) was extremely resistant to basic hydrolysis, again indicating the steric crowding caused by the *N*-benzyl group; however, after being heated with 30% potassium hydroxide in 50% aqueous ethanol at 150–170° for 7 days, the cyclic urea group was hydrolyzed. Work-up by acetylation in aqueous acetic acid gave a crystalline monoacetyl derivative (XXX) in 82% yield for the two steps; that the monoacetyl group was on the primary amine group as expected was shown by the amide-NH band at 6.57 μ.

Although it should be possible to remove the *N*-benzyl group from either XXVII or XXX by hydrogenolysis or by sodium–ammonia reduction to give the desired 2,3-diamino-D-alloside derivative, these reactions have not yet been investigated.

(9) R. W. Jeanloz and D. A. Jeanloz, *J. Am. Chem. Soc.*, **80**, 5692 (1958).

(10) B. R. Baker and T. Neilson, *J. Org. Chem.*, **29**, 1063 (1964), paper LXI of this series.

Experimental[11]

Methyl 4,6-*O*-Benzylidene-*N*-cyano-2,3-dideoxy-2,3-imino-α,D-allopyranoside (VI).—To a solution of 500 mg. of V[2] in 10 ml. of absolute ethanol at room temperature was added 2 ml. of 1 *N* methanolic sodium methoxide. A yellow coloration immediately formed that bleached in a few minutes as the product separated. The product was collected on a filter and washed with water. Recrystallization from ethanol gave 360 mg. (88%) of white needles, m.p. 183–184°; $[\alpha]^{22}D$ +135 ± 1° (1.1%); λ_{max} 4.53 (C≡N), 13.2, 14.3 (C_6H_5—), and no NH near 3 and no sulfonate near 7.4 or 8.5 μ.

Anal. Calcd. for $C_{15}H_{16}N_2O_4$: C, 62.5; H, 5.61; N, 9.73; S, 0.0. Found: C, 62.4; H, 5.66; N, 9.88; S, 0.0.

Methyl 4,6-*O*-Benzylidene-*N*-carbamyl-2,3-dideoxy-2,3-imino-α,D-allopyranoside (VIII). **A.**—A solution of 500 mg. of VI in 20 ml. of 0.25 *N* sodium hydroxide in 90% ethanol was warmed on a steam bath for 10 min., then spin evaporated *in vacuo*. The residue was extracted with two 20-ml. portions of chloroform. The combined extracts, washed with two 2-ml. portions of water and dried with magnesium sulfate, were spin evaporated *in vacuo*. Recrystallization from ethanol gave 390 mg. (74%) of white needles, m.p. 197–198°; $[\alpha]D$ + 141 ± 1° (0.94%); λ_{max} 2.92, 3.02, 3.13 (NH), 5.90, 6.05 (C=O), 6.30 (amide II), and 13.4, 14.5 μ (C_6H_5—).

Anal. Calcd. for $C_{15}H_{18}N_2O_5$: C, 58.8; H, 5.94; N, 9.15. Found: C, 58.6; H, 5.77; N, 8.90.

B.—To a solution of 1.00 g. of VII (prepared *via* XVI) in 10 ml. of absolute ethanol was added 1 ml. of 1 *N* methanolic sodium methoxide. After being refluxed for 1 hr., the mixture was processed as in method A to yield 520 mg. (68%) of recrystallized product, m.p. 199–200°, that was identical with preparation A. Similarly, VII prepared *via* XII gave 73% yield of VIII.

Anal. Found: C, 58.9; H, 5.83; N, 8.95.

Methyl 4,6-Benzylidene-2,3-dideoxy-2,3-imino-α,D-allopyranoside (IX). **A.**—A solution of 500 mg. of V[2] in 25 ml. of 0.2 *N* aqueous sodium hydroxide was refluxed for 2 hr., then cooled, and extracted with two 25-ml. portions of chloroform. The combined extracts, washed with two 20-ml. portions of water and dried with magnesium sulfate, were spin evaporated *in vacuo*. Recrystallization from ethyl acetate–petroleum ether (b.p. 30–60°) gave 310 mg. (90%) of product, m.p. 143–144°, that was identical with an authentic sample.[3,5]

B.—Treatment of 500 mg. of VI as in method A gave 350 mg. (75%) of recrystallized product, m.p. 143–144°, identical with an authentic sample.[3,5]

C.—Treatment of 230 mg. of VIII (prepared from VI) as in method A gave 180 mg. (91%) of recrystallized product, m.p. 143–144°, identical with an authentic sample.[3,5] Similarly VIII, prepared *via* VII gave 68% of recrystallized product, m.p. 143–144°.

Methyl 3-Amino-*N*-benzylidene-4,6-*O*-benzylidene-3-deoxy-α,D-altropyranoside (XI).—A mixture of 1.5 g. of X,[18] 10 ml. of absolute ethanol and 0.75 g. of benzaldehyde was refluxed for 30 min. After being cooled overnight at 0–3°, the mixture was filtered and the white prisms were washed with ethanol to yield 1.7 g. (87%), m.p. 188–189°; $[\alpha]D$ + 129 ± 1° (1.1%); λ_{max} 2.92 (OH), 6.10 (C=N), 6.35 (C=C), and 13.2, 14.2, 14.4 μ (C_6H_5—).

Anal. Calcd. for $C_{21}H_{23}NO_5$: C, 68.4; H, 6.27; N, 3.80. Found: C 68.5; H, 6.18; N, 3.92.

When this anil was refluxed in 50% ethanol for 2 hr., 89% of X was regenerated.

Methyl 3-Amino-*N*-benzylidene-4,6-*O*-benzylidene-3-deoxy-2-*O*-mesyl-α,D-altropyranoside (XII).—To a stirred solution of 1.7 g. of XI in 8 ml. of pyridine cooled in an ice bath was added dropwise 0.4 ml. of methanesulfonyl chloride over a period of 15 min., the temperature being maintained at 0–10°. After standing at 0–3° for about 18 hr. in a stoppered flask, the mixture was diluted with 40 ml. of chloroform and poured onto 50 g. of ice. The separated aqueous layer was extracted with two more 30-ml. portions of chloroform. The combined chloroform solutions, washed with two 40-ml. portions of water and dried with magnesium sulfate, were spin evaporated *in vacuo*. Traces of pyri-

(11) Melting points were taken in capillary tubes in a Mel-Temp block and those below 230° were corrected. Infrared spectra were determined in Nujol mull (unless otherwise indicated) with a Perkin-Elmer 137B recording spectrophotometer. Optical rotations were run in a 1-dm. microtube in *N,N*-dimethylformamide. Petroleum ether was a fraction boiling at 30–60°.

dine in the residue were removed by spin evaporation *in vacuo* with toluene (two 15-ml. portions) to yield 1.7 g. (97%) of a gum that could not be crystallized; λ_{max}^{film} 6.11 (C=N), 6.35 (C=C), 7.50, 8.53 (sulfonate), 13.25, 14.35 (C_6H_5—), no OH or NH absorption near 3 μ.

This compound was characterized as follows. A mixture of 2.0 g. of XII and 30 ml. of 0.2 *N* aqueous sodium hydroxide was refluxed for 2 hr., during which time the gum gradually changed to a solid. The cooled mixture was extracted with two 30-ml. portions of chloroform. The combined extracts, washed with two 30-ml. portions of water and dried with magnesium sulfate, were spin evaporated *in vacuo*. Crystallization of the residue from ethyl acetate gave 500 mg. (32%) of the benzylidenebisaziridine (XIII), m.p. 211–212°; λ_{max} 13.38, 14.43 (C_6H_5—), no NH or OH near 3, and no C=O or C=N near 6 μ.

Anal. Calcd. for $C_{35}H_{38}N_2O_8$: C, 68.4; H, 6.24; N, 4.57; S, 0.0. Found: C, 68.3; H, 5.89; N, 4.63; S, 0.0.

Addition of petroleum ether to mother liquor gave 240 mg. of the aziridine (IV), m.p. 143–144°, that was identical with an authentic sample.[3,5]

Methyl 4,6-*O*-Benzylidene-2-*O*-carbophenoxy-3-carbophenoxyamino-3-deoxy-α,D-altropyranoside (XIV).—To a stirred mixture of 1.00 g. of X[8] and 10 ml. of dichloromethane cooled in an ice bath was added in one portion a mixture of 0.55 g. of phenyl chloroformate, 10 ml. of dichloromethane, and 5 ml. of pyridine precooled to 0°. After being stirred in an ice bath for 1 hr., the mixture was diluted with 25 ml. of ice–water. The separated aqueous layer was extracted with additional dichloromethane (two 25-ml. portions). The combined dichloromethane extracts, washed with two 20-ml. portions of water and dried with magnesium sulfate, were spin evaporated *in vacuo*. Crystallization from ethanol gave 390 mg. (21%) of white crystals, m.p. 140–141°; $[\alpha]_D$ + 37 ± 1° (1.44%); λ_{max} 2.90 (NH), 5.72 (broad, C=O of ester and amide), 6.30 (amide II), 8.10, 8.40 (ester C—O—C), and 13.3, 14.3 μ (C_6H_5—).

Anal. Calcd. for $C_{28}H_{27}NO_9$: C, 64.5; H, 5.22; N, 2.69. Found: C, 64.5; H, 4.93; N, 2.72.

The mother liquor upon evaporation gave crude XV, as shown by its infrared spectrum.

Methyl 4,6-*O*-Benzylidene-3-carbophenoxyamino-3-deoxy-α,D-altropyranoside (XV).—A mixture of 3.0 g. of X[8] and 6.75 g. of diphenyl carbonate was heated on a steam bath for 3 hr. Phenol and excess diphenyl carbonate were removed by extraction with three 50-ml. portions of hot petroleum ether (b.p. 30–60°) to yield 4.1 g. (96%) of a colorless oil which could not be crystallized; λ_{max}^{film} 2.93 (OH, NH), 5.8 (broad C=O), 6.32 (amide II), 8.33 (ester C—O—C), and 13.3, 14.5 μ (C_6H_5—).

This oil was characterized as follows. To a solution of 500 mg. of XV in 10 ml. of ethanol was added 5 ml. of concentrated ammonia water. After being heated on a steam bath for 1 hr., the solution was cooled to give 265 mg. (65%) of IV, m.p. 230–231°, that was identical with an authentic sample[2]; no attempt was made to obtain a second crop.

Methyl 4,6-*O*-Benzylidene-3-carbophenoxyamino-3-deoxy-2-*O*-mesyl-α,D-altropyranoside (XVI).—To a magnetically stirred solution of 4.1 g. of XV in 25 ml. of reagent pyridine cooled in an ice bath was added dropwise 1.6 ml. of methanesulfonyl chloride at such a rate that the temperature was 0–5° (about 15 min.). After standing overnight at 0–3° in a stoppered flask, the mixture was diluted with 100 ml. of iced water and extracted with three 25-ml. portions of chloroform. The combined extracts, washed with two 30-ml. portions of water and dried with magnesium sulfate, were spin evaporated *in vacuo;* the last traces of pyridine were removed by spin evaporation *in vacuo* of toluene (two 20-ml. portions) to yield 4.5 g. (92%) of an oil that could not be crystallized; λ_{max}^{film} 2.92 (NH), 5.78 (C=O), 6.31 (amide II), 7.39, 8.52 (sulfonate), and 13.3, 14.5 μ (C_6H_5—).

Methyl 4,6-*O*-Benzylidene-3-deoxy-2-*O*-mesyl-3-ureido-α,D-altropyranoside (VII). A.—To a solution of 4.5 g. of XVI in 20 ml. of ethanol was added 30 ml. of concentrated ammonia water. After standing about 18 hr. at ambient temperature, the mixture was spin evaporated *in vacuo*. The residue was dissolved in 50 ml. of chloroform, washed with two 25-ml. portions of water, dried with magnesium sulfate, and spin evaporated *in vacuo* to yield 3.5 g. (92%) of a colorless glass containing some phenol that could not be crystallized but was estimated from the combustion values to be at least 80% pure; λ_{max}^{film} 2.87, 2.93, 3.10 (NH), 5.91 (broad C=O), 6.27, 6.50 (broad amide II), 7.35, 8.50 (sulfonate), and 13.2, 14.3 μ (C_6H_5—).

Anal. Calcd. for $C_{16}H_{22}N_2O_8S$: C, 47.8; H, 5.52; N, 6.97; S, 7.96. Found: C, 50.6; H, 5.51; N, 5.59; S, 7.81.

The conversion of VII to crystalline VIII can be considered as additional characterization of VII.

B.—To a solution of 2.0 g. of XII in 10 ml. of ethanol was added a solution of 0.71 g. of potassium cyanate in 10 ml. of water followed by 0.53 ml. of glacial acetic acid. The mixture was warmed on a steam bath for 15 min., then spin evaporated *in vacuo* to about 10 ml. The mixture was then processed by chloroform extraction as in method A. Benzaldehyde was removed by spin evaporation of water (two 20-ml. portions) *in vacuo* leaving 1.4 g. (78%) of a glass that had an infrared spectrum essentially identical with preparation A. From the combustion values, this material was estimated to be at least 85% pure.

Anal. Found: C, 47.2; H, 5.37; N, 7.28; S, 6.87.

Methyl 3-Amino-4,6-*O*-benzylidene-3-deoxy-α,D-allopyranoside (XIX).—A mixture of 1.00 g. of VII, 0.80 g. of anhydrous sodium acetate, and 15 ml. of 2-methoxyethanol was refluxed for 20 hr., during which time some sodium methanesulfonate separated. The reaction mixture was diluted with 20 ml. of water and extracted with three 20-ml. portions of chloroform. The combined extracts, washed with two 20-ml. portions of water and dried with magnesium sulfate, were spin evaporated to dryness *in vacuo* to yield 0.63 g. (82%) of a glassy mixture of XVII and XVIII; λ_{max}^{film} 2.95 (NH), 5.73, 5.90 (C=O), 6.05 (C=N), 6.30 (amide II), 13.2, 14.4 (C_6H_5—), and no sulfonate absorption near 7.4 or 8.6 μ.

A solution of 600 mg. of this mixture in 5 ml. of ethanol and 0.2 *N* aqueous sodium hydroxide was refluxed for 4 hr., then cooled, and extracted with two 25-ml. portions of chloroform. The combined extracts, washed with two 20-ml. portions of water and dried with magnesium sulfate, were spin evaporated *in vacuo* leaving 430 mg. (78%) of glassy residue. When 200 mg. of this material was allowed to stand in ethanol, white crystals of XIX separated slowly with poor recovery to yield 80 mg. (31%), m.p. 231–233°; $[\alpha]^{22}_D$ + 133 ± 1.5° (0.44%); λ_{max} 2.85, 2.95 (NH, OH), 6.05, 6.55 (NH_2), and 13.3, 14.2 μ (C_6H_5—).

Anal. Calcd. for $C_{14}H_{19}NO_5$: C, 59.8; H, 6.82; N, 4.97. Found: C, 59.7; H, 6.97; N, 5.06.

This compound is clearly isomeric to X which has been reported[12] to have m.p. 188° and $[\alpha]_D$ +90° (chloroform). Acetylation of XIX in 50% aqueous acetic acid with acetic anhydride gave XXI, while acetic anhydride in pyridine[8] gave XX as a glass; both had infrared spectra identical with respective authentic samples.[8]

Methyl 3-Acetamido-4,6-*O*-benzylidene-3-deoxy-α,D-altropyranoside.—Treatment of X with acetic anhydride in 50% acetic acid gave the *N*-acetyl derivative as a glass, as previously described.[8] This compound has now been crystallized from ethyl acetate–petroleum ether (b.p. 30–60°) as white crystals, m.p. 136–137°; $[\alpha]_D$ + 102 ± 1° (1.1%); λ_{max} 2.92 (NH, OH), 6.03 (amide C=O), 6.62 (amide II), and 13.0, 14.2 μ (C_6H_5—).

Anal. Calcd. for $C_{16}H_{21}NO_6$: C, 59.5; H, 6.54; N, 4.34. Found: C, 59.4; H, 6.55; N, 4.52.

A mixture with the alloside (XXI) melted at 90–95°.

Methyl 3-Acetamido-4,6-*O*-benzylidene-3-deoxy-α,D-allopyranoside (XXI). A.—By treatment of methyl 3-acetamido-4,6-*O*-benzylidene-3-deoxy-2-*O*-mesyl-α,D-altropyranoside[8] with sodium acetate in boiling ethanol 700 mg. (79%) of glassy XX was obtained by the previously described method.[8] This compound has now been crystallized from ethyl acetate–petroleum ether (b.p. 30–60°) as white crystals to yield 350 mg. (40%), m.p. 120–121°; $[\alpha]_D$ + 107 ± 1°; λ_{max} 2.97, 3.13 (NH, OH), 6.08 (amide C=O), 6.60 (amide II), and 13.3, 14.4 μ (C_6H_5—).

Anal. Calcd. for $C_{16}H_{21}NO_6$: C, 59.5; H, 6.54; N, 4.34. Found: C, 59.4; H, 6.41; N, 4.46.

B.—A solution of 1.00 g. of VII in 10 ml. of reagent pyridine was refluxed for 3 hr., diluted with 50 ml. of water, and extracted with three 20-ml. portions of chloroform. The combined extracts, washed with two 20-ml. portions of water and dried with magnesium sulfate, were spin evaporated *in vacuo*. Traces of residual pyridine were removed by spin evaporation of toluene (two 10-ml. portions) *in vacuo* to yield 0.65 g. (84%) of XVII as a glass; λ_{max} 2.88, 2.95 (NH), 6.00, 6.32 (NH, C=N), 13.25, 14.45 (C_6H_5—), and no sulfonate near 7.4 or 8.5 μ.

When XVII was stirred with 0.2 *N* aqueous sodium hydroxide at room temperature, the infrared spectrum shifted to that of the

(12) W. H. Myers and G. J. Robertson, *J. Am. Chem. Soc.*, **65**, 8 (1943).

cyclic urethane (XVIII). When XVII was refluxed with 0.2 *N* aqueous sodium hydroxide as described for the conversion of XVIII to XIX, XIX was obtained as a glass in 72% yield that had an infrared spectrum identical with glassy XIX prepared from XVIII. Instead of crystallization at this point, XIX was acetylated in 50% acetic acid with acetic anhydride to give, in poor yield, XX as crystals identical with those of preparation A.

Methyl 3-Benzylamino-4,6-*O*-benzylidene-3-deoxy-α,D-altropyranoside (XXIII). A.—To a warm solution of 5.0 g. of X in 50 ml. of ethanol was added 1.0 ml. of benzyl bromide in 5 ml. of ethanol. The solution was heated to boiling, then allowed to stand at ambient temperature for about 20 hr. After removal of the solvent by spin evaporation *in vacuo*, the residue was partitioned with 50 ml. of chloroform and 30 ml. of water. The separated aqueous layer was neutralized immediately for recovery of the excess X. The chloroform solution, washed further with water (three 30-ml. portions) and dried with magnesium sulfate, was evaporated *in vacuo* to yield 3.9 g. (91% based on benzyl bromide) of an oil that could not be crystallized; λ_{max}^{film} 2.9–3.0 (broad, NH, OH), 6.33 (C=C), 13.3, 13.6, 14.4 μ (C_6H_5—).

B.—To a solution of 1.00 g. of XI in 10 ml. of ethanol was added a solution of 0.50 g. of sodium borohydride in 2 ml. of water. After standing for about 18 hr. at ambient temperature, the solution was processed as in method A to yield 0.88 g. (82%) of an oil that had an infrared spectrum identical with preparation A, including no C=N absorption near 6.1 μ.

Methyl 3-Benzylamino-4,6-*O*-benzylidene-*N*-cyano-3-deoxy-D-altropyranoside (XXIII).—To a solution of 2.0 g. of XXII in 20 ml. of absolute ethanol was added a solution of 0.30 g. of cyanogen bromide in 5 ml. of absolute ethanol. After 2 hr. at 50–60°, the solution was allowed to stand overnight. Solvent was removed *in vacuo* and the residue was dissolved in 25 ml. of chloroform and 25 ml. of water. The separated chloroform layer was washed once more with water. The combined aqueous extracts were made strongly alkaline with 2 *N* sodium hydroxide and the recovered XXII (0.80 g.) was isolated by chloroform extraction.

The chloroform solution of XXIII, dried with magnesium sulfate, was evaporated *in vacuo* to yield 1.0 g. (94% based on cyanogen bromide or 79% based on XXII not recovered) of a gum that could not be crystallized; λ_{max}^{film} 2.95 (OH), 4.54 (C≡N), and 13.3, 13.8, 14.4 μ (C_6H_5—).

Anal. Calcd. for $C_{22}H_{24}N_2O_3$: C, 66.7; H, 6.11; N, 7.07. Found: C, 66.7; H, 6.11; N, 6.92.

Methyl 3-Benzylamino-4,6-*O*-benzylidene-*N*-cyano-3-deoxy-2-*O*-mesyl-α,D-altropyranoside (XXVI).—Mesylation of 1.1 g. of XXIII in 10 ml. of reagent pyridine with 0.30 ml. of methanesulfonyl chloride as described for the preparation of XVI gave 1.20 g. (91%) of product as a glass; λ_{max}^{film} 4.53 (C≡N), 7.40, 8.55 (sulfonate), 13.3, 13.8, 14.4 μ (C_6H_5—), and no OH or NH near 3 μ.

Anal. Calcd. for $C_{23}H_{26}N_2O_7S$: C, 58.2; H, 5.53; N, 5.91; S, 6.74. Found: C, 58.4; H, 5.54; N, 5.74; S, 6.43.

4′,6′-*O*-Benzylidene-1-benzyl-1′-*O*-methyl-2-oxo-α,D-allopyrano[2′,3′:4,5]imidazolidine (XXVII).—To 2.0 g. of XXVI was added 30 ml. of methanol previously saturated with ammonia. When solution was complete, it was transferred to a steel bomb and heated at 130–150° for 7 days. On being cooled and opened, the bomb contained crystals suspended in the solution and some fastened to the side; an odor of methylamine was noticeable. The product was collected on a filter and washed with methanol to yield 0.70 g. (42 or 70% based on XXVI not recovered), m.p. 250–258°, suitable for further transformation. Recrystallization from ethanol gave white needles, m.p. 258–260°; $[\alpha]^{24}D$ + 72 ± 1° (0.83%); λ_{max} 3.05 (NH), 5.91, 6.05 (C=O, NH), 6.78, 13.1, 13.3, 14.4 (C_6H_5), and no C≡N near 4.5 or sulfonate near 7.5 or 8.5 μ.

Anal. Calcd. for $C_{22}H_{24}N_2O_5$: C, 66.6; H, 6.11; N, 7.08. Found: C, 66.5; H, 6.21; N, 7.06.

The methanolic ammonia mother liquor was concentrated to give an additional 50 mg. (3%) of product. The filtrate was further processed for recovery of starting material by evaporation *in vacuo*. The residue was extracted with chloroform. The combined extracts, washed with water, dried with magnesium sulfate, and clarified with decolorizing carbon, gave on evaporation 0.80 g. (40%) of starting material (XXVI) that was recycled to XXVII.

Methyl 2-Acetamido-3-benzylamino-4,6-*O*-benzylidene-2,3-dideoxy-α,D-allopyranoside (XXX).—A solution of 10 g. of potassium hydroxide in 10 ml. of water and 10 ml. of ethanol was added to 350 mg. of XXVII. The mixture was heated in a steel bomb at 150–170° for 7 days. The cooled solution was transferred from the bomb with the aid of water. The solution containing XXIX was spin evaporated *in vacuo* until most of the ethanol was removed, then neutralized to about pH 9 with glacial acetic acid. To the stirred solution at 25° was added 1 ml. of acetic anhydride. After being stirred for 1 hr. at ambient temperature, the mixture was extracted with three 25-ml. portions of chloroform. Washed with three 20-ml. portions of water and dried with magnesium sulfate, the combined extracts were spin evaporated *in vacuo* to a crystalline residue, m.p. 142–143°, yield 300 mg. (82%). Recrystallization from a small volume of ethanol gave white needles, m.p. 142–143°; $[\alpha]^{24}D$ + 27 ± 1° (0.09%); λ_{max} 3.00 (NH), 6.13 (amide C=O), 6.57 (amide II), and 6.75, 13.3, 13.6, 14.4 μ (C_6H_5—).

Anal. Calcd. for $C_{23}H_{28}N_2O_5$: C, 67.9; H, 6.85; N, 6.80. Found: C, 67.9; H, 7.00; N, 6.61.

Acknowledgment.—We wish to thank the Cancer Chemotherapy National Service Center, National Cancer Institute, and Starks Associates, Inc., for large scale preparation of certain intermediates, mediated by Contract No. SA-43-ph-4346.

Synthetic Nucleosides. LXI.[1,2] Studies on the Synthesis of *cis*-2,3-Diamino Sugars. IV. The Guanidine Neighboring Group

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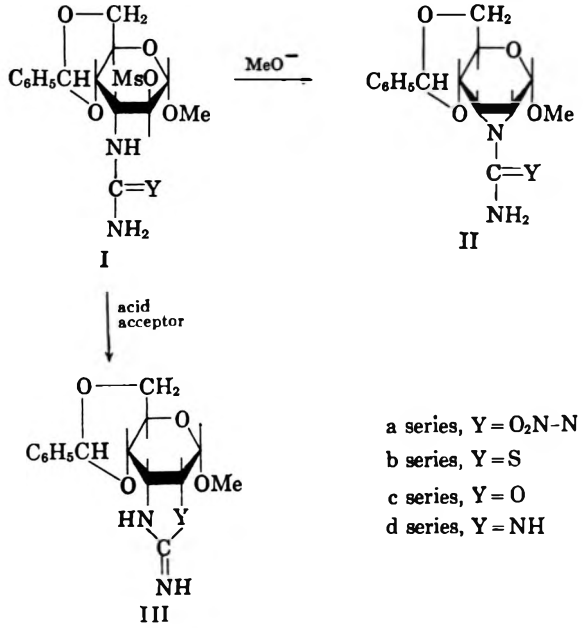
September 25, 1963

The cyanamido group of methyl 4,6-*O*-benzylidene-3-cyanamido-3-deoxy-2-*O*-mesyl-α,D-altropyranoside (IV) was a sufficiently strong acid to be converted to an anion with ammonia which rapidly cyclized to the cyanoimino alloside (VI) rather than adding ammonia to form a guanidino derivative (V). However, aniline was not sufficiently basic to cause anionic ring closure; instead aniline slowly added to the cyanamido group of IV to give a phenylguanidine derivative that cyclized to a 1-phenyl-2-imino imidazoline (XXIII) faster than addition occurred. Vigorous basic hydrolysis of XXIII afforded methyl 3-amino-2-anilino-4,6-*O*-benzylidene-2,3-dideoxy-α,D-allopyranoside (XXV), a derivative of a *cis*-2,3-diamino sugar. Similarly, reaction of IV with *N*-methylaniline gave methyl 3-amino-4,6-*O*-benzylidene-2,3-dideoxy-2-(*N*-methylanilino)-α,D-allopyranoside (XXIX).

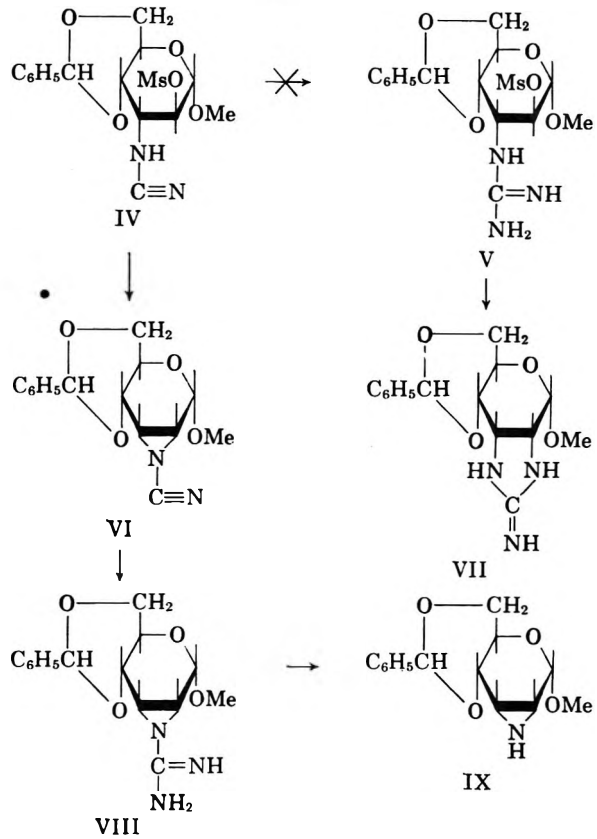
The rationale for synthesis of nucleosides derived from 2,3-diamino-2,3-dideoxy-D-ribofuranose has been presented in a previous paper.[3] The availability of methyl 3-amino-4,6-*O*-benzylidene-3-deoxy-α,D-altropyranoside (X)[4,5] makes this compound useful for study of neighboring group reactions that have the potential of introducing a second amino in the 2-position *cis* to the 3-amino group. Study of "complex" neighboring groups[6] such as nitroguanidino (Ia),[3] thioureido (Ib),[7] and ureido (Ic)[2] has been reported in the accompanying papers. In all three cases, when I was converted to an anion with sodium methoxide,

SCHEME I



ring closure to an aziridine derivative (II) took place (Scheme I). In the presence of an acid acceptor such as sodium acetate or pyridine ring closure to IIIb and IIIc took place, but Ia failed to cyclize under these conditions; thus oxygen or sulfur could be introduced,

SCHEME II



but not a usable nitrogen function. Blocking of the secondary nitrogen of Ic was one solution to the problem.[2] Another possible solution to this enigma would be the use of a guanidine neighboring group (Id) so that ring closure under acid acceptor (nonanionic) conditions which usually forms a five-membered ring (IIId) could only proceed by nitrogen attack; studies on the preparation of Id, derivatives, and their mode of ring closure is the subject of this paper.

Methyl 4,6-*O*-benzylidene-3-cyanamido-3-deoxy-2-*O*-mesyl-α,D-altropyranoside (IV)[7] appeared to be an attractive starting material for preparation of V and VII. Attempts to add ammonia to the C≡N of IV with ammonium chloride or ammonium mesylate in alcohol led to the partial loss of the benzylidene group and no detectable addition to the triple bond took place; if the reaction was run in dry pyridine to avoid loss of the benzylidene group, decomposition occurred.

(1) This work was generously supported by Grant CY-5845 from the National Cancer Institute, U. S. Public Health Service.

(2) For the previous paper of this series, see B. R. Baker and T. Neilson, *J. Org. Chem.*, **29**, 1057 (1964).

(3) B. R. Baker and T. Neilson, *ibid.*, **29**, 1047 (1964), paper LVIII of this series.

(4) B. R. Baker and R. E. Schaub, *ibid.*, **19**, 646 (1954).

(5) W. H. Myers and G. J. Robertson, *J. Am. Chem. Soc.*, **65**, 8 (1943).

(6) S. Winstein and R. Boschan, *ibid.*, **72**, 4669 (1950).

(7) See ref. 2, LX paper of this series.

The use of the relatively neutral ammonium acetate in alcohol gave the same results as ammonium hydroxide described subsequently.

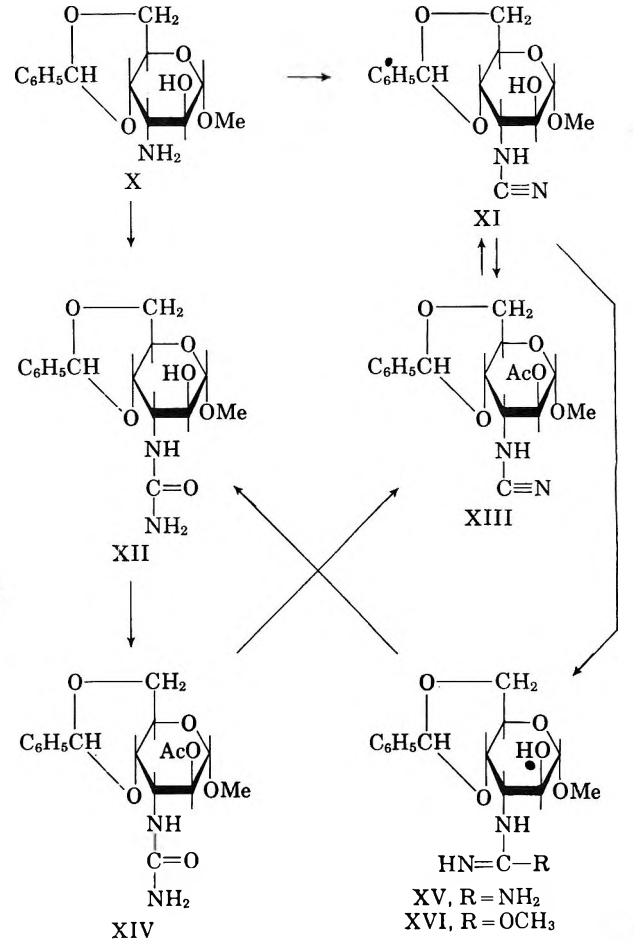
When IV was allowed to react with ammonia in dilute alcohol at ambient temperature after 5-min. warming at 50°, a crystalline amidine base separated in 19% yield (presumed to be VII) which was insoluble in all solvents except hot dimethylformamide; when the filtrate was processed through water and chloroform, an oil was obtained which was soluble in ethyl acetate and could be crystallized in 58% yield (m.p. 201°) by addition of petroleum ether (b.p. 30–60°) and which showed combustion values in agreement with the amidine containing a covalent mesylate (V). The solubility properties were certainly compatible with a covalent mesylate. However, the C=N absorption of V at 6.00 μ was more characteristic of C=NH$^+$, than C=N which usually appears at 6.1–6.3 μ; in addition the covalent sulfonate band was not near 8.55 μ as usual, but was at 8.18 μ which is more typical of an ionic sulfonate. That the compound was actually ionic rather than a covalent compound was shown by treatment with cold methanolic sodium hydroxide; the free base obtained was identical with the free base obtained directly from the reaction mixture in 19% yield. Basic hydrolysis of the presumed imidazoline (VII) did not afford a 2,3-diamino allose derivative, but instead formed the imino alloside (IX),[3] showing the amidine and its methanesulfonate salt did not have structure VII, but structure VIII.

The mode of formation of VIII from IV (Scheme II) was shown to be as follows. Treatment of a suspension of the cyanamido mesylate (IV) in ethanol with aqueous ammonia at 25° gave a yellow color; the cyanamido mesylate (IV) rapidly dissolved, the color bleached, and another compound rapidly separated. This compound proved to be the cyano imine (VI), identical with a sample prepared from IV with methanolic sodium methoxide.[7] When VI was warmed briefly with ammonia in dilute alcohol, then allowed to stand, a 69% yield of the crystalline amidinyl imine (VIII) separated from solution; this compound was identical with that prepared directly from IV with ammonia in dilute alcohol that was earlier presumed to be VII. Apparently the cyanamide (IV) is a sufficiently strong acid to be converted to the anion with dilute ammonia, said anion then rapidly ring closing to the cyano imine (VI).

Two approaches were then envisioned to overcome the difficulty of the rapid anionic ring closure of IV to VI. The first was to put the guanidine residue in place before introduction of the mesylate into V, and the second was to add an amine to the nitrile of IV that was a sufficiently weak base not to convert IV to an anion.

The ureido altroside (XII), prepared earlier[7] from the amino altroside (X) and potassium cyanate, was acetylated with acetic anhydride in pyridine to give XIV as a glass. When XIV was dehydrated with mesyl chloride in pyridine, the crystalline cyanamido acetate (XIII) was obtained in 60% yield. Short treatment with warm aqueous ammonia gave the desired XI in 72% yield (Scheme III). A shorter route also was formed for XI which involved treating the amino altroside (X) with one-half equivalent of

SCHEME III



cyanogen bromide, the excess X being used as an acid acceptor and being recovered.[8]

When XI reacted with ammonia in dilute methanol at 100° under pressure for 18 hr., the resultant oil had lost the C≡N bond near 4.5 μ and now showed C=N absorption at 6.12 μ. However, the low nitrogen analysis indicated that ammonia did not add to the triple bond to give XV, but, most likely, methanol had added to give the *O*-methylurea (XVI); when the crude oil was allowed to stand several days in water, crystals of the urea derivative (XII) gradually separated.

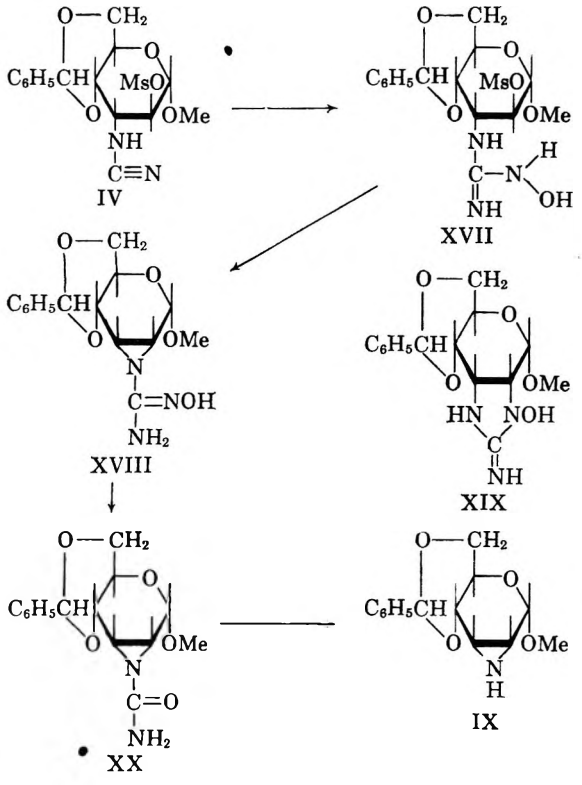
It is notable that the cyano imine (VI) adds ammonia very rapidly to give the amidine (VIII), whereas the cyanamido altrose (XI) was recovered unchanged under the same conditions. Apparently the imine activates the C≡N in the same way that the C=O of an acylated aziridine is activated.[9] Although it may have been possible to form XV in an aprotic solvent, these studies were discontinued when concurrent studies to be described on the addition of aniline to the cyanamide (IV) were successful.

Attention was then turned to the addition of amines to the cyanamide (IV) that were sufficiently weak not to convert IV to an anion in order to avoid cyclization to the cyano imine (VI). Hydroxylamine and

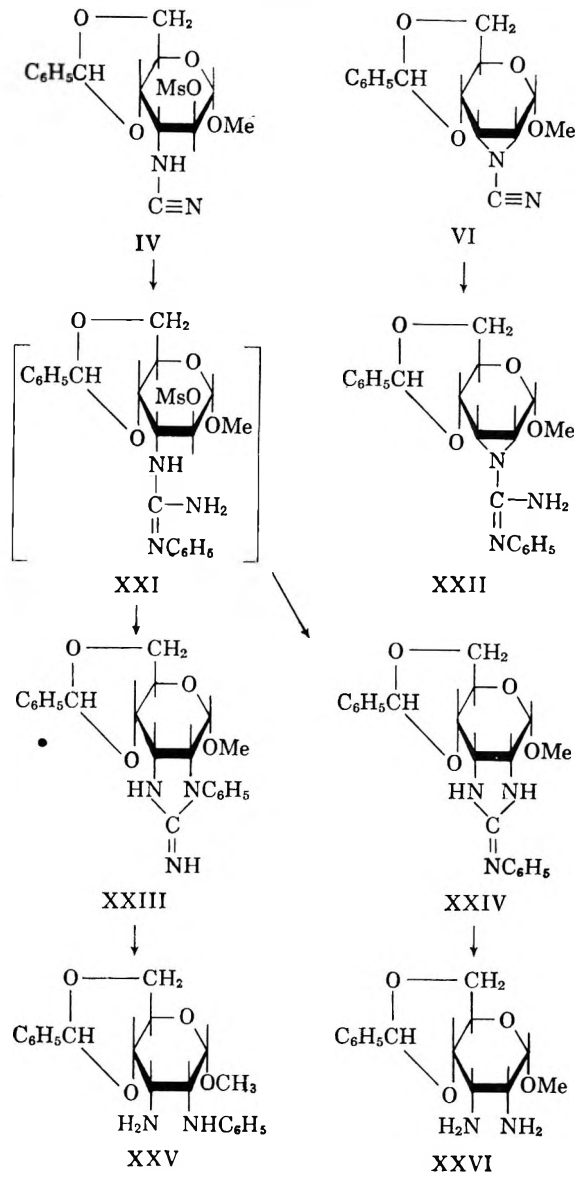
(8) The amino altroside (X) failed to condense with cyanamide in dilute alcohol to give the corresponding guanidine altroside (XV).

(9) The higher reactivity of the carbonyl of an acylaziridine compared to an ordinary *t*-amide has been noted previously: H. C. Brown and A. Tsukamoto, *J. Am. Chem. Soc.*, **83**, 4549 (1961); and H. W. Heine, M. A. Fetter, and E. M. Nicholson, *ibid.*, **81**, 2202 (1959).

SCHEME IV



SCHEME V



aniline were investigated. When IV reacted with hydroxylamine hydrochloride in boiling pyridine[10] for 10 min., the hydroxyguanidine mesylate (XVII) was obtained as a glass in 92% yield with no C≡N absorption; that cyclization had not taken place was shown by covalent sulfonate absorption at 8.55 μ and a 3:1 ratio of nitrogen to sulfur. Attempts to ring close XVII with boiling pyridine to XIX or the isomeric 2-hydroxylamino imidazoline led to tars. Cyclization with methanolic sodium methoxide led to imine derivatives; this could now be anticipated since the hydroxyguanidine group can form an anion. A mixture of XVIII and XX was obtained from which 41% of crystalline XX[2] could be isolated; the presence of some other product in the mother liquor, presumably the base sensitive XVIII, was shown by basic hydrolysis to give the imine IX in 39% yield (Scheme IV).

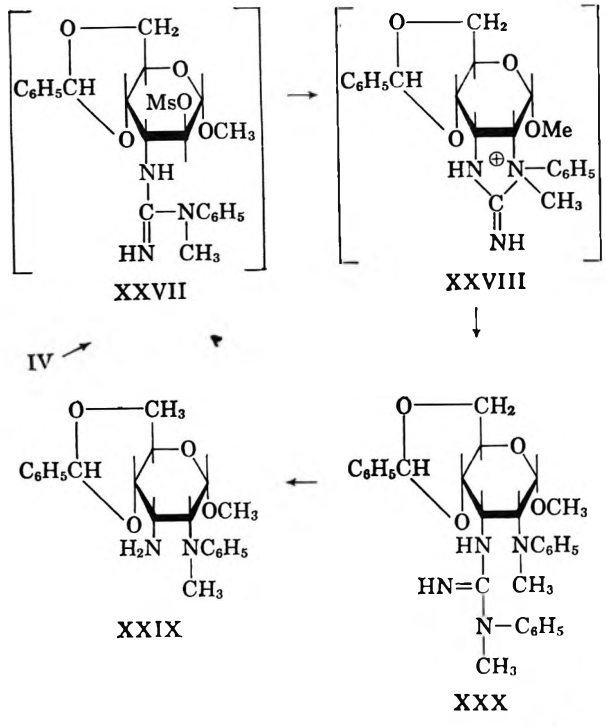
Aniline added slowly to the triple bond of the cyanamido mesylate (IV); after 1 day in boiling alcohol IV was still present showing that the aniline was a sufficiently weak base not to cyclize IV to the imine VI. After 2–5 days in boiling alcohol, depending on the ratio of aniline to IV, the C≡N absorption near 4.5 μ had disappeared; when processed by washing a chloroform solution with dilute base, the resultant product contained no sulfonate bands. Thus, ring closure of the presumed amidine (XXI) with elimination of methanesulfonate was more rapid from the addition of aniline to IV. Although this analytically pure amidine could not be crystallized, its infrared spectrum clearly showed it to be different from the isomeric amidino imine (XXII), formed by addition of aniline to the cyano imine (VI). This aniline addition product of IV could be either the imino imidazolidine (XXIII) or the anil (XXIV) or a mixture of the two (Scheme V).

Both XXII and XXIII (or XXIV) were stable to boiling 2 *N* aqueous sodium hydroxide. However, that ring closure to XXIII had occurred predominantly could be shown by hydrolysis to the *N*-phenyl diaminoalloside (XXV) in 72% yield with 30% potassium hydroxide in 50% ethanol at 140° for 4 days. The relatively high yield of 52% for three steps from IV (average yield, 80%) indicated that little, if any, cyclization to the isomeric imidazoline (XXIV) had occurred.

The addition of *N*-methylaniline to the cyanamide (IV) was then investigated, since cyclization of the adduct (XXVII) might be expected to occur by NH attack rather than form the quaternary salt (XXVIII). Surprisingly, basic hydrolysis of the ring closed product gave the crystalline *N*-methylanilino sugar derivative (XXIX) in 34% over-all yield from IV rather than the diamine XXVI. Presumably the intermediate adduct (XXVII) cyclized to the quaternary salt (XXVIII), then XXVIII further reacted with *N*-methylaniline to give the methanesulfonate salt of XXX as an oil (Scheme VI). The only evidence that

(10) J. U. Nef, *Ann.*, **280**, 320 (1894); N. P. Buu-Hoï and J. Lecocq, *Bull. soc. chim. France*, 139 (1946).

SCHEME VI



XXX had formed was based on the loss of a C=NH$^+$ bond in the infrared at 6.0 μ when XXX was converted to the free base; no C=O absorbtion appeared in the free base, thus indicating that *N*-methylaniline had split the quaternerized imidazolidine to XXX. This reaction sequence was not investigated in further detail.

Although the phenyl group was not removed to provide XXVI, further work will be necessary to see if a labile (to basic hydrolysis or oxidation) substituted phenyl group can be employed successfully in such a transformation.

Experimental[11]

Methyl 4,6-*O*-Benzylidene-*N*-cyano-2,3-dideoxy-2,3-imino-α,D-allopyranoside (VI).—To a solution of 1.00 g. of IV in 20 ml. of ethanol was added 10 ml. of concentrated ammonia water. The mixture became momentarily yellow; then the product separated to yield 0.46 g. (61%), m.p. 183–184°. Recrystallization from ethanol gave white needles identical with an authentic sample of VI.[2]

From the filtrate, after standing overnight, could be isolated the amidine (VIII)-methanesulfonate, identical with an authentic sample described subsequently.

Methyl *N*-Amidino-4,6-*O*-benzylidene-2,3-dideoxy-2,3-imino-α,D-allopyranoside (VIII). A.—To a warm solution of 150 mg. of VI in 5 ml. of ethanol was added 5 ml. of concentrated ammonia water. After being refluxed for 10 min., the solution was allowed to stand overnight at ambient temperature. The amidine base (VIII) was collected on a filter and washed with aqueous alcohol to yield 110 mg. (69%), m.p. 242–243°. Recrystallization from hot *N,N*-dimethylformamide by addition of water gave white crystals of unchanged melting point; $[\alpha]^{22}D$ + 97 ± 3° (0.29%); λ_{max} 2.95, 3.15 (NH), 6.20 (C=N), 6.40 (NH), 13.41, 14.45 (C_6H_5—), and no C≡N near 4.5 μ.

Anal. Calcd. for $C_{15}H_{19}N_3O_4$: C, 59.1; H, 6.27; N, 13.8. Found: C, 59.1; H, 6.07; N, 13.6.

B.—To a warm solution of 500 mg. of IV in 10 ml. of ethanol was added 5 ml. of concentrated ammonia water. After being warmed to about 50° for 5 min., the solution was allowed to stand overnight at ambient temperature. The white crystals that had separated were collected by filtration and washed with dilute alcohol to yield 85 mg. (19%) of amidine free base identical with preparation A.

The combined filtrate and washings were spin evaporated *in vacuo* and the residue extracted with two 20-ml. portions of chloroform. The combined extracts, washed with two 20-ml. portions of water and dried with magnesium sulfate, were spin evaporated *in vacuo*. The oily residue was crystallized from ethyl acetate–petroleum ether (b.p. 30–60°) to yield 300 mg. (58%) of VIII methanesulfonate salt, m.p. 199–201°; λ_{max} 2.90, 3.17, 3.25 (NH), 6.00 (C=NH$^+$), 6.55 (NH_2), 7.31, 8.18 (ionic sulfonate), 13.3, 14.15 (C_6H_5—), and no C≡N near 4.5 μ.

Anal. Calcd. for $C_{16}H_{23}N_2O_7S$: C, 47.9; H, 5.79; N, 10.5; S, 8.00. Found: C, 47.9; H, 5.72; N, 10.4; S, 7.98.

C.—To a solution of 200 mg. of the methanesulfonate salt of VIII, prepared by method B, in 5 ml. of 95% ethanol was added 1 ml. of 1 *N* methanolic sodium methoxide. Immediate precipitation took place. The amidine free base (VIII) was collected on a filter and washed with ethanol to yield 130 mg. (85%), m.p. 240–241°; its infrared spectrum was identical with that of preparation A.

D.—A solution of 600 mg. of amidine free base (VIII), prepared by method A, in 2 ml. of concentrated ammonia water containing 200 mg. of methanesulfonic acid was spin evaporated *in vacuo*. Crystallization of the gummy residue from ethyl acetate gave 620 mg. (79%) of the methanesulfonate salt of VIII, m.p. 198–199°, that was identical with preparation B.

Ammonium methanesulfonate in excess ammonia water was used rather than aqueous methanesulfonic acid in order to preserve the acid-sensitive benzylidene group.

Methyl 4,6-*O*-Benzylidene-2,3-dideoxy-2,3-imino-α,D-allopyranoside (IX).—A mixture of 250 mg. of VIII, 3 ml. of 2 *N* aqueous sodium hydroxide, 10 ml. of water, and 10 ml. of 2-methoxyethanol was refluxed for 3 hr., then processed as described earlier for IX[2,3] to yield 150 mg. (70%) of white crystals, m.p. 143–144°, that were identical with an authentic sample of IX.[3]

Methyl 2-*O*-Acetyl-4,6-*O*-benzylidene-3-deoxy-3-ureido-α,D-altropyranoside (XIV).—A mixture of 1.00 g. of XII,[7] 5 ml. of reagent pyridine, and 0.70 ml. of acetic anhydride was stirred in an ice bath until solution was complete; then it was allowed to stand about 18 hr. at 0–3° in a stoppered flask. After dilution with 25 ml. of water, the mixture was extracted with three 20-ml. portions of chloroform. The combined extracts, washed with two 20-ml. portions of water and dried with magnesium sulfate, were spin evaporated *in vacuo* leaving 0.75 g. (66%) of a glass that could not be crystallized; λ_{max}^{film} 2.85, 2.95, 3.11 (NH), 5.77 (ester C=O), 6.05 (amide C=O), 6.60 (amide II), and 13.3, 14.3 μ (C_6H_5—).

Anal. Calcd. for $C_{17}H_{22}N_2O_7$: C, 55.7; H, 6.06; N, 7.65. Found: C, 55.9; H, 6.12; N, 7.42.

Methyl 2-*O*-Acetyl-4,6-*O*-benzylidene-3-cyanamido-3-deoxy-α,D-altropyranoside (XIII). A.—To a stirred solution of 700 mg. (XIV) in 5 ml. of reagent pyridine cooled in an ice bath was added 0.2 ml. of methanesulfonyl chloride. After standing about 18 hr. at 0–3° in a stoppered flask, the mixture was poured into 20 ml. of ice–water and processed as described for XIV. The chloroform residue was spin evaporated with toluene (two 10-ml. portions) to remove the last traces of pyridine. Recrystallization from alcohol gave 400 mg. (60%) of white needles, m.p. 176–177°; $[\alpha]^{22}D$ +65 ± 1° (1.02%); λ_{max} 3.14 (NH), 4.51 (C≡N), 5.80 (ester C=O), 8.23 (ester C—O—C), 13.3, 14.4 (C_6H_5—), and no urea carbonyl near 6 μ.

Anal. Calcd. for $C_{17}H_{20}N_2O_6$: C, 58.6; H, 5.79; N, 8.05. Found: C, 58.5; H, 5.84; N, 7.94.

B.—Acetylation of 300 mg. of XI (prepared from X) in 2 ml. of reagent pyridine with 0.2 ml. of acetic anhydride at room temperature for 18 hr., then work-up, as described for XIV, gave 230 mg. (67%) of recrystallized product, m.p. 176–177°, that was identical with preparation A.

Methyl 4,6-*O*-Benzylidene-3-cyanamido-3-deoxy-α,D-altropyranoside (XI). A.—To a mixture of 5.0 g. of X[4] and 100 ml. of ethanol was added 1.0 g. of cyanogen bromide. The mixture was heated on a steam bath at about 70° for 1 hr., then spin evaporated *in vacuo*. The residue was partitioned between 25 ml. of chloroform and 50 ml. of water. The separated aqueous

(11) Melting points were taken in capillary tubes in a Mel-Temp block; those below 230° are corrected. Infrared spectra were determined in Nujol mull, unless otherwise indicated, with a Perkin-Elmer 137B spectrophotometer. Optical rotations were determined in a 1-dm. microtube in *N,N*-dimethylformamide and concentrations are recorded in %. Petroleum ether was a fraction boiling at 30–60°.

layer was extracted with additional chloroform (two 25-ml. portions). The combined chloroform extracts were washed with two 25-ml. portions of water. The combined aqueous layer and washings were made basic with 2 *N* sodium hydroxide, then spin evaporated *in vacuo* to about 25 ml.; 1.5 g. (30%) of unchanged X separated from the solution.

The chloroform solution, dried with magnesium sulfate, was spin evaporated *in vacuo*. Recrystallization from ethanol gave 2.0 g. (73% based on cyanogen bromide or 52% based on X not recovered) of white needles, m.p. 175–176°; $[\alpha]^{22}D$ + 85 ± 1° (0.62%); λ_{max} 2.89, 3.05 (NH, OH), 4.51 (C≡N), and 13.1, 14.3 μ (C_6H_5—).

Anal. Calcd. for $C_{15}H_{18}N_2O_5$: C, 58.8; H, 5.93; N, 9.15. Found: C, 58.8; H, 6.05; N, 8.95.

B.—A solution of 250 mg. of XIII (prepared from XIV) in 5 ml. of ethanol was diluted with 10 ml. of 3 *N* aqueous ammonia, then warmed at about 60° for 30 min. The cooled solution was extracted with three 20-ml. portions of chloroform. The combined extracts, washed with two 20-ml. portions of water and dried with magnesium sulfate, were spin evaporated *in vacuo* leaving 200 mg. (91%) of a white solid. Recrystallization from alcohol gave 150 mg. (72%) of product, m.p. 175–176°, that was identical with preparation A.

Methyl 4,6-*O*-Benzylidene-3-deoxy-3-(3-hydroxyguanidino)-2-*O*-mesyl-α,D-altropyranoside (XVII).—A solution of 2.0 g. of IV and 0.36 g. of hydroxylamine hydrochloride in 20 ml. of pyridine was refluxed for 10 min., then cooled, diluted with 30 ml. of water, and extracted with three 25-ml. portions of chloroform. The combined extracts, washed with three 20-ml. portions of water and dried with magnesium sulfate, were spin evaporated *in vacuo*. The last traces of pyridine were removed by spin evaporation of two 10-ml. portions of toluene *in vacuo* to yield 2.0 g. (92%) of a glass that was estimated to be about 80% pure by combustion analyses; λ_{max}^{film} 2.85, 2.95, 2.99 (NH, OH), 6.05 (C=N), 6.31 (NH), 6.59 (N—O), 7.41, 8.53 (sulfonate, 13.3, 14.3 (C_6H_5—), and no C≡N near 4.5 μ.

Anal. Calcd. for $C_{16}H_{23}N_3SO_8$: N, 10.07; S, 7.68; N:S, 3.0. Found: N, 8.35; S, 6.46; N:S, 2.9.

When XVII was refluxed in pyridine, tar formation occurred before appreciable amounts of the covalent mesylate had disappeared. When 1.00 g. of XVII in 20 ml. of methanol and 4 ml. of 1 *N* sodium methoxide were warmed to 50° on a steam bath, then cooled, sodium methanesulfonate separated. When processed by chloroform–water, then crystallized from ethanol, 300 mg. (41%) of XX, m.p. 197–198°, was obtained that was identical with an authentic sample.[2] Evaporation of the filtrate and hydrolysis of the residue with 0.5 *N* sodium hydroxide gave 250 mg. (39%) of the imino alloside (IX), m.p. 143–144°, that was identical with an authentic sample.[3]

Methyl 4,6-*O*-Benzylidene-2,3-dideoxy-2,3-imino-*N*-(phenylamidino)-α,D-altropyranoside (XXII).—A solution of 450 mg. of VI and 0.30 ml. of aniline in 10 ml. of ethanol was refluxed for 3 days. The solvent was removed *in vacuo* and the residue partioned between 20 ml. each of water and chloroform. The aqueous layer was extracted with additional two 20-ml. portions of chloroform. The combined chloroform extracts, washed with two 20-ml. portions of water and dried with magnesium sulfate, were spin evaporated *in vacuo*. The residue was extracted with four 20-ml. portions of warm petroleum ether (b.p. 30–60°) to remove aniline, which left 450 mg. (76%) of a glass; λ_{max}^{film} 2.95 (NH), 6.05, 6.27, 6.70 (NH, C=N, C_6H_5—), 13.3, 14.4 (C_6H_5—), no C≡N near 4.5, and no bands at 6.15 and 6.35 μ (present in the isomeric XXIII).

Anal. Calcd. for $C_{21}H_{23}N_3O_4$: C, 66.2; H, 6.09; N, 11.0. Found: C, 66.1; H, 6.13; N, 10.8.

4′,6′-*O*-Benzylidene-2-imino-1′-*O*-methyl-1-phenyl-α,D-allopyrano[2′,3′:5,4]imidazolidine (XXIII).—A solution of 500 mg. of IV and 0.5 ml. (4 equiv.) of aniline in 15 ml. of ethanol was refluxed for 5 days when C≡N absorption near 4.5 μ finally had disappeared. The solvent was spin evaporated *in vacuo*. The residue was processed as described for XXII with an additional washing of the combined chloroform extracts with 25 ml. of 0.2 *N* aqueous sodium hydroxide prior to the water washings to yield 355 mg. (72%) of a glass; λ_{max}^{film} 2.95 (NH), 6.15, 6.29, 6.35, 6.73 (C=N, NH, C_6H_5—), 13.3, 14.4 (C_6H_5—), no C≡N near 4.5, no sulfonate near 7.4 and 8.5, and no band at 6.05 μ (present in XXII).

Anal. Calcd. for $C_{21}H_{23}N_3O_4$: C, 66.2; H, 6.09; N, 11.0. Found: C, 66.4; H, 6.21; N, 10.9.

When the aniline was increased to 8 equiv./mole in 12 ml. of alcohol per gram of IV, the reaction was complete in 2 days.

Methyl 3-Amino-2-anilino-4,6-*O*-benzylidene-2,3-dideoxy-α,D-allopyranoside (XXV).—To a solution of 0.75 g. of XXIII in 10 ml. of ethanol in a steel bomb was added a solution of 10 g. of potassium hydroxide in 10 ml. of water. The contents were sealed and heated at 130–140° for 4 days. The bomb contents were spin evaporated *in vacuo* to about one-half volume when the product began to separate. The crystalline product (0.5 g.) was collected on a filter and washed with water. Recrystallization from ethanol gave 0.48 g. (72%) of pure product as white needles, m.p. 166–167°; $[\alpha]^{23}D$ −2.7 ± 0.4° (0.9%); λ_{max} 2.94, 3.03 (NH), 6.22 (NH, phenyl), and 6.52, 6.68, 13.3, 14.3, 14.45 μ (phenyl).

Anal. Calcd. for $C_{20}H_{24}N_2O_4$: C, 67.4; H, 6.81; N, 7.87. Found: C, 67.1; H, 6.71, N, 7.74.

Methyl 3-Amino-4,6-*O*-benzylidene-2,3-dideoxy-3-(*N*-methylanilino)-α-D-allopyranoside (XXIX).—Treatment of 1.00 g. of IV with 2 ml. of *N*-methylaniline in 15 ml. of boiling ethanol for 2 days, as described for XXIII, gave 1.00 g. of crude methanesulfonate salt of a base presumed to be XXX. Conversion to the free base and hydrolysis with potassium hydroxide as described for the preparation of XXV gave a solution which was concentrated by spin evaporation *in vacuo* to remove ethanol. Extraction of the aqueous mixture with three 25-ml. portions of chloroform left 0.50 g. of residue after evaporation of the dried extracts. Recrystallization from ethyl acetate–petroleum ether (b.p. 30–60°) afforded 0.32 g. (34% based on IV) of white crystals, m.p. 143–144°; λ_{max} 2.93 (NH), 6.26 (NH, phenyl), and 6.39, 6.70, 13.3, 13.4, 14.4 μ (phenyl).

Anal. Calcd. for $C_{21}H_{26}N_2O_4$: C, 68.2; H, 7.09; N, 7.57. Found: C, 68.1; H, 7.12; N, 7.66.

Attempts to add phenylhydrazine or *N*,*N*-dimethyl-*p*-phenylenediamine to the triple bond of IV gave dark tars.

Acknowledgment.—We wish to thank the Cancer Chemotherapy National Service Center, National Cancer Institute, and Starks Associates, Inc., for large scale preparation of certain intermediates, mediated by Contract No. SA-43-ph-4346.

Synthetic Nucleosides. LXII.[1,2] Facile Displacement Reactions in the D-Mannitol Series. V. Studies on the Selective Conversion of Some Hexitol Derivatives to Aldoses

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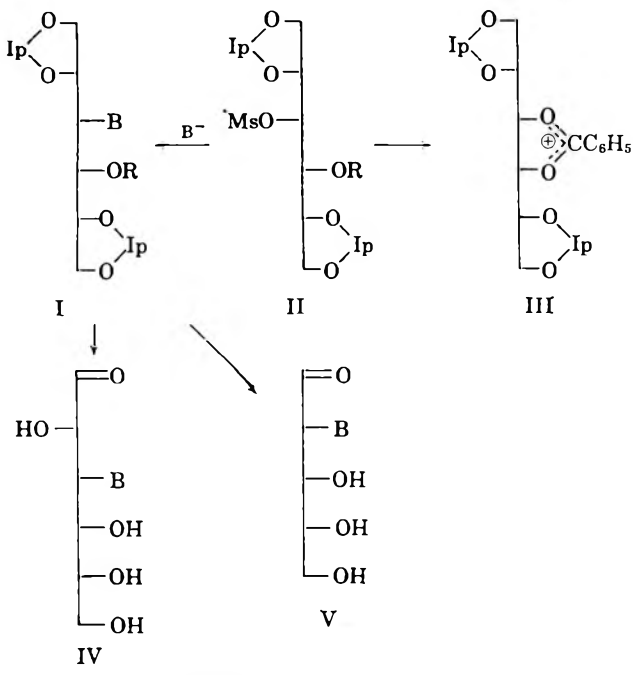
November 19, 1963

Hydrolysis studies showed there was no selectivity in removing one isopropylidene group from 3-amino-3-deoxy-1,2:5,6-di-*O*-isopropylidene-D-altritol (VIa), its *N*-benzoyl derivative (VIc), or its di-*O*,*N*-benzoyl derivative (VIb), in order that periodate oxidation could give a single pentose. Successful blocking was ultimately achieved by an unsymmetrical blocking technic; 3-amino-4-*O*-benzoyl-*N*-carbophenoxy-3-deoxy-1,2:5,6-di-*O*-isopropylidene-D-altritol (XXXI) could be cyclized by short boiling in pyridine to the unsymmetrical cyclic carbonate, 3-amino-4-*O*-benzoyl-3-deoxy-D-altritol 2,3-carbonate (XXXV), although benzoyl migration to the 6-*O*-benzoyl derivative (XXXIV) was a slower side reaction. As a model series to show the feasibility of the unsymmetrical blocking technic for conversion of a hexitol to a pentose, 4-*O*-benzoyl-3-*O*-carbomethoxy-1,2:5,6-di-*O*-isopropylidene-D-mannitol (XVI) was deacetonated, then cyclized in pyridine to 4-*O*-benzoyl-D-mannitol 2,3-carbonate (XIX); periodate oxidation of XIX and deblocking afforded crystalline D-arabinose.

Earlier work in this area on displacement reactions of the 4-*O*-mesyl group of the D-mannitol derivative (IIa) has shown that the reaction can proceed by direct Sn2 reaction (IIa → I) or by anchimeric formation of the ortho ester ion (III)—depending upon the relative strengths of the anchimeric group and the attacking group (B^-)[3,4] (Scheme I).[5] With a strong nucleophile such as azide ion, formation of I ($B{=}N_3^-$) was favorably competitive; with a weaker nucleophile, such as acetate, the anchimeric reaction predominated.

SCHEME I



a series, R = Bz—
b series, R = CH_3—
c series, R = 2-tetrahydropyranyl-

By replacing the benzoate group with an ether function such as methyl (IIb) or 2-tetrahydropyranyl (IIc),[6] only the bimolecular reaction took place, even with a weak nucleophile to give Ib and Ic, respectively. Thus, the use of hexitol derivatives (I) in displacement reactions was successful, whereas the same reactions on displacement of a ring sulfonate of a glycoside were almost always unsuccessful.[7] In order for the greater flexibility in synthetic transformation on hexitol derivatives to be useful for the synthesis of unusual pentoses or hexoses, it would be necessary to find good routes for the selective conversion of the transformed hexitol (I) to pentoses such as V and hexoses such as IV; initial studies on the possible routes for the conversion of I to aldoses (IV and V) are the subject of this paper.

Although the field of hexitol chemistry has been sufficiently established to warrant a review,[8] surprisingly little work has been done on the selective conversion of hexitols to aldoses. Conversion of a hexitol to a lower aldose is certainly possible when the hexitol is blocked in such a way that only one *vic*-glycol is present; an example is the well-known conversion of 1,2:5,6-di-*O*-isopropylidene-D-mannitol with lead tetraacetate to 2,3-*O*-isopropylidene-D-glyceraldehyde.[9] Furthermore, if all the groups of a hexitol except a primary hydroxyl group are blocked, it should be feasible to convert this primary hydroxyl to an aldehyde function either directly or indirectly. For our initial studies we chose to seek blocked hexitols with only one *vic*-glycol group that could be cleaved with periodate or lead tetraacetate to an aldose; thus, this study is concerned mainly with the selective blocking of appropriate hexitols.

Since several derivatives (VI) of 3-amino-3-deoxy-1,2:5,6-di-*O*-isopropylidene-D-altritol were available[4] by suitable Sn2 transformation of the D-mannitol derivative (IIa), the possible selective hydrolysis of these derivatives (VI) to a monoisopropylidene derivative, VII or VIII, was investigated (Scheme II) by

(1) This work was supported generously by Grant No. CY-5845 from the National Cancer Institute, U. S. Public Health Service.

(2) For the previous paper of this series, see B. R. Baker and T. Neilson, *J. Org. Chem.*, **29**, 1063 (1964).

(3) B. R. Baker and A. H. Haines, *ibid.*, **28**, 438 (1963), paper LIV of this series.

(4) B. R. Baker and A. H. Haines, *ibid.*, **28**, 442 (1963), paper LV of this series.

(5) Abbreviations used in structural formulas: Ip is isopropylidene; Bz is benzoyl; Ms is methanesulfonyl.

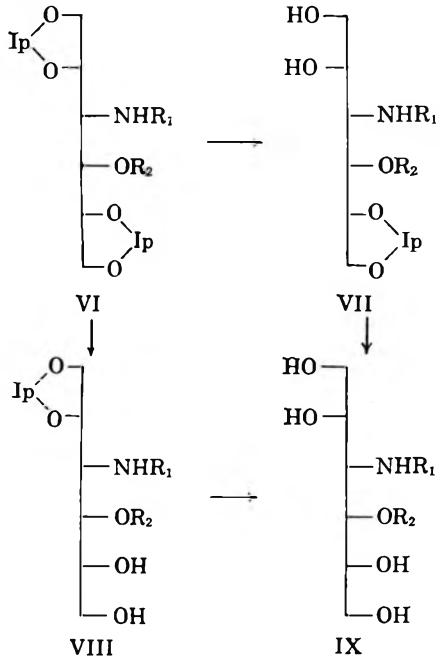
(6) B. R. Baker and H. S. Sachdev, *J. Org. Chem.*, **28**, 2132 (1963), paper LVI of this series.

(7) B. R. Baker and H. S. Sachdev, *ibid.*, **28**, 2135 (1963), paper LVII of this series.

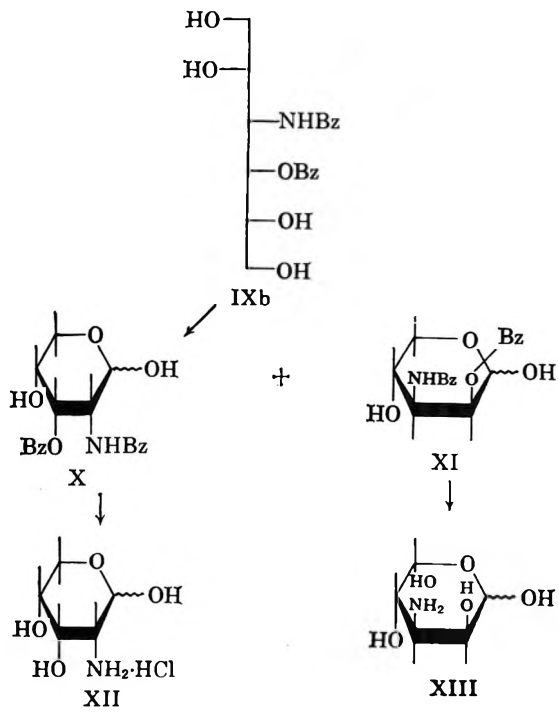
(8) S. A. Barker and E. J. Bourne, *Advan. Carbohydrate Chem.*, **7**, 137 (1952).

(9) E. Baer and H. O. L. Fischer, *J. Biol. Chem.*, **128**, 463 (1939).

SCHEME II



SCHEME III



time–product studies using thin layer chromatography (t.l.c.) or paper chromatography.

The glycoside linkage of methyl 2-amino-2-deoxy-D-glucopyranoside is stable to acid hydrolysis, presumably owing to the protonation of the amino group repelling further protonation of the acetal linkage[10]; it was, therefore, considered possible that the protonated 3-amino group of VIa would slow the hydrolysis of the 1,2-*O*-isopropylidene group compared to the 5,6-*O*-isopropylidene which should result in a favored formation of VIIIa. A solution of VIa in 70% aqueous ethanol containing 0.24 *N* hydrochloric acid was allowed to react at 20°; aliquots were removed at appropriate times and quenched with excess sodium bicarbonate. When the aliquots were investigated by t.l.c. (acetone–chloroform, 2:3), four spots could be detected by ninhydrin. After 60–240 min., the fastest moving spot was starting material (VIa), the slowest moving spot (at the origin) was the fully hydrolyzed product (IXa), and the intermediate spots were presumably VIIa and VIIIa. By the time the intermediate spots were detectable (60 min.), the fully hydrolyzed product was already detectable and later times showed no accumulation of a mono-*O*-isopropylidene derivative. Apparently both isopropylidene groups hydrolyze at similar rates; presumably the acetal-oxygen at C-1 can still be protonated even though the amino group is protonated, thus resulting in no appreciable selective hydrolysis. Complete hydrolysis of VIa with 0.4 *N* hydrochloric acid to IXa required 7 hr. at 0°.

Similar time studies on the hydrolysis of the dibenzoyl derivative (VIb) or the *N*-benzoyl derivative (VIc) showed that selective hydrolysis to VII or VIII was not feasible, since none of the intermediate mono-*O*-isopropylidene derivative accumulated and the final product (IX) began to appear soon after VII–VIII. The fully de-acetonated products (IXb and IXc) were isolated in crystalline form in 79 and 76% yields, respectively, when hydrolysis was allowed to go to completion.

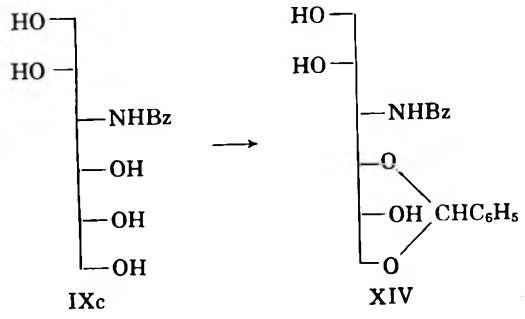
When the dibenzoyl derivative (IXb) was treated with periodate in aqueous dimethylformamide, 1 mole of periodate was consumed in less than 15 min.; about 2 days is necessary for a 2nd mole of periodate to be consumed. Thus, when IXb consumes 1 mole of periodate, the resultant pentose immediately cyclizes to X or XI (Scheme III); the ratio of X to XI is of course dependent upon the relative rate of cleavage of the two *vic*-glycol groups in IXa. The resultant X or XI or mixture of the two could then be expected to react with periodate slowly, since only the open-chain forms of X and XI have a *vic*-glycol system. The oxidation product(s) moved as a single spot (detected by aniline phthalate) on paper chromatography; however, hydrolysis of X–XI did not give a single aminopentose (XII or XIII), but a mixture as shown by paper chromatography.

When the di-*O*-isopropylidenealtritol (VIb) hydrolysis was quenched when the largest quantity of VIIb and VIIc were present and then the mixture subjected to periodate oxidation followed by acid hydrolysis, the same two spots (XII and XIII) were obtained. Thus neither route was considered to be sufficiently selective to be of preparative utility.

By use of the "Barker and Bourne rules,"[11] it might be anticipated that IXc would react preferentially with benzaldehyde to give a mono-4,6-*O*-benzylidene derivative (XIV), which then has a single *vic*-glycol system oxidatively cleavable to a derivative of 2-amino-2-deoxy-D-ribose. Unfortunately—owing to its insolubility—IXc failed to react appreciably when only 1 mole of benzaldehyde was present in reaction mixtures; with excess benzaldehyde in benzene on the presence

(10) R. C. G. Maggride and A. Neuberger, *J. Chem. Soc.*, 745 (1938).

(11) S. A. Barker and E. J. Bourne, *ibid.*, 905 (1952).



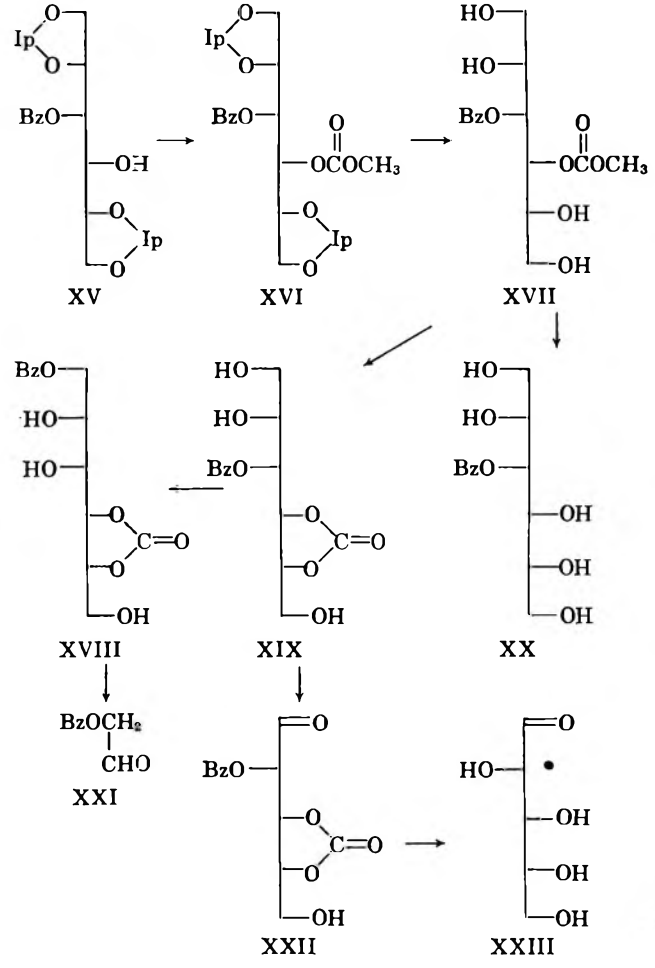
of *p*-toluenesulfonic acid or cupric sulfate, a non-crystalline product was obtained which had properties expected for a di-*O*-benzylidene derivative.

From the preceding studies on derivatives of VI and IX, it was clear that selective reactions involving the 1, 2, 4, and 5 hydroxyls were not likely to be found that would lead to suitable preparative methods. We, therefore, turned our attention to derivatives of I with an R group that could be cyclized onto the 4-hydroxyl group after the isopropylidene groups had been removed; such an unsymmetrical cyclization would then give a system with only one remaining *vic*-glycol. A model series starting with 3-*O*-benzoyl-1,2:5,6-di-*O*-isopropylidene-D-mannitol (XV)[12] was first explored to see if the key cyclization step (XVII → XIX), followed by oxidation to the D-arabinose derivative (XXII), was feasible.

Reaction of XV with methyl chlorocarbonate in pyridine to give the crystalline mixed carbonate (XVI) was sluggish. The best conditions found were 1:1 chloroform–pyridine as solvent with excess methyl chlorocarbonate at 65° for 2 days; under these conditions, 46% of XVI was obtained and 33% of unchanged XV was recovered. When XVI was hydrolyzed under excessively strenuous conditions, not only were the isopropylidene groups removed, but the carbomethoxy group also was lost and crystalline 3-*O*-benzoyl-D-mannitol (XX) was obtained. As a result, it was necessary to do a time study of the hydrolysis; 0.5 *N* hydrochloric acid in 56% aqueous tetrahydrofuran at 23° was chosen as the hydrolysis medium and neutralized aliquots were subjected to t.l.c. After 9 hr., only a trace of starting material could be detected and only a trace of 3-*O*-benzoyl-D-mannitol (XX) had formed; the main spot (R_f 0.27) appeared to be that of the desired product (XVII). When the reaction was extended to 19 hr., considerable XX had formed (Scheme IV).

When a preparative-sized hydrolysis of XVI was run for 12 hr. in aqueous tetrahydrofuran at 20–25°, the resultant oily product showed both cyclic and linear carbonate carbonyls at 1780 and 1740 cm.$^{-1}$, corresponding to XIX and XVII, respectively. This sirup was treated further with boiling pyridine, 5 hr. being required to complete the cyclization of XVII to XIX—as shown by the loss of the 1740-cm.$^{-1}$ linear carbonate carbonyl band.[13] From this syrup could then be isolated 3% of crystalline 3-*O*-benzoyl-D-mannitol (XX), and a varying amount (depending on the hydrolysis conditions) of a crystalline benzoyl

SCHEME IV



carbonate derivative also was isolated which was ultimately shown to be the 6-benzoate (XVIII) by periodate oxidation to glycol aldehyde benzoate (XXI); the major product was still a sirup, presumably XIX. If the reaction temperature was raised to 35°, then the yields of XVIII and XX were increased to 17 and 11%, respectively, but cyclization to XIX was nearly complete without pyridine treatment; after removal of the crystalline 6-benzoate (XVIII), the remaining crude 3-benzoate (XIX) was treated with pyridine, oxidized with periodate to XXII, then deblocked to give crystalline D-arabinose. Although the yield of D-arabinose was low, the feasibility of the method was shown; rather than spend further development time on this sequence, we turned our attention back to the more important 3-amino-D-altritol derivative (VIa).

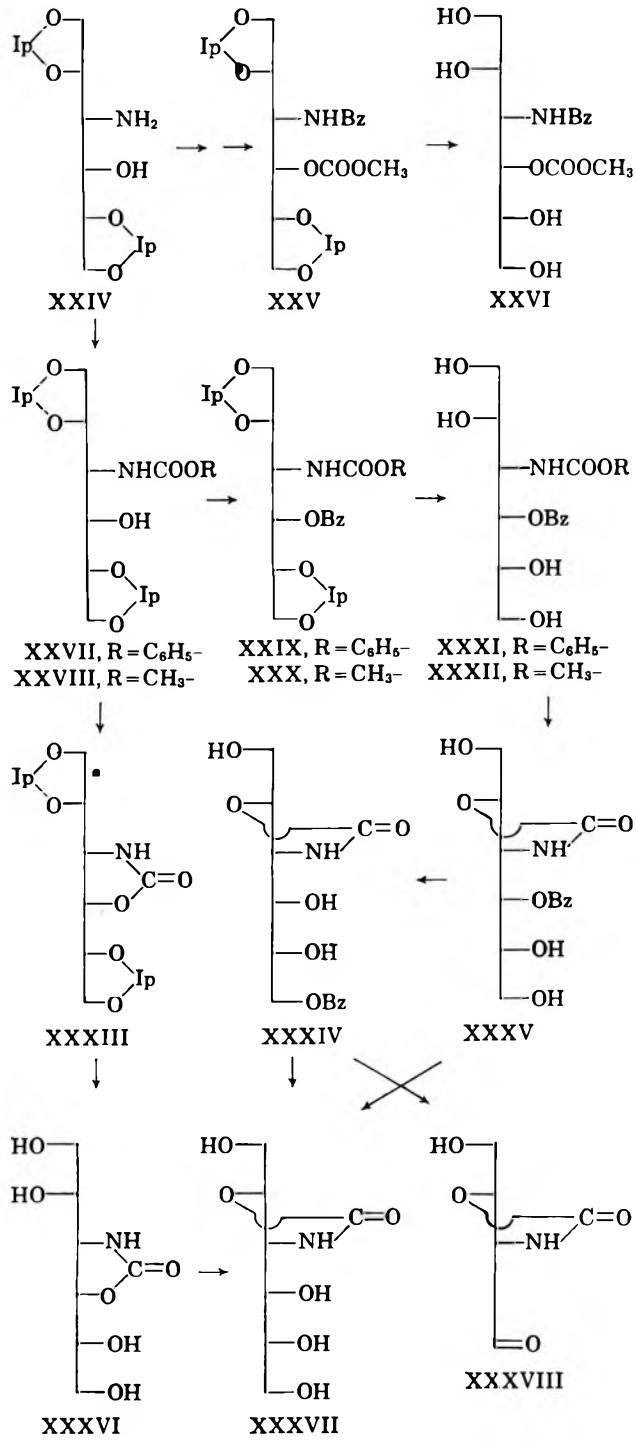
Dependent upon whether the carbomethoxy function is placed on the 3-amino group (XXXII) or on the 4-hydroxyl group (XXVI) of the 3-amino-D-altritol system (XXIV), it should be possible to obtain 3-amino-D-lyxose *via* XXXV or 2-amino-D-ribose, respectively, under controlled conditions. Initial attention was directed towards the *N*-carbomethoxy series. Reaction of XXIV with methyl chloroformate in methylene chloride in the presence of triethylamine afforded a 66% yield of crystalline XXVIII (Scheme V). Benzoylation to crystalline XXX proceeded smoothly with pyridine–benzoyl chloride.

A kinetic study on the hydrolysis of the isopropylidene groups in XXX was run in acidic aqueous tetrahydrofuran as described for the mannitol series

(12) J. M. Sugihara and G. U. Yuen, *J. Am. Chem. Soc.* **79**, 5780 (1957).

(13) The cyclization of a linear carbonate to a cyclic carbonate in boiling pyridine has been demonstrated previously by E. J. Reist, R. R. Spencer, and B. R. Baker, *J. Org. Chem.* **23**, 1958 (1958).

SCHEME V



(XVI → XVII); t.l.c. in benzene–methanol (5:1) showed that all the starting material was gone after 12 hr. at room temperature in the presence of 0.4 *N* hydrochloric acid, resulting in a major product with R_f 0.21. Further reaction time did not cause appearance of further cleavage products as in the case of XX. The product from a 12-hr. preparative run was a sirup that showed broad infrared absorption of the carbonyls of benzoate and linear urethane at 1720 cm.$^{-1}$ and NH deformation of a linear urethane at 1510 cm.$^{-1}$. Gomper and Herlinger[14] have indicated that the infrared spectra of oxazolones show carbonyl absorption at 1740–1750 cm.$^{-1}$, but show no amide–NH bond near 1510 cm.$^{-1}$. It was concluded that this hydrolysis product was mainly the linear urethane (XXXII) which was further substantiated by the presence of 0.6 equiv. of O–CH_3 in the n.m.r.

When the linear urethane (XXXII) was boiled in pyridine for 5 hr.—conditions used for cyclization of XVII to XIX—no reaction occurred as shown by the unchanged infrared spectrum. Although XXXII could be cyclized initially to XXXV in the higher boiling collidine—as shown by the appearance of a 1740-cm.$^{-1}$ band of a cyclic urethane and the disappearance of the 1510-cm.$^{-1}$ NH band—the t.l.c. pattern showed a series of spots indicating acyl migration under these strenuous conditions.

Attempted cyclization of XXXII with a catalytic quantity of solid sodium methoxide in dimethylformamide[15] was successful, as shown by the appearance of the 1740-cm.$^{-1}$ band, but again t.l.c. indicated acyl migration. With methanolic sodium methoxide cyclization of XXXII took place, but the benzoyl group simultaneously was removed as could be anticipated; the resultant crystalline product was later shown unequivocally to have structure XXXVII.

Since the linear urethane (XXXII) cyclized so slowly to XXXV that acyl migration appeared to be a serious side reaction, the more base-reactive *O*-phenylurethane (XXXI) was synthesized and its cyclization studied. Reaction of the amino-D-altritol derivative (XXIV) with phenyl chloroformate in dichloromethane containing triethylamine gave 86% yield of the carbophenoxy derivative (XXVII) in two dimorphic forms. Benzoylation with pyridine–benzoyl chloride afforded the crystalline benzoate (XXIX) in 94% yield. A time study on acid hydrolysis of the isopropylidene group of XXIX under the now standard conditions by use of the t.l.c. technic showed that hydrolysis was complete in 18 hr. at room temperature and that no further reaction occurred in 24 hr. A preparative run afforded the crystalline carbophenoxy-amino hexitol (XXXI) in 70% yield.

Since benzoyl migration during cyclization of XXXI to XXXV in boiling pyridine was a probable side reaction, a time–product study was made of aliquots by use of t.l.c. and infrared spectra. At the end of 30-min. reflux, t.l.c. in benzene–methanol (4:1) showed that starting material (R_f 0.44) had disappeared and a new major product with R_f 0.35 appeared along with a minor product at R_f 0.40; the infrared spectrum showed the loss of the 1510-cm.$^{-1}$ amide–NH band. At the end of 10 min., starting material and some product at R_f 0.35 were present; the side product at R_f 0.40 was not apparent. At the end of 9-hr. reflux, only one spot (R_f 0.40) was detectable; these results indicated that the desired cyclization to XXXV was probably taking place followed by a slower benzoate migration. When the reaction mixture was processed at the end of 30 min., no crystalline product could be isolated; however, at the end of 3-hr. reflux, a crystalline benzoate could be isolated in 62% yield.

That this benzoate had the rearranged structure, XXXIV, was shown as follows. There are four possible monobenzoates of XXXVII, including XXXIV and XXXV. If the cyclic urethane also rearranged to XXXVI, then there are four more possible mono-

(14) R. Gomper and H. Herlinger, *Ber.*, **89**, 2825 (1956).

(15) B. R. Baker and J. P. Joseph, *J. Am. Chem. Soc.*, **77**, 15 (1955).

benzoates. A quantitative periodate tetration showed the uptake of a single mole (complete in 24 hr.), and *O*-benzoylglycolaldehyde (XXI) could be isolated as the 2,4-dinitrophenylhydrazone in 44% yield; only structure XXXIV is compatible with this data.

Debenzoylation of the crystalline monobenzoyl urethane (XXXIV) with methanolic sodium methoxide afforded a cyclic urethane, identical with that obtained, as described earlier, from treatment of XXXII under the same conditions; this urethane could have structure XXXVII if no rearrangement of the oxazolidone had occurred, or it could have structure XXXVI if the oxazolidone did rearrange. That the debenzoylation product had structure XXXVII was shown by synthesis of the isomeric XXXVI by an alternate route and comparison of their n.m.r. spectra.

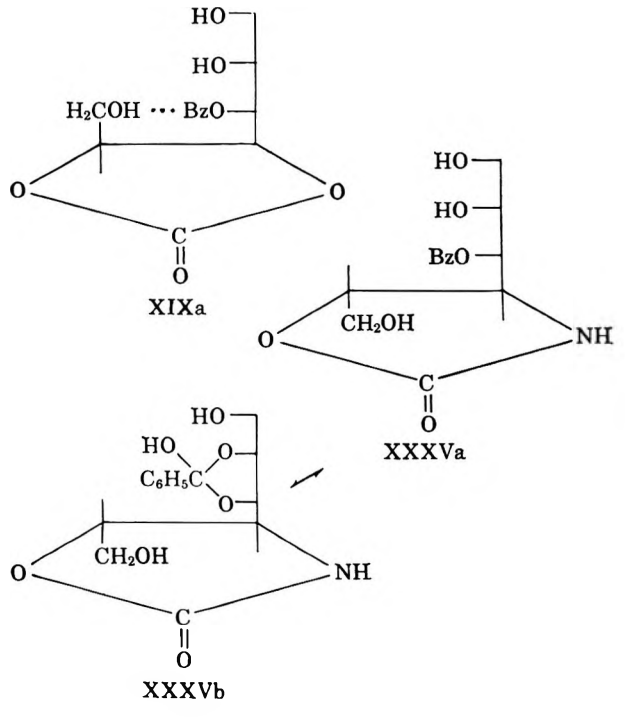
When the *O*-phenylurethane (XXVII) was refluxed in pyridine, cyclization to the crystalline oxazolidone (XXXIII) occurred in 56% yield; this compound also could be prepared by direct fusion of XXIV with diphenyl carbonate. Acid hydrolysis of XXXIII afforded 83% of the deacetonated oxazolidone (XXXVI), clearly isomeric to XXXVII. In order to show that the structural assignments were not the reverse as a result of acid-catalyzed rearrangement, the oxazolidone (XXXVII) was shown to be stable under the conditions used for the preparation of XXXVI—unequivocal proof for the structural assignments.

Attempted confirmation of the structural assignment by n.m.r. was equivocal. The proton of the carbinyl group of an ester—in this case the oxazolidone proton on the carbon bearing the cyclic acyloxyl group—usually gives a signal downfield from a proton attached to the carbinyl group of an alcohol. It can be calculated that the splitting pattern of the proton in question by adjacent protons should be simpler in the case of the *cis*-oxazolidone (XXXVI) than the *trans*-oxazolidone (XXXVII). In deuterium oxide, resolution was insufficient at 20–80° to make an unequivocal assignment of structure by *J* values, but XXXVI appeared to give a simpler spectrum than XXXVII in this carbinyl region.

Although XXXVI and XXXVII were both stable to dilute acid at room temperature, such was not the case with base. Treatment of XXXVI with methanolic sodium methoxide readily rearranged it to XXXVII, presumably *via* a linear methyl urethane. Thus, the *trans* conformation (XXXVII) is apparently more stable than the *cis* conformation XXXVI.

An interesting contrast is the ready migration of the *O*-benzoate of XXXVa in boiling pyridine compared to the stability of the *O*-benzoate (XIXa) under the same conditions. Benzoyl migration to the 5-hydroxyl could occur readily in XXXVa *via* the ortho ester (XXXVb), then migrate further to the 6-hydroxyl by the same mechanism.[16] Although XIXa could form a similar ortho ester with the adjacent 5-hydroxyl group, the *cis*-hydroxymethyl of XIXa could hydrogen bond to the 4-benzoate, hence competing with the tendency to form an ortho ester; in contrast, the *trans*-hydroxymethyl group of XXXVa cannot hydrogen bond intramolecularly with the 4-benzoate.

Further work will be necessary to see if a *p*-nitrobenzoyl or *p*-chlorobenzoyl blocking group for the 4-hydroxyl of XXXa will be somewhat more stable towards acyl migration or if a *p*-nitrocarbophenoxy group will ring close more rapidly. Since ring closure of XXXI to XXXV is complete in 30 min. in boiling pyridine, whereas benzoyl migration is only about half complete in 3 hr., an acyl blocking group with no more than twice the stability of benzoate or a ring-closing group with no less than twice the reactivity should suffice to complete the synthesis of 3-amino-3-deoxy-D-lyxose *via* an ester such as XXXV. Additional studies on conversion of XXXVII to 2-amino-2-deoxy-D-threose, XXXV to 3-amino-3-deoxy-D-altrose, and 4-amino-D-talose *via* XXVI are worthy of exploration; in this way it could be determined whether or not unusual hexitols derivable by displacement reactions in the D-mannitol series can be converted to unusual tetroses, pentoses, or hexoses by the unsymmetrical blocking technics described in this paper.



Experimental[17]

3-Benzamido-3-deoxy-D-altritol (IXc).—To a solution of 1.5 g. of VIc in 15 ml. of methanol was added 10 ml. of cold 1 *N* aqueous hydrochloric acid. After 7 hr. at 0°, the solution was neutralized by stirring with excess silver carbonate, then clarified by filtration through a Celite pad. The solution was spin evaporated *in vacuo* and the residue was further dried by spin evaporation *in vacuo* of several portions of 1:1 ethanol–benzene. Crystallization of the sirup from ethyl acetate–ethanol gave 0.64 g. (55%)

(16) (a) Base-catalyzed *O*-benzoyl migration directly from the 3-hydroxyl to the 6-hydroxyl has been observed with 1,2-*O*-isopropylidene-D-glucose; *cf.* H. Ohle, *Ber.*, **57B**, 403 (1924), and E. J. Reist, R. R. Spencer, and B. R. Baker, *J. Org. Chem.*, **23**, 1757 (1958). Therefore, direct 4-benzoate migration in XXXVa to the 6-benzoate (XXXIV) is also a possibility; see also (b) E. Pascu, *Advan. Carbohydrate Chem.*, **1**, 109 (1945); and (c) M. L. Wolfrom, E. P. Swan, K. S. Ennor, and A. Chaney, *J. Am. Chem. Soc.*, **81**, 5701 (1959).

(17) Melting points were determined in capillary tubes with a Mel-Temp block and those below 230° are corrected. Infrared spectra were determined in Nujol mull with a Perkin-Elmer Model 137B spectrophotometer. Optical rotations were measured in a 1-dm. microtube in *N,N*-dimethylformamide; per cent concentrations are grams per 100 ml. Thin layer chromatograms were performed with silica gel G in 5:1 benzene–methanol and spots were detected by iodine vapor, unless otherwise indicated. Paper chromatograms were performed on Whatman No. 1 paper with the upper phase of 1-butanol–ethanol–water (4:1:5); spots were detected by ninhydrin if a free amino group was present, by aniline hydrogen phthalate if a reducing sugar was present, or by an ultraviolet lamp if benzoate was present.

of product, m.p. 105–108°. The analytical sample was obtained by recrystallization from the same solvent as white crystals, m.p. 108–110°; ν_{max} 3500, 3350, 3200 (NH, OH), 1640 (amide C=O), 1510 (amide II), and 720, 690 cm.$^{-1}$ (CH of benzoate); $[\alpha]^{23}D$ + 22 ± 3° (0.16%).

Anal. Calcd. for $C_{13}H_{19}NO_6$: C, 54.7; H, 6.73; N, 4.91. Found: C, 54.2; H, 6.68; N, 4.96.

In a later run a different dimorph, m.p. 116–118°, was obtained in 76% yield; ν_{max} 3650, 3400, 3300 (NH, OH), 1625 (amide C=O), 1540 (amide II), 690 cm.$^{-1}$ (CH of benzoate).

Anal. Found: C, 54.7; H, 6.47; N, 4.88.

This compound (IXc) consumed 4.7 moles of periodate in 10 min. and 6 moles in 20 hr., indicating overoxidation.

The possibility of obtaining a monoisopropylidene derivative of VIIc or VIIIc was shown to be unfeasible by a time study. A solution of 0.15 g. of VIc in 1.5 ml. of methanol and 1 ml. of 0.01 *N* aqueous hydrochloric acid was stored at 20°; 0.1-ml. aliquots were removed at time intervals and immediately neutralized with sodium bicarbonate. Paper chromatograms were run with 20 λ of each aliquot, using VIc (R_f 0.90) and IXc (R_f 0.52) as standards. After 9 hr., starting material VIc and monoisopropylidene derivatives VIIc and VIIIc (R_f 0.80) were present; before all the starting material had been consumed, the nonacetonated hexitol (IXc) at R_f 0.52 was present, thus showing that there was no selectivity in hydrolysis of the isopropylidene groups of VIc. All of VIc was consumed after 20 hr., but a strong spot of IXc was present; at no time was there an accumulation of monoacetone derivatives.

3-Benzamido-4-*O*-benzoyl-3-deoxy-D-altritol (IXb).—To a stirred solution of 6.3 g. of VIb[4] in 300 ml. of tetrahydrofuran was added 300 ml. of 1 *N* aqueous hydrochloric acid. Some VIb separated which gradually redissolved on stirring. After 18 hr., the solvent was concentrated by spin evaporation *in vacuo* until most of the tetrahydrofuran had been removed. The product was collected on a filter, washed with water, and dried, then leached with 100 ml. of chloroform to remove any intermediate hydrolysis products. Recrystallization from methanol gave 4.1 g. (79%) of white crystals, m.p. 189–192°. The melting point of IXb varied with each preparation within the range of 179–195°, although it was usually sharp. The infrared spectra of the materials with different melting points were indistinguishable. The analytical sample had m.p. 179–181°; $[\alpha]^{23}D$ + 13 ± 1° (1.08%); ν_{max} 3400 (broad OH and NH), 1690 (ester C=O), 1610 (amide C=O), 1510 (amide NH), and 718 cm.$^{-1}$ (CH of benzoate).

Anal. Calcd. for $C_{20}H_{23}NO_7$: C, 61.7; H, 5.97; N, 3.60. Found: C, 61.5; H, 5.60; N, 3.67.

This compound in 10% aqueous dimethylformamide consumed 1.0 moles of periodate in 15 min., 1.2 moles in 75 min., and 2.5 moles in 46 hr. In a preparative run, the reaction was stopped after 45 min. by addition of a slight excess of ethylene glycol and the products (X and XI) isolated by extraction with dichloromethane. Paper chromatography of the sirup showed only a single spot when detected by aniline hydrogen phthalate. That this was a mixture of X and XI was indicated by hydrolysis with boiling 1 *N* hydrochloric acid for 48 hr. Spin evaporation of the charcoal-clarified solution *in vacuo* at room temperature gave a glass that showed on paper chromatography a series of spots positive to ninhydrin; the major spots (XII and XIII) had R_f 0.09 and 0.01.

Reaction of IXc with 3 moles of benzaldehyde in boiling benzene in the presence of a trace of *p*-toluenesulfonic acid, after removal of water under a Dean–Stark trap, gave an oil which had characteristics of a dibenzylidene derivative rather than XIV; with 1 mole of benzaldehyde, starting material was recovered after water removal was complete, also indicating formation of a dibenzylidene derivative. With anhydrous copper sulfate as a catalyst, similar results were obtained.

3-*O*-Benzoyl-4-*O*-carbomethoxy-1,2:5,6-di-*O*-isopropylidene-D-mannitol (XVI).—To a stirred solution of 3.0 g. of XV[3,12] in 10 ml. of chloroform and 20 ml. of pyridine cooled in an ice bath and protected from moisture was added dropwise a solution of 3 ml. of methyl chloroformate in 10 ml. of chloroform over a period of 15 min. After being heated in a bath at 65° for 2 days, the mixture was cooled and poured into 200 ml. of ice–water with good stirring. The separated aqueous layer was extracted with additional chloroform (two 20-ml. portions). The combined chloroform extracts were washed with two 30-ml. portions of water, dried with magnesium sulfate, then spin evaporated to residue *in vacuo*. Traces of pyridine were removed from the residue by spin evaporation of toluene (two 30-ml. portions). Crystallization of the residue from methanol gave 1.4 g. (40%) of white crystals, m.p. 86–87°; $[\alpha]^{24}D$ + 21.9 ± 0.7° (0.46%); ν_{max} 1740 (carbonate C=O), 1710 (benzoate C=O), and 705 cm.$^{-1}$ (benzoate CH).

Anal. Calcd. for $C_{21}H_{28}O_9$ C, 59.4; H, 6.60. Found: C, 59.4; H, 6.42.

The mother liquor was spin evaporated *in vacuo* and the residue recrystallized from ethyl acetate–petroleum ether (b.p. 30–60°) to give 1.0 g. (33%) of unchanged XV. An additional 0.2 g. (total 46%) of product XVI could be obtained by evaporation of the filtrate and crystallization from methanol.

Although the carbomethoxylation of XV was explored in depth, no conditions could be found that converted more of XV to the product. However, 5 days at room temperature gave the same yield as 2 days at 65°.

3-*O*-Benzoyl-D-mannitol (XX).—This compound was isolated as a by-product in the acid hydrolysis of XVI, as described subsequently. Recrystallization from ethanol gave white crystals, m.p. 173–174°; $[\alpha]^{24}D$ + 5.7 ± 0.6° (0.76%); ν_{max} 3450, 3300, (OH), 1690 (hydrogen-bonded C=O of benzoate), and 715 cm.$^{-1}$ (CH of benzoate).

Anal. Calcd. for $C_{13}H_{18}O_7$: C, 54.5; H, 6.29. Found: C, 54.7; H, 6.13.

Sugihara and Yuen[12] have prepared this compound by ion-exchange-catalyzed hydrolysis of XV and have recorded m.p. 177–178° and $[\alpha]^{22}D$ +6.35° (2.9% in acetone). Although they believed the structure to be the 3-benzoate (XX) because of the mild conditions used, there was a possibility for our more severe conditions to cause rearrangement of the 3-benzoate to the 1-benzoate, particularly since 1-*O*-benzoyl-D-mannitol 4,5-carbonate (XVIII) also was isolated in our hydrolysis. However, XX is clearly isomeric to 1-*O*-benzoyl-D-mannitol,[16c] m.p. 121–122°, $[\alpha]^{18}D$ +9° (5.22% in ethanol).

The following preparative method was developed. A solution of 500 mg. of XV in 22 ml. of methanol and 20 ml. of 1 *N* aqueous hydrochloric acid was allowed to stand at room temperature for about 18 hr. The solution was neutralized by stirring with Dowex 21K (carbonate form), then spin evaporated *in vacuo*. The solid residue (0.34 g.) was recrystallized from ethanol to yield 0.25 g. (64%) with m.p. 173–174° that was identical with the preparation isolated from hydrolysis of XVII.

1-(and 3)-*O*-Benzoyl-D-mannitol 4,5-Carbonate (XVIII and XIX).

A. Kinetic Study of Hydrolysis.—A solution of 100 mg. of XVI in 10 ml. of tetrahydrofuran and 8 ml. of 1 *N* hydrochloric acid was stirred at 23°. Aliquots were removed at intervals and neutralized with Dowex 21K (carbonate form). Each aliquot was analyzed by t.l.c. using as standards XVI (R_f 0.92) and XX (R_f 0.16). At the end of 2 hr., a spot at R_f 0.7 was detectable (monoisopropylidene derivative of XVII) and starting material was still present. At the end of 7–9 hr., all the starting material was consumed and the major spot was at R_f 0.27 (a mixture of XVII and XIX). After 9 hr., XX (R_f 0.16) began to appear and, at the end of 52 hr., was one of the two major spots along with R_f 0.30. It appears that XX is formed by the hydrolysis of XVII competing with ring closure to XIX.

B. Cyclization of XVII.—The infrared spectrum of the hydrolysis products after a 12-hr. hydrolysis showed carbonyl absorption of benzoate at 1710, linear carbonate (of XVII) at 1740, and cyclic carbonate (of XIX) at 1780 cm.$^{-1}$. After longer reaction time or warmer temperature, the 1740-cm.$^{-1}$ band gradually decreased and the 1780-cm.$^{-1}$ band increased showing acid-catalyzed cyclization of XVII to XIX; however, these more strenuous conditions also led to a greater proportion of the rearranged product (XVIII) and the overhydrolyzed product (XX). Thus, the ratio of XVII, XIX, and XX will vary somewhat depending upon the reaction conditions. The XX present was readily removed by crystallization and the linear carbonate (XVII) could be cyclized to XIX in boiling pyridine. A kinetic study showed that cyclization was complete after 5-hr. reflux in pyridine.

C. Preparative Method.—A solution of 4.0 g. of XVI in 160 ml. of tetrahydrofuran and 120 ml. of 1 *N* aqueous hydrochloric acid was stirred for 12 hr. at 30–35°. The solution was neutralized with Dowex 21K (carbonate form), then spin evaporated *in vacuo*. Crystallization of the residue from methanol gave 0.50 g. (17%) of XVIII, m.p. 163–165°. Recrystallization from ethanol gave white prisms, m.p. 164–166°; $[\alpha]^{24}D$ 0.5 ± 0.8° (0.65%); ν_{max} 3400, 3250, (OH), 1810 (cyclic carbonate C=O), 1690 (benzoate C=O), and 715 cm.$^{-1}$ (benzoate CH).

Anal. Calcd. for $C_{14}H_{16}O_8$: C, 53.8; H, 5.13. Found: C, 54.0; H, 5.21.

The filtrate from the 0.50 g. was spin evaporated *in vacuo*. Crystallization from ethyl acetate containing ethanol gave 0.3 g. (11%) of XX. Spin evaporation of the filtrate *in vacuo* gave a residue which was dissolved in 30 ml. of reagent pyridine and the solution refluxed for 5 hr. The residue remaining after spin evaporation *in vacuo* was partitioned between 20 ml. of benzene and 20 ml. of water. The separated aqueous layer was washed once more with 20 ml. of benzene; the benzene washings containing by-products were rejected. The aqueous solution was spin evaporated *in vacuo* leaving a sirup of crude XIX that could not be crystallized, but was used for periodate oxidation; yield 1.6 g. (54%); ν_{max}^{film} 1790 (cyclic carbonate C=O), 1710 (benzoate C=O), and no 1740-cm.$^{-1}$ linear carbonate carbonyl. Thin layer chromatography showed one major spot at R_f 0.45 in 4:1 benzene–methanol.

Conversion of XIX to D-Arabinose (XXIII).—A solution of the above 1.6 g. of XIX in 110 ml. of water containing 4.4 g. of sodium periodate was allowed to stand. After 30 min. the solution was extracted with benzene to remove by-products resulting from oxidation of mannitol monobenzoates; infrared examination showed no carbonate carbonyl absorption. After 8 hr., the periodate solution was extracted with five 50-ml. portions of ethyl acetate. The combined extracts were dried with magnesium sulfate, then spin evaporated *in vacuo*. The residue was dissolved in ethanol and stirred with Dowex 21K (carbonate form), until neutral when spotted on moist indicator paper which removed traces of acetic acid that interfered with the next step; yield 0.85 g. (59%) of crude XXII; ν_{max}^{film} 1780 (cyclic carbonate C=O), and 1710 cm.$^{-1}$ (benzoate C=O); t.l.c. in 10:1 benzene–methanol showed a single spot at R_f 0.30.

To a solution of 0.80 g. of crude XXII in 10 ml. of methanol was added 0.3 ml. of 1 *N* methanolic sodium methoxide. After standing for 18 hr. at room temperature in a closed flask, the solution was neutralized with Dowex 50W-X8 (H^+ form). The filtrate was evaporated to a sirup *in vacuo* and the residue crystallized from a small amount of methanol to yield 0.10 g. (23%) of D-arabinose (XXIII), m.p. 154–155°. Recrystallization from methanol gave white crystals of D-arabinose, m.p. 159–160°, $[\alpha]^{24}D$ −42.1 ± 0.6° (0.92%). A mixture with authentic D-arabinose (m.p. 159–160°) gave no depression in melting point and the infrared spectra of the two samples were identical.

In some runs the D-arabinose was isolated as the tosylhydrazone, m.p. 153°, that was identical with a sample, m.p. 156°, prepared from authentic D-arabinose.

3-Benzamido-4-*O*-carbomethoxy-3-deoxy-1,2:5,6-di-*O*-isopropylidene-D-altritol (XXV). A.—Treatment of 3-benzamido-3-deoxy-1,2:5,6-di-*O*-isopropylidene-D-altritol[4] with methyl chloroformate in chloroform–pyridine, as described for the preparation of XVI, after crystallization from ethanol, gave 34% of crude XXV, m.p. 138–142°. Recrystallization from methanol–water afforded white crystals, m.p. 155–157°; $[\alpha]^{24}D$ + 8.9 ± 0.5° (0.72%); ν_{max} 3500 (NH), 1740 (linear carbonate C=O), and 1640, 1610 cm.$^{-1}$ (amide I and II).

Anal. Calcd. for $C_{21}H_{29}NO_8$: C, 59.6; H, 6.86; N, 3.31. Found: C, 59.5; H, 6.63; N, 3.32.

B.—Preparation by the sodium salt method as described for the corresponding carboisobutoxy derivative gave, after crystallization from ethyl acetate–petroleum ether (b.p. 30–60°), 30 mg. (26%) of product, m.p. 155–157°, that was identical with preparation A.

3-Benzamido-4-*O*-carboisobutoxy-3-deoxy-1,2:5,6-di-*O*-isopropylidene-D-altritol.—A stirred mixture of 100 mg. of 3-benzamido-3-deoxy-1,2:5,6-di-*O*-isopropylidene-D-altritol,[4] 5 ml. of toluene, and 12 mg. of a 55% suspension of sodium hydride, protected from moisture, was stirred for 15 min. at 30–35° when hydrogen evolution was complete. After the addition of 1.1 equiv. of isobutyl chloroformate, the mixture was stirred in a bath at 50° for 18 hr. The toluene solution was washed with water, dried with magnesium sulfate, and spin evaporated. The crystalline residue was recrystallized from ethyl acetate–petroleum ether (b.p. 30–60°) to give 60 mg. (47%) of product, m.p. 158–160°; no attempt was made to get a second crop. Recrystallization again from the same solvents gave white crystals, m.p. 160–161°; $[\alpha]^{24}D$ + 5.1 ± 0.9° (0.39%); ν_{max} 3400 (NH), 1740 (carbonate C=O), and 1640, 1510 cm.$^{-1}$ (amide I and II).

Anal. Calcd. for $C_{24}H_{35}NO_8$: C, 61.9; H, 7.53; N, 3.01. Found: C, 62.0; H, 7.72; N, 2.82.

3-Amino-*N*-carbophenoxy-3-deoxy-1,2:5,6-di-*O*-isopropylidene-D-altritol (XXVII).—To a stirred solution of 2.0 g. of XXIV[4] in 80 ml. of methylene chloride and 2 ml. of triethylamine, protected from moisture and cooled in an ice bath, was added 1.1 ml. of phenyl chloroformate. The mixture was stirred at ambient temperature for 75 min. after the addition, then washed with water, 100 ml. of ice-cold 0.2 *N* hydrochloric acid, and again with water (two 50-ml. portions). Dried with magnesium sulfate, the solution was spin evaporated *in vacuo*. Crystallization from ethyl acetate–petroleum ether (b.p. 30–60°) gave 2.6 g. (94%) of white crystals as a mixture of fine needles and heavy prisms. The needles were readily separated by swirling the mixed crystals with petroleum ether (b.p. 30–60°) and decanting the suspension of needles from the heavy prisms; in this way 2.5 g. of prisms, m.p. 54–65°, and 0.10 g. of needles, m.p. 62–65°, were obtained. A mixture of the two melted at 54–65°; they are apparently dimorphs since both give proper combustion analyses for XXVII. The needles had ν_{max} 3450, 3300 (NH, OH), 1720 (urethane C=O), and 1590 cm.$^{-1}$ (amide NH). The prisms had $[\alpha]^{24}D$ + 5.4 ± 0.3° (1.15%) and ν_{max} 3450, 3300 (NH, OH), 1720 (urethane C=O), and 1590 cm.$^{-1}$ (amide NH).

Anal. Calcd. for $C_{19}H_{27}O_7N$: C, 59.8; H, 7.09; N, 3.67. Found (prisms): C, 60.0; H, 7.26; N, 3.39. Found (needles): C, 60.0; H, 7.15.

Recrystallization of the prisms from ethyl acetate–petroleum ether (b.p. 30–60°) again gave a few needles, but mostly the prismatic dimorph of unchanged melting point range.

3-Amino-*N*-carbomethoxy-3-deoxy-1,2:5,6-di-*O*-isopropylidene-D-altritol (XXVIII).—XXVIII was prepared with methyl chloroformate as described for the preparation of XXVII. Recrystallization from ethyl acetate–petroleum ether (b.p. 30–60°) afforded 0.40 g. (66%) of white needles, m.p. 97–98°; $[\alpha]^{24}D$ + 19.0 ± 0.5° (0.86%); ν_{max} 3500 (NH, OH), 1710 (urethane C=O), and 1510 cm.$^{-1}$ (amide NH).

Anal. Calcd. for $C_{14}H_{25}NO_7$: C, 52.7; H, 7.84; N, 4.39. Found: C, 52.7; H, 7.61; N, 4.38.

3-Amino-4-*O*-benzoyl-*N*-carbophenoxy-3-deoxy-1,2:5,6-di-*O*-isopropylidene-D-altritol (XXIX).—To a stirred and ice-cooled solution of 2.6 g. of XXVII in 50 ml. of reagent pyridine, protected from moisture, was added 3.0 ml. of benzoyl chloride dropwise over a period of about 10 min. After an additional 18 hr. at ambient temperature, the mixture was poured into 500 ml. of ice-cold 1% aqueous sodium bicarbonate. The product was collected on a filter, washed with water, and dried. Recrystallization from ethyl acetate–petroleum ether (b.p. 30–60°) gave 3.1 g. (94%) of white needles, m.p. 167–168°; $[\alpha]^{24}D$ + 5.9 ± 0.5° (0.65%); ν_{max} 3450 (NH), 1720 (benzoate and urethane C=O), 1510 (amide NH), and 710 cm.$^{-1}$ (benzoate CH).

Anal. Calcd. for $C_{26}H_{31}NO_8$: C, 64.3; H, 6.39; N, 2.89. Found: C, 64.5; H, 6.57; N, 2.69.

Similarly, **3-amino-4-*O*-benzoyl-*N*-carbomethoxy-3-deoxy-1,2:5,6-di-*O*-isopropylidene-D-altritol (XXX)** was prepared and, after recrystallization from ethanol–water, 0.27 g. (68%) was obtained as white crystals, m.p. 138–139°; $[\alpha]^{24}D$ + 8.3 ± 1.2° (0.40%); ν_{max} 3500 (NH), 1700 (benzoyl and urethane C=O), 1510 (amide NH), and 710 cm.$^{-1}$ (benzoate CH).

Anal. Calcd. for $C_{21}H_{27}NO_8$: C, 59.6; H, 6.86; N, 3.31. Found: C, 59.7; H, 6.91; N, 3.46.

3-Amino-3-deoxy-1,2:5,6-di-*O*-isopropylidene-D-altritol 3,4-Carbonate (XXXIII). A.—A solution of 0.75 g. of XXVII in 50 ml. of reagent pyridine was refluxed for 18 hr., then spin evaporated *in vacuo*. Traces of pyridine were removed by spin evaporation of toluene (two 10-ml. portions) *in vacuo*. Recrystallization of the residue from ethyl acetate–petroleum ether (b.p. 30–60°) gave 0.35 g. (56%) long, white needles, m.p. 202–203°; $[\alpha]^{24}D$ − 36.3 ± 0.9° (0.57%); ν_{max} 3300 (NH), and 1750, 1730 (d) cm.$^{-1}$ (cyclic carbonate C=O).

Anal. Calcd. for $C_{13}H_{21}NO_6$: C, 54.4; H, 7.32; N, 4.88. Found: C, 54.5; H, 7.26; N, 5.03.

No attempt was made to obtain a second crop.

B.—A mixture of 100 mg. of XXIV and 82 mg. of diphenyl carbonate were fused on a steam bath for 2.5 hr. The semicrystalline mass was recrystallized from methanol to give 30 mg. (27%) of product, m.p. 201–202°, that was identical with preparation A. The yield could probably be improved by using a larger excess of diphenyl carbonate and either a longer reaction time or higher fusion temperature.

3-Amino-3-deoxy-D-altritol 3,4-Carbonate (XXXVI).—A mixture of 150 mg. of XXXIII, 10 ml. of tetrahydrofuran, and 7 ml. of 1 *N* aqueous hydrochloric acid was stirred at room temperature for 18 hr., then neutralized with Dowex 1-X8 (carbonate form). Spin evaporation *in vacuo* gave a residue that was recrystallized from methanol to yield 90 mg. (83%) of white needles, m.p. 180–

181°; $[\alpha]^{24}D$ − 79 ± 2° (0.38%); ν_{max} 3300 (NH, OH), and 1750, 1730 (d) cm.$^{-1}$ (cyclic carbonate C=O).

Anal. Calcd. for $C_7H_{13}NO_6$: C, 40.6; H, 6.28; N, 6.76. Found: C, 40.8; H, 6.15; N, 7.04.

3-Amino-4-*O*-benzoyl-*N*-carbophenoxy-3-deoxy-D-altritol (XXXI).—A preliminary kinetic study on the hydrolysis of XXIX with 3:2 tetrahydrofuran–aqueous hydrochloric acid (1 *N*) showed that hydrolysis was complete in 18 hr. at 23°; at that time, t.l.c. in 5:1 benzene–methanol showed that the starting material (R_f 0.95) had disappeared and only a single spot with R_f 0.30 remained.

A mixture of 3.0 g. of XXIX, 180 ml. of tetrahydrofuran, and 120 ml. of 1 *N* aqueous hydrochloric acid was stirred at room temperature for 18 hr., then neutralized with Dowex 1-X8 (carbonate form). The residue remaining after spin evaporation *in vacuo* was further dried by spin evaporation *in vacuo* of an ethanol solution. Crystallization from 1:1 ethyl acetate–benzene gave 1.75 g. (70%) of white crystals, m.p. 127–129°; $[\alpha]^{24}D$ − 11 ± 1° (0.33%); ν_{max} 3500, 3350 (NH, OH), 1700 (benzoate and urethane C=O), and 715 cm.$^{-1}$ (benzoate CH).

Anal. Calcd. for $C_{20}H_{23}NO_8$: C, 59.2; H, 5.68; N, 3.46. Found: C, 59.1; H, 5.73; N, 3.39.

Similarly, hydrolysis of XXX gave XXXII as a glass that gave a single spot (R_f 0.36) on t.l.c.; however, the infrared spectrum indicated a mixture of XXXII and the cyclized urethane (XXXV) since the carbonyl absorption was broadened to 1700–1730 cm.$^{-1}$.

3-Amino-6-(and 4)-*O*-benzoyl-3-deoxy-D-altritol 2,3-Carbonate (XXXIV and XXXV). A.—A kinetic study on ring closure of XXXI was necessary since it soon became apparent that benzoyl migration in XXXV to give XXXIV was taking place. A solution of XXXI in pyridine was refluxed and aliquots at time intervals were examined by t.l.c. with 4:1 benzene–methanol and by the disappearance of the amide NH of XXXI at 1510 cm.$^{-1}$. After 10 min., starting material XXXI with R_f 0.43 was still present and a new spot appeared at R_f 0.35. At the end of 30 min. starting material was absent by t.l.c. and the product showed no NH band at 1510 cm.$^{-1}$; at this point, a major spot at R_f 0.35 was present and minor spot at R_f 0.40. By 90 min., both spots at R_f 0.35 and 0.40 were about equal intensity, but after 3 hr. only a trace of the spot at R_f 0.35 was present. As shown subsequently, the crystalline, rearranged benzoate (XXXIV) isolated at the end of 3 hr. had R_f 0.40.

B.—A solution of 400 mg. of XXXI in 25 ml. of pyridine was refluxed for 3 hr., then spin evaporated *in vacuo*. Traces of pyridine were removed by spin evaporation of toluene (two 10-ml. portions). Crystallization of the residue as rosettes from ethyl acetate in an open flask occurred slowly as the hydrate of the 6-benzoate (XXXIV) formed; yield 200 mg. (62%), m.p. 82–85°. Repeated recrystallization from ethyl acetate was still slow, indicating that water vapor was necessary for crystallization. The melting point remained at 82–85°; $[\alpha]^{24}D$ + 52.2 ± 0.5° (0.75%); ν_{max} 3500, 3300 (NH, OH), 1740 (cyclic carbonate C=O), 1710 (benzoate C=O), 1650 (weak, water), 705 (benzoate CH), and no amide NH near 1510 cm.$^{-1}$.

Anal. Calcd. for $C_{14}H_{17}NO_7 \cdot H_2O$: C, 51.1; H, 5.78; N, 4.26; O, 38.9. Found: C, 51.5; H, 5.87; N, 4.43; O, 38.9.

This compound consumed 1/2 mole of periodate in 5 hr., 1 mole in 18 hr., and no additional periodate in 24 hr.; the slow uptake was compatible with the nonterminal *vic*-glycol structure of XXXIV.

C.—A reaction run as in B, but for 30-min. reflux, gave a glass that was mainly XXXV, but could not be crystallized.

2-*O*-Benzoylglycolaldehyde (XXI) 2,4-Dinitrophenylhydrazone. A.—A solution of 0.75 g. of XXXIV in 200 ml. of water containing 1.0 g. of sodium metaperiodate was allowed to stand at room temperature for 24 hr., then extracted with methylene chloride. Evaporation of the combined extracts *in vacuo* gave 310 mg. of crude XXI. Conversion to the 2,4-dinitrophenylhydrazone in the usual manner gave 450 mg. (44% based on XXXIV) of orange crystals, m.p. 183–185°; ν_{max} 3300 (NH), 1710 (benzoate C=O), 1500 (NO_2), and 710 cm.$^{-1}$ (benzoate CH).

Anal. Calcd. for $C_{14}H_{12}N_4O_5$: C, 52.3; H, 3.49; N, 16.3. Found: C, 52.4; H, 3.69; N, 16.2.

Ohle and Melkonian[18] have recorded m.p. 185° for this compound prepared by a different route.

The other fragment (XXXVIII) was isolated as a glass by spin evaporation of the aqueous periodate solution *in vacuo* and extraction with absolute ethanol. This glass had ν_{max} 3300 (broad NH, OH), and 1750–1710 (broad, cyclic urethane C=O and aldehyde C=O); since a band near 710 cm.$^{-1}$ was absent, no benzoate was present. This glass could not be crystallized and was resistant to boiling with 2.5 *N* hydrochloric acid for 18 hr. Further studies on the preparation of XXXVIII (*via* XXXVII) and its conversion to the free tetrose will be pursued.

B.—Oxidation of crystalline XVIII, as described in A, gave an oil which was converted to the 2,4-dinitrophenylhydrazone, m.p. 183–185°, that was identical with preparation A.

3-Amino-3-deoxy-D-altritol 2,3-Carbonate (XXXVII). A.—A solution of 50 mg. of XXXIV in 3 ml. of 0.3 *N* methanolic sodium methoxide was allowed to stand at room temperature for 18 hr. in a stoppered flask. The solution was neutralized with Dowex 50W-X8 (H^+ form), then evaporated to residue *in vacuo*. Crystallization from ethanol–ethyl acetate gave 21 mg. (63%) of white plates, m.p. 166–167°; $[\alpha]^{24}D$ + 68 ± 1° (0.30%); ν_{max} 3300 (NH, OH), 1740 (cyclic urethane C=O), and no benzoate CH near 710 cm.$^{-1}$.

Anal. Calcd. for $C_7H_{13}NO_6$: C, 40.8; H, 6.17; N, 6.76. Found: C, 40.8; H, 6.17; N, 7.00.

This compound was recovered unchanged under the acid conditions used for hydrolysis of XXXIII to XXXVI.

B.—A solution of 70 mg. of XXXVI in 3 ml. of reagent methanol containing a drop of 1 *N* methanolic sodium methoxide was allowed to stand 18 hr., then processed as in A to yield 50 mg. (71%), m.p. 166–167°, that was identical with preparation A.

3-Amino-3-deoxy-1,2:5,6-di-*O*-isopropylidene-D-altritol (VIa) and -D-mannitol.—The availability of 4-*O*-benzoyl-1,2:5,6-di-*O*-isopropylidene-D-arabo-3-hexulose[12] suggested that it be investigated as a source of VIa by oximation and reduction. This route was much less effective for preparation of VIa than the azide displacement route (II → I) described earlier,[4] since both VIa and the corresponding mannitol isomer were obtained; separation by crystallization gave large losses.

A solution of 1.8 g. of the keto sugar[12] in 50 ml. of ethanol was added to a solution of 1.05 g. of hydroxylamine and 2.0 g. of anhydrous sodium acetate in 10 ml. of water. After being refluxed for 2 hr., the mixture was poured into 500 ml. of water and extracted with five 100-ml. portions of chloroform. The combined extracts were washed with 50 ml. of water, dried with magnesium sulfate, and spin evaporated *in vacuo;* the residue was dissolved in ether, clarified with charcoal, and again spin evaporated. The residual oxime (1.3 g., 70%), which failed to crystallize, had ν^{film} 3400 (OH), 1725 (benzoate C=O), 1700 (sh) (C=N), and 710 cm.$^{-1}$ (benzoate CH).

A solution of 1.3 g. of the oxime in 20 ml. of reagent ether was added to a stirred mixture of 1.3 g. of lithium aluminum hydride in 40 ml. of reagent ether. After being refluxed for 2 hr., the reaction mixture was processed as previously described for preparation of VIa.[4] Spin evaporation *in vacuo* of the combined chloroform–ether solutions gave 0.74 g. (83%) of mixed isomers as a semicrystalline mass.

For crystallization, 0.42 g. was dissolved in ethyl acetate, petroleum ether (b.p. 30–60°) was added to turbidity, and the solution was seeded with VIa to yield 0.10 g. (24% recovery, 14% based on ketone) of VIa, m.p. 111–114°. 3-Amino-3-deoxy-1,2:5,6-di-*O*-isopropylidene-D-mannitol could be isolated by chromatography on neutral alumina as previously described.[4] Elution with chloroform containing 1% methanol gave VIa in the early fractions and later fractions eluted the mannitol isomer, m.p. 80–83°, with 14% recovery.

Acknowledgment.—We wish to thank Professor A. J. Solo for interpretation of the n.m.r. spectra. We are grateful also to Starks Associates and the Cancer Chemotherapy National Service Center, mediated by Contract No. SA-43-ph-4346, for large scale preparation of VIa.

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Reduction of the Products of Periodate Oxidation of Carbohydrates. XIII. Determination of Sugars in Polysaccharides Oxidized by Periodate[1]

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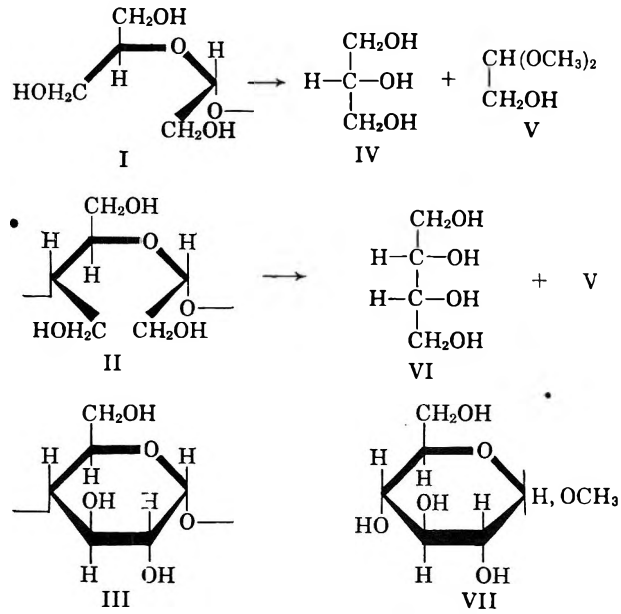
A method is described for the quantitative determination of sugar in periodate-oxidized polysaccharides. This is accomplished by reducing the polyaldehyde with sodium borohydride and subjecting the polyalcohol so formed to the action of methanolic hydrogen chloride which forms a mixture of alditols, methyl glycoside, and glycolic aldehyde dimethylacetal. Distillation under reduced pressure removes the glycolic aldehyde dimethylacetal, after which the residue is analyzed for sugar by the phenol–sulfuric acid method.

Periodate oxidation studies on polysaccharides[2] have necessitated the development of a simple method for determining the proportion of sugar units which survive oxidation. In a number of instances, the proportion of sugar residues in periodate-oxidized polysaccharides has been deduced indirectly from the periodate consumption[3] and from the results of the action of sodium hydroxide,[4] sodium borohydride,[5] or *p*-nitrophenylhydrazine[6] on the derived polyaldehyde.

Another approach in the case of glucans is to determine glucose in the hydrolysate of the polyaldehyde by means of glucose oxidase.[7] In other procedures, the hydrolysate of a polyalcohol obtained by reduction[8] of the corresponding polyaldehyde may be separated by paper chromatography and the reducing sugar determined by the Nelson–Somogyi[9,10] or by the phenol–sulfuric acid method.[11] The anthrone and orcinol reagents have been used for the determination of sugar in periodate-oxidized and reduced oligosaccharides[12] and glycopeptides,[13] respectively.

This article describes a simple and general method for the determination of sugar residues in polysaccharides which have been subjected to periodate oxidation. The procedure involves reducing the polyaldehyde to the polyalcohol with sodium borohydride, after which the polyalcohol is boiled with methanolic hydrogen chloride. This results in total cleavage giving glycerol and/or erythritol, the methyl glycosides of the sugar residues which survive periodate oxidation, and glycolic aldehyde dimethylacetal. Thus, in the case of a terminal, nonreducing glucose residue, periodate oxidation and reduction gives the residue I which upon methanolysis yields glycerol (IV) and glycolic aldehyde dimethylacetal (V). By the same procedure, a (1→4)-linked glucose unit will provide the residue II which in turn will give rise to erythritol (VI) and V, whereas any glucose unit surviving periodate oxidation, such as that depicted in III, will furnish methyl D-glucoside (VII). Evaporation of the neutralized solution removes



the glycolic aldehyde dimethylacetal which interferes with the phenol–sulfuric acid method and leaves a mixture of methyl glycosides and sugar alcohol(s). This residual mixture is dissolved in water and the sugar is determined by the phenol–sulfuric acid method in the usual way.[11]

Although the present study deals only with the glucans, glycogen, and starch, the method is applicable to polysaccharides in general and, since protein does not interfere[14] with the phenol–sulfuric acid method, the procedure proposed herein is also applicable to glycoproteins and glycopeptides.

Experimental

The apparatus used was a spectrophotomer (Coleman Junior or its equivalent) and a set of matched test tubes (18 × 150 mm.). The reagents used were phenol reagent,[11] prepared by dissolving freshly distilled phenol (5 g.) in distilled water (95 ml.), and sulfuric acid, reagent grade 95.5%, Spectro Grade 1.84.

I. Periodate Oxidation of the Polysaccharide.—A known weight of glycogen from calf liver was treated with an amount of 0.1 *N* sodium periodate calculated to bring about the desired level of oxidation, the reaction mixture being kept in the dark at 5°. A blank experiment was carried out at the same time. After about 3 weeks, the periodate consumption was determined volumetrically.[3] From the amount of periodate consumed, the degree of oxidation of the polysaccharide was calculated, assuming that 1 mole of periodate is consumed per glucose unit. The periodate-oxidized glycogen was isolated by freezing the reaction mixture and then allowing it to thaw,[15] after which the precipi-

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tated glycogen polyaldehyde was washed repeatedly with water until the washings were free from iodate (tested with acidified potassium iodide–starch solution). The periodate-oxidized glycogen was washed successively with ethanol (to remove water), ether, and petroleum ether (b.p. 30–60°) and dried *in vacuo*. Three samples of partially ozidized glycogen of 50, 75, and 90% oxidation were prepared in this manner.

A modified procedure can be used for polysaccharides which are soluble in the periodate oxidation reaction mixture. An aqueous solution of barium acetate is added until no more precipitate of barium iodate or periodate is formed. The solution is then filtered, the residue is washed with water, and the filtrate is treated as in section II below.

II. Determination of Glucose in Periodate-Oxidized Polysaccharides.—It is recommended that for 99% oxidized polysaccharides a 100-mg. sample should be used, and for 1% oxidized polysaccharides 10 mg. is a suitable quantity.

A. By the Phenol–Sulfuric Acid Method.[11] **Example 1.**—Periodate-oxidized glycogen (100.6 mg. oxidized to 90% of theory required for complete cleavage) was treated with 0.5% sodium borohydride solution (10 ml.), and the reaction mixture was allowed to stand overnight. A test portion of the solution, after acidification with dilute acetic acid, gave a negative Fehling's test. The solution was neutralized with dilute hydrochloric acid and concentrated to dryness under reduced pressure (35–40°), the last traces of water being removed by repeated addition and distillation of absolute ethanol. The dry residue was refluxed with 2.5% methanolic hydrogen chloride (5 ml.) for 2 hr. (or until the mixture gave a negative Fehling's test). The solution was neutralized by the addition of lead carbonate and filtered, and the filtrate was concentrated to dryness. The residue was dissolved in dry methanol (20 ml.) and the solution concentrated to dryness. This was repeated twice, and the product was heated finally for 2 hr. at 80–90° under reduced pressure to ensure complete removal of glycolic aldehyde dimethylacetal and trimethyl borate to give a residue R. This residue (R) was dissolved in water, the solution was filtered, and the volume was adjusted to 500 ml. by adding water.

Aliquots (1 ml.) of the solution in 18 × 150 mm. tubes were treated with the phenol reagent (1 ml.), followed by concentrated sulfuric acid (5 ml.), the latter being added quickly against the liquid surface to ensure rapid mixing.[11] The tubes were allowed to cool to room temperature, and the absorbancy of the characteristic orange-yellow color was determined at λ 490 mμ. Analyses were carried out in triplicate. The amount of glucose in each tube was computed by reference to a standard curve for glucose (10–50 μg.).[11]

Example 2.—Periodate-oxidized starch (30.4 mg. of 95% oxidation) was suspended in water (15 ml.) and treated with sodium borohydride (50 mg. in 10 ml. of water), and the mixture was kept for 24 hr. at room temperature. The procedure described above in example 1 was then followed except that methanolysis was continued for 7 hr. The solution was filtered, and the volume was adjusted to 50 ml. by the addition of water. The glucose content of 1-ml. aliquots was determined by the phenol–sulfuric acid method as described above.

B. By the Glucose Oxidase Method.[16,17]—The enzyme solution was prepared by combining a solution of glucose oxidase[18] (10 ml., 0.01% in 0.05 *M* acetate buffer of pH 4.8), peroxidase[19] (10 ml., 0.025% in the buffer), *o*-dianisidine (1 ml., 0.5% in 95% ethanol), and 0.05 *M* acetate buffer, pH 4.8 (20 ml.).

The residue (such as R, see example 1) was hydrolyzed by heating for 5 hr. at 100° with 1 *N* sulfuric acid (5 ml.). The solution was neutralized with barium carbonate and filtered, and the residue was washed well with water. The volume of the filtrate was adjusted to 100 ml. with 0.05 *M* acetate buffer, pH 4.8. Duplicate aliquots (1 ml., containing 20–80 μg. of glucose) were pipeted into 18 × 150 mm. tubes and allowed to equilibrate at 37° in a constant temperature bath. The enzyme solution (4 ml.), preheated to 37°, was pipeted into each tube, and the digest was incubated at 37°. The reaction was stopped after exactly 30 min. by rapid addition of 0.5 *N* hydrochloric acid (1 ml.), and the tubes were cooled in water for 20 min. The absorbancy of each tube was measured at λ 420 mμ. Glucose standards (20–80 μg./ml.) were analyzed concurrently in duplicate and a standard curve was constructed. The amount of glucose present in a 1-ml. aliquot was determined by reference to the standard curve.

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(18) Nutritional Biochemicals Corp., pure grade glucose oxidase.

(19) Worthington Biochemical Corp., recrystallized horse radish peroxidase.

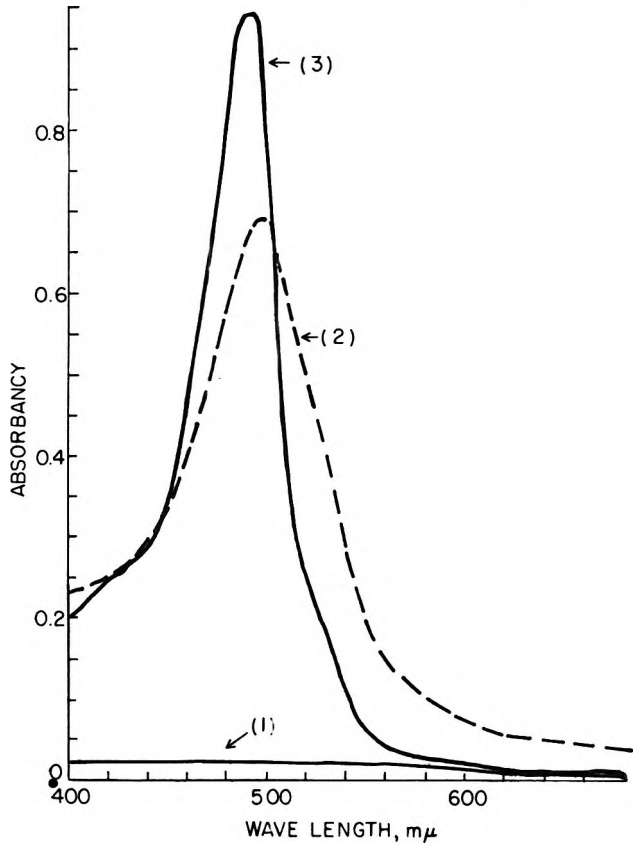

Fig. 1.—Test solutions contained an aqueous solution (1 ml.) of (1) glycerol and erythritol (45 μg., 730 μg.), (2) glycolic aldehyde (470 μg.), and (3) glucose (85 μg.), together with 5% aqueous phenol (1 ml.) and concentrated sulfuric acid (5 ml.).

Results and Discussion

The analyses of three glycogen polyaldehydes and three starch polyaldehydes are summarized in Table I.

TABLE I

GLUCOSE CONTENT OF PERIODATE-OXIDIZED GLYCOGENS AND STARCHES

	Weight of sample, mg.	Degree of oxidation, %	% Glucose, determined by— Periodate consumption	Phenol–sulfuric acid	Glucose oxidase
Glycogen	57.3	50	50.0	46.3	44.2
	73.2	75	25.0	27.6	24.5
	110.6	90	10.0	14.2	13.8
Starch	28.0	3	97.0	95.0	
	27.4	60	40.0	41.0	
	30.4	95	5.0	5.3	

With specimens of periodate-oxidized glycogen, good agreement was obtained between the expected glucose content based on the periodate consumption data, and the glucose content as determined by the phenol–sulfuric acid method and by the glucose oxidase method.

The success of this simple method is dependent on complete removal of interfering compounds. Glycolic aldehyde, which is derived from C-1 and C-2 of the glucose units, produces a pink coloration with the phenol–sulfuric acid reagent (λ_{max} 495 mμ, Fig. 1), and boric acid, generated in the sodium borohydride reduction,

decreases the color yield in the phenol–sulfuric acid reaction in an undefined manner.[20] Both of these compounds are converted to volatile derivatives (glycolic aldehyde dimethylacetal and trimethyl borate) by methanolysis and are eliminated by evaporation of the solvent. The complete removal of glycolic aldehyde dimethylacetal may be checked by testing the residue with the diphenylamine reagent.[21] In the event of incomplete removal of the aldehyde, the methanolysis and subsequent distillation is repeated. Glycerol, formed from terminal nonreducing hexopyranose and pentofuranose units, and erythritol, formed from nonterminal (1→4)-linked hexopyranose units, do not interfere with the glucose determination (Fig. 1).

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Polynucleotides. II. Synthesis of (3′→5′)-Linked Diribonucleoside Phosphates Containing Uridine

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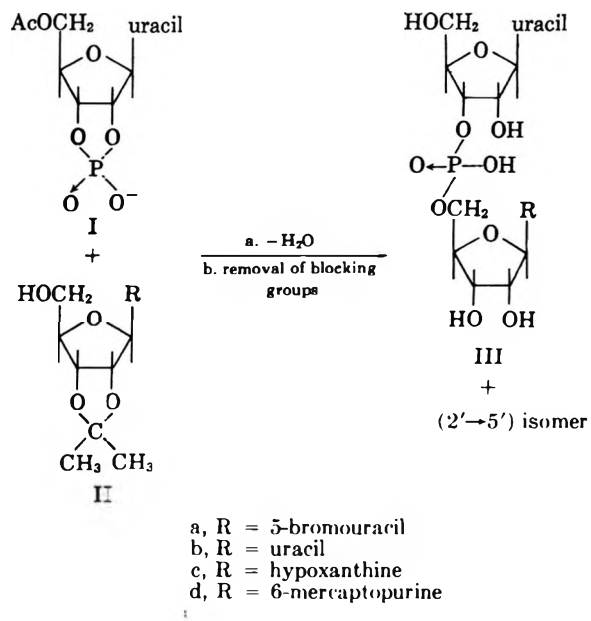
In the past few years, the syntheses of several (3′→5′)-linked diribonucleoside phosphates have been reported.[1-5] These syntheses fall into two groups, namely those which produce the (3′→5′) internucleotide bond and those which produce a mixture of (2′→5′)- and (3′→5′)-linked isomers. The second type of synthesis was utilized by us, and an ion-exchange procedure was developed which resolves the mixed isomers. The internucleotide bond was formed by treating 5′-*O*-acetyluridine-2′,3′ cyclic phosphate with a nucleoside blocked in the 2′- and 3′-positions in the presence of diphenyl phosphorochloridate. The following diribonucleoside phosphates have been prepared: uridylyl(3′→5′)-5-bromouridine, uridylyl(3′→5′)uridine, uridylyl(3′→5′)-6-thioinosine, and uridylyl(3′→5′)inosine.

One of the major problems in the synthesis of (3′→5′)-linked diribonucleoside phosphates stems from the requirement for an intermediate blocked in the 2′- and 5′-positions. The key intermediate can be prepared either by acetylation of the 2′-position of nucleoside-3′ phosphates[6] or by phosphorylation of ribonucleosides blocked in the 2′- and 5′-positions such as the easily prepared 2′,5′-di-*O*-trityluridine.[7] The first approach relies on the ability to obtain pure 3′-ribonucleotides and the second is limited to those nucleosides for which selective blocking of the 2′- and 5′-positions is practical. The difficulties in preparing diribonucleoside phosphates can be ameliorated to some extent if selective blocking of the 2′- or 3′-position is eliminated with the result that the final product becomes a mixture of (2′→5′)- and (3′→5′)-linked isomers. The usefulness of this method, therefore, rests on the ability to resolve the isomers. One of the first exponents of this approach to oligonucleotide syntheses was Michelson,[5] who prepared a series of [2′(3′)′→5′]-linked diribonucleoside phosphates and in some cases was able to separate the isomers. Such an approach to the synthesis of diribonucleoside phosphates results in a reduction of the number of steps and increased over-all yields. We have examined this approach with the intention of ascertaining its general usefulness for the synthesis of oligonucleotides and this paper describes the preparation of diribonucleoside phosphates in which uridylyl-3′ phosphate is linked to the 5′-position of 5-bromouridine, uridine, inosine, and 6-thioinosine.

The internucleotide bond was formed according to the method developed by Michelson[5] in which a ribonucleoside-2′,3′ cyclic phosphate (I) reacts with a 2′,3′-isopropylidene derivative of a ribonucleoside (II) under the influence of diphenyl phosphorochloridate and in the presence of tri-*n*-butylamine. Ready availability of ribonucleoside-2′,3′ cyclic phosphates is essential to



a, R = 5-bromouracil
b, R = uracil
c, R = hypoxanthine
d, R = 6-mercaptopurine

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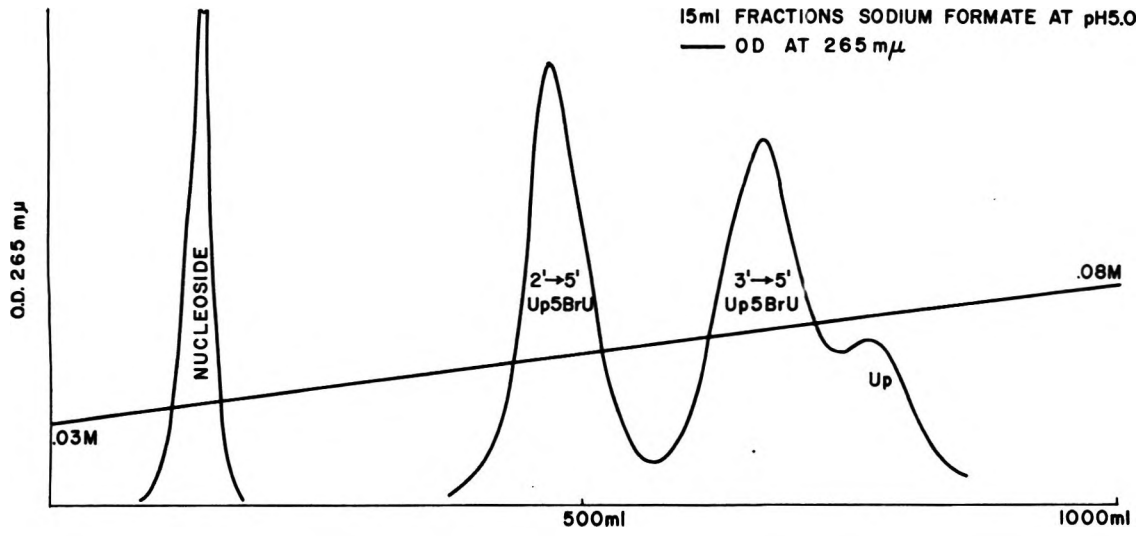

Fig. 1.—Ion-exchange chromatographic separation of uridylyl[2′(3′)→5′]-5-bromouridine—[2′(3′)→5′]Up5BrU, 0.1-mmole scale, using a Dowex-1X2 formate column, 14 × 0.9 cm.

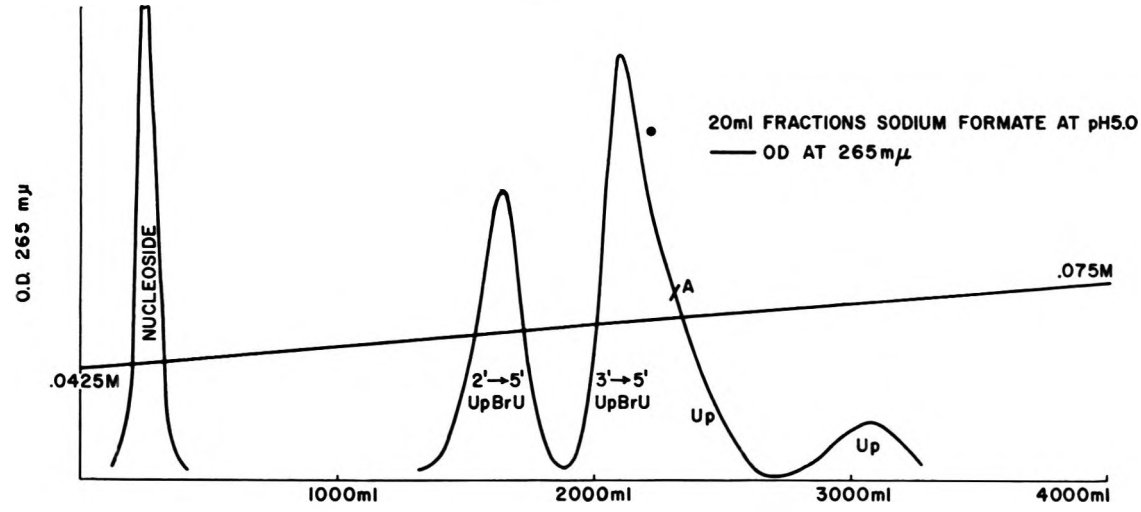

Fig. 2.—Ion-exchange chromatographic separation of uridylyl[2′(3′)→5′]-5-bromourid ne—[2′(3′)→5′]Up5BrU, 1.0-mmole scale, using a Dowex-1X2 formate column, 42 × 1.2 cm.

the usefulness of this method and a number of methods have been described for their preparation. For our purposes the ethyl chloroformate method of Michelson[5] with some modifications was found to be the most satisfactory route to the formation of nucleoside-2′,3′ cyclic phosphates. Ethyl chloroformate can be used in aqueous solution, but the hydrochloric acid which is released during the reaction must be effectively neutralized since cyclic phosphates are unstable at pH values of less than 4.0 or more than 9.0.[8] Using the reaction conditions as previously described[5] for the preparation of uridine-2′,3′ cyclic phosphate, only 70% of cyclized phosphate was obtained, but, upon addition of a greater excess of tri-*n*-butylamine, a yield of 100% was obtained. Since tri-*n*-butylamine has only a limited solubility in water, there was no danger of hydrolyzing the cyclic phosphate by making the reaction medium too basic.

The first diribonucleoside phosphate prepared in this series was uridylyl(3′→5′)-5-bromouridine (IIIa). The nucleotide intermediate, 5′-*O*-acetyluridine-2′,3′ cyclic phosphate (I), had been prepared previously by Smrt and Šorm[3] who used dicyclohexyl carbodiimide (DCC) for the preparation of the cyclic phosphate. For our purposes, we found the ethyl chloroformate method more suitable, as it was not necessary to isolate the product before it was treated with IIa. Compound IIa was prepared by the method developed by Hampton[9] and the product was conveniently isolated from the reaction mixture by using partition chromatography on Celite-545 according to the method of Hall.[10] This compound had been prepared previously by Smrt and Šorm,[11] and Ueda.[12] Formation of the internucleotide bond to form uridylyl[2′(3′)→5′]-5-bromouridine (IIIa) was carried out in anhydrous dioxane. In order to ensure that the intermediates of the reaction were scrupulously dry, tri-*n*-butylammonium 5′-*O*-acetyluridine-2′,3′ cyclic phosphate and 2′,3′-isopropylidene-5-bromouridine were dissolved previously in dioxane

(8) D. M. Brown, C. A. Dekker, and A. R. Todd, *J. Chem. Soc.*, 2715 (1952).

(9) A. Hampton, *J. Am. Chem. Soc.*, **83**, 3640 (1961).

(10) R. H. Hall, *J. Biol. Chem.*, **237**, 2283 (1962).

(11) J. Smrt and F. Šorm, *Collection Czech. Chem. Commun.*, **25**, 553 (1960).

(12) T. Ueda, *Chem. Pharm. Bull.* (Tokyo), **8**, 455 (1960).

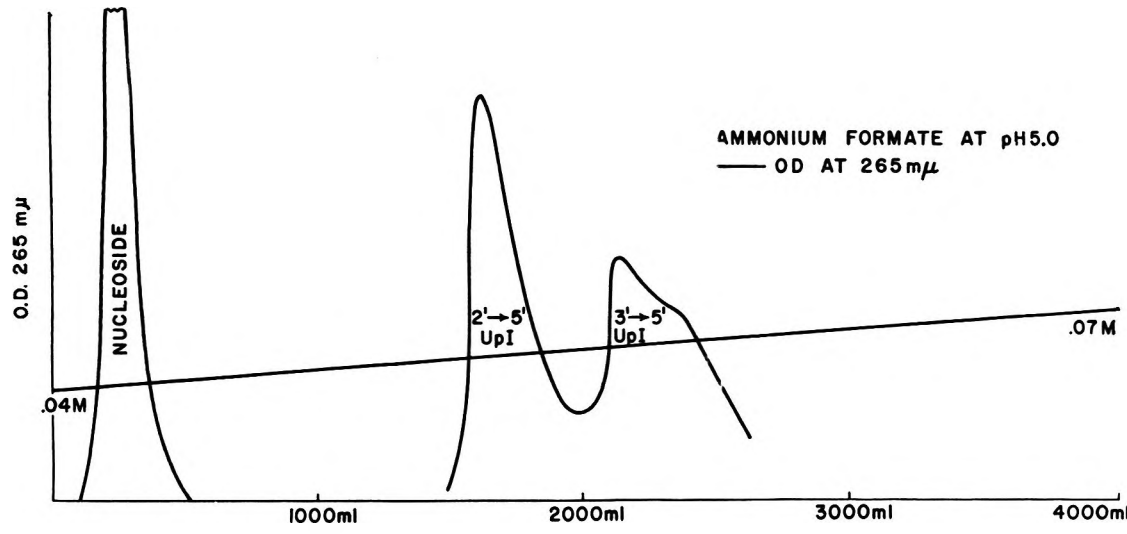

Fig. 3.—Ion-exchange chromatographic separation of uridylyl[2′(3′)→5′]inosine—[2′(3′)→5′]UpI, 1.0-mmole scale, using a Dowex-1X2 formate column, 42 × 1.2 cm.

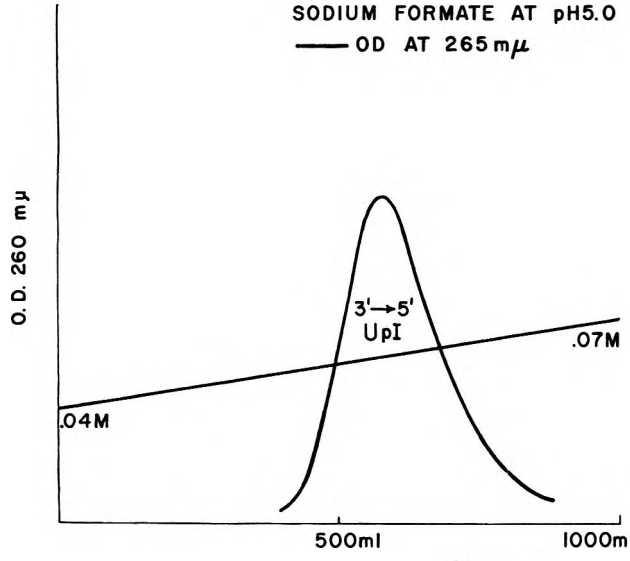

Fig. 4.—Ion-exchange chromatographic purification of uridylyl-(3′→5′)inosine isolated from peak shown in Fig. 3, using a Dowex 1X2 formate column, 25 × 0.9 cm.

and the solution was freeze-dried.[13] Freeze-drying was repeated three times after which the residue was dissolved in dioxane and diphenyl phosphorochloridate was added. The diphenylphosphorochloridate, although a phosphorylating agent, does not appear to phosphorylate the free nucleoside 5′-hydroxyl group but presumably reacts with the cyclic phosphate, providing energy for the desired phosphorylation.[14]

Dowex-1X2 (formate) ion-exchange resin was used for the chromatographic separation. Separation of the reaction products was undertaken on a 0.1-mmole scale, using a small column and a fairly steep formate gradient as shown in Fig. 1. Chromatography was then scaled up to a 1-mmole level using a less steep formate gradient (Fig. 2). Attempts to separate the products of the reaction at pH below 5.0 were made, but the separation was not satisfactory. The optimum pH for this type of separation appears to lie between 5.0 and 5.5, which corresponds to the conditions required for separation of uridine-2′ phosphate and uridine-3′ phosphate.[15] The choice of cation to be used in the buffer solutions, *i.e.*, sodium *vs.* ammonium, appeared to make little difference in the degree of separation. The use of sodium formate, however, did tend to reduce tailing of the peaks, as shown by the resolution of uridylyl[3′(2′)→5′]inosine (IIIc) illustrated in Fig. 3 and 4. When the fraction containing the (3′→5′) isomer (Fig. 3) was rechromatographed using a sodium formate elution gradient, a single bell-shaped peak was obtained (Fig. 4), although the relatively smaller loading of the column during the rerun may have contributed toward this improved elution pattern. It was not possible to separate completely uridylyl(3′→5′)-5-bromouridine from uridylic acid (Fig. 2); therefore, the material eluted after point A was discarded and the material from the major part of the peak was rechromatographed in the same system to give pure uridylyl(3′→5′)-5-bromouridine (IIIa). The total yield of the diribonucleoside phosphates based on uridine-2′(3) phosphate averaged 40–50%. The ratio of the amounts of the two isomers approximated 1:1, so that the effective yield of the desired isomer was 20–25%. The identity of the two isomers of uridylyl[2′-(3′)→5′]-5-bromouridine was established by the action of pancreatic ribonuclease, which brought about the complete hydrolysis of uridylyl(3′→5′)-5-bromouridine to uridine-3 phosphate, and 5-bromouridine, and had no detectable effect on the (2′→5′)-linked isomer. The complete hydrolysis by ribonuclease also indicated that no migration of the phosphate bond from the 3′-position to the 2′-position occurred under the conditions used for the final isolation of the products.

Identical procedures were used for the synthesis of uridylyl(3′→5′)uridine (IIIb), uridylyl(3′→5′)inosine (IIIc), and uridylyl(3′→5′)-6-thioinosine (IIId). Compound IIId, when directly obtained from the column, ran as a single spot on paper chromatography and, upon treatment with ribonuclease, yielded 1 equiv. each of 6-thioinosine and uridylic acid, but, after lyophilization

(13) 2′,3′-Isopropylidene-5-thioinosine was dried at 109° under vacuum, not as described for the other isopropylidene derivatives, and the internucleotide linkage was formed in a mixture of dioxane and *N,N*-dimethylformamide (1:1).

(14) R. Letters and A. M. Michelson, *J. Chem. Soc.*, 71 (1962).

(15) W. E. Cohn, in "Nucleic Acids," Vol. 1, Chargaff and Davison, Ed., Academic Press, New York, N. Y., 1955, pp. 211–242.

of the entire fraction, the product became yellow. An ultraviolet absorbing impurity, the identity of which has not yet been established, was separated from the product by high voltage electrophoresis.

Synthesis of uridylyl(3′→5′)uridine in the present series offers an opportunity for comparison of this general method with those used previously for this synthesis. For example, Hall and Thedford[1] directly obtained the (3′→5′)-linked diribonucleoside phosphate *via* a uridine intermediate specifically blocked at the 2′- and 5′-positions. The synthesis required four steps and the over-all yield was 7.4%, based on uridine as the starting material. Starting from commercially available uridylic acid, the present method also consists of four steps and yields the diribonucleoside phosphate in over-all yield of 23%. Since the specific synthesis of the (3′→5′)-linked isomer requires an ion-exchange column procedure for final purification, the separation of the mixed (2′→5′)- and (3′→5′)-linked isomers in the method reported here represents no additional burden. Thus, depending on the available starting materials, the synthesis of certain diribonucleoside phosphates *via* the mixed (2′→5′)- and (3′→5′)-linked isomers may be the method of choice.

Experimental

Paper Chromatography.—Paper chromatography was carried out on Whatman No. 3 MM chromatograms which were developed in each of two descending solvent systems for 16 hr.: A, isopropyl alcohol–concentrated ammonium hydroxide–water (7:1:4), and B, isopropyl alcohol–aqueous ammonium sulfate, 1% (2:1).

Paper Electrophoresis.—Paper electrophoresis was carried out for 1 hr. in a Gilson Electrophorator on Whatman No. 3 MM chromatography paper in a buffer of 0.05 *M* formic acid adjusted to pH 3.0 with ammonia (4500 volts, 1 hr.). Results are expressed as a fraction of the mobility of uridylic acid [(3′),2′ mixture] which, under the previous conditions, moves as a single spot approximately 25 cm. from the origin.

Unless stated otherwise, all evaporations referred to were carried out in a rotary evaporator at temperatures up to 30°. Samples for analyses were dried at 25° to constant weight over phosphorus pentoxide and under vacuum. Melting points are uncorrected. Spectra were obtained on a Cary Model 14 spectrophotometer.

Uridine-2′,3′ Cyclic Phosphate (Modification of the Method of Michelson[6]).—Uridine-2′(3′) phosphate (324 mg., 1 mole) was dissolved in water (3 ml.) and the solution was treated with tri-*n*-butylamine (1.1 ml., 7.6 mmoles) and ethyl chloroformate (0.2 ml., 2.1 mmoles) and shaken vigorously in a stoppered flask for 5 min. The reaction mixture was allowed to stand for a further 10 min. with occasional agitation before being evaporated to a thick gum. Paper chromatography of the crude gum in the two systems, A and B, and electrophoresis showed 100% conversion to cyclic phosphate; R_f, solvent A, 0.28, and B, 0.43; electrophoretic mobility, 1.12. The gum was washed several times with anhydrous ether and evaporated from anhydrous pyridine solution repeatedly until the product, pyridinium uridine-2′,3′ cyclic phosphate, crystallized.

Anal. Calcd. for $C_{14}H_{16}N_3O_8P$: C, 43.6; H, 4.19; N, 10.90. Found: C, 43.94; H, 4.32; N, 10.94.

Preparation and Purification of 2′,3′-Isopropylidene-6-thioinosine (IId).—This intermediate was prepared according to the method of Hampton.[9] The difficulties in isolating the product were overcome by employing a partition column as follows. Following the reaction on a 1-mmole scale, the solution was chilled to 0°, poured into dilute ammonium hydroxide, and this solution was evaporated to dryness. The residue was dissolved in 10 ml. of the lower phase of the solvent system *n*-butyl alcohol–aqueous ammonium hydroxide, 10% (3:1). This was mixed with 22 g. of Celite-545 and the mixture was packed on top of a previously packed partition column containing 140 g. of Celite-545 and 63 ml. of lower phase (column size, 2.54 × 80 cm.). The column was developed with the upper phase and the desired product was obtained within the first hold-back volume. (See ref. 10 for complete details of this technique for partition columns.) The product which moved as a single spot on paper chromatography (R_f, solvent A, 0.67, and B, 0.65) was crystallized from hot water; m.p. 268°. dec., yield 72%.

Anal. Calcd. for $C_{13}H_{16}N_4O_4S$: C, 48.13; H, 4.93; N, 17.28; S, 9.88. Found: C, 48.24; H, 4.94; N, 16.99; S, 9.89.

Uridylyl(3′→5′)-5-bromouridine (III). A Formation of the Internucleotide Bond.—The product of 1-mmole preparation of 5′-*O*-acetyluridine-2′,3′ cyclic phosphate[16] was dissolved in anhydrous dioxane (10 ml.) containing 2′,3′-isopropylidene-5-bromouridine[9,11,12] (726 mg., 2 mmoles). The mixture was freeze-dried from dioxane (3 × 10 ml.) before being dissolved in 5 ml. of dioxane. To this solution was added tri-*n*-butylamine (0.6 ml., 4.16 mmoles), followed by diphenyl phosphorochloridate (0.3 ml.). The flask was sealed and shaken for 5 min., then set aside for the reaction to continue for 24 hr., after which time the solvent was removed by evaporation. The resulting gum was dissolved in cold water (10 ml.), and the pH of the solution was adjusted to 9.5 with ammonium hydroxide (7.5 *M*). The aqueous solution was extracted with ether (four 20-ml. portions); pH was readjusted to 9.5 with ammonia. The alkaline solution was incubated at 37° for 24 hr. to remove the acetyl group. The acid labile isopropylidene group was removed as follows. A slight excess of Dowex 50-W-X8 (H^+ form) ion-exchange resin was added to the solution to remove all the cations and the solution was stirred at 35° for 1.5 hr. in the presence of the resin. The ion-exchange resin was removed from solution by filtration, and the pH of the solution was adjusted to 8.5 with ammonium hydroxide (7.5 *M*)

Ion-Exchange Chromatography.—Commercially available Dowex-1X2 (chloride) ion-exchange resin (200–400 mesh) was prepared for chromatography by washing in a column (30 × 1 in.) with 2 *N* sodium hydroxide solution until no further trace of chloride ion was found in the effluent. The resin was then washed with distilled water to neutrality followed by 4 *N* formic acid (4:1.). Finally the resin was washed with 80% formic acid (1 l.) and distilled water until the effluent was neutral. After adjustment of the solution to pH 8.5, the solution was absorbed onto the top of a column (40 × 1.2 cm) of Dowex-1X2 formate ion-exchange resin and the column was washed with a little distilled water (100–150 ml.). Gradient elution with formate was commenced (see Fig. 2 for conditions), and 20-ml. fractions were collected. The solutions of formate buffer containing uridylyl-(3′→5′)-5-bromouridine[17] and the (2→5′) isomer were cooled to 0° and run under pressure through a column of Dowex-50-WX8 (H^+ form) ion-exchange resin, 50–100 mesh, to remove the cations. The resulting acidic solutions were immediately frozen and lyophilized to yield white powders. The products were redissolved, frozen and relyophilized. The (2→5′)-linked isomer was chromatographically pure and weighed 128 mg. (20.4%). The (3′→5′)-linked product was contaminated with approximately 3% uridylic acid as shown by paper chromatography. This sample was refractionated on the same size column under conditions identical with those described in Fig. 2. In this manner 126 mg. of analytically and chromatographically pure uridylyl(3′→5′)-5-bromouridine was obtained; paper chromatography gave R_f, system A, 0.51, and B, 0.57; electrophoretic mobility, 0.71.

Anal. Calcd. for $C_{18}H_{22}BrN_4O_{14}P$: C, 34.4; H, 3.57; N, 8.9; Br, 12.7. Found: C, 34.54; H, 3.83; N, 8.67; Br, 13.0.

Uridylyl(3′→5′)uridine.—5′-*O*-Acetyluridine-2′,3′ cyclic phosphate (1 mmole) was treated with 2′,3′-isopropylideneuridine (2 mmoles) in the same way as for the preparation of uridylyl-[2′(3′→5′]-3-bromouridine. The blocking groups were removed under the same conditions as previously described, and the conditions for the ion-exchange chromatography are shown in Fig. 5. The yields of the diribonucleoside phosphate isomers, which were obtained as white lyophilized powders, were 127 mg. (23%) and 134.5 mg. (24.5%) for the (2′→5′)- and (3′→5′) isomers, respectively. The triethylammonium salt was prepared by dissolving the free acid in water and titrating with triethylamine to pH 7.0. The solution was filtered and lyophilized yielding triethylammonium uridylyl(3′→5′)uridine:

(16) Acetylation of uridine-2′,3′ cyclic phosphate was performed according to the method of Smrt and Šorm.[3]

(17) Because the fraction containing the (3′→5′)-linked isomer also contained a small amount of uridylic acid, it was collected only to point A, Fig. 2.

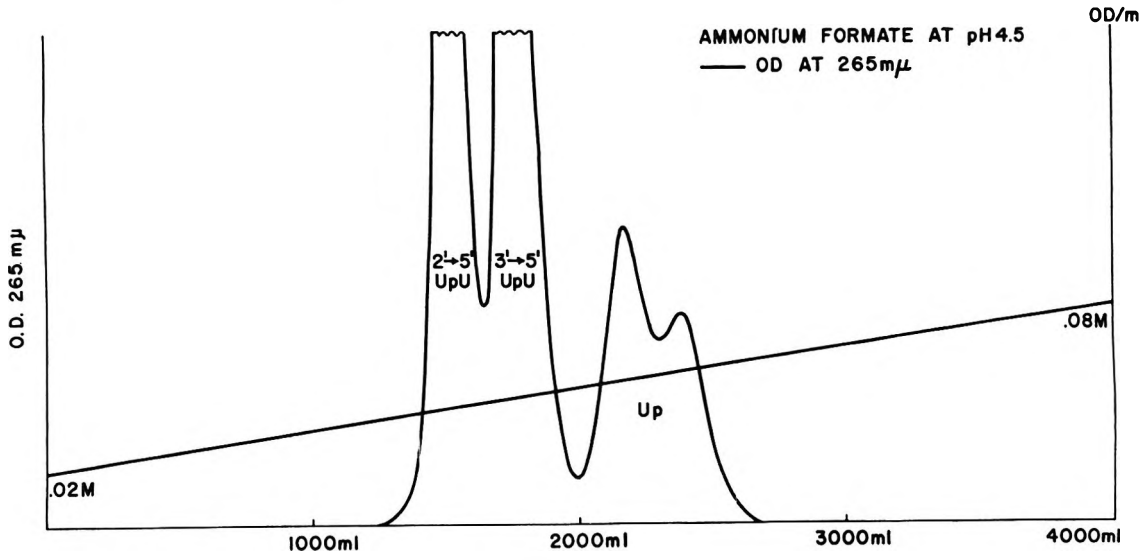

Fig. 5.—Ion-exchange chromatographic separation of uridylyl[2′(3′)→5′]uridine—[2′(3′)→5′]UpU; 1-mmole scale using a Dowex 1X2 formate column, 42 × 1.2 cm.

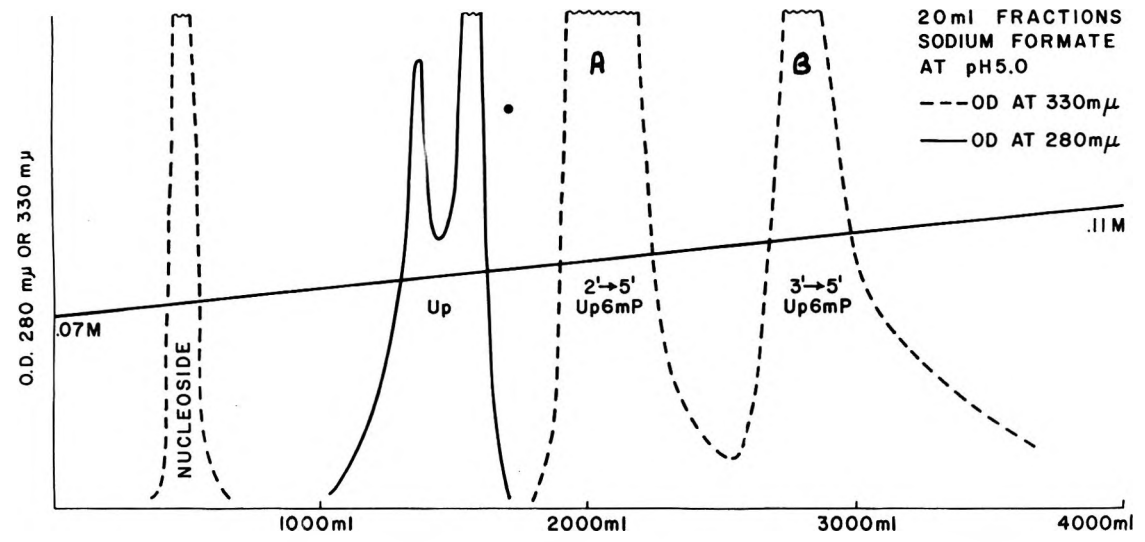

Fig. 6.—Ion-exchange chromatographic separation of uridylyl[2′(3′)→5′]-6-thioinosine—[2′(3′)→5′]Up6MP, using a Dowex 1X2 formate column, 42 × 1.2 cm.

paper chromatography gave R_f, solvent A, 0.26, and B, 0.30; electrophoretic mobility, 0.67.

Anal. Calcd. for $C_{24}H_{38}N_5O_{14}P \cdot 4H_2O$: C, 39.9; H, 6.36; N, 9.68. Found: C, 39.85; H, 6.36; N, 9.96.

Uridylyl(3′→5′)inosine (IIIc).—Uridylyl[2′(3′)→5′]inosine was prepared under conditions described for uridylyl[2′(3′)→5′]-uridine, from 5′-*O*-acetyluridine-2′3′ cyclic phosphate (1 mmole) and 2′,3′-isopropylideneinosine (2 mmoles). Conditions for the separation of the components of the reaction mixture are shown in Fig. 3. Although the (3′→5′) isomer, which was obtained white and amorphous, was homogeneous on paper chromatography in two systems (R_f, A, 0.23, and B, 0.30) and electrophoresis (mobility, 0.67), no satisfactory analysis was obtained (weight 151 mg., 27%).

Uridylyl(3′→5′)6-thioinosine (IIId).—5-*O*-Acetyluridine-2′,5′ cyclic phosphate (2 mmoles) was treated with 2′,3′-isopropylidene-6-thioinosine (1 mmole) in dioxane (2 ml.) and *N*,*N*′-dimethylformamide (2 ml.) as previously described. Only the nucleotide was dried by lyophilization from dioxane; the nucleoside was dried at 109° under vacuum. The hydrolytic removal of the blocking groups was carried out as described earlier. The conditions for the ion-exchange chromatography of the mixed isomers are shown in Fig. 5. The fractions were treated with Dowex-50 as described before and lyophilized in the dark. The yields were (2′→5′) isomer, 48.2 mg., and (3′→5′) isomer, 50.0 mg. Paper chromatography gave R_f, solvent A, 0.058, and B, 0.26; electrophoretic mobility, 0.60. Electrophoresis of the lyophilized material for 1 hr. at 4500 v. (pH 3.0) yielded the desired product and an impurity.[18] No satisfactory analysis for uridylyl(3′→5′)-6-thioinosine was obtained.

TABLE I

ULTRAVIOLET ABSORPTION DATA

	$\lambda_{max.}$ pH 2.0 mμ	ε	$\lambda_{max.}$ pH 7.0 mμ	ε	$\lambda_{max.}$ pH 11.0 mμ	ε
(3′→5′)Up5BrU	267	15,000	267	15,000	266	11,500
(3′→5′)UpI	252		252		256	
(3′→5′)UpU	262	19,100	262	19,100	262	14,800
(3′→5′)-Up6MPR	262 321		262 317		260 310	

Ribonuclease Treatment.—One milligram of each of the diribonucleoside phosphates was dissolved in 0.5 ml. of water and

(18) Although the product contained in the fractions corresponding to peak B, Fig. 6, was colorless and homogeneous so far as could be detected by chromatography in systems A and B and by electrophoresis, some degradation occurred during lyophilization and the product was obtained as a yellow powder. Ultraviolet spectral data (Table I) was obtained by eluting the compound from a paper electrophoretogram.

the pH was adjusted to 7.0. Magnesium sulfate (5 λ of a 1 *M* solution) and 0.1 mg. of crystalline ribonuclease were added. The pH was adjusted from time to time as required. After 6 hr., the whole sample was streaked on Whatman 3 MM paper which was developed in solvent A. Each of the (3′→5′)-linked isomers was completely degraded to uridylic acid and the free nucleoside.

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Neighboring Group Participation in the Elimination of the Exocyclic Secondary *p*-Tolylsulfonyloxy Group in D-Glucofuranose Derivatives[1,2]

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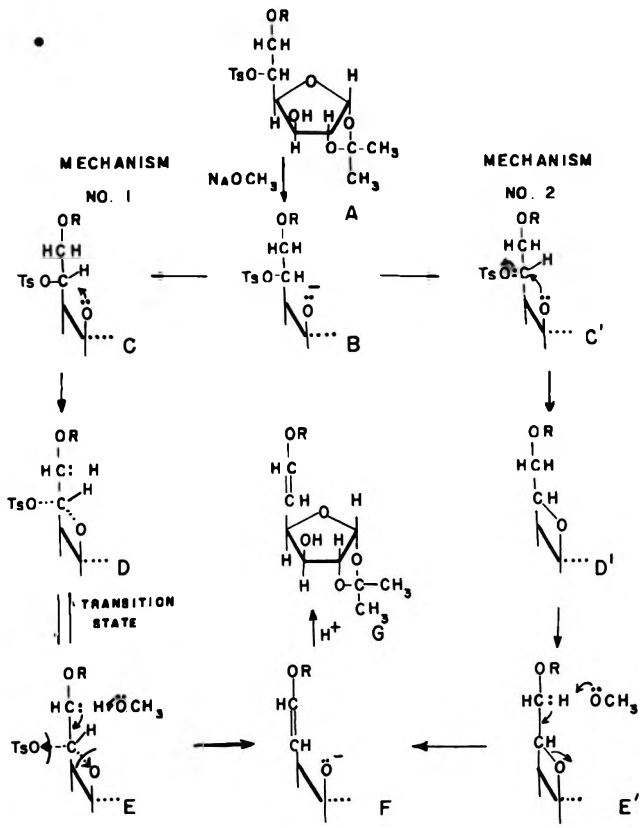
Base-catalyzed elimination of the exocyclic secondary tosyloxy group in a D-glucofuranose structure is dependent on the participation of a neighboring alkoxide group. Model tosylated D-glucofuranose derivatives with a stereochemical configuration similar to 6-*O*-benzyl-1,2-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-α-D-glucofuranose are synthesized and treated with sodium methoxide to substantiate an anchimeric assistance in desulfonyloxylation. Tosyloxy elimination is always accompanied by β-proton elimination, with subsequent formation of 5-deoxy-α-D-*xylo*-hexofuran-5-enose derivatives when specific 5-*O*-*p*-tolylsulfonyl-α-D-glucofuranose derivatives contain a free C-3 hydroxyl group. Since increased yield of olefin is observed when the sodium methoxide concentration is raised from 1 to 4 moles per mole of tosylate, it is suggested that tosyloxy elimination is dependent on the concentration of an ionized C-3 hydroxyl group, and that protonization of the β-hydrogen with subsequent formation of olefin is dependent on the concentration of methoxide ion.

Desulfonyloxylation and β-elimination of 6-*O*-benzyl-1,2-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-α-D-glucofuranose (V) in the presence of sodium methoxide, with subsequent formation of 6-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuran-5-enose (XI) has been recently reported.[3] This reaction reveals that, although the stereochemical configuration of V would seem to permit a 3,5-anhydro ring, olefin formation is dominant. This elimination of an exocyclic secondary tosyloxy group, as observed in a selected series of D-glucofuranose derivatives, is now examined in greater detail and two mechanisms for a β-proton elimination in the formation of olefins are proposed (see col. 2).

Four pairs of 5-*O*-*p*-tolylsulfonyl-α-D-glucofuranose derivatives, all of which contain an alkali stable R group substituted for the hydrogen on the C-6 hydroxyl group, were synthesized. One derivative in each pair has its C-3 hydroxyl group protected with an alkali stable R group. Each compound was treated with sodium methoxide, and the products were characterized. A scheme for the synthesis of compounds I to VIII (Table I) is as follows. Unimolar tosylation of 6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose[4] gave 6-deoxy-1,2-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-α-D-glucofuranose (I). The catalytic hydrogenation of 5,6-anhydro-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-glucofuranose[5] and subsequent tosylation furnished 6-deoxy-1,2-*O*-isopropylidene-3-*O*-methyl-5-*O*-*p*-tolylsulfonyl-α-D-glucofuranose (II). Treatment of 5,6-anhydro-1,2-*O*-isopropylidene-α-D-glucofuranose[6] with sodium methoxide, followed by a monotosylation of the product[7] therefrom, furnished 1,2-*O*-isopropylidene-6-*O*-methyl-5-*O*-*p*-tolylsulfonyl-α-D-glucofuranose (III). The reaction of 5,6-anhydro-3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose[4] with sodium methoxide and subsequent tosylation of the product obtained produced 3-*O*-benzyl-1,2-*O*-isopropylidene-6-*O*-methyl-5-*O*-*p*-tolylsulfonyl-α-D-glucofuranose (IV). A preparation for the compound which initiated the study of olefin formation, namely 6-*O*-benzyl-1,2-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-α-D-glucofuranose (V), is described in an earlier paper.[3] When 5,6-anhydro-3-*O*-benzyl-1,2-*O*-



(1) Journal Paper No. 2237 of the Purdue University Agricultural Experiment Station.

(2) Presented before the Division of Carbohydrate Chemistry at the 145th National Meeting of the American Chemical Society, New York, N. Y., Sept., 1963.

(3) R. E. Gramera, T. R. Ingle, and R. L. Whistler, *J. Org. Chem.*, **29**, 878 (1964).

(4) A. S. Meyer and T. Reichstein, *Helv. Chim. Acta*, **29**, 152 (1946).

(5) E. Vischer and T. Reichstein, *ibid.*, **27**, 1332 (1944).

(6) R. L. Whistler and M. L. Wolfrom, "Methods in Carbohydrate Chemistry," Vol. II, Academic Press, New York, N. Y., 1963, p. 190.

(7) H. Ohle and Von Vargha, *Ber.*, **62**, 2435 (1929).

isopropylidene-α-D-glucofuranose[4] was treated with sodium benzyl alkoxide and the product obtained was tosylated, 3,6-di-*O*-benzyl-1,2-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-α-D-glucofuranose (VI) was produced. Tosylation of 3-*O*-acetyl-1,2-*O*-isopropylidene-6-*O*-triphenylmethyl-α-D-glucofuranose[8] afforded 3-*O*-acetyl-1,2-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-6-*O*-triphenylmethyl-α-D-glucofuranose (VII). A synthesis of 3-*O*-benzyl-1,2-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-6-*O*-triphenylmethyl-α-D-glucofuranose (VIII) is described.[9]

Products obtained when compounds I, III, V, and VII were treated with sodium methoxide under experimental conditions usually adopted for anhydro ring formation are identified as 5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuran-5-enose (IX), 5-deoxy-1,2-*O*-isopropylidene-6-*O*-methyl-α-D-*xylo*-hexofuran-5-enose (X), 6-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuran-5-enose (XI), and 5-deoxy-1,2-*O*-isopropylidene-6-*O*-triphenylmethyl-α-D-*xylo*-hexofuran-5-enose (XII), respectively (Table I).

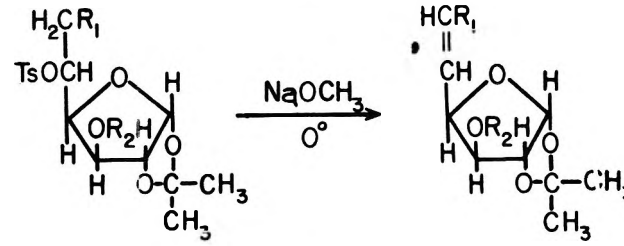
Structural identity of olefin IX was made by comparison with a known compound.[10] Isolation and identification of 1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose,[11] after a reductive ozonolysis of olefins X, XI,[3] and XII, showed that the position of the double bond in the above-mentioned compounds is between C-5 and C-6.

Maximum yield of olefins IX, X, XI, and XII was obtained when the concentration of sodium methoxide in the base-catalyzed elimination reaction was increased from 1 to 4 moles per mole of tosylate. This observation suggests that a sufficiently ionized C-3 hydroxyl group is necessary to facilitate tosyloxy elimination, and that protonization of the β-hydrogen in the formation of an olefin is dependent on the concentration of methoxide ion. A decrease in the yield of olefin formation in systems containing less than 3 moles of sodium methoxide per mole of tosylate is undoubtedly due in part to a repressed ionization of the C-3 hydroxyl group in the chloroform–sodium methoxide system. For example, if dimethylformamide (DMF) is substituted for chloroform, olefin formation in near quantitative yield is complete in a very short time, even when a lower sodium methoxide concentration is employed. The results obtained in DMF can best be explained by an increased ionization of the C-3 hydroxyl group.

Compounds II, IV, VI, and VIII, when treated with sodium methoxide at 0°, gave mostly unchanged starting compound, a small amount of detosylated material, but no detectable olefin. Isolation of sodium *p*-tolylsulfinate supports a detosylation rather than desulfonyloxylation of the reacted compounds.

Two mechanisms, both of which indicate that desulfonyloxylation is facilitated by a neighboring C-3 alkoxy anion, can explain β-proton elimination with the formation of olefin. Mechanism 1 suggests that ionization of the C-3 hydroxyl group is necessary to facilitate an anchimeric assistance in tosyloxy elimination. The stereochemistry and nucleophilicity of the alkoxy anion

TABLE I



MODEL COMPOUNDS		OLEFINS
I	R_1 = H, R_2 = H	IX
II	R_1 = H, R_2 = CH_3	No Olefin
III	R_1 = OCH_3, R_2 = H	X
IV	R_1 = OCH_3, R_2 = $CH_2Ø$	No Olefin
V	R_1 = $OCH_2Ø$, R_2 = H	XI
VI	R_1 = $OCH_2Ø$, R_2 = $CH_2Ø$	No Olefin
VII	R_1 = $OC(Ø)_3$, R_2 = $CO\,CH_3$	XII
VIII	R_1 = $OC(Ø)_3$, R_2 = $CH_2Ø$	No Olefin

B allows an intramolecular approach of the latter, illustrated in C, to displace the tosyloxy group. However, prior to displacement, delocalization of electron density between the tosyloxy group and C-5 would be necessary, since partial bond breaking (TsO. . . .C_5) and partial bond forming (C-3. . . .O. . . .C-5) are visualized in the transition state of an S_N2 reaction.[12] It is quite conceivable that at the moment the tosyloxy bond is weakening and the 3,5-anhydro ring is forming, a β-proton is eliminated *via* an E2 mechanism. A transition state D ⇋ E in all probability is of such a nature that an anchimeric-assisted desulfonyloxylation and β-proton elimination occur in a synchronous process. The olefinic anion F picks up a proton and gives olefin G.

If mechanism 1 is operative, protonization of the β-hydrogen occurs, or is facilitated to a greater extent, while the tosyloxy carbon bond is weakening and the 3,5-anhydro ring is forming. If D ⇋ E is an acceptable transition state, it can be postulated that greater stabilization of the system may be achieved when a β-proton is eliminated rather than combined; for, if recombination of the β-proton and subsequent formation of a 3,5-anhydro ring requires more energy, or is a less stable system than transition state D ⇋ E, olefin formation would predominate.

The possibility of an initial desulfonyloxylation followed by the formation of a 3,5-anhydro intermediate,

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which in turn loses a β-proton to give the respective olefin, is suggested in mechanism 2. Here again, as in mechanism 1, formation of the alkoxy anion B is necessary in order to initiate the reaction. In contrast to mechanism 1, however, mechanism 2 shows that the alkoxy anion C′ actually displaces the tosyloxy group to give the 3,5-anhydro intermediate D′. Elimination of a β-proton in E′ results in the formation of anion F. Anion F picks up a proton to give olefin G.

Formation of a 3,5-anhydro intermediate illustrated in mechanism 2 is suggested, since the products obtained after hydrazinolysis[13] and subsequent hydrogenolysis of V are identified as 5-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose and two amino sugars, none of which are identical with 5-amino-5-deoxy-1,2-*O*-isopropylidene-β-L-idofuranose.[8] Isolation of the deoxy sugar as the major product proves that olefin formation during hydrazinolysis of V is the dominant reaction. The significant observation that two different amino sugars are produced suggests that a 3,5-anhydro ring is formed during hydrazinolysis, and nucleophilic substitution on the ring at C-3 or C-5 by hydrazine takes place.

One of the amino sugars obtained in higher yields is identified as 5-amino-5-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose,[14] while the other sugar is thought to be the 3-amino-3-deoxy-L-talose derivative. Since the solvent, hydrazine, acts as the proton acceptor as well as the nucleophile, it is not surprising that substitution of an anhydro intermediate occurs.

When an attempt was made to trap the proposed oxetane intermediate by treating V with sodium azide in boiling methanol, unchanged starting material was recovered. This indicates that, although the nucleophilicity of the azide ion would have been sufficient to open an oxetane ring, the basicity of the reaction medium is insufficient to promote significant ionization of the C-3 hydroxyl group, the latter of which is necessary in facilitating desulfonyloxylation. This experiment supports the theory that an ionized C-3 hydroxyl group is necessary to initiate the olefin-forming reaction.

If mechanism 2 is operative, elimination of a β-proton from intermediate D′ with subsequent formation of an olefin, rather than a nucleophilic substitution on the ring of D′ by methoxide ion, can be explained by consideration of the experimental conditions used in this work for base catalysis. It is known[15] that bimolecular elimination is usually facilitated at the expense of substitution, especially when there is extensive branching at either α- or β-carbons (as would be the case of a 3,5-anhydro intermediate D′), using strong bases at high concentrations, and when the reaction is conducted in an aprotic, nonpolar solvent. Since these conditions would exist in a chloroform–sodium methoxide system, β-elimination is not unexpected. On the other hand, if intermediate D′ is in a high energy state or strained, elimination of a β-proton may reduce the energy, or increase stability of the system by formation of an olefin.

Although mechanisms 1 and 2 illustrate slightly different views in the elimination of a β-proton, the experimental facts prove that desulfonyloxylation of the D-glucofuranose structures studied requires the assistance of a neighboring C-3 alkoxy anion.

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Experimental

Analytical Methods.—Variance in the proportion of products formed during the course of the base-catalyzed elimination reaction was followed by thin layer chromatography on 1 × 3 in. silica gel G[16] coated glass plates, irrigated with A, chloroform–acetone (1:1 v./v.), and B, 1-butanol saturated with water. Plates were sprayed with a dilute ethanolic solution containing 5% sulfuric acid and charred at 110° until permanent spots developed. Chromatographic separations and identification of sugar derivatives were performed at 25° on Whatman No. 1 filter paper developed in irrigants C, 1-butanol–ethanol–water (40:11:19 v./v.), and D, ethyl acetate–pyridine–water (10:4:3 v./v.). Indicators consisted of E, potassium permanganate–periodate spray reagent, and F, iodine vapor. Evaporations were done at reduced pressure and reported melting points were obtained on a calibrated Fisher-Johns apparatus.

5,6-Dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuran-5-enose (IX).—A solution containing 3 g. of 6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose[4] dissolved in 10 ml. of pyridine was cooled with stirring to −5°. A one-half portion of 3.0 g. of tosyl chloride (*p*-toluenesulfonyl chloride) was added to the solution over a period of 2 hr. After maintaining the solution at 25° for 5 hr., it was cooled again to −5°, and the remaining half portion of tosyl chloride was added as before. After an additional 10 hr. at 25°, the reaction mixture was treated with ice and stirred for 0.5 hr., after which 10 ml. of chloroform was added and the total mixture was poured into ice–water. The chloroform layer was washed sequentially with water, an ice-cold solution of dilute hydrochloric acid until slightly acidic (pH 4.0), and an aqueous solution of sodium bicarbonate until neutral. After several washings with water, the chloroform layer was dried over anhydrous sodium sulfate, filtered, and evaporated below 40° to a sirup (3.7 g.) which contained 6-deoxy-5-*O*-*p*-tolylsulfonyl-1,2-*O*-isopropylidene-α-D-glucofuranose (I). A 2-g. portion of the sirupy product containing I was dissolved in 15 ml. of alcohol-free chloroform, The mixture was cooled to 0°, and 8 ml. of a methanolic solution containing 12.5% of sodium methylate was added. The solution was stirred at 0° for 1 hr. and then at 25° for an additional 16 hr. After the addition of a saturated solution of potassium bicarbonate, the mixture was evaporated to remove methanol. The residue was extracted six times with 25-ml. portions of chloroform; the latter was dried over anhydrous sodium sulfate and evaporated to a sirup which absorbed bromine from a bromine–carbon tetrachloride solution and instantaneously decolorized a solution of potassium permanganate. Examination of this sirup by thin layer chromatography in irrigants A and B revealed that the major component, IX, migrated the same as the known compound recorded in the literature.[10] After compound IX was isolated from paper chromatograms, it crystallized from petroleum either (b.p. 40–60°), m.p. 64°, $[\alpha]^{25}D$ −60.5° (*c* 2.0, water); the melting point remained undepressed when admixed with an authentic sample.

6-Deoxy-1,2-*O*-isopropylidene-3-*O*-methyl-5-*O*-*p*-tolylsulfonyl-α-D-glucofuranose (II).—Three grams of 6-deoxy-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-glucofuranose[5] was dissolved in 10 ml. of dry pyridine to which was added 8 ml. of alcohol-free chloroform containing 3 g. of tosyl chloride. After the reaction mixture was maintained at 37° for 3 days, it was cooled to 0° and 2 ml. of water were added to hydrolyze excess tosyl chloride. Within 0.5 hr. the solution was poured into 100 ml. of ice–water and 20 ml. of chloroform then was added. The aqueous layer was drawn off, extracted twice with chloroform, and the combined organic layer was washed free of pyridine with several portions of a cold dilute solution of hydrochloric acid to pH 4.0. The organic extract was neutralized with a dilute solution of sodium bicarbonate, washed free of salts, and dried over anhydrous magnesium sulfate. After filtration and evaporation a light yellow sirup (4.93 g.) was obtained, $[\alpha]^{25}D$ −25.1° (*c* 1.84, chloroform). Thin layer chromatograms of II showed the material was essentially pure. A 500-mg. portion of II was chromatographed on alumina and sequentially eluted with a mixture of benzene–petroleum ether of increasing benzene concentration. A main

(16) Brinkman Instruments, Inc., Great Neck, L. I., N. Y.

fraction (376 mg.) was chromatographically pure but could not be induced to crystallize, $[\alpha]^{26}D$ −21.5° (*c* 2.0, chloroform).

Anal. Calcd. for $C_{17}H_{24}O_7S$ (372.41): OCH_3, 11.56; S, 8.61. Found: OCH_3, 11.28; S, 8.47.

5-Deoxy-1,2-*O*-isopropylidene-6-*O*-methyl-α-D-*xylo*-hexofuran-5-enose (X).—Unimolar tosylation of 10.6 g. of pure distilled 1,2-*O*-isopropylidene-6-*O*-methyl-α-D-glucofuranose,[7] b.p. 148–150° (0.04 mm.), $[\alpha]^{25}D$ −6.0° (*c* 2.3, chloroform), was performed by the method described for I. A sirupy product (12 g.) obtained after tosylation, containing 1,2-*O*-isopropylidene-6-*O*-methyl-5-*O*-*p*-tolylsulfonyl-α-D-glucofuranose (III), was treated with sodium methoxide by the procedure given for I. A crystalline product obtained from the base catalysis of II was identified as X, 2.3-g. yield, m.p. 112.5°, $[\alpha]^{25}D$ −171° (*c* 0.75 g., chloroform). Chromatography of X in irrigants C and D when sprayed with indicator E or subjected to indicator F revealed a single component. Compound X instantaneously decolorized a solution of potassium permanganate and absorbed bromine from a bromine–carbon tetrachloride solution.

Anal. Calcd. for $C_{10}H_{16}O_5$ (216.23): C, 55.53; H, 7.45; OCH_3, 14.35. Found: C, 55.30; H, 7.34; OCH_3, 14.24.

3-*O*-Benzyl-1,2-*O*-isopropylidene-6-*O*-methyl-5-*O*-*p*-tolylsulfonyl-α-D-glucofuranose (IV).—Eight grams of 5,6-anhydro-3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose[4] was dissolved in 125 ml. of absolute methanol containing 0.75 g. of sodium. After 3 days at 30°, the reaction mixture was cooled to 5°, neutralized with a dilute solution of sulfuric acid, filtered, and evaporated to remove methanol. The remaining residue was extracted with chloroform; the latter was washed with water and concentrated to a sirup which was subjected to high vacuum distillation. Pure distilled 3-*O*-benzyl-1,2-*O*-isopropylidene-6-*O*-methyl-α-D-glucofuranose [3.55 g., b.p. 170–172° (0.02 mm.), $[\alpha]^{2t}D$ −40.4° (*c* 2.0, chloroform), methoxyl, 9.46%] was obtained and 3 g. was tosylated by the conditions described for II. Compound IV was obtained as a light yellow sirup which on thin layer chromatography in irrigants A or B migrated as a single component to yield 4.36 g., $[\alpha]^{26}D$ −14.5° (*c* 2.0, in chloroform).

Anal. Calcd. for $C_{24}H_{30}O_8S$ (478.33): OCH_3, 6.48; S, 6.70. Found: OCH_3, 6.21; S, 6.53.

6-*O*-Benzyl-5-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuran-5-enose (XI).—Preparation of XI by base catalysis of 6-*O*-benzyl-1,2-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-α-D-glucofuranose (V) was described in an earlier paper.[3]

3,6-Di-*O*-benzyl-1,2-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-α-D-glucofuranose (VI).—In 200 ml. of a cooled, continuously stirred solution of benzyl alcohol which contained 1.7 g. of sodium, 15 g. of 5,6-anhydro-3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose[4] was dissolved. After the reaction was maintained at 25° for 3 days, it was slowly neutralized with a chilled dilute solution of sulfuric acid. Sodium sulfate was filtered from solution and washed with two 10-ml. portions of benzyl alcohol. The combined washings and filtrate were extracted with two 25-ml. portions of water and then dried over anhydrous magnesium sulfate. After filtration, the excess benzyl alcohol was removed by high vacuum distillation. A 5-g. portion of the remaining residue was subjected to high vacuum distillation from which 3.2 g. of a colorless sirup, namely, 3,6-di-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose, was obtained, b.p. 170–175° (0.02 mm.), $[\alpha]^{25}D$ −42.6° (*c* 1.5, chloroform). After 3 g. of the benzylated derivative was tosylated by the method described for II, compound VI was obtained as a light yellowish sirup in a 3.95-g. yield, $[\alpha]^{25}D$ −14.1° (*c* 2.0, chloroform). A 250-mg. portion of VI was chromatographed on alumina by the procedure described for II. The main fraction (186 mg.) migrated as a single component when examined by thin layer chromatography in irrigants A or B, but could not be induced to crystallize.

Anal. Calcd. for $C_{30}H_{34}O_8S$ (554.63): S, 5.78. Found: S, 5.64.

5-Deoxy-1,2-*O*-isopropylidene-6-*O*-triphenylmethyl-α-D-*xylo*-hexofuran-5-enose (XII).—Tosylation of 12 g. of 3-*O*-acetyl-1,2-*O*-isopropylidene-6-*O*-triphenylmethyl-α-D-glucofuranose[8] by the usual method gave amorphous 3-*O*-acetyl-1,2-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-6-*O*-triphenylmethyl-α-D-glucofuranose (VII) in 14.7-g. yield, $[\alpha]^{25}D$ −21.4° (*c* 1.8 g., chloroform). When 2 g. of VII was treated with sodium methoxide by the method described for I, a crystalline product identified as XII was obtained from a mixture of benzene and petroleum ether in a 1.86-g. yield, m.p. 83°, $[\alpha]^{25}D$ −15.4° (*c* 1.4 g., chloroform). Chromatography of XII in irrigants C and D revealed a single component. Compound XII decolorized a solution of potassium permanganate and absorbed bromine from a bromine–carbon tetrachloride solution.

Anal. Calcd. for $C_{28}H_{28}O_5$ (444.30): C, 75.66; H, 6.34. Found: C, 75.38; H, 6.42.

3-*O*-Benzyl-1,2-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-6-*O*-triphenylmethyl-α-D-glucofuranose (VIII).—A procedure for the preparation of VII has been described in an earlier paper.[14]

Reaction of II, IV, VI, and VIII with Sodium Methoxide.—Experimental conditions employed for the base catalysis of compounds I, III, V, and VII were applied to compounds II, IV, VI, and VIII. Thin layer chromatography of the reaction products indicated that mostly starting compound and some detosylated product were produced. Olefin was not detected in any of the reaction products when the usual tests for unsaturation were employed. A small amount of sodium *p*-tolylsulfinate was isolated as a by-product in these reactions.

Reductive Ozonolysis of X and XII.—Compounds X and XII, when subjected to reductive ozonolysis by a specific procedure described in a recent paper,[3] gave sirupy 1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose,[11] which was converted to its crystalline hydrazone,[11,17] m.p. 141°, $[\alpha]^{25}D$ −42° (*c* 2.0, chloroform). Nucleation of aged sirupy 1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose with an authentic sample of it's crystalline dimer[18] gave bis(1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose)-5,5′:3′,5 cyclic acetal, m.p. 183°.

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5-Thio-D-Xylopyranosylamines[1]

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5-Thio-D-xylopyranose reacts with arylamines to produce glycosylamines in a similar way to normal oxygen ring sugars. The glycosylamines also appear to undergo the normal Amadori rearrangement to produce 1-amino-1-deoxy-2-ketoses.

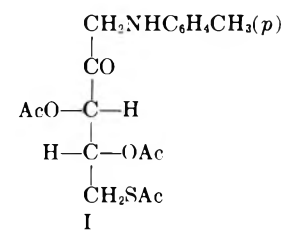
Several reports have appeared on the formation of 5-thio-D-pentoses[2-4] and -hexoses[5,6] and their derivatives. This work describes the preparation of glycosylamines of 5-thio-D-xylopyranose and their Amadori rearrangement.

5-Thio-D-xylopyranose reacts with aromatic amines in the presence of a small amount of acid such as acetic acid. Using this procedure, a number of crystalline glycosylamines are obtained in good yields. Alkylamines such as *n*-propyl- or *n*-butylamine or arylalkylamines such as benzylamine give dark-colored sirups which are not investigated further.

The ease of formation of the glycosylamines depends on the position of any substituent present in the aromatic amine,[7] the order being *para* > *meta* > *ortho*. *ortho*-Substituted amines require a reaction time of eight hours as compared to the usual two hours at 100° for *para*-substituted amines. With *o*-nitroaniline, no glycosylamine is obtained even after more extended heating. Various 5-thio-D-xylopyranosylamines are listed in Table I. These compounds are quite stable at 25°, but they decompose and darken at the elevated temperatures encountered during melting point determination.

An Amadori rearrangement of the glycosylamines occurs but to a minor extent when they are refluxed in either (1) isopropyl alcohol containing anhydrous oxalic acid, acetic acid, or concentrated hydrochloric acid, or (2) ethanol containing an active methylene compound such as diethyl malonate.[8] A solution of the glycosylamines in pyridine and ethanol with a small amount of acetic acid will produce, under reflux conditions, more extensive rearrangement and yield some free 5-thio-D-xylopyranose. Pyridine containing 10% acetic acid[9,10] at reflux temperature brings about an extensive Amadori rearrangement. Formation of Amadori products is followed by titration of the solution with 2,6-dichlorophenolindophenol.[9] The rearrangement is always accompanied by color formation. Micheel[11] found that *ortho–para*-directing substituents in the 2- and 4-position and *meta*-directing substituents in the 3-position, relative to the nitrogen atom in the glycosylamine, facilitated the rearrangement. This observation is verified here. Thus, the *N*-*p*-tolylglycosylamine rearranges much more readily than the *N*-phenyl compound. Reaction of 5-thio-D-xylopyranose with *m*-aminobenzoic acid does not produce the expected *N*-glycosylamine, but gives a dark tar, possibly from the Amadori rearrangement. The volumes of standard 2,6-dichlorophenolindophenol reagent required after definite reaction periods, per 0.1-ml. aliquots of alkaline reaction mixture containing equal glycosylamine concentration, are shown in Table II.

N-*p*-Tolyl-5-thio-D-xylosylamine under rearrangement conditions produces a compound with a slightly higher R_f value on thin layer chromatography than the starting material. After three hours of reaction other artifacts also appear. The reaction mixture has a strong reaction with alkaline triphenyltetrazolium chloride, methylene blue, and nitroprusside. The Amadori product could not be isolated by chromatography or by Kuhn's[10] procedure of forming the triazene. Acetylation of the reaction mixture gives two compounds on thin layer chromatography with quite different R_f values. The acetylated reaction mixture on separation on a silica gel column gives approximately a 65% yield of crystalline 2,3,4-tri-*O*-acetyl-1-*N*-(*p*-tolyl)-5-thio-D-xylopyranosylamine and a dark sirup. Decolorization and rechromatography on silica gel gives a light yellow sirup, which has a strong reaction with alkaline triphenyltetrazolium chloride, methylene blue, and 2,6-dichlorophenolindophenol, but gives a negative test with alkaline nitroprusside. Infrared spectra of the yellow sirup as a thin film shows the absence of hydroxyl groups and the presence of three carbonyl absorptions at 5.76, 5.91, and 6.02 μ which are ascribed to the presence of *O*-acetyl, *S*-acetyl, and a free keto group, respectively. Ultraviolet spectra reveal the presence of *S*-acetyl,[12] λ_{max}^{MeOH} 225 mμ (ϵ 9420). These observations and elemental analysis suggest the following open chain structure. It is observed[10] that Amadori products assume the pyranose structure if possible or occur in the open chain form.



I

Experimental

Preparation of 5-Thio-D-xylosylamines.—A 0.55-g. (0.0033 mole) sample of 5-thio-D-xylopyranose was added to 0.004 mole of

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TABLE I

5-THIO-D-XYLOPYRANOSYLAMINES

Amine	Yield, %	M.p. dec., °C.	$[\alpha]^{20}D$ (c 1.00, pyridine	Formula	% N Calcd.	% N Found	% S Calcd.	% S Found
Aniline	83	206–207	−279	$C_{11}H_{15}NO_3S$	5.81	5.62	13.28	13.14
o-Toluidine	33	170–171	−316	$C_{12}H_{17}NO_3S$	5.49	5.43	12.54	12.59
m-Toluidine	66	185–186	−238	$C_{12}H_{17}NO_3S$	5.49	5.45	12.54	12.63
p-Toluidine	78	181–182	−265	$C_{12}H_{17}NO_3S$	5.49	5.33	12.54	12.46
o-Anisidine	61	194–195	−242	$C_{12}H_{17}NO_4S$	5.17	5.34	11.81	11.79
m-Anisidine	49	184–185	−222	$C_{12}H_{17}NO_4S$	5.17	5.29	11.81	11.72
p-Anisidine	80	172–173	−278	$C_{12}H_{17}NO_4S$	5.17	5.10	11.81	11.93
o-Bromoaniline	12	184–185	−250	$C_{11}H_{14}BrNO_3S$	4.38	4.17	10.00	10.04
m-Bromoaniline	60	196–197	−214	$C_{11}H_{14}BrNO_3S$	4.38	4.48	10.00	10.07
p-Bromoaniline	55	182–183	−196	$C_{11}H_{14}BrNO_3S$	4.38	4.35	10.00	9.92
α-Naphthylamine	68	200–201	−310	$C_{15}H_{17}NO_3S$	4.81	4.95	11.00	10.96
β-Naphthylamine	63	193–194	−202	$C_{15}H_{17}NO_3S$	4.81	4.64	11.00	10.93
m-Nitroaniline	29	203–204	−246	$C_{11}H_{14}N_2O_5S$	9.80	9.78	11.18	11.09
p-Nitroaniline	35	223–224	−116	$C_{11}H_{14}N_2O_5S$	9.80	9.72	11.18	11.17
o-Aminobenzoic Acid	82	199–200	−98	$C_{12}H_{15}NO_5S$	4.92	4.73	11.23	11.29
p-Aminobenzoic Acid	52	202–203	+58	$C_{12}H_{15}NO_5S$	4.92	4.97	11.23	11.17

TABLE II

GLYCOSYLAMINE REACTION TIME UNDER REFLUX[a]

	Hr. 1	2	3	4	5	6
N-Phenyl-5-thio-D-xylosylamine	5.0 ml.	10.0[b]	14.5	14.5	11.0	...
N-*p*-Tolyl-5-thio-D-xylosylamine	8.5	13.0	17.5[b]	24.0	23.0	19.0
N-*p*-Anisyl-5-thio-D-xylosylamine	11.5[b]	14.5	17.5	14.5	12.0	10.0

[a] The values in the table represent the volume (ml.) of 2,6-dichlorophenolindophenol reagent required after definite reaction periods (hr.) per 0.1-ml. aliquots of alkaline reaction mixture containing equal glycosylamine concentration. [b] At this point the reaction mixture turned dark.

TABLE III

N-SUBSTITUTED 2,3,4-*O*-TRIACETYL-5-THIO-D-XYLOPYRANOSYLAMINE

N-Substitution group	M.p., °C.	$[\alpha]^{20}D$ (c 1.00, pyridine)	Formula	% N Calcd.	% N Found
Phenyl	220	−148	$C_{17}H_{21}NO_6S$	3.81	3.84
o-Tolyl	184	−184	$C_{18}H_{23}NO_6S$	3.67	3.81
m-Tolyl	207	−138	$C_{18}H_{23}NO_6S$	3.67	3.66
p-Tolyl	212	−132	$C_{18}H_{23}NO_6S$	3.67	3.70
o-Anisyl	165	−134	$C_{18}H_{23}NO_7S$	3.53	3.50
m-Anisyl	155	−116	$C_{18}H_{23}NO_7S$	3.53	3.64
p-Anisyl	173	−130	$C_{18}H_{23}NO_7S$	3.53	3.59
o-Bromphenyl	160	−146	$C_{17}H_{20}BrNO_6S$	3.14	3.12
m-Bromphenyl	208	−122	$C_{17}H_{20}BrNO_6S$	3.14	3.18
p-Bromphenyl	217	−102	$C_{17}H_{20}BrNO_6S$	3.14	3.22
α-Naphthyl	190	−242	$C_{21}H_{23}NO_6S$	3.36	3.31
β-Naphthyl	227	−162	$C_{21}H_{23}NO_6S$	3.36	3.46
m-Nitrophenyl[a]	256	+56	$C_{17}H_{20}N_2O_8S$	6.80	6.92
p-Nitrophenyl[a]	241	−108	$C_{17}H_{20}N_2O_8S$	6.80	6.85
o-Carboxyphenyl	195	−98	$C_{18}H_{21}NO_8S$	3.40	3.46
p-Carboxyphenyl	197	+144	$C_{18}H_{21}NO_8S$	3.40	3.49

[a] Crystallized from dilute pyridine.

the appropriate amine, 0.5 ml. of ethanol, 0.1 ml. of water, and 0.02 ml. of glacial acetic acid, and the mixture was heated at 100° for 2 hr. For amines containing *ortho* substituents the reaction time was increased to 8 hr. The glycosylamines separated during the heating period and were washed with ethanol and ether. The compounds were crystallized from isopropyl alcohol. Yield and analytical data are given in Table I. The compounds do not reduce 2,6-dichloroindophenol, methylene blue, 2,3,5-triphenyl-2*H*-tetrazolium chloride, or dinitrobenzene in 0.1 *N* sodium hydroxide solution at 15°.

The triacetates were prepared by treating 100 mg. of the appropriate glycosylamine with 1 ml. of pyridine and 1 ml. of acetic anhydride at 25° for 18 hr. The mixture was then poured into water and crystallized from methanol (see Table III).

Amadori Rearrangement.—A 250-mg. sample of the glycosylamine (*N*-phenyl-, *N*-*p*-tolyl-, *N*-*p*-anisyl-) was refluxed with 9.0 ml. of pyridine and 1.0 ml. of glacial acetic acid. At intervals, 0.10-ml. portions were withdrawn, made alkaline by addition of 1.2 ml. of 1 *N* sodium hydroxide solution, and titrated against 2,6-dichlorophenolindophenol by the procedure described by Rosen, *et al.*[9] The results are given in Table II.

In the case of *N*-*p*-tolyl-5-thio-*p*-xylosylamine, the reaction mixture was examined at intervals by thin layer chromatography on silica gel G with 15% methanol in benzene as developer and concentrated sulfuric acid or alkaline triphenyltetrazolium chloride as spray reagents. After 1 hr., the reaction mixture contained the starting material, R_f 0.18, and a substance with R_f 0.23. After 3.5–4 hr., the component with R_f 0.23 was in greatest concentration and other components, with R_f 0.53 and 0.60, appeared. The reaction mixture darkened appreciably. This reaction mixture was cooled and 1 ml. of acetic anhydride was added. After standing overnight, it was evaporated under reduced pressure at 50°, and the residue was distilled with water to remove pyridine. It was then distilled with benzene. Thin

layer chromatography on kieselgel G with 4% methanol in benzene as developer and concentrated sulfuric acid as a spray reagent revealed the presence of components with R_f 0.14 and 0.46. The faster moving component was identified as 2,3,4-tri-*O*-acetyl-1-*N*-(*p*-tolyl)-5-thio-D-xylosylamine by comparison with authentic material. After a similar reaction sequence on 2.5 g. of *N*-*p*-tolyl-5-thio-D-xylosylamine the residue was taken up in 10 ml. of benzene containing 4% methanol, the mixture was cooled, and the undissolved 2,3,4-tri-*O*-acetyl-1-*N*-(*p*-tolyl)-5-thio-D-xylosylamine was removed by filtration. The filtrate was applied to a column of 200 g. of silica gel, the column was eluted with benzene containing 4% methanol, and the fractions were examined by a thin layer chromatography. The total amount of solid acetate recovered was 2.44 g. or 65%. A further 1.33 g. (35% yield) of a dark sirup was decolorized by stirring for 4 hr. with an equal weight of activated charcoal in 25 ml. of methanol. It was filtered through Celite, and the filter was washed twice with 10 ml. of methanol. Evaporation of the filtrate gave a yellow sirup which was rechromatographed on silica gel using 4% methanol in benzene. The fraction with R_f 0.14 was concentrated and dried over phosphorus pentoxide, $[\alpha]^{20}D$ $-1°$ (*c* 0.79, methanol).

Anal. Calcd. for $C_{18}H_{23}NO_6S$: C, 56.6; H, 6.04; N, 3.69. Found: C, 56.3; H, 6.15; N, 3.62.

Attempted deacetylation of this sirup with barium hydroxide, sodium methoxide, sodium hydroxide, or acid led to complex mixtures. Examination of these reaction mixtures by thin layer chromatography showed the absence of an Amadori product.

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Furano Compounds. II[1a]

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The greater ease of synthesis of simple or condensed furanopyrones carrying a β-methyl substituent in the furan ring over similar compounds lacking such a substituent is discussed. Further, the significance of the presence of a C-methyl group in a number of simple or condensed benzo-γ-pyrone derivatives of plant origin and that of a β-methyl substituent in the furan ring of a few naturally occurring benzofurans has been stressed. This is illustrated by a typical synthesis of 4′-methylfurano(3′,2′:4,3)xanthone and 4′,6-dimethylfurano-(3′,2′:4,3)xanthone.

In part I[1b] of this series, the occurrence of a furan nucleus in a number of related natural products, *viz.*, furanocoumarins, -chromones, -flavones, -isoflavones, and -xanthones, was discussed, and the synthesis of furano(3′,2′:4,3)xanthone, the xanthone analog of the well-known furanoflavone Karanjin, was recorded. This synthesis employs one of the typical methods for the preparation of benzofuran derivatives, *viz.*, a mixed Claisen-type condensation or internal aldol condensation using the appropriately substituted aldehyde or ketone and bromoacetic or bromomalonic ester. Thus, 4-formyl-3-hydroxyxanthone obtained from 3-hydroxyxanthone was submitted to such a condensation employing bromomalonic ester which effected simultaneous esterification and internal aldol condensation (cyclization).

On the other hand, the corresponding ketones, *viz.*, 4-acetyl-3-hydroxyxanthones, which can also be submitted to a similar internal Claisen condensation leading to the formation of a furan skeleton, can be more easily prepared and in better yields from the hydroxyxanthones through a Friedel–Crafts–Fries reaction. However, while aldehydo esters give rise to furano compounds unsubstituted in the furan ring, the use of substituted ketones for such an internal Claisen condensation results in furano compounds carrying a methyl substituent in the β-position. It may be pointed out that the occurrence in nature of furano compounds carrying a methyl substituent is not uncommon. Thus menthofuran,[2] the chemical constituent of various peppermint oils, and Evodon,[3] a crystalline ketone from the essential oil of *Evodia hortensis*, are β-methylbenzofurans. It could also be expected that a methyl substituent in the β-position may affect the physiological properties of the furano compounds concerned. Further, the presence of a C-methyl group in the benzenoid ring of a number of related, naturally occurring, simple or condensed benzo-γ-pyrone derivatives[4] and its significance in the biogenetic evolution of such compounds made us attempt the synthesis of two typical examples of furanoxanthones, *viz.*, 4′-methylfurano(3′,2′:4,3)xanthone and 4′,6-dimethylfurano(3′,2′:4,3)xanthone, carrying a methyl substituent in the furan ring alone or with such substituents both in the furan ring and in the benzenoid nucleus. The first step in such synthesis, *viz.*, the preparation of the 4-acetyl derivatives from 3-hydroxyxanthone and 3-hydroxy-6-methylxanthone, is based on the valuable observations of Mustafa and Hishmat[5] and of Davies, Scheinmann, and Suschitzky.[6]

Thus, 3-hydroxyxanthone and 3-hydroxy-6-methylxanthone on treatment with acetyl chloride in the presence of aluminum chloride yield the appropriate 4-acetyl derivatives. These have been condensed with bromoacetic ester in presence of potassium carbonate to yield the 3-O-carbethoxy derivatives which on hydrolysis with aqueous potassium hydroxide give the corresponding carboxylic acids. The internal Claisen condensation (cyclization) of the acids has been effected by sodium acetate and acetic anhydride to yield 4′-methylfurano(3′,2′:4,3)xanthone (IIa) and 4′,-

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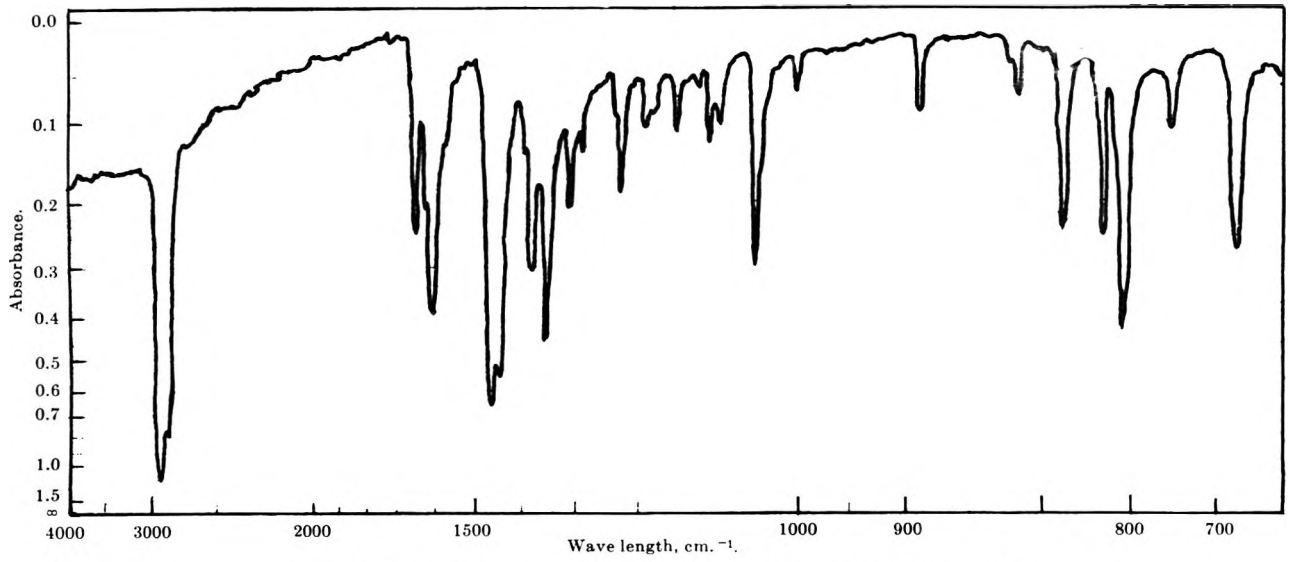


Fig. 1.—Infrared spectrum of 4′-methylfurano(3′,2′:4,3)xanthone (IIa) in Nujol.

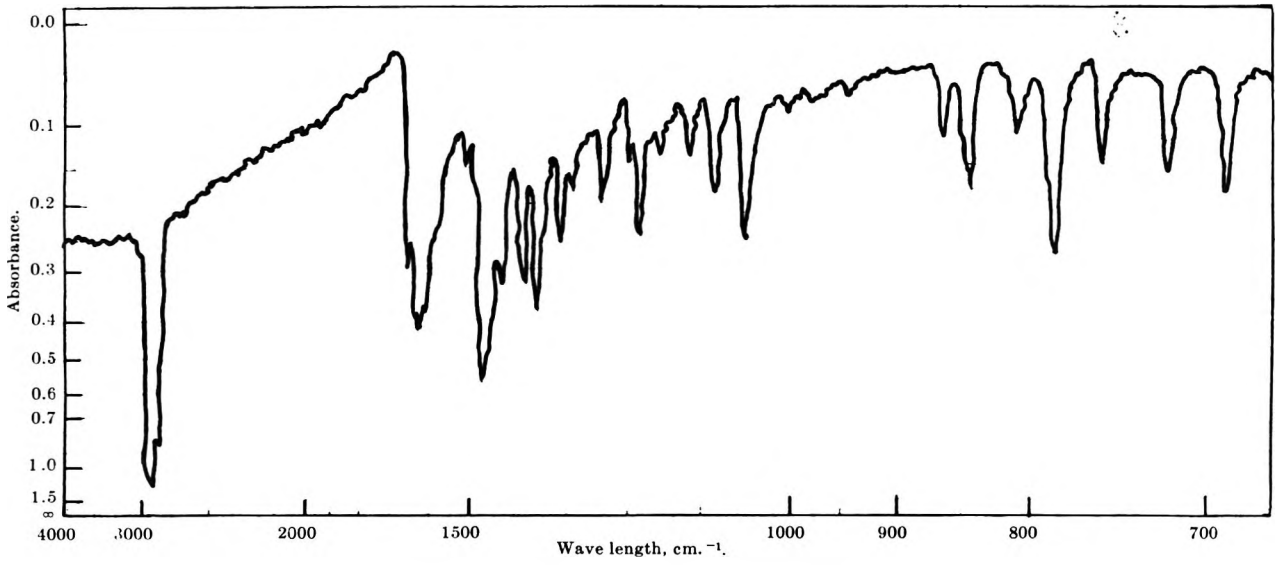
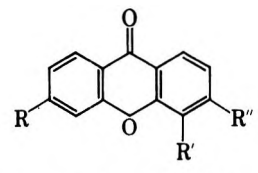


Fig. 2.—Infrared spectrum of 4′,6-dimethylfurano(3′,2′:4,3)xanthone (IIb) in Nujol.

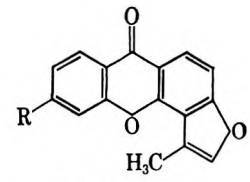
6-dimethylfurano(3′,2′:4,3)xanthone (IIb), cyclization and decarboxylation having occurred simultaneously.

It may be pointed out that 3-hydroxy-6-methylxanthone has been prepared earlier by Shah, *et al.*,[7] by condensing *m*-cresotic acid with resorcinol in the presence of fused zinc chloride and phosphorus oxychloride and subsequently heating the resulting benzophenone with water under pressure. The present procedure involves the modified Ullmann condensation of 2-chloro-4-methylbenzoic acid[8] with *m*-methoxyphenol and subsequent cyclization of the phenoxybenzoic acid and demethylation of the resulting 3-methoxy-6-methylxanthone, thereby dispensing with any reaction under pressure.

The infrared absorption spectra (Fig. 1 and 2) of these furanoxanthenes (IIa and IIb) show the following characteristics (the values in parentheses refer to compound IIb while the other ones refer to compound IIa): strong bands at (a) 1645, 1600 (1645, 1625) characteristic of xanthone carbonyl[9-12]; (b) 1460 (1460) characteristic of C–C and C–O stretching in



Ia, R = R′ = R″ = H
b, R = H; R′ = $COCH_3$; R″ = H
c, R = H; R′ = $COCH_3$; R″ = $CH_2COOC_2H_5$
d, R = H; R′ = $COCH_3$; R″ = CH_2COOH
e, R = CH_3; R′ = R″ = H
f, R = CH_3; R′ = $COCH_3$; R″ = H
g, R = CH_3; R′ = $COCH_3$; R″ = $CH_2COOC_2H_5$
h, R = CH_3; R′ = $COCH_3$; R″ = CH_2COOH



IIa, R = H
b, R = CH_3

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TABLE I

Compound	Recrystn. solvent	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
4-Acetyl-3-acetoxy-6-methylxanthone	Ethanol	167	$C_{18}H_{14}O_5$	69.68	69.72	4.51	4.82
Ethyl 4-acetyl-6-methyl-9-oxo-3-xanthyloxyacetate (Ig)	Ethanol	154	$C_{20}H_{18}O_6$	67.79	67.48	5.09	5.21
4-Acetyl-6-methyl-9-oxo-3-xanthyl-oxyacetic acid (Ih)	Acetic acid	260	$C_{18}H_{14}O_6$	66.27	66.51	4.29	4.61
4′,6-Dimethylfurano(3′,2′:4,3)-xanthone (IIb)	Ethanol	227	$C_{17}H_{12}O_3$	77.27	77.32	4.55	4.62

derivatives of furan[13-17]; (c) 1044 (1044) characteristic of C–H out-of-plane deformation of furan derivatives[13-17]; and (d) 889 (840) due to "furan ring breathing".[13-17]

Experimental

All melting points are corrected and were determined in open capillary tubes.

4-Acetyl-3-hydroxyanthone (Ib).—A mixture of 3-hydroxyxanthone (Ia, 2.12 g.) in redistilled nitrobenzene (25 ml.) and acetyl chloride (1.6 g.) was treated with aluminum chloride (3.5 g.) in portions as rapidly as it dissolved. The reaction mixture was heated for 3 hr. (steam bath) and kept at room temperature overnight. It was poured into ice–water (150 ml.) containing concentrated hydrochloric acid (25 ml.) and then was steam distilled. The solid residue in the flask then was extracted with hot ethyl acetate. Concentration of the ethyl acetate extract by slow evaporation gave the 4-acetyl-3-hydroxyxanthone, which crystallized from alcohol as pale yellow needles, m.p. 205–206°, 1.4 g. yield. It gave a scarlet-red color with ethanolic ferric chloride.

Anal. Calcd. for $C_{15}H_{10}O_4$: C, 70.87; H, 3.94. Found: C, 70.58; H, 4.12.

Its 2,4-dinitrophenylhydrazone, which was obtained as orange needles from acetic acid, had m.p. 267°.

Anal. Calcd. for $C_{21}H_{14}N_4O_7$: N, 12.90. Found: N, 12.62.

4-Acetyl-3-acetoxyanthone.—This was prepared by heating 4-acetyl-3-hydroxyxanthone (0.1 g.) with acetic anhydride (2 ml.) and few drops of pyridine for 2 hr. and working up in the usual manner. On crystallization from alcohol, it was obtained as colorless needles, m.p. 145°; it gave no color with ethanolic ferric chloride.

Anal. Calcd. for $C_{17}H_{12}O_5$: C, 68.92; H, 4.05. Found: C, 68.67; H, 4.05.

Ethyl 4-Acetyl-9-oxo-3-xanthyloxyacetate (Ic).—4-Acetyl-3-hydroxyxanthone (Ib, 0.64 g.) in acetone (120 ml.) was treated with bromoacetic ester (1.3 g.) and anhydrous potassium carbonate (2.5 g.), and the mixture refluxed vigorously for 20 hr. The reaction product was filtered from the potassium salts and the solvent was removed from the filtrate. The residual oily product on crystallization from alcohol gave ethyl 4-acetyl-9-oxo-3-xanthyloxyacetate as colorless shiny rectangular plates, m.p. 165°, 0.82 g. yield.

Anal. Calcd. for $C_{19}H_{16}O_6$: C, 67.05; H, 4.71. Found: C, 67.21; H, 4.62.

4-Acetyl-9-oxo-3-xanthyloxyacetic Acid (Id).—Ethyl 4-acetyl-9-oxo-3-xanthyloxyacetate (Ic, 0.68 g.) was macerated with potassium hydroxide (10%, 15.0 ml.) and left overnight at room temperature. The orange solution was filtered and chilled and then acidified carefully with dilute hydrochloric acid when a precipitate was obtained. This was filtered and washed with small amount of water. 4-Acetyl-9-oxo-3-xanthyloxyacetic acid crystallized from acetic acid as colorless shiny rods, m.p. 249° dec., 0.58 g. yield.

Anal. Calcd. for $C_{17}H_{12}O_6$: C, 65.37; H, 3.85. Found: C, 65.42; H, 3.92.

4′-Methylfurano(3′,2′:4,3)xanthone (IIa).—4-Acetyl-9-oxo-3-xanthyloxyacetic acid (Id, 0.31 g.) in acetic anhydride (2 ml.) and sodium acetate (1.0 g.) were heated under reflux for 2 hr. The reaction product was diluted with water, and the precipitate thus obtained was filtered and treated with hot sodium hydrogen carbonate. It was filtered and washed with water. On crystallization from alcohol 4′-methylfurano(3′,2′:4,3)xanthone was obtained as rectangular shiny plates, m.p. 216°, 0.20 g. yield.

Anal. Calcd. for $C_{16}H_{10}O_3$: C, 76.81; H, 4.00. Found: C, 76.92; H, 4.21.

3-Hydroxy-6-methylxanthone (Ie). A. 2-Carboxy-5-methyl-3′-methoxydiphenyl Ether.—2-Chloro-4-methylbenzoic acid (17.5 g.), potassium carbonate (34 g.), *m*-methoxyphenyl (16.5 g.), copper bronze (0.2 g.), cuprous iodide (0.2 g.), and nitrobenzene (175 g.) were stirred at 160° for 6 hr. The mixture was cooled and diluted with water, the solvent was removed in steam, and the residual aqueous solution was filtered from tar. Acidification to pH 6 precipitated more tar, after removal of which the filtrate was adjusted to pH 2 and the carboxydiphenyl ether was collected. It crystallized from benzene–petroleum ether (b.p. 40–60°) as colorless needles, m.p. 124°, 10.2-g. yield.

Anal. Calcd. for $C_{15}H_{14}O_4$: C, 69.77; H, 5.43. Found: C, 69.48; H, 5.61.

B. 3-Methoxy-6-methylxanthone (Cyclization).—2-Carboxy-5-methyl-3′-methoxydiphenyl ether (7.5 g.) was dissolved in acetyl chloride (75 ml.) and cooled in ice. Concentrated sulfuric acid (1.5 ml.) was added, and the reaction mixture was left for an hour at room temperature. Then acetyl chloride was removed by distillation and the reaction product was poured in ice. The resulting precipitate was collected and crystallized from alcohol when 3-methoxy-6-methylxanthone was obtained as needles, m.p. 132°, 5.80 g. yield.

Anal. Calcd. for $C_{15}H_{12}O_3$: C, 75.01; H, 5.00. Found: C, 74.87; H, 5.12.

C. Demethylation.—3-methoxy-6-methylxanthone (4.5 g.) dissolved in xylene (100 ml.) was treated with aluminum chloride (9.0 g.) and kept on a boiling water bath for 2 hr. The reaction mixture, after decomposition with ice, was steam distilled to remove the solvent. The solid residue thus obtained was dissolved in sodium hydroxide (10%) and, after treatment with animal charcoal, was acidified to get the hydroxyxanthone. It crystallized from acetic acid in small yellow needles, m.p. 318–319°, 4.2 g. yield (Shah, *et al.*,[7] report the same melting point).

Anal. Calcd for $C_{14}H_{10}O_3$: C, 74.33; H, 4.33. Found: C, 74.52; H, 4.51.

4-Acetyl-3-hydroxy-6-methylxanthone (If). A.—3-Hydroxy-6-methylxanthone (Ie, 2.26 g.) in redistilled nitrobenzene (25 ml.) and acetyl chloride (1.6 g.) was treated with aluminum chloride (3.5 g.) in portions as rapidly as it dissolved. The reaction mixture was heated for 3 hr. (steam bath) and kept at room temperature overnight. Subsequent work-up of the reaction product as in the case of 4-acetyl-3-hydroxyxanthone gave the crude 4-acetyl-3-hydroxy-6-methylxanthone and If on crystallization from alcohol was obtained as shiny needles, m.p. 243°, 1.68 g. yield. It gave a scarlet-red color with ethanolic ferric chloride.

Anal. Calcd. for $C_{16}H_{12}O_4$: C, 71.64; H, 4.48. Found: C, 71.91; H, 4.51.

Its 2,4-dinitrophenylhydrazone which was obtained as orange needles from acetic acid had m.p. 276°.

Anal. Calcd. for $C_{22}H_{16}N_4O_7$: N, 12.50. Found: N, 12.32.

B.—Redistilled acetic anhydride (5.0 g.) in *sym*-tetrachloroethane (30.00 ml.) was added dropwise to a stirred suspension of powdered aluminum chloride (13.3 g.) and 3-hydroxy-6-methylxanthone (4.1 g.) in *sym*-tetrachloroethane (90.00 ml.). The dark mixture was heated with stirring on a steam bath for 3 hr. and then poured onto crushed ice and concentrated hydrochloric acid (50.00 ml.). The resulting mixture was steam distilled to remove *sym*-tetrachloroethane, and the residue was taken up in ethyl

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acetate. Removal of the solvent left a residue which on crystallization from alcohol gave 4-acetyl-3-hydroxy-6-methylxanthone as long shiny needles, m.p. and m.m.p. 243–244°, 1.94 g. yield.

Employing the same sequence of reactions and identical experimental conditions as given for the preparation of 4′-methylfurano(3′,2′:4,3)xanthone, 4-acetyl-3-hydroxy-6-methylxanthone has been converted into the 3-O-carbethoxy ester which has been subsequently hydrolyzed and allowed to undergo internal cyclization. The physical constants of the intermediates, as well as the final compound, and the analysis values are recorded in Table I.

Acknowledgment.—Our thanks are due to Professor S. Siddappa for his kind interest. We also record our thanks to the Government of India, Ministry of Scientific Research and Cultural Affairs, for the award of a Research Training Scholarship to G. S. Puranik.

Seven-Membered Heterocycles. III. Homoallylic Resonance and a Unique Sulfur Extrusion Reaction in Seven-Membered Sulfur Heterocycles[1-3]

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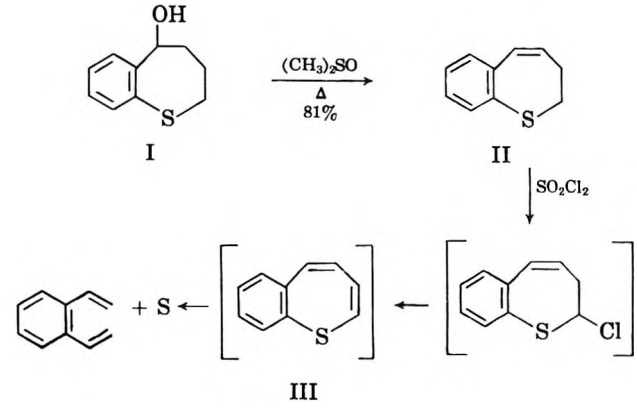
This paper describes some observations made during a study directed toward the synthesis of benzo[*b*]thiepin. The synthesis and structure of 5-hydroxy-2-chloro-4,5-dihydrobenzo[*b*]thiepin (VII) and its acetate (VIII) are reported. Treatment of VII with *p*-toluenesulfonic acid produced an ester (XI). In rationalizing the origin of XI, homoallylic resonance stabilization of the intermediate carbonium ion becomes important. Since carbonium ions appeared to promote a ring contraction, the pyrolysis of VIII was studied. The pyrolysis products were α-chloronaphthalene and 1,1′-naphthyl disulfide, which suggested the intermediate formation of 2-chlorobenzo[*b*]thiepin. A reaction of extruded sulfur and 2-chloronaphthalene is reported.

A number of papers dealing with the preparation and properties of thiepin derivatives have appeared during the past decade; however, the synthesis of benzo[*b*]thiepin remains to be accomplished. In previous reports we have reviewed the known thiepin derivatives,[5] described the synthesis of benzo[*b*]thiepin 1,1-dioxide,[5] and discussed its chemical properties.[1] This paper presents some unexpected reactions encountered in work directed toward the synthesis of benzo[*b*]thiepin.

In the initial synthetic approach toward benzo[*b*]thiepin, the introduction of the 4,5-double bond preceded the 2,3-double bond. The key material for this scheme, 2,3-dihydrobenzo[*b*]thiepin (II), was available readily by dehydration in dimethyl sulfoxide[6] of the known 5-hydroxy-2,3,4,5-tetrahydrobenzo[*b*]thiepin (I).[5] Attempts to introduce the 2,3-double bond by dehydrogenation or *via* allylic bromination with N-bromosuccinimide, followed by reaction with base, were unsuccessful.[7] When II was subjected to chlorination with sulfuryl chloride,[8] sulfur (2.5%, expt. 2 4.5%), naphthalene (9.6%, expt. 2 5.3%), and a dichlorination product of II (22%, the structure of this material has not been established) were isolated. The appearance of sulfur and naphthalene in similar amounts leads one to suspect the presence of benzo[*b*]thiepin (III) which suffered sulfur extrusion.[9] The origin of benzo[*b*]thiepin could be rationalized by a thermal elimination of hydrogen chloride from the 2-chloro derivative of II, the expected product of the chlorination reaction.



These results suggested a limited thermal stability for benzo[*b*]thiepin and the need for an alternate synthetic approach. In this alternate pathway the 2,3-double bond was introduced first, followed by attempts to insert the 4,5-double bond. The compounds utilized in these studies were 5-substituted 2-chloro-4,5-dihydrobenzo[*b*]thiepins. The chloro group in the 2-position was a consequence of the synthetic method employed to introduce the 2,3-double bond.

The reaction sequence which conveniently led to the preparation of the desired starting materials is outlined in Scheme 1.

When IV was subjected to the chlorination procedure of Truce, Birum, and McBee[8] using at least 2 moles of sulfuryl chloride, substitution proceeded, in good yield, α to the sulfur and gave 5-(*p*-nitrobenzoyloxy)-2,2-dichloro-2,3,4,5-tetrahydrobenzo[*b*]thiepin (V) as a white crystalline product. Attempts to monochlorinate IV produced amorphous solids which could not be crystallized and purified. During the melting point determination of V, the evolution of a gas was evident

(1) For part II in this series, see V. J. Traynelis and R. F. Love, *J. Org. Chem.*, **29**, 366 (1964).

(2) Presented before the Organic Division at the 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., Sept., 1962.

(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) Smith Kline and French Foundation Fellow, 1959–1960; Eastman Kodak Fellow, 1960–1961. Abstracted from part of the Ph.D. dissertation of J. R. Livingston, Jr., March, 1962.

(5) V. J. Traynelis and R. F. Love, *J. Org. Chem.*, **26**, 2728 (1961).

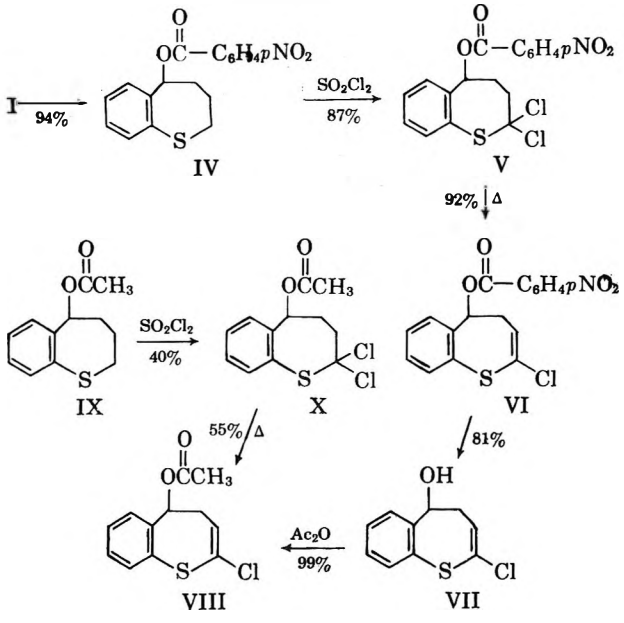
(6) V. J. Traynelis, W. L. Hergenrother, J. R. Livingston, and J. A. Valicenti, *ibid.*, **27**, 2377 (1962).

(7) R. F. Love, Ph.D. dissertation, University of Notre Dame, 1960.

(8) (a) W. E. Truce, G. H. Birum, and E. T. McBee, *J. Am. Chem. Soc.*, **72**, 3594 (1952); (b) F. G. Bordwell and B. M. Pitt, *ibid.*, **77**, 572 (1955).

(9) For a review of sulfur extrusion reactions, see J. D. Loudon, "Organic Sulfur Compounds," Vol. I, N. Kharasch, Ed., Pergamon Press, New York, N. Y., 1961, p. 299; also, see ref. 1.

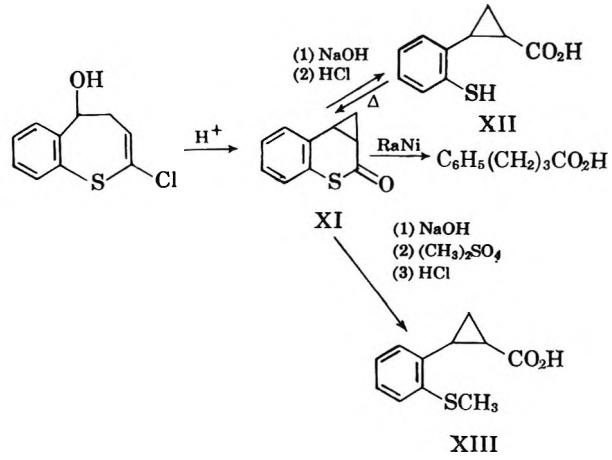
SCHEME I



and, when V was heated in refluxing xylene for a few hours, 1 mole of hydrogen chloride was lost and 5-(*p*-nitrobenzoyloxy)-2-chloro-4,5-dihydrobenzo[*b*]thiepin-(VI) was isolated in good yield. Alkaline hydrolysis of VI in aqueous *t*-butyl alcohol produced the first key intermediate, 5-hydroxy-2-chloro-4,5-dihydrobenzo[*b*]-thiepin (VII), and a simple acetylation of VII afforded the second key intermediate, 5-acetoxy-2-chloro-4,5-dihydrobenzo[*b*]thiepin (VIII). An alternate approach to the preparation of VIII involved the acetylation of I to 5-acetoxy-2,3,4,5-tetrahydrobenzo[*b*]thiepin (IX); dichlorination with sulfuryl chloride gave X followed by the pyrolytic elimination of hydrogen chloride to give VIII. The structural assignments for compounds VII and VIII were based on elemental analysis, infrared (in particular the observation of functional group changes as one proceeds through the reaction scheme), ultraviolet, and n.m.r. spectra. The n.m.r. spectral data, along with proton assignments, are recorded in the Experimental section.

The initial experiments to introduce the final double bond in the sulfur ring involved a dehydration study of VII. When VII was heated with a trace of *p*-toluenesulfonic acid in benzene, some water distilled as an azeotrope with benzene and also hydrogen chloride was formed. A white crystalline product was isolated in 30% yield and was assigned the structure of 2-oxo-1a,7b-dihydrocyclopropa[*c*][1]benzothiapyran[10] (XI) on the basis of the following chemical and physical evidence.

(1) Compound XI was dissolved in hot aqueous sodium hydroxide solution and upon acidification gave the acid XII. When XII was heated under reduced pressure, the starting cyclic ester (XI) was recovered as a sublimate. Treatment of a solution of XI in aqueous sodium hydroxide with methyl sulfate produced the methylmercapto acid (XIII). These data are rationalized conveniently by the presence of a cyclic thiol ester function.



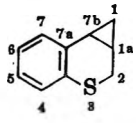
(2) The infrared spectrum of XI had a strong absorption at 6.05 μ which is attributed to the thiol ester carbonyl. Hurd and Kreuz[11] have prepared 2-thienol and reported a carbonyl absorption at 6.0 μ, which may arise from one of two tautomeric structures.[11] In considering the structural effects in XI such as the conjugative effect of a cyclopropyl ring, the presence of a benzo fused ring and the ring size, the appearance of the carbonyl band for XI at 6.05 μ is compatible with the carbonyl band in 2-thienol at 6.0 μ. The infrared spectra of XII and XIII were consistent with the assigned structures for these compounds.

(3) A Raney nickel desulfurization of XI gave γ-phenylbutyric acid, identified by spectral comparison and mixture melting points of the free acid and its amide with authentic samples.

(4) The strongest support for the presence of a cyclopropane ring comes from the n.m.r. spectra of XI, XII, and XIII. These spectra showed complex multiplets in the region of τ 7–9 and were similar to the n.m.r. spectra of *cis*- and *trans*-2-phenylcyclopropanecarboxylic acids. Compounds XI and XII showed complex multiplets in three regions which centered at τ 8.72, 8.25, and 7.45 (determined in deuteriochloroform) and 8.78, 8.27, and 7.36 (determined in trifluoroacetic acid), respectively. However, compound XIII, *cis*- and *trans*-2-phenylcyclopropanecarboxylic acids (each measured in trifluoroacetic acid solution), had complex multiplets in only two regions centered at τ 8.19 and 7.50 (τ 7.60 S–CH_3 absorption), 8.40 and 7.16, and 8.49 and 7.35, respectively. The absence of olefinic protons excluded consideration of a seven-membered thiol ester with a double bond in the hetero ring in XI.[12]

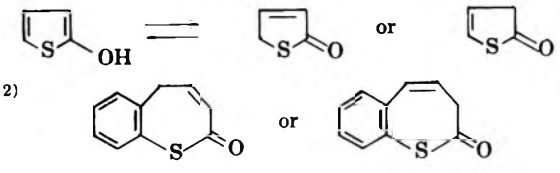
(5) Some confirmatory evidence in favor of the cyclopropane ring in preference to a double bond was the failure of XI to add hydrogen catalytically or decolorize bromine in carbon tetrachloride.

(10) For the numbering of XI according to A. M. Patterson, L. T. Capell, and D. F. Walter, "The Ring Index," 2nd Ed., American Chemical Society, Washington, D. C., 1960, see p. 275.

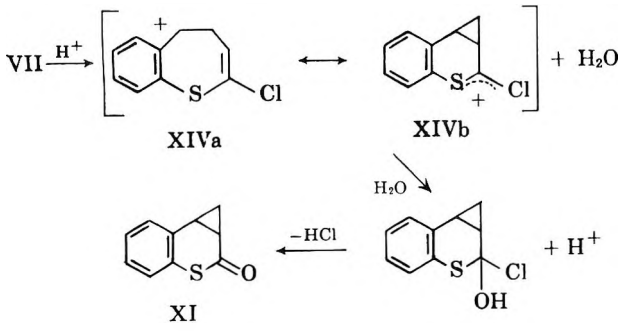


(11) C. D. Hurd and K. L. Kreuz, *J. Am. Chem. Soc.*, **72**, 5543 (1950).

(12)



The origin of the cyclic ester XI can be nicely rationalized by application of carbonium ions stabilized by homoallylic resonance. In this case the contribution of structure XIVb to the resonance hybrid of the car-

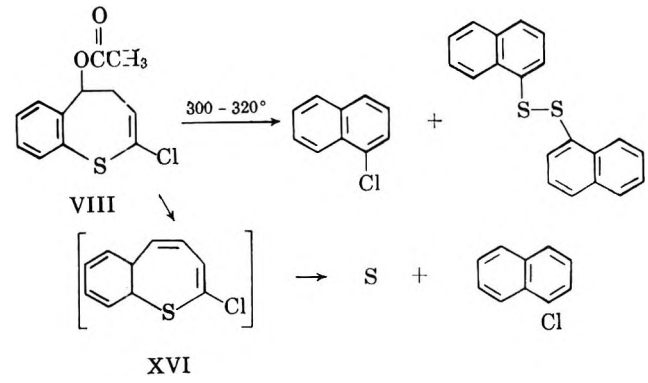


bonium ion XIV becomes appreciable because of the presence of two electron-releasing atoms (sulfur and chlorine) which help delocalize the positive charge from C-2. This effect is reflected in the isolation of the cyclopropyl ester (XI) in 30% yield. The remaining 70% for the reaction is still under investigation.

Since elimination reactions which proceed *via* carbonium ions would be prone to the above homoallylic resonance, the next approach to introduce the 4,5-double bond of benzo[*b*]thiepin utilized an acetate pyrolysis which involves a *cis* cyclic elimination. Thus, VIII was distilled into a tube heated to about 300° and the pyrolysis products were separated by column chromatography. The first compound eluted was α-chloronaphthalene (10%), identified by comparison of its infrared and ultraviolet spectra with that of an authentic sample, and by a mixture melting point of its picrate with an authentic sample. A second fraction was recovered as a yellow viscous oil from which was isolated 1,1′-naphthyl disulfide (11%) as a yellow crystalline solid. The remaining oil possessed infrared and ultraviolet spectra identical with 1,1′-naphthyl disulfide and most likely was a mixture of 1,1′-naphthyl disulfide and 1,1′-naphthyl polysulfides. The yield based on the initial yellow viscous oil being 1,1′-naphthyl disulfide was 20%.

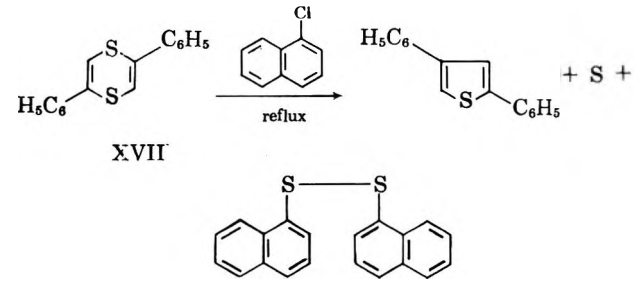
The identity of 1,1′-naphthyl disulfide was established by analysis, molecular weight determination, comparison of infrared and ultraviolet spectra with an authentic sample, and melting point and mixture melting point with an authentic sample. A reduction of the disulfide was accomplished by zinc and hydrochloric acid and was followed by conversion of the mercaptan to the known α-napthylthioacetic acid. A mixture melting point with an authentic sample was not depressed. Evidence for the presence of some 1,1′-napthyl polysulfides was found when hydrogen sulfide was liberated during reduction of the liquid mixture containing this compound with zinc and hydrochloric acid. The resulting mercaptan was converted to α-naphthylthioacetic acid.

In order to rationalize the products isolated, one can picture the expected pyrolysis of the acetate VIII leading to 2-chlorobenzo[*b*]thiepin (XVI). Since these seven-membered sulfur systems are known to extrude sulfur,[9,13,14] such a reaction proceeding with XVI



would form sulfur and α-chloronaphthalene. In a recent report Parham and Koncos[13] suggested the formation of 3-chlorobenzo[*b*]thiepin as an intermediate which under reaction conditions was converted to the isolated product, β-chloronaphthalene.

Such an extrusion of sulfur nicely accounts for α-choronaphthalene. As for the formation of 1,1′-naphthyl disulfide, one possibility may involve a reaction of sulfur with α-chloronaphthalene. A mixture of elemental sulfur and pure α-chloronaphthalene was refluxed; however, only starting materials were recovered. This failure of reaction could be attributed to the different nature of sulfur, as extruded in the pyrolysis, and elemental sulfur. Another compound known to extrude sulfur at a temperature which would permit pyrolysis in refluxing α-chloronaphthalene is 1,4-dithiadiene (XVII).[15] When XVII was added to refluxing α-chloronaphthalene, about 4% of 1,1′-naphthyl disulfide was isolated. Identification was by com-



parison of its infrared spectrum with an authentic sample. The nature of this reaction is under further investigation.

In conclusion, the pyrolytic method of introducing a double bond suffers from the disadvantage (as a method for making benzo[*b*]thiepin) of requiring temperatures at which the desired product loses sulfur and is converted to a more stable naphthalene system. Other pathways toward benzo[*b*]thiepin are now being studied.

Experimental[16]

5-Hydroxy-2,3,4,5-tetrahydrobenzo[*b*]thiepin (I).—This starting material was prepared by the sequence of reactions described

(13) W. E. Parham and R. Koncos, *J. Am. Chem. Soc.*, **83**, 4034 (1961).

(14) G. P. Scott, *ibid.*, **75**, 6332 (1953); K. Dimroth and G. Lenke, *Chem. Ber.*, **89**, 2608 (1956); J. D. Loudon, A. D. B. Sloan, and L. A. Summers, *J. Chem. Soc.*, 3814 (1957).

(15) W. E. Parham and V. J. Traynelis, *J. Am. Chem. Soc.*, **76**, 4960 (1954).

(16) All melting points and boiling points are uncorrected. The microanalyses were carried out by Midwest Microlab, Inc., Indianapolis, Ind., and Schwartzkopf Microanalytical Laboratories, Woodside, N. Y. Infrared spectra were determined on a Baird Associates infrared spectrophotometer by J. R. L., Jr.; ultraviolet spectra were recorded by Mr. Fred Klebacher on a Perkin-Elmer Spectracord; the n.m.r. spectra were determined by Dr. M. Gianni and Mr. B. Nowak with a Varian Associates 60-Mc. high resolution n.m.r. spectrometer, Model V-4300B.

by Traynelis and Love.[5] Thiophenol (0.50 mole) and butyrolactone (0.50 mole) were converted in 86% yield to γ-phenylmercaptobutyric acid which was cyclodehydrated with polyphosphoric acid to 5-oxo-2,3,4,5-tetrahydrobenzo[*b*]thiepin (85% yield); reduction with sodium borohydride gave 5-hydroxy-2,3,4,5-tetrahydrobenzo[*b*]thiepin (96%), m.p. 69–70.5°, lit.[5] m.p. 70–71°.

2,3-Dihydrobenzo[*b*]thiepin (II).—Dehydration of the preceding alcohol in dimethyl sulfoxide was described previously[6] and supplied the material used in this work.

Reaction of 2,3-Dihydrobenzo[*b*]thiepin with Sulfuryl Chloride.—Following the procedure of Bordwell and Pitt,[8] a solution of sulfuryl chloride (8.4 g., 0.062 mole) in 20 ml. of petroleum ether (b.p. 30–60°) was added dropwise over a period of 45 min. to 2,3-dihydrobenzo[*b*]thiepin (10.0 g., 0.062 mole) in 20 ml. of petroleum ether. After the solution was refluxed 55 min., sodium bicarbonate (5.0 g., 0.055 mole) was added, and the solution refluxed 1 hr. The reaction mixture was dried over anhydrous magnesium sulfate and distilled rapidly under nitrogen. Chromatography of the distillate (9.35 g.) on Alcoa F-20 alumina (450 g.) using dry petroleum ether as eluent gave 0.05 g. (2.5%) of elemental sulfur, m.p. 111–112°. Recrystallization from ethyl acetate produced 0.025 g. (1.2%) of sulfur, m.p. 118–119°, which showed no depression in melting point when mixed with an authentic sample recrystallized in the same manner. Naphthalene (0.77 g., 9.6%), m.p. 72–78°, was eluted next and upon recrystallization from ethanol gave 0.34 g. (4.3%) of pure naphthalene, m.p. 79–80.5°, lit.[17] m.p. 79–80°. A mixture melting point with an authentic sample was not depressed, and the infrared spectra of the two samples were identical. The third compound eluted from the column was 2,3-dihydrobenzo[*b*]thiepin (0.09 g., 1%), identified by its infrared spectrum. A final component (3.25 g.) was eluted with ether–petroleum ether (20:80) and contained chlorine. Distillation of this material gave a mixture, b.p. 83–86° (0.02 mm.), $n^{20}D$ 1.6329–1.6345, which appeared to be primarily a dichlorination product. The structure of this material has not been established.

In a second experiment the reaction mixture was heated under nitrogen at 85° for 24 hr. and gave sulfur (4.5%) and naphthalene (5.3%).

5-(*p*-Nitrobenzoyloxy)-2,3,4,5-tetrahydrobenzo[*b*]thiepin (IV).—Solid *p*-nitrobenzoyl chloride (23.0 g., 0.124 mole) was added in one portion to a solution of 5-hydroxy-2,3,4,5-tetrahydrobenzo[*b*]thiepin (19.0 g., 0.105 mole) in 60 ml. of pyridine, and the mixture refluxed for 15 min. after all the solid dissolved. The reaction mixture was poured into water and the solid was collected, triturated with saturated sodium bicarbonate solution, washed with water, dried, and crystallized from a benzene–petroleum ether (b.p. 60–70°) mixture. The yield of 5-(*p*-nitrobenzoyloxy)-2,3,4,5-tetrahydrobenzo[*b*]thiepin as pale yellow needles, m.p. 149–150°, lit.[5] m.p. 149–150°, was 32.3 g. (94%).

2,2-Dichloro-5-(*p*-nitrobenzoyloxy)-2,3,4,5-tetrahydrobenzo[*b*]thiepin (V).—Sulfuryl chloride (22.0 g., 0.17 mole) was added dropwise with stirring to a solution of 5-(*p*-nitrobenzoyloxy)-2,3,4,5-tetrahydrobenzo[*b*]thiepin (25.0 g., 0.076 mole) in 100 ml. of methylene chloride at a rate sufficient to keep the solution refluxing gently. After addition was complete, the solution was refluxed for an additional 40 min. and then one-third of the solvent was removed under reduced pressure. Petroleum ether (b.p. 30–60°, 200 ml.) was added, and the precipitate was filtered and washed with petroleum ether (b.p. 30–60°). The yield of 2,2-dichloro-5-(*p*-nitrobenzoyloxy)-2,3,4,5-tetrahydrobenzo[*b*]thiepin, m.p. 112°, was 26.2 g. (82%).

Anal. Calcd. for $C_{17}H_{13}Cl_2NO_4S$: C, 51.27; H, 3.29; Cl, 7.81; N, 3.52. Found: C, 51.21; H, 3.17; Cl, 17.91; N, 3.79.

2-Chloro-5-(*p*-nitrobenzoyloxy)-4,5-dihydrobenzo[*b*]thiepin (VI).—A solution of 2,2-dichloro-5-(*p*-nitrobenzoyloxy)-2,3,4,5-tetrahydrobenzo[*b*]thiepin (5.0 g., 0.0125 mole) in 20 ml. of sodium-dried xylene was refluxed vigorously for 4 hr. and cooled to 0°; the precipitate of 2-chloro-5-(*p*-nitrobenzoyloxy)-4,5-dihydrobenzo[*b*]thiepin, 4.15 g. (92%), m.p. 199–201°, was collected. An analytical sample was prepared by repeated recrystallization from benzene, m.p. 201–202°.

Anal. Calcd. for $C_{17}H_{12}ClNO_4S$: C, 56.43; H, 3.34; Cl, 9.80; N, 3.87. Found: C, 56.67; H, 3.47; Cl, 10.02; N, 3.96.

(17) G. Egloff, "Physical Constants of Hydrocarbons," Vol. IV, Reinhold Publishing Corp., New York, N. Y., 1947, p. 77.

2-Chloro-5-hydroxy-4,5-dihydrobenzo[*b*]thiepin (VII).—A mixture of potassium hydroxide (5.0 g., 0.088 mole), water (10 ml.), 2-chloro-5-(*p*-nitrobenzoyloxy)-4,5-dihydrobenzo[*b*]thiepin (25.2 g., 0.069 mole), and *t*-butyl alcohol (100 ml.) was refluxed until all materials dissolved and then for an additional 15 min. After the reaction mixture was poured into water, the solid was isolated, and recrystallization from petroleum ether (b.p. 60–70°) gave 11.6 g. of white needles of 2-chloro-5-hydroxy-4,5-dihydrobenzo[*b*]thiepin, m.p. 98–99°; $\lambda_{max}^{heptane}$ 217, 240, and 273 mμ (ε 8800, 3640, and 4200). Concentration of the mother liquor followed by treatment with Norit gave an additional 0.45 g. of alcohol, m.p. 97.5–98.5°, for a total yield of 12.0 g. (81%).

Anal. Calcd. for $C_{10}H_9ClOS$: C, 56.47; H, 4.27; Cl, 16.67; S, 15.08. Found: C, 56.51; H, 4.26; Cl, 16.89; S, 14.90.

The n.m.r. spectrum[18] had the following peaks: multiplet, τ 3.00 center, wt. of 4 (aromatic protons); triplet,[19] 4.31 center, wt. of 1 (C_3–H olefinic proton); quartet,[19] 4.51 center, wt. of 1 (C_5–H, benzylic proton); singlet, 6.75, wt. of 1 (OH proton); and multiplet, 7.44 center, wt. of 2 (C_4–H allylic protons).

2-Chloro-5-acetoxy-4,5-dihydrobenzo[*b*]thiepin (VIII). Method A.—A solution of 2-chloro-5-hydroxy-4,5-dihydrobenzo[*b*]thiepin (4.70 g., 0.022 mole), acetic anhydride (10 g., 0.098 mole), and pyridine (20 ml.) was refluxed for 20 min. and after cooling poured into water. Recrystallization of the resulting solid from petroleum ether (b.p. 60–70°) gave 5.55 g. (99%) of 2-chloro-5-acetoxy-4,5-dihydrobenzo[*b*]thiepin, m.p. 110–111°. An analytical sample, m.p. 111–112°, obtained by recrystallization from the same solvent, had $\lambda_{max}^{heptane}$ 240 mμ (ε 3570) and 274 (5250).

Anal. Calcd. for $C_{12}H_{11}ClO_2S$: C, 56.57; H, 4.34. Found: C, 56.29; H, 4.54.

The n.m.r. spectrum had the following peaks: multiplet, τ 2.64 center, wt. of 4 (aromatic protons); quartet, 3.30 center, wt. of 1 (C_5–H, benzylic proton); triplet, 4.03 center, wt. of 1 (C_3–H, olefinic proton); multiplet 7.15 center, wt. of 2 (C_4–H, allylic protons); and singlet, 7.83, wt. of 3 (methyl protons).

Method B.—Sulfuryl chloride (7.30 g., 0.054 mole) was added dropwise to a well-stirred solution of 5-acetoxy-2,3,4,5-tetrahydrobenzo[*b*]thiepin[5] (5.45 g., 0.0245 mole) in methylene chloride (10 ml.). After the solution was refluxed until the evolution of hydrogen chloride ceased, the methylene chloride was removed and petroleum ether (b.p. 30–60°) was added. The resulting solid was isolated and recrystallization from petroleum ether (b.p. 60–70°) gave 3.0 g. (40%) of 2,2-dichloro-5-acetoxy-2,3,4,5-tetrahydrobenzo[*b*]thiepin, m.p. 75–77°.

A solution of the above dichloro derivative (2.30 g., 0.0079 mole) in xylene (10 ml.) was refluxed 2.5 hr.; then most of the xylene was removed under reduced pressure. Petroleum ether (b.p. 30–60°) was added and the precipitate was collected. Recrystallization from a mixture of benzene petroleum ether (b.p. 60–70°) after a Norit treatment gave 1.1 g. (55%) of 2-chloro-5-acetoxy-4,5-dihydrobenzo[*b*]thiepin, m.p. 110–111°.

2-Oxa-1a,7b-dihydrocyclopropa[*c*][1]benzothiapyran (XI).—A solution of 2-chloro-5-hydroxy-4,5-dihydrobenzo[*b*]thiepin (2.0 g., 0.0094 mole), *p*-toluenesulfonic acid (0.2 g.), and anhydrous benzene (15 ml.) was allowed to reflux for 3 hr. during which time hydrogen chloride was evolved. The benzene was removed, 20 ml. of petroleum ether (b.p. 60–70°) was added, and, after a Norit treatment, 0.54 g. (30%) of colorless plates of 2-oxa-1a,7b-dihydrocyclopropa[*c*][1]benzothiapyran, m.p. 79–80°, was isolated. Further recrystallization from petroleum ether (b.p. 60–70°) produced an analytical sample, m.p. 80.5–81°, $\lambda_{max}^{heptane}$ 255 mμ (ε 4450) and 280 inf. (1635).

Anal. Calcd. for $C_{10}H_8OS$: C, 68.15; H, 4.58; S, 18.19. Found: C, 68.21; H, 4.58; S, 17.83.

A solution of 2-oxa-1a,7b-dihydrocyclopropa[*c*][1]benzothiapyran in 10 ml. of dioxane and 33 mg. of 10% palladium on charcoal were stirred at atmospheric pressure in a semimicro hydrogenation apparatus[20] for 5 hr. Since no significant uptake of hydrogen occurred, the reaction mixture was transferred to a Paar hydrogenation apparatus and kept at 50 p.s.i. of hydrogen for 2 hr. When the solvent was removed, starting material with m.p. 80–81° was recovered.

When 2-oxo-1a,7b-dihydrocyclopropa[*c*][1]benzothiapyran was treated with an excess of bromine in carbon tetrachloride for 2

(18) The n.m.r. spectrum was determined in deuteriochloroform solution with tetramethylsilane as an internal standard.

(19) One band of the C_3–H triplet was superimposed on one band of the C_5–H quartet.

(20) For a diagram of the apparatus, see A. A. Baldoni, Ph.D. dissertation, University of Notre Dame, 1951, p. 54.

hr., no decolorization of bromine took place and only unchanged starting material was recovered.

2-(2-Mercaptophenyl)cyclopropanecarboxylic Acid (XII).—2-Oxo-1a,7b-dihydrocyclopropa[*c*][1]benzothiapyran (100 mg., 0.568 mmole) and 10 ml. of 10% sodium hydroxide solution were heated until the solid dissolved. After the solution was acidified, the resulting solid was crystallized from ethanol–water to give 78 mg. (71%) of 2-(2-mercaptophenyl)cyclopropanecarboxylic acid, m.p. 146–150°.

Anal. Calcd. for $C_{10}H_{10}O_2S$: C, 61.83; H, 5.19. Found: C, 61.71; H, 5.23.

Ring Closure of 2-(2-Mercaptophenyl)cyclopropanecarboxylic Acid.—2-(2-Mercaptophenyl)cyclopropanecarboxylic acid (100 mg., 0.52 mmole) was sublimed slowly and gave 62 mg. (69%) of 2-oxo-1a,7b-dihydrocyclopropa[*c*][1]benzothiapyran, m.p. 75–80°. The infrared spectrum was identical with that of an authentic sample, and a mixture melting point with an authentic sample was 77–79.5°.

2-(2-Methylthiophenyl)cyclopropanecarboxylic Acid (XIII).—Dimethyl sulfate (700 mg., 5.5 mmoles) was added to a solution of 2-oxo-1a,7b-dihydrocyclopropa[*c*][1]benzothiapyran (200 mg., 1.4 mmoles) in 10 ml. of sodium hydroxide (2.0 g., 0.05 mole), and the resulting solution was heated for 5 min. The solution was cooled, strongly acidified with sulfuric acid, and the precipitate was collected. The yield of 2-(2-methylthiophenyl)cyclopropanecarboxylic acid, m.p. 165–166°, was 210 mg. (89%). Recrystallization from benzene–petroleum ether (b.p. 60–70°) produced an analytical sample, m.p. 168–169°.

Anal. Calcd. for $C_{11}H_{12}O_2S$: C, 63.42; H, 5.80; S, 15.39. Found: C, 63.45, 63.27; H, 5.92, 5.83; S, 15.51, 15.23.

Desulfurization of 2-Oxa-1a,7b-dihydrocyclopropa[*c*][1]benzothiapyran.—To a solution of 2-oxo-1a,7b-dihydrocyclopropa[*c*][1]benzothiapyran (200 mg., 1.2 mmoles) in 30 ml. of 6.7% sodium hydroxide solution was added slowly and with stirring 2.0 g. of Raney nickel alloy. The mixture was heated for 2 hr. on a steam bath and filtered through Celite; the filtrate strongly was acidified with concentrated hydrochloric acid. A precipitate of 93 mg. (50%) of γ-phenylbutyric acid, m.p. 50–52°, was collected and an additional 54 mg. (30%), m.p. 50–52°, was obtained by extraction of the acidic filtrate with methylene chloride. A mixture melting point with an authentic sample was not depressed.

The amide was prepared in the usual manner[21] and melted at 84–86°. A mixture melting point with an authentic sample was undepressed. The infrared spectra of both the acid and the amide were identical with those of authentic samples.

γ-Phenylbutyric Acid.—Addition of 200 g. of crushed Dry Ice to the Grignard reagent prepared from γ-phenylpropyl chloride (15.5 g., 0.10 mole), magnesium (3.0 g., 0.12 g.-atom), and 40 ml. of ether produced 7.6 g. (44%) of γ-phenylbutyric acid, m.p. 48–51.5°, lit.[22] m.p. 51°, isolated by ether extraction of the acidified reaction mixture.

The amide was prepared in the usual manner and after recrystallization from benzene–petroleum ether (b.p. 60–70°) melted at 84–86°, lit.[23] m.p. 84.5°.

2-Phenylcyclopropanecarboxylic Acid.—Employing the procedure of Burger and Yost,[24] the reaction of ethyl diazoacetate[25] (18.3 g., 0.161 mole) and styrene (16.7 g., 0.161 mole plus 8.35 g., 0.08 mole) produced 19.4 g. (63% based on ethyl diazoacetate) of ethyl 2-phenylcyclopropanecarboxylate, b.p. 91–93° (0.4 mm.), $n^{20}D$ 1.5192, lit.[24] b.p. 103–105° (0.5–0.7 mm.). Saponification of a portion of the above ester followed by fractional crystallization according to the procedure of Burger and Yost[24] gave *trans*-2-phenylcyclopropanecarboxylic acid, m.p. 92–93°, lit.[24] m.p. 93°, and *cis*-2-phenylcyclopropanecarboxylic acid, m.p. 106–107°, lit.[24] m.p. 106–107°.

Pyrolysis of 2-chloro-5-acetoxy-4,5-dihydrobenzo[*b*]thiepin.—After 2-chloro-5-acetoxy-4,5-dihydrobenzo[*b*]thiepin (5.55 g., 0.022 mole) was distilled slowly at 0.05-mm. pressure into a jacketed, electrically heated, 13 × 2.3 mm. glass tube packed loosely with glass wool and maintained at 300–320°, the apparatus was cooled and the pyrolysis tube and condenser were washed with carbon tetrachloride. Removal of the solvent left 5.2 g. of a black residue which was redissolved in carbon tetrachloride, placed on 70 g. of Alcoa F-20 activated alumina, and washed with 500 ml. of petroleum ether (b.p. 30–60°). When the eluate was concentrated, 0.70 g. (12.6%) of starting material with m.p. 109–111° crystallized. An infrared spectrum was identical with that of an authentic sample. The remainder of the solvent was removed and the 2.1 g. of residue was chromatographed on 120 g. of Alcoa F-20 activated alumina. Elution with petroleum ether (b.p. 30–60°) gave 350 mg. (10%) of α-chloronaphthalene. The infrared spectrum was identical with that of authentic material.

The picrate was prepared by the method of Vogel[26] and had m.p. 133–136°, and a mixture melting point with an authentic sample was not depressed.

A second substance eluted with petroleum ether (b.p. 30–60°) was a viscous yellow oil which, when mixed with acetic acid, gave a yellow crystalline solid (1st crop, m.p. 88–89.5°; 2nd crop, m.p. 79–82°; 3rd crop, m.p. 80–85°) in 387-mg. total yield. An analytical sample, m.p. 88.5–91°, was prepared by recrystallization from methanol.

Anal. Calcd. for $C_{20}H_{14}S_2$: C, 75.43; H, 4.42; mol. wt., 318. Found: C, 75.72; H, 4.72; mol. wt., 332.

The ultraviolet spectrum determined in *n*-heptane showed λ_{max} 299 mμ (ϵ_{max} 11,950).

The infrared and ultraviolet spectra of the solid were identical with those of 1,1′-naphthyl disulfide, and a mixture melting point of the first crop of crystals with an authentic sample was not depressed. Removal of the solvent from the mother liquors left 300 mg. of yellow oil which had infrared and ultraviolet spectra identical with 1,1′-naphthyl disulfide. The total yield of oil plus solid was 687 mg. (32% considering this as 1,1-naphthyl disulfide).

1,1-Naphthyl Disulfide.—Employing the procedure of Taboury,[27] the α-mercaptonaphthalene resulting from α-bromonaphthalene (12.5 g., 0.061 mole), magnesium (1.47 g., 0.061 g.-atom), and sulfur (1.94 g., 0.061 mole) was extracted into 20% sodium hydroxide that had been freed of dissolved air. This solution was treated with 30% hydrogen peroxide (5.0 ml.), and the precipitate (3.5 g.) was collected after 1 hr. Recrystallization from ethanol gave 2.8 g. (29%) of 1,1′-naphthyl disulfide, m.p. 88.5–90°, lit.[28] m.p. 91°.

α-Naphthylthioacetic Acid.—Zinc dust (2.0 g., 0.03 g.-atom) was added in small portions to a slurry of 1,1′-naphthyl disulfide (1.0 g., 0.0031 mole) in ethanol (30 ml.) and concentrated hydrochloric acid (10 ml.). After the mixture was heated on a steam bath until solution was complete and the color was discharged, the solution was made basic with potassium hydroxide, and chloroacetic acid (1.5 g., 0.016 mole) was added. The mixture was heated 1 hr. on a steam bath, cooled, and acidified; the resulting solid was crystallized from benzene–petroleum ether (b.p. 60–70°). The yield of α-naphthylthioacetic acid, m.p. 102–104°, lit.[29] m.p. 111–112°, was 600 mg. (45%).

When the yellow oil (300-mg. fraction) from the above pyrolysis experiment was treated as above, some hydrogen sulfide was evolved (trapped as lead sulfide), and the yield of α-naphthylthioacetic acid, m.p. 102–104°, was 147 mg. (37%). A mixture melting point with an authentic sample was not depressed.

Attempted Reaction of α-Chloronaphthalene with Elemental Sulfur.—Sulfur (0.20 g., 0.0063 g.-atom) and α-chloronaphthalene (1.0 g., 0.0062 mole) were refluxed for 5 min. and cooled; 5 ml. of petroleum ether (b.p. 30–60°) was added. The solid isolated was 140 mg. of sulfur. The mother liquor was placed on 60 g. of Alcoa F-20 activated alumina and washed with petroleum ether (b.p. 30–60°). The first fraction contained 10 mg. of sulfur (total sulfur, 150 mg., 75%), and fractions 2 and 3 contained 900 mg. (90%) of α-chloronaphthalene identified by its infrared spectrum.

2,5-Diphenyl-1,4-dithiadiene.—This material was prepared according to the procedure of Barker and Barkenbus.[30]

Pyrolysis of 2,5-Diphenyl-1,4-dithiadiene in α-Chloronaphthalene.—A suspension of 2,5-diphenyl-1,4-dithiadiene (1.50 g., 5.6 mmoles) in α-chloronaphthalene (3.00 g.) was added to refluxing

(21) 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. 200.

(22) E. Fischer and W. Schmitz, *Ber.*, **39**, 2208 (1906).

(23) C. Willgerodt and F. H. Merk, *J. prakt. Chem.*, [2]**80**, 197 (1909).

(24) A. Burger and W. L. Yost, *J. Am. Chem. Soc.*, **70**, 2198 (1948).

(25) F. B. LaForge, W. A. Gersoff, N. Green, and H. S. Schechter, *J. Org Chem.*, **17**, 381 (1952).

(26) A. I. Vogel, "Practical Organic Chemistry," 3rd Ed., Longmans Green and Co., New York, N. Y., 1957, p. 578.

(27) M. F. Taboury, *Compt. rend.*, **138**, 982 (1904).

(28) R. Leuckart, *J. prakt. Chem.*, [2]**41**, 217 (1890).

(29) German Patent 414,853; *Chem. Zentr.*, **96** II, 774 (1925).

(30) R. H. Barker and C. Barkenbus, *J. Am. Chem. Soc.*, **58**, 262 (1936).

α-chloronaphthalene (0.50 g.) over a 5-min. period. After allowing the mixture to cool, 2.0 g. of α-chloronaphthalene was removed by distillation and had b.p. 125° (12 mm.). The residue was triturated with petroleum ether (b.p. 30–60°), and the resulting solution was chromatographed on 120 g. of Alcoa F-20 activated alumina. The materials to come off the column were 10 mg. (5.8%) of sulfur, m.p. 119–120°; 835 mg. of α-chloronaphthalene (a total recovery of α-chloronaphthalene was 2.84 g., 81%); 200 mg. (15.2%) of 2,4-diphenylthiophene, m.p. 118–119°, lit.[15] m.p. 121.5–123°; and 31.2 mg. (3.7%) of a yellow oil–crystal mixture which had an infrared spectrum identical with that of authentic 1,1-naphthyl disulfide.

2-Hydroxycyclohexylhydrazines. I.[1] Synthesis, Acylation, Acyl Migration, and Dihydrooxadiazine Ring Formation

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DL-*trans*- and DL-*cis*-2-hydroxycyclohexylhydrazines (*trans*- and *cis*-I) were prepared. The *trans* isomer was correlated with DL-*trans*-2-aminocyclohexanol in two ways, confirming the configuration of *trans*-I and accordingly of *cis*-I. N-Monobenzoyl, N_1,N_2-dibenzoyl, and N_1,N_2,O-tribenzoyl derivatives were derived from I. The N-benzoylated derivatives were treated with hydrogen chloride in anhydrous ethanol (method A) and in water (method B). Method A converted both forms of DL-2-benzoyl-1-(2-hydroxycyclohexyl)hydrazine (VI) and DL-*cis*-1,2-dibenzoyl-1-(2-hydroxycyclohexyl)hydrazine (*cis*-V) to dihydrooxadiazine derivatives (*trans*-X, *cis*-X, and *cis*-IX) with retention. On the same treatment, each form of DL-1-benzoyl-1-(2-hydroxycyclohexyl)hydrazine (IV) was converted to DL-4a,5,6,7,8,8a-hexahydro-3-phenyl-1H-4,1,2-benzoxadiazine (X) with retention, which was identical with the product from VI. This indicated that the reaction involved $N_1 \rightarrow N_2$ acyl migration followed by cyclization reaction to X. This new mode of acyl migration from N_1 to N_2 was found and confirmed in treatments of IV by method B and also with 10% anhydrous ethanolic hydrogen chloride for less time than in method A.

A few studies[2] have been carried out on 2-hydroxyalkyl hydrazines, mainly for synthetic purposes, but nothing appears to be reported concerning the stereochemistry of diastereomeric 2-hydroxyalkyl hydrazines. This prompted us to investigate the stereochemical behavior of DL-2-hydroxycyclohexylhydrazines (I) in comparison with that of the DL-2-aminocyclohexanols which have been widely studied.

DL-*trans*-2-Hydroxycyclohexylhydrazine (*trans*-I) was prepared by the action of hydrazine on *meso*–*cis*-cyclohexene oxide in ethanol. The *trans* assignment was established by correlating it with DL-*trans*-2-aminocyclohexanol[3] in three ways, of which two are described below and the other will appear in the next paper.[4] Treatment with hydroxylamine O-sulfonic acid[2g] converted DL-*trans*-2-aminocyclohexanol to a hydrazine derivative which was identical with *trans*-I. *trans*-I was condensed with acetone to give the N_2-isopropylidene derivative (*trans*-II), the structure of which was supported by the ultraviolet and the infrared spectra: λ_{max}^{EtOH} 227 mμ (ε 8092) (C=N), ν_{max}^{Nujol} 1634 cm.$^{-1}$ (C=N). The Schotten–Baumann benzoylation converted *trans*-II to the N_1-benzoyl, N_2-isopropylidene derivative (*trans*-III) which gave DL-*trans*-2-benzamidocyclohexanol on treatment with sodium amalgam in acetic acid. Thus the results confirmed the configuration of *trans*-I.

Benzoyl derivatives of *trans*-I were prepared and characterized as follows. The N_1-benzoyl, N_2-isopropylidene compound (*trans*-III) underwent deacetonization to give DL-*trans*-1-benzoyl-1-(2-hydroxycyclohexyl)hydrazine hydrochloride (*trans*-IV·HCl) by adding ether as soon as dissolved in 20% anhydrous ethanolic hydrogen chloride in the cold.[5] Support for the structure of *trans*-IV was presented when the compound reverted to *trans*-III by condensation with acetone. Moreover, the infrared spectrum also supported the structure: ν_{max}^{Nujol} 1647 (–CON<) and 1610 cm.$^{-1}$ (–NH_2). *trans*-IV was further treated with benzoyl chloride in aqueous sodium hydroxide to afford a dibenzoyl derivative which was identified as DL-*trans*-1,2-dibenzoyl-1-(2-hydroxycyclohexyl)hydrazine (*trans*-V) by infrared spectrum determination (lack of the ester carbonyl bands). *trans*-V was converted to the N_1,N_2,O-tribenzoate (*trans*-VII) on heating with benzoyl chloride in pyridine; ν_{max}^{Nujol} 1692, 1292, and 1120 (ester), and 1684 and 1664 cm.$^{-1}$ (amide). On the other hand, acylation of *trans*-I with boiling ethyl benzoate gave rise to a monobenzoyl derivative which was identified as DL-*trans*-2-benzoyl-1-(2-hydroxycyclohexyl)hydrazine (*trans*-VI) because of nonidentity with the N_1-benzoyl derivative (*trans*-IV) and also with the O-benzoate (see below) by mixture melting point and infrared comparison. An alternative preparation of *trans*-VI concerns application of the acyl migration reaction described later. In the Schotten–Baumann benzoylation of *trans*-I with 1 equiv. of benzoyl chloride, reaction temperature was found to govern product formation. Room temperature favored the formation of *trans*-V, while chilling at 0–5° resulted in the formation of *trans*-IV accompanied by a small amount of *trans*-VI.

(1) Studies in Stereochemistry. XXXI. Part XXX, *Tetrahedron Letters*, **3**, 131 (1963).

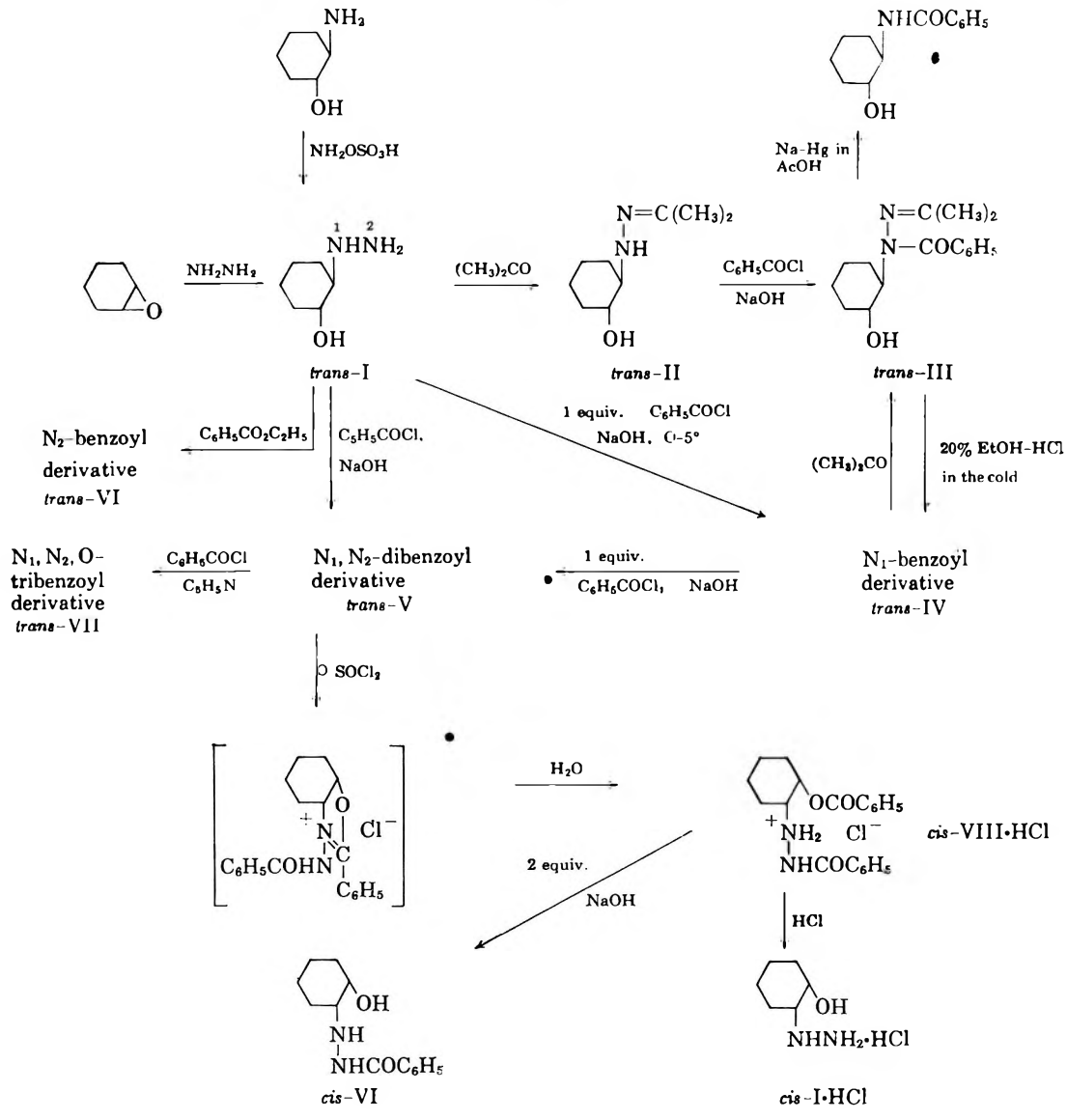
(2) (a) A. K. Plisov, *Ukr. Khim. Zh.*, **3**, 125 (1928); *Chem. Abstr.*, **22**, 3392 (1928); (b) S. Gabriel, *Ber.*, **47**, 3028 (1914); (c) G. Benoit, *Bull. soc. chim. France*, 242 (1947); (d) R. Gösl and A. Meuwsen, *Ber.*, **92**, 2521 (1959); (e) G. Gever, *et al.*, *Chem. Abstr.*, **48**, 12,168 (1954); (f) N. Rabjohn and M. S. Cohen, *J. Am. Chem. Soc.*, **76**, 1282 (1954); (g) G. Gever and K. Hayes, *J. Org. Chem.*, **14**, 813 (1949); (h) J. C. Howard, G. Gever, A. B. Neill, and P. H. I. Wei, *ibid.*, **26**, 1082 (1961).

(3) G. E. McCasland and co-workers, *J. Am. Chem. Soc.*, **71**, 637 (1949); **72**, 2190 (1950); W. S. Johnson and E. N. Schubert, *ibid.*, **72**, 2187 (1950); S. Winstein and R. Boschan, *ibid.*, **72**, 2311, 4699 (1950); T. Taguchi and M. Nakayama, *ibid.*, **73**, 5679 (1951).

(4) T. Taguchi, J. Ishibashi, T. Matsuo, and M. Kojima, *J. Org. Chem.*, **29**, 1104 (1964). The correlation was achieved by the conversion of *trans*-I to DL-*trans*-2-aminocyclohexanol through the deamination reaction.

(5) Treatment for a prolonged time or hot caused $N_1 \rightarrow N_2$ benzoyl migration affording *trans*-VI and the use of 10% anhydrous ethanolic hydrogen chloride hot caused ring closure to *trans*-X, as discussed later.

CHART I

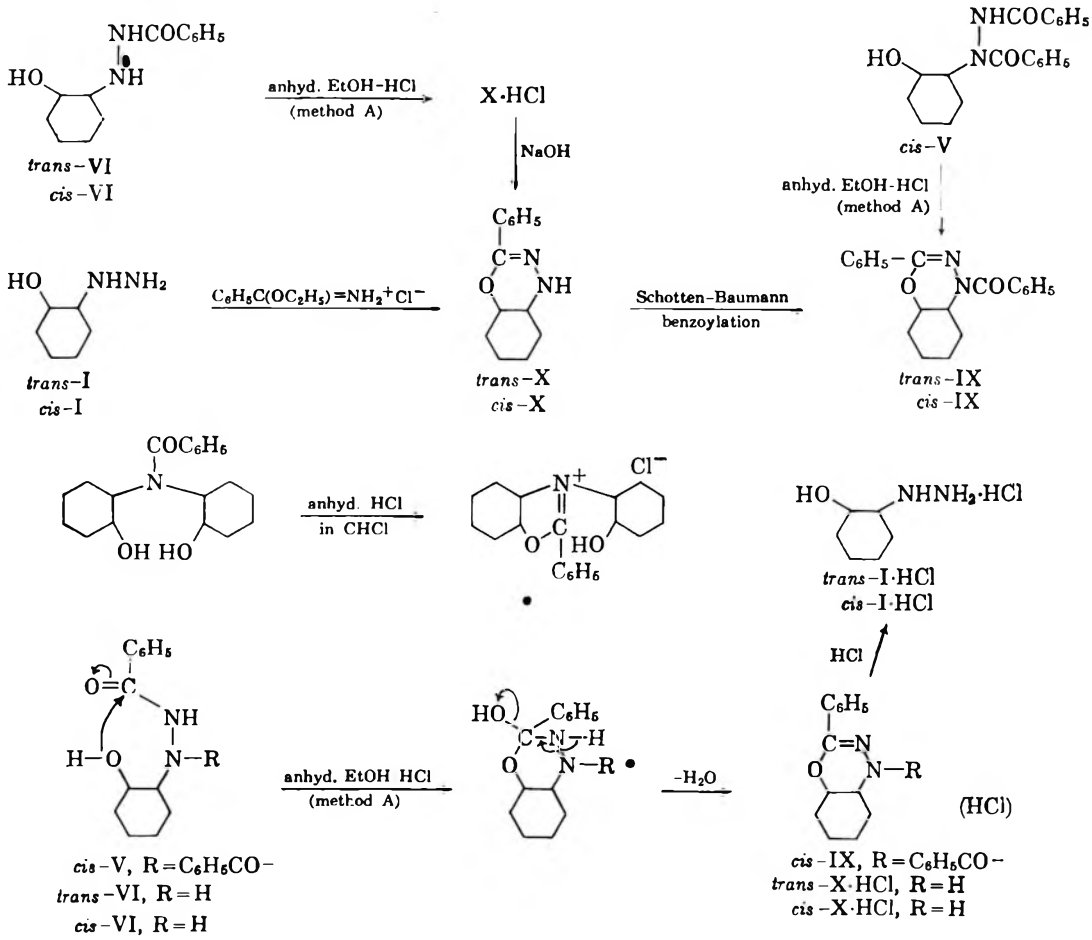


DL-*cis*-2-Hydroxycyclohexylhydrazine (*cis*-I) and its benzoylated derivatives were prepared as follows. The *trans*-N_1,N_2-dibenzoyl compound (*trans*-V) was treated with thionyl chloride to give a crystalline product, $C_{20}H_{22}N_2O_3 \cdot HCl$. Hydrolysis of the product in aqueous hydrochloric acid gave rise to the other DL isomer of 2-hydroxycyclohexylhydrazine hydrochloride which must be the *cis* form (*cis*-I·HCl). The compound, $C_{20}H_{22}N_2O_3 \cdot HCl$, was submitted to hydrolysis with 2 equiv. of sodium hydroxide to yield DL-*cis*-2-benzoyl-1-(2-hydroxycyclohexyl)hydrazine (*cis*-VI), an authentic sample of which was prepared as described later. This shows that one of two benzoyl groups in $C_{20}H_{22}N_2O_3 \cdot HCl$ attaches to N_2 and the existence in the salt form shows that the other combines with O, thus suggesting that the compound is DL-*cis*-2-benzoyl-1-(2-benzoyloxycyclohexyl)hydrazine hydrochloride (*cis*-VIII·HCl). In addition, the infrared spectrum, ν_{max}^{Nujol} 1733, 1280, and 1105 (ester), and 1694 cm.$^{-1}$ (secondary amide), agreed with it. The Walden inversion involved in the course from *trans*-V to *cis*-VIII seems to occur passing through an oxazolinium salt in analogy with the same treatment of DL-*trans*-2-benzamidocyclohexanol[3] (see Chart I). N_1-Benzoyl, N_2-benzoyl, N_1,N_2-dibenzoyl, and N_1,N_2,O-tribenzoyl derivatives of *cis*-I (*cis*-IV, -VI, -V, and -VII, respectively) were obtained and characterized by methods exactly similar to those used for the corresponding *trans* isomers (see Chart I).

Acyl migration in N-benzoyl derivatives of *trans*- and *cis*-I were carried out under two conditions: method A, boiling in twenty parts of 10% anhydrous ethanolic hydrogen chloride for 30 min.; method B, heating in 3 *N* aqueous hydrochloric acid on a water bath for 30 min.

Materials treated by method A and the resulting products are shown in Table I. As indicated in Table I and Chart II, of the N-benzoyl derivatives (IV, V, and VI) treated, only the *trans*-N_1,N_2-dibenzoyl compound (*trans*-V) underwent acyl migration, while the others suffered dehydrative ring closure. The migration product from *trans*-V was formulated as DL-*trans*-2-benzoyl-1-(2-benzoyloxycyclohexyl)hydrazine hydrochloride (*trans*-VIII·HCl) on the grounds that it exists in the salt form and was converted to the *trans*-N_2-benzoyl compound (*trans*-VI) on treatment with 2 equiv. of sodium hydroxide. The infrared spectrum also supported the identification. From *trans*- and

CHART II



cis-VI, respectively, was obtained DL-4a,5,6,7,8,8a-hexahydro-3-phenyl-1H-4,1,2-benzoxadiazine (X) of the same configuration, together with some starting material. The infrared spectra supported the structure of X (presence of C=N, -NH-, and C-O-C). The retention of configuration in the reaction was clear from the finding that hydrolysis of X gave I·HCl keeping the configuration. *cis*-V treated by method A also gave a dehydration product, $C_{20}H_{20}N_2O_2$, which was identified as DL-*cis*-1-benzoyl-4a,5,6,7,8,8a-hexahydro-3-phenyl-1H-4,1,2-benzoxadiazine (*cis*-IX), because the product was identical with the one formed by the introduction of a benzoyl group into *cis*-X by the Schotten-Baumann method; the infrared spectrum supported the structure (presence of C=N, -CON<, and C-O-C). *trans*-IX was also prepared by the Schotten-Baumann benzoylation of *trans*-X (see Chart II).

TABLE I

TREATMENT OF N-BENZOYLATED DL-2-HYDROXYCYCLOHEXYLHYDRAZINES WITH HYDROGEN CHLORIDE

Compound treated	Solvent (method)[a]	Product (yield, %)
trans-V	Anhyd. EtOH (A)	*trans*-VIII·HCl (71)
cis-V	Anhyd. EtOH (A)	*cis*-IX·HCl (87)
trans-VI	Anhyd. EtOH (A)	*trans*-X·HCl (54)[b]
	Water (B)	*trans*-XII·HCl (43)[b]
cis-VI	Anhyd. EtOH (A)	*cis*-X·HCl (56)[b]
	Water (B)	*cis*-XII·HCl (42)[b]
trans-IV	Anhyd. EtOH (A)	*trans*-X·HCl + *trans*-VI·HCl (48:52)[c]
	Water (B)	*trans*-XII·HCl + *trans*-VI·HCl (42:58)[c]
cis-IV	Anhyd. EtOH (A)	*cis*-X·HCl + *cis*-VI·HCl (63:37)[c]
	Water (B)	*cis*-XII·HCl + *cis*-VI·HCl (42:58)[c]
trans-III	Anhyd. EtOH (A)	*trans*-XI (52)
	Water (B)	*trans*-XII·HCl + *trans*-VI·HCl (73:27)[c]
cis-III	Anhyd. EtOH (A)	*cis*-XI (50)
	Water (B)	*cis*-XII·HCl + *cis*-VI·HCl (86:14)[c]

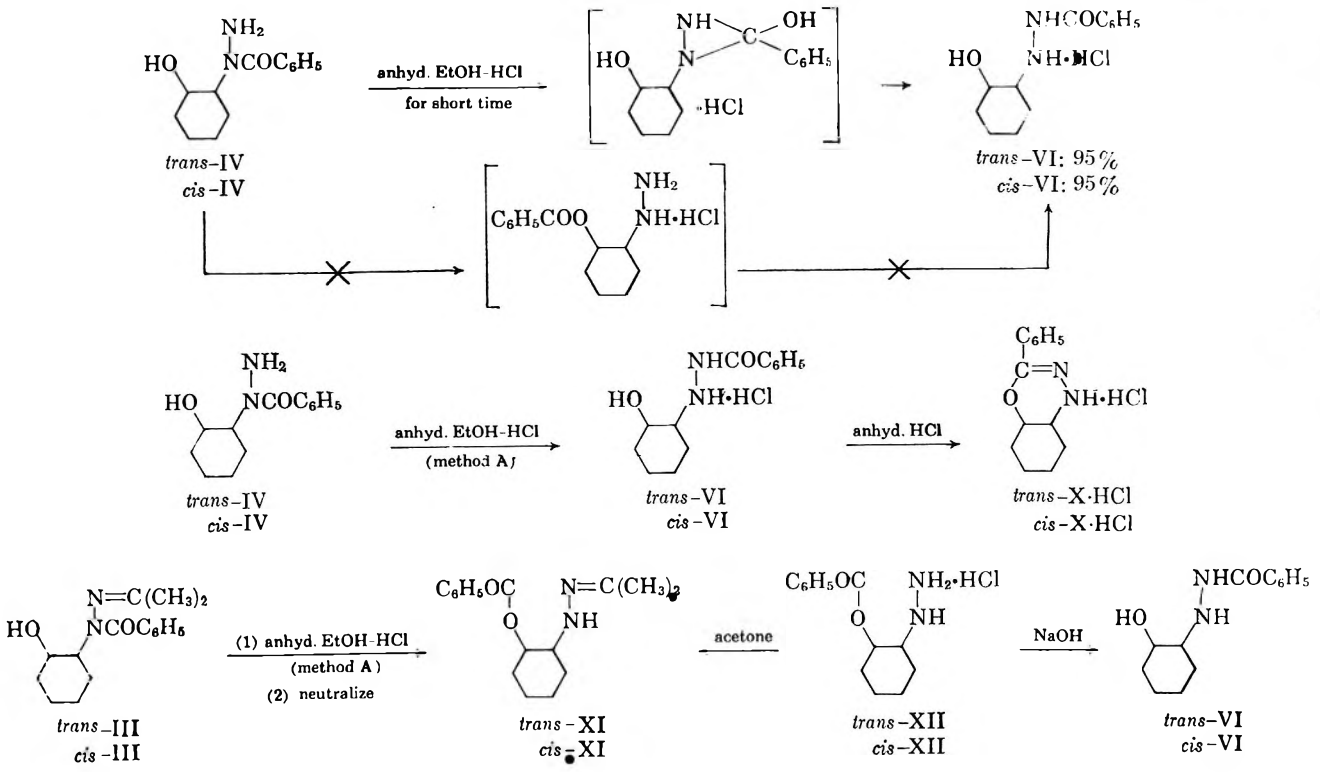
[a] See the text. [b] The formation ratio of product to the starting material recovered. [c] The formation ratio of products.

Condensation of ethyl benzimidate hydrochloride with *trans*- and *cis*-I gave compounds $C_{13}H_{16}N_2O$, which were identical with *trans*- and *cis*-X, respectively, thus indicating that the condensation occurred between the hydroxyl and the N_2-benzoyl groups with retention (see Chart II).

Previously, Taguchi and Hayashida[6] had reported that DL-(*trans*-*cis*-2,2′-dihydroxydicyclohexyl)benzamide with anhydrous hydrogen chloride caused ring closure giving DL-3-(*trans*-2-hydroxycyclohexyl)-2-phenyl-*cis*-4,5-cyclohexanooxazolinium chloride with retention. By analogy with this report, the formation of the 4a,5,6,7,8,8a-hexahydro-3-phenyl-1H-4,1,2-benzoxadiazines, *cis*-IX, *trans*-X, and *cis*-X, respectively from *cis*-V, *trans*-VI, and *cis*-VI, by method A seems to proceed through attack of the hydroxyl group to the carbon of the N_2-carbonyl followed by dehydration (see Chart II). However, it appeared strange that the N_1-benzoyl com-

(6) T. Taguchi and K. Hayashida, *J. Am. Chem. Soc.*, **80**, 2522 (1958).

CHART III



pounds, *trans*-IV and *cis*-IV, treated by method A gave *trans*-X and *cis*-X, respectively, the products identical with those from the N_2-benzoyl compounds (*trans*-VI and *cis*-VI) by the same treatment. In addition, the reactions also caused the formation of VI·HCl with retention.

To throw light upon the case, the action of anhydrous hydrogen chloride was carefully examined. As soon as *trans*- and *cis*-IV were dissolved in 10% anhydrous ethanolic hydrogen chloride, ethanol was removed by vacuum distillation. The treatments afforded DL-*trans*- and DL-*cis*-2-benzoyl-1-(2-hydroxycyclohexyl)-hydrazines (*trans*- and *cis*-VI), respectively, which might be formed *via* $N_1 \rightarrow N_2$ acyl migration, in yields up to 95%. The other migration route, $N_1 \rightarrow O \rightarrow N_2$, is entirely excluded, because the acyl migration from O to N is improbable in an acidic medium, though $N \rightarrow O$ migration seems probable. This supports the direct migration of the benzoyl group from N_1 to N_2, a new mode of migration as shown in Chart III. Moreover, this also suggests that the first step of the reaction of IV, when treated by method A, is the formation of VI, which was then partially converted to X (see Chart III).

The compounds in which the 2-amino group of IV was blocked with acetone, *trans*- and *cis*-III, were also treated by method A, followed by neutralization. The reactions caused acyl migration to afford DL-*trans*- and DL-*cis*-2-isopropylidene-1-(2-benzoyloxycyclohexyl)hydrazines (*trans*- and *cis*-XI), respectively (see Chart III). Structural proof was provided for *cis*-XI by its identity with the condensation product of DL-*cis*-2-benzoyloxycyclohexylhydrazine (*cis*-XII) with acetone described below. This supported also the structure of *trans*-XI by analogy. Moreover the specific absorption bands in the infrared spectra, ν_{max}^{Nujo} 1698, 1271, and 1114 (*trans*-XI, ester), and 1718, 1285, and 1117 cm.$^{-1}$ (*cis*-XI, ester), confirmed the structure of XI. Hence the behavior of IV on treatment by method A reveals that $N_1 \rightarrow O$ acyl migration can occur only when the 2-amino group is blocked with the isopropylidene radical; otherwise, $N_1 \rightarrow N_2$ acyl migration preferentially occurs and favors formation of X.

In comparison with method A, method B (the treatment in aqueous hydrochloric acid) was applied to the N-benzoyl derivatives of I which are listed with products in Table I. Consequently, both forms of the N_2-benzoyl derivative (VI) underwent $N_2 \rightarrow O$ acyl migration with retention to give DL-2-benzoyloxycyclohexylhydrazine hydrochlorides (XII·HCl). Of the resulting O-benzoyl compounds (XII·HCl), the *cis* isomer was a liquid substance; therefore, it was condensed with acetone to a crystalline substance, which was identical with the *cis*-N_2-isopropylidene-O-benzoate (*cis*-XI). Treatment of *trans*- and *cis*-XII·HCl in alkaline media caused the reverse acyl migration, $O \rightarrow N_2$ not $O \rightarrow N_1$, to reproduce *trans*- and *cis*-VI with retention (see Chart III).

These findings and the infrared data supported the structures of the products (XII).

On treatment by method B, each form of the N_1-benzoyl derivative (IV) gave XII·HCl with retention in addition to the N_2-benzoyl derivative (VI) of the same configuration, a product resulting from $N_1 \rightarrow N_2$ acyl migration. As described above, this mode of migration was found also in the short treatment of IV with 10% anhydrous ethanolic hydrogen chloride (see Chart III). The N_1-benzoyl-N_2-isopropylidene derivative (III) showed the same behavior as IV toward method B treatment in the formation of products.

Experimental[7]

DL-*trans*-**2-Hydroxycyclohexylhydrazine** (*trans*-**I**). **A.**—To a solution of 7.0 g. of DL-*trans*-2-aminocyclohexanol[3] in 40 ml. of 3% aqueous potassium hydroxide was added an aqueous solution of 1.2 g. of hydroxylamine O-sulfonic acid in drops for 15 min. at 95–96°. After heating for 15 min. more and then chilling, 15 ml. of glacial acetic acid and 1.7 g. of benzaldehyde were added to the solution and stirred vigorously for 10 min. at 55°. The reaction mixture was extracted with ether and the ether layer was evaporated to dryness. To the residue was added 10 ml. of water containing 1.7 g. of oxalic acid, and it was steam distilled to remove benzaldehyde completely. The remainder was evaporated to dryness, washed with a small amount of ethanol, and recrystallized from ethanol to give colorless scales, m.p. 165° dec., yield 0.7 g. (5.2%).

Anal. Calcd. for $C_6H_{14}N_2O \cdot C_2H_2O_4$ (*trans*-I hydrogen oxalate): C, 43.63; H, 7.32; N, 12.72. Found: C, 43.59; H, 7.25; N, 12.47.

B.—To a mixture of cyclohexene oxide (78 g.) and 80% hydrazine hydrate (250 g.) was added ethanol (170 ml.) and the mixture was refluxed for 2.5 hr. After removal of ethanol and surplus hydrazine by evaporation, the residue was distilled under reduced pressure, b.p. 137° (8.5 mm.), and the distillate crystallized in the receiver and had m.p. 80°, yield 85 g. (83%). The crystals were hygroscopic and became colored on standing in air.

Hydrochloride.—On treatment with hydrochloric acid, *trans*-I gave a dihydrochloride, m.p. 160°.

Anal. Calcd. for $C_6H_{14}N_2O \cdot 2HCl$: C, 35.47; H, 7.94; N, 13.78. Found: C, 35.61; H, 7.95; N, 14.26.

The dihydrochloride changed to the monohydrochloride on recrystallization from ethanol and yielded colorless needles of m.p. 126°.

Anal. Calcd. for $C_6H_{14}N_2O \cdot HCl$: C, 43.24; H, 9.07; N, 16.81. Found: C, 43.22; H, 9.01; N, 16.68.

Hydrogen oxalate had m.p. 165° dec. A mixture melting point with an authentic sample prepared by A showed no depression.

DL-*trans*-**1-Benzoyl-2-isopropylidene-1-(2-hydroxycyclohexyl)-hydrazine** (*trans*-**III**). **A.**—Twenty grams of *trans*-I was dissolved in acetone by heating on a water bath. It was freed of acetone and distilled *in vacuo* to give hygroscopic crystals of DL-*trans*-2-isopropylidene-1-(2-hydroxycyclohexyl)hydrazine (*trans*-II), b.p. 117–118° (2 mm.), m.p. 35–37°, yield 22 g. (85%), λ_{max}^{EtOH} 227 mμ (ε 8092) (C=N), ν_{max}^{Nujol} 1634 cm.$^{-1}$ (C=N). To a mixture of an ethereal solution of *trans*-II (22 g.) and 5% aqueous sodium hydroxide was added an ethereal solution of benzoyl chloride (18 g.) with ice cooling to cause precipitation. After filtration, recrystallization from methanol gave colorless plates, m.p. 132–134°, yield 19 g. (54%).

Anal. Calcd. for $C_{16}H_{22}N_2O_2$: C, 70.03; H, 8.08; N, 10.21. Found: C, 70.09; H, 8.06; N, 10.05.

B.—A solution of 0.3 g. of *trans*-IV (described below) in acetone was refluxed for 1.5 hr. and evaporated to dryness to leave colorless plates, yield 0.34 g. (97%), m.p. 133–134° after recrystallization from methanol, which were identical with a sample of *trans*-III prepared by A on a mixture melting point determination.

Treatment of DL-*trans*-**1-Benzoyl-2-isopropylidene-1-(2-hydroxycyclohexyl)hydrazine** (*trans*-**III**) **with Sodium Amalgam. The Formation of** DL-*trans*-**2-Benzamidocyclohexanol.**—To a solution of *trans*-III (1 g.) in ethanol (10 ml.) and glacial acetic acid (6 g.) was added, little by little, 2% sodium amalgam (22 g.) with stirring at 30–35°. The resulting reaction mixture was stirred for 30 min. more, and the precipitated mercury was removed and concentrated, furnishing a solid. Repeated recrystallization from ethanol gave colorless needles, m.p. 165–167°, yield 0.11 g. (12.4%), which were identical with DL-*trans*-2-benzamidocyclohexanol[3] by a mixture melting point determination.

DL-*trans*-**1-Benzoyl-1-(2-hydroxycyclohexyl)hydrazine** (*trans*-**IV**).—Immediately after *trans*-III (13 g.) was dissolved in 20% ethanolic hydrochloric acid at 0–5°, ether was added to the solution to cause precipitation of crystals, yielding 11.5 g. (90%) of colorless needles of m.p. 170.5° dec. after recrystallization from ethanol.

Anal. Calcd. for $C_{13}H_{18}N_2O_2 \cdot HCl$ (*trans*-IV·HCl): C, 57.67; H, 6.70. Found: C, 57.62; H, 7.18.

trans-IV·HCl was neutralized with sodium hydroxide in ethanol, the precipitated sodium chloride was filtered off, and the solution was evaporated to dryness to give colorless needles, m.p. 132–133° after recrystallization from benzene.

Anal. Calcd. for $C_{13}H_{18}N_2O_2$: C, 66.63; H, 7.74; N, 11.95. Found: C, 66.85; H, 7.81; N, 11.90.

DL-*trans*-**1,2-Dibenzoyl-1-(2-hydroxycyclohexyl)hydrazine** (*trans*-**V**). **A.**—To a benzene solution containing 0.2 g. of *trans*-IV and 0.13 g. of benzoyl chloride (1 equiv.) was added 5% aqueous sodium hydroxide while stirring until crystals ceased to deposit. Filtration, followed by recrystallization from ethanol, gave colorless needles of m.p. 218–218.5°, yield 0.27 g. (94%).

Anal. Calcd. for $C_{20}H_{22}N_2O_3$: C, 70.98; H, 6.55; N, 8.28. Found: C, 70.84; H, 6.77; N, 8.24.

B.—An aqueous solution of *trans*-I (50 g.) was mixed with an ethereal solution of 2 equiv. of benzoyl chloride (108 g.), and to the mixture was slowly added 5% aqueous sodium hydroxide with stirring and ice chilling until the precipitation of crystals ceased. After filtration, recrystallization from ethanol gave colorless needles, m.p. 218° alone and on admixture with authentic *trans*-V, yield 125 g. (96%).

The use of 1 equiv. of benzoyl chloride in the benzoylation reaction gave *trans*-V when the reaction was carried out at room temperature, yielding 24%.

DL-*trans*-**2-Benzoyl-1-(2-hydroxycyclohexyl)hydrazine** (*trans*-**VI**). **A.**—One gram of *trans*-I was combined with 3 g. of ethyl benzoate and heated at 130–150° for 5 hr. After cooling, the resulting precipitate was filtered and recrystallized from ethanol, yielding 0.27 g. (15%) of colorless needles, m.p. 155–156°. A mixture melting point with authentic *trans*-IV showed no depression.

Anal. Calcd. for $C_{13}H_{18}N_2O_2$: C, 66.63; H, 7.74; N, 11.95. Found: C, 66.43; H, 7.88; N, 12.16.

Hydrochloride.—Colorless needles had m.p. 189° dec., ν_{max}^{Nujol} 1695 and 1563 cm.$^{-1}$ (amide).

Anal. Calcd. for $C_{13}H_{18}N_2O_2 \cdot HCl$: C, 57.66; H, 6.67; N, 10.35. Found: C, 58.13; H, 7.19; N, 10.78.

B.—To a mixture of an aqueous solution (10 ml.) of *trans*-I (0.5 g.) and an ethereal solution (5 ml.) containing 1 equiv. of benzoyl chloride (0.54 g.) was added in drops 5% aqueous sodium hydroxide with stirring and cooling at 0–5° to deposit crystals. Filtration followed by recrystallization from ethanol gave colorless needles of m.p. and m.m.p. (with authentic *trans*-VI) 155°, yield 0.53 g. (59%). From the mother liquor a small amount of *trans*-IV was obtained.

C.—A solution of DL-*trans*-2-benzoyl-1-(2-benzoyloxycyclohexyl)hydrazine (*trans*-VIII, described below, 0.5 g.) in 15 ml. of aqueous ethanol containing 1 equiv. of sodium hydroxide (0.06 g.) was refluxed on a water bath for 30 min. and ethanol was evaporated. To the cooled residue was added 10% aqueous sodium hydroxide; it was extracted with ether and evaporated to dryness, yielding 0.3 g. (87%), m.p. 156° after recrystallization from ethanol and also on admixture with authentic *trans*-VI.

DL-*trans*-**1,2-Dibenzoyl-1-(2-benzoyloxycyclohexyl)hydrazine** (*trans*-**VII**).—A mixture of *trans*-V (1 g.), benzoyl chloride (0.42 g.), and pyridine (20 ml.) was heated at reflux for 5 hr. The reaction mixture was evaporated to dryness leaving crystals, and the crystals were recrystallized from ethanol as colorless plates of m.p. 181°, yield 0.64 g. (49%); ν_{max}^{Nujol} 1692, 1292, and 1120 (ester), 1684 and 1664 cm.$^{-1}$ (amide).

Anal. Calcd. for $C_{27}H_{26}N_2O_4$: C, 73.28; H, 5.93; N, 6.33. Found: C, 72.94; H, 6.31; N, 6.30.

The Action of Thionyl Chloride on *trans*-**V. The Formation of** DL-*cis*-**2-Benzoyl-1-(2-benzoyloxycyclohexyl)hydrazine** (*cis*-**VIII**).—To 1 g. of *trans*-V was added 1 ml. of thionyl chloride and set aside for 6–7 hr. at room temperature (25°). The reaction mixture was poured on ice to precipitate a gummy mass which crystallized slowly. Filtration followed by recrystallization from ethanol gave colorless needles of m.p. 168.5°, yield 1 g. (91%); ν_{max}^{Nujol} 1733, 1280, and 1105 (ester), and 1694 cm.$^{-1}$ (–CON<).

Anal. Calcd. for $C_{20}H_{22}N_2O_3 \cdot HCl$ (*cis*-VIII·HCl): C, 64.07; H, 6.18; N, 7.47. Found: C, 64.33; H, 6.29; N, 7.25.

The filtrate was made alkaline to afford an additional crop of *cis*-VIII (free base), yielding 0.05 g. Recrystallization from acetone–water gave colorless needles of m.p. 117–118°; ν_{max}^{Nujol} 1691, 1297, and 1114 (ester), 1668, and 1555 cm.$^{-1}$ (—CON<).

Anal. Calcd. for $C_{20}H_{22}N_2O_3$ (*cis*-VIII): C, 70.98; H, 6.55; N, 8.28. Found: C, 71.17; H, 6.60; N, 8.11.

(7) Melting and boiling points are uncorrected.

DL-*cis*-2-**Hydroxycyclohexylhydrazine** (*cis*-**I**).—A suspension of *cis*-VIII (70 g.) in 20% aqueous hydrochloric acid (1 l.) was vigorously refluxed to get a clear solution and then for an additional hour. The reaction time needed over-all was 7–8 hr. After cooling, the precipitated benzoic acid was filtered off, and the filtrate was evaporated to dryness. The residue was recrystallized from ethanol furnishing colorless needles of m.p 110–111°, yield 26 g. (84%).

Anal. Calcd. for $C_6H_{14}N_2O \cdot HCl$ (*cis*-I·HCl): C, 43.24; H, 9.07; N, 16.81. Found: C, 43.28; H, 9.03; N, 16.97.

cis-I, which was obtained by neutralization of *cis*-I·HCl with sodium hydroxide, boiled at 119° (4 mm.) and crystallized to colorless needles, m.p. 78°, which were hygroscopic and turned pale yellow on standing in air.

Alkaline Hydrolysis of *cis*-VIII·HCl with Two Equivalents of Sodium Hydroxide. The Formation of DL-*cis*-2-**Benzoyl-1-(2-hydroxycyclohexyl)hydrazine** (*cis*-**VI**).—To an ethanolic solution of *cis*-VIII·HCl (0.5 g.) was added an ethanolic solution containing 2 equiv. of sodium hydroxide (0.11 g.). The solution was refluxed on a water bath for 30 min.

To the reaction mixture freed of ethanol was added a small amount of 10% aqueous sodium hydroxide solution; the solution was extracted with ether and evaporated to dryness. The residue was recrystallized from ethanol as colorless needles, yielding 0.28 g. (89%), m.p. 162° alone and on admixture with authentic *cis*-VI (described below).

Benzoyl Derivatives of *cis*-**I.**—The following *cis* compounds were prepared analogously by the method applied to the corresponding *trans* isomer. (Headings A, B, and C correspond to those of methods in *trans* series.)

DL-*cis*-1-**Benzoyl-2-isopropylidene-1-(2-hydroxycyclohexyl)-hydrazine** (*cis*-**III**). **A.**—Colorless plates had m.p. 160–161° from methanol, and a 94% yield from the intermediate, DL-*cis*-2-isopropylidene-1-(2-hydroxycyclohexyl)hydrazine (*cis*-II).

Anal. Calcd. for $C_{16}H_{22}N_2O_2$: C, 70.03; H, 8.08; N, 10.21. Found: C, 69.88; H, 8.10; N, 10.12.

The intermediate (*cis*-II) had b.p. 110° (3 mm.), and deposited hygroscopic colorless needles m.p. 46–48°, in 87% yield: λ_{max}^{EtOH} 227 mμ (ε 9290), ν_{max}^{Nujol} 1629 cm.$^{-1}$ (C=N).

B.—The yield was 93%, m.p. 160–161° alone and on admixture with a sample prepared by **A.**

DL-*cis*-1-**Benzoyl-1-(2-hydroxycyclohexyl)hydrazine** (*cis*-**IV**), colorless needles, m.p. 134–135° from benzene, had a yield of 46%.

Anal. Calcd. for $C_{13}H_{18}N_2O_2$: C, 66.63; H, 7.74; N, 11.95. Found: C, 67.00; H, 7.78; N, 11.72.

The hydrochloride (*cis*-IV·HCl) did not crystallize.

DL-*cis*-1,2-**Dibenzoyl-1-(2-hydroxycyclohexyl)hydrazine** (*cis*-**V**), colorless needles, m.p. 201° from ethanol, had yields of (A) 90% and (B) 98%.

Anal. Calcd. for $C_{20}H_{22}N_2O_3$: C, 70.98; H, 6.55; N, 8.28. Found: C, 71.16; H, 6.61; N, 7.91.

DL-*cis*-2-**Benzoyl-1-(2-hydroxycyclohexyl)hydrazine** (*cis*-**VI**), colorless needles, m.p. 161.5–162.5° from ethanol, had yields of (A) 25%, (B) 67%, and (C) 89%.

Anal. Calcd. for $C_{13}H_{18}N_2O_2$: C, 66.63; H, 7.74; N, 11.95. Found: C, 66.74; H, 7.80; N, 11.89.

Hydrochloride, colorless needles, had m.p. 193° dec. from ethanol: ν_{max}^{Nujol} 1667 and 1546 cm.$^{-1}$ (amide).

Anal. Calcd. for $C_{13}H_{18}N_2O_2 \cdot HCl$: C, 57.66; H, 6.67; N, 10.35. Found: C, 57.70; H, 7.23; N, 10.30.

DL-*cis*-1,2-**Dibenzoyl-1-(2-benzoyloxycyclohexyl)hydrazine** (*cis*-**VII**), colorless needles, m.p. 212° from ethanol, had a 52% yield: ν_{max}^{Nujol} 1706, 1287, and 1112 (ester), and 1684, 1664, and 1527 cm.$^{-1}$ (amide).

Anal. Calcd. for $C_{27}H_{26}N_2O_4$: C, 73.28; H, 5.93; N, 6.33. Found: C, 73.10; H, 5.98; N, 5.95.

Treatments of N-Benzoyl Derivatives of I with Hydrogen Chloride by Two Methods. Method A.—The derivatives were refluxed in twenty parts of 10% anhydrous ethanolic hydrogen chloride on a water bath for 30 min. and concentrated.

(1). **The Formation of** DL-*trans*-2-**Benzoyl-1-(2-benzoyloxy-cyclohexyl)hydrazine Hydrochloride** (*trans*-**VIII·HCl**) **from** *trans*-**V.**—After treatment of *trans*-V·HCl (0.5 g.) by method, A, recrystallization from ethanol gave colorless needles, m.p. 169° dec., yield 0.42 g. (71%); ν_{max}^{Nujol} 1724, 1282, and 1109 (ester), 1672 and 1529 cm.$^{-1}$ (amide).

Anal. Calcd. for $C_{20}H_{22}N_2O_3 \cdot HCl$: C, 64.07; H, 6.18; N, 7.47. Found: C, 63.79; H, 6.15; N, 7.38.

The Free Base (*trans*-**VIII**).—Treatment of the hydrochloride with a 10% cold, aqueous solution of sodium hydroxide followed by extraction with ether and by evaporation furnished colorless needles, m.p. 151–152° after recrystallization from ethanol; ν_{max}^{Nujol} 1724, 1277, and 1110 (ester), 1642 and 1520 cm.$^{-1}$ (amide).

Anal. Calcd. for $C_{20}H_{22}N_2O_3$: C, 70.98; H, 6.55; N, 8.28. Found: C, 70.92; H, 6.72; N, 8.46.

(2). **The Formation of** DL-*cis*-1-**Benzoyl-4a,5,6,7,8,8a-hexahydro-3-phenyl-1H-4,1,2-benzoxadiazine** (*cis*-**IX**) **from** *cis*-**V.**—Method A followed by neutralization and recrystallization from ethanol converted 0.5 g. of *cis*-V to colorless needles, m.p. 163–164°, yield 0.41 g. (87%); ν_{max}^{Nujol} 1629 (C=N), 1624 (amide), and 1096 cm.$^{-1}$ (C–O–C).

Anal. Calcd. for $C_{20}H_{20}N_2O_2$: C, 74.97; H, 6.29; N, 8.75. Found: C, 74.99; H, 6.34; N, 8.42.

The product in 20% aqueous hydrochloric acid was refluxed for 10 hr. and cooled. The precipitated benzoic acid was filtered, and the filtrate was washed with ether and evaporated to dryness furnishing *cis*-I·HCl.

(3). **The Formation of** DL-*trans*-**4a,5,6,7,8,8a-Hexahydro-3-phenyl-1H-4,1,2-benzoxadiazine** (*trans*-**X**) **from** *trans*-**VI.**—Treatment of *trans*-VI (0.5 g.) by method A left a solid mass. The mass was combined with 10% aqueous sodium hydroxide solution and extracted repeatedly with ether. After evaporation of ether, the remainder was divided into two portions by extraction from ether. The soluble portion, 0.25 g. yield, was recrystallized from ethanol, m.p 128–128.5°; ν_{max}^{Nujol} 1637 (C=N), 3322 (–NH), and 1092 cm.$^{-1}$ (C–O–C).

Anal. Calcd. for $C_{13}H_{16}N_2O$ (*trans*-X): C, 72.18; H, 7.45; N, 12.95. Found: C, 72.28; H, 7.52; N, 12.94.

Hydrochloride (*trans*-**X·HCl**).—Recrystallization from ethanol gave product with m.p. 208–209° dec.; ν_{max}^{Nujol} 2390, 2457, and 2525–2730 cm.$^{-1}$ ($-NH_2^+$).

Anal. Calcd. for $C_{13}H_{16}N_2O \cdot HCl$: C, 61.77; H, 6.78; N, 11.08. Found: C, 61.97; H, 6.70; N, 10.89.

The less soluble portion, yield 0.23 g., was converted to the hyrochloride and identified as *trans*-VI·HCl. The ratio of product to recovered material was 54:46. The acidic hydrolysis of *trans*-X, worked up as for *cis*-IX, furnished *trans*-I·HCl.

(4). **Formation of** DL-*cis*-**4a,5,6,7,8,8a-Hexahydro-3-phenyl-1H-4,1,2-benzoxadiazine** (*cis*-**X**) **from** *cis*-**VI.**—Method A converted 0.5 g. of *cis*-VI to a mixture of crystals, yield 0.24 g., and an oil, yield 0.30 g. The crystals were *cis*-VI·HCl. The oil was mixed with 10% aqueous sodium hydroxide, extracted with ether, and evaporated to dryness, leaving an oil again. The primary and the secondary oily products were identified as *cis*-X·HCl and *cis*-X, respectively, by the finding that the Schotten–Baumann benzoylation converted the secondary oily product to crystals, m.p. 163°, which were identical with *cis*-IX by a mixture melting point determination.

(5). **The Formation of** *trans*-**X and** *trans*-**VI from** *trans*-**IV.**—Treatment of *trans*-IV (0.25 g.) by method A furnished 0.27 g. of crystals. Fractional recrystallization from ethanol gave two compounds. Mixture melting point determinations indicated that one, m.p. 208–209° dec., 0.11 g. yield, was identical with *trans*-X·HCl and the other, m.p. 185–188° dec., 0.13 g. yield, was identical with *trans*-VI·HCl. The ratio of the compounds was 48:52.

(6). **The Formation of** *cis*-**X and** *cis*-**VI from** *cis*-**IV.**—*cis*-IV (0.20 g.) was submitted to treatment by method A furnishing a crystalline product, 0.04 g. yield, and an oily product, 0.17 g. yield. The ratio of products was 37:63. The crystals were recrystallized from ethanol as colorless plates, m.p. 191–192° dec., and identified as *cis*-VI·HCl by a mixture melting point determination. The oily product underwent the Schotten–Baumann benzoylation to form crystals as colorless needles, m.p. 163–164°, which were identical with *cis*-IX by a mixture melting point determination. The oily product was characterized as *cis*-X·HCl.

(7). **Formation of** DL-*trans*-2-**Isopropylidene-1-(2-benzoyloxy-cyclohexyl)hydrazine** (*trans*-**XI**) **from** *trans*-**III.**—An oily product from *trans*-III (1 g.) by method A was neutralized with 10% aqueous sodium hydroxide, extracted with ether, and the ether solution was evaporated to leave a solid residue, yield 0.52 g. (52%), as colorless needles, m.p. 107–108° after recrystallization from ethanol; ν_{max}^{Nujol} 1698, 1271, and 1114 cm.$^{-1}$ (ester).

Anal. Calcd. for $C_{16}H_{22}N_2O_2$ (*trans*-XI): C, 70.03; H, 8.08; N, 10.21. Found: C, 70.06; H, 8.11; N, 10.35.

(8). **Formation of** DL-*cis*-2-**Isopropylidene-1-(2-benzoyloxy-cyclohexyl)hydrazine** (*cis*-**XI**) **from** *cis*-**III.**—An oily product

obtained on treatment of *cis*-III (2 g.) by method A was neutralized with 10% aqueous sodium hydroxide, extracted with ether, and evaporated to dryness. Distillation of the residue, b.p. 174–176° (3.5 mm.), gave an oil which crystallized in the receiver as colorless needles, m.p. 78° after recrystallization from petroleum ether (b.p. 30–70°), yield 1 g. (50%); ν_{max}^{Nujol} 1718, 1285, and 1117 cm.$^{-1}$ (ester).

Anal. Calcd. for $C_{16}H_{22}N_2O_2$ (*cis*-XI): C, 70.03; H, 8.08; N, 10.21. Found: C, 70.18; H, 8.03; N, 10.00.

Method B.—The derivatives were heated in five parts of 3 *N* aqueous hydrochloric acid solution on a water bath for 30 min. and concentrated.

(1). **The Formation of DL-*trans*-2-Benzoyloxycyclohexylhydrazine Hydrochloride (*trans*-XII·HCl) from *trans*-VI.**—Treatment of *trans*-VI(0.5 g.) by method B left crystals. Fractional recrystallization from ethanol gave 0.27 g. of *trans*-VI·HCl unchanged and 0.20 g. of *trans*-XII·HCl as colorless granules, m.p. 173–174° dec.; ν_{max}^{Nujol} 1715, 1294, and 1117 cm.$^{-1}$ (ester). The ratio of *trans*-XII·HCl and *trans*-VI·HCl recovered was 43:57.

Anal. Calcd. for $C_{13}H_{18}N_2O_2$·HCl: C, 57.66; H, 6.67; N, 10.35. Found: C, 58.04; H, 7.11; N, 10.54.

The product was converted to *trans*-VI on treatment with alkali, as described below.

(2). **The Formation of DL-*cis*-2-Benzoyloxycyclohexylhydrazine Hydrochloride (*cis*-XII·HCl) from *cis*-VI.**—Treatment of *cis*-VI (0.5 g.) by method B afforded 0.25 g. of crystals, that were identical with *cis*-VI·HCl unchanged, and 0.18 g. of an oil. The oil was neutralized with 10% aqueous sodium hydroxide, extracted with ether, and evaporated to dryness leaving an oil again with ν_{max}^{Nujol} 1721, 1276, and 1110 cm.$^{-1}$ (ester). The secondary oily product was refluxed in acetone to yield crystals as colorless needles, m.p. 78° after recrystallization from petroleum ether, which were identical with authentic DL-*cis*-2-isopropylidene-1-(2-benzoyloxycyclohexyl)hydrazine (*cis*-XI) on a mixture melting point determination, thus indicating the secondary oily product to be *cis*-XII·HCl. The ratio of *cis*-XII·HCl and *cis*-VI·HCl recovered was 42:58.

(3). **The Formation of *trans*-XII·HCl and *trans*-VI·HCl from *trans*-IV.**—Treatment of *trans*-IV (0.25 g.) by method B left 0.25 g. of crystals. Fractional recrystallization from ether–ethanol effected the separation of the crystals to two compounds. One, m.p. 186–189° dec., 0.13 g. yield, was identical with authentic *trans*-VI·HCl and the other, m.p. 168–173° dec., 0.09 g. yield, was identical with authentic *trans*-XII·HCl. The ratio of *trans*-VI·HCl and *trans*-XII·HCl was 58:42.

(4). **The Formation of *cis*-XII·HCl and *cis*-VI·HCl from *cis*-IV.**—Treatment of *cis*-IV (0.20 g.) by method B left a mixture of crystals and an oil. The crystals, 0.03 g. yield, were recrystallized from ethanol furnishing colorless plates, m.p. 190–191.5° dec. alone and on admixture with authentic *cis*-VI·HCl.

The oily product, 0.15 g. yield, was neutralized with 10% aqueous sodium hydroxide, extracted with ether, and evaporated to dryness affording an oil, which then was refluxed in acetone to turn into a crystalline product, 0.02 g. yield, as colorless needles, m.p. 77.5–78° after recrystallization from petroleum ether. The condensation product with acetone was identical with authentic *cis*-XI by a mixture melting point determination, and accordingly the primary oily product was characterized as *cis*-XII·HCl.

(5). **The Formation of *trans*-XII·HCl and *trans*-VI·HCl from *trans*-III.**—Work-up of *trans*-III (0.5 g.) was exactly the same as 3, giving 0.30 g. of *trans*-XII·HCl and 0.12 g. of *trans*-VI·HCl which were the same as the products under 3. The ratio of *trans*-XII·HCl and *trans*-VI·HCl was 73:27.

(6). **The Formation of *cis*-XII·HCl and *cis*-VI·HCl from *cis*-III.**—Treatment of *cis*-III (0.5 g.) and identification of products were exactly the same as 4, affording 0.45 g. of *cis*-XII HCl and 0.08 g. of *cis*-VI·HCl (ratio 86:14), which were same as the products under 4.

Short Treatment of DL-1-Benzoyl-1-(2-hydroxycyclohexyl)-hydrazines (IV) with Anhydrous Ethanolic Hydrogen Chloride at Room Temperature. A.—As soon as *trans*-IV (0.25 g.) was completely dissolved in 10% anhydrous ethanolic hydrogen chloride, ethanol was distilled *in vacuo*. The residue which was recrystallized from ethanol gave colorless needles, 0.28 g. yield (95%), m.p. 188–189° dec. alone and on admixture with authentic *trans*-VI·HCl.

B.—*cis*-IV was treated just like A, furnishing colorless plates which were recrystallized from ethanol, 95% yield, m.p. 193° dec. alone and on admixture with *cis*-VI·HCl.

Treatments of DL-2-Benzoyloxycyclohexylhydrazine Hydrochlorides (XII·HCl) with an Aqueous Sodium Hydroxide Solution. The Formation of VI *via* O → N_2 Migration. A.—*trans*-XII·HCl (0.5 g.) was neutralized with 10% aqueous sodium hydroxide, extracted with ether and evaporated to dryness. Recrystallization from ethanol gave colorless needles, 0.28 g. (64%) yield, m.p. 156° alone and on admixture with authentic *trans*-VI.

B.—*cis*-XII·HCl (0.5 g.) was treated exactly as in A, furnishing colorless needles which were recrystallized from ethanol, 0.35 g. (81%) yield, m.p. 162.5° alone and on admixture with *cis*-VI.

DL-*trans*-1-Benzoyl-4a,5,6,7,8,8a-hexahydro-3-phenyl-1H-4,1,2-benzoxadiazine (*trans*-IX).—To an ethereal solution (15 ml.) of *trans*-X (0.5 g.) and benzoyl chloride (0.33 g.) was added 5% aqueous sodium hydroxide until precipitation of crystals was complete. Recrystallization from ethanol afforded colorless needles, m.p. 135.5–136.5°, 0.65 g. (88%) yield, ν_{max}^{Nujol} 1664 (amide) and 1645 cm.$^{-1}$ (C=N).

Anal. Calcd. for $C_{20}H_{20}N_2O_2$: C, 74.97; H, 6.29; N, 8.75. Found: C, 75.01; H, 6.38; N, 8.70.

The Action of Ethyl Benzimidate Hydrochloride on DL-2-Hydroxycyclohexylhydrazines (I). The Formation of DL-4a,-5,6,7,8,8a-Hexahydro-3-phenyl-1H-4,1,2-benzoxadiazines (X). A.—An ethanolic solution (75 ml.) of *trans*-I (2.00 g.) and ethyl benzimidate hydrochloride (2.90 g.) was refluxed for 1 hr. and evaporated to dryness. The residue was mixed with water, extracted with ether, dried over anhydrous sodium sulfate, and evaporated to dryness, furnishing an oil which crystallized while cooling to yield 0.87 g. (26%). Recrystallization from ethanol gave colorless needles, m.p. 128–129° alone and on admixture with authentic *trans*-X.

B.—*cis*-I (1.20 g.) was treated exactly as described under A furnishing an oily product, 1.20 g. (60%) yield, which was identified as *cis*-X by the fact that the Schotten–Baumann benzoylation in pyridine converted it to *cis*-IX, m.p. 163–164°.

Acknowledgment.—This work was supported in part by the Grant-in-Aid for Scientific Research from the Ministry of Education, Japan, which the authors gratefully acknowledge. Thanks are also due to the Analytical Section of this institute for the determinations of infrared spectra and microanalyses.

2-Hydroxycyclohexylhydrazines. II.[1] Reaction with Nitrous Acid

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DL-2-Hydroxycyclohexylhydrazines (I) were treated with sodium nitrite in aqueous acetic acid solution. When one equivalent of sodium nitrite was used, *trans*-I gave DL-*trans*-2-cyclopentylmethylene-1-nitroso-1-(2-hydroxycyclohexyl)hydrazine (*trans*-II) and cyclopentanecarboxaldehyde (III), while *cis*-I gave *cis*-II, III, DL-*cis*-2-cyclohexylidene-1-nitroso-1-(2-hydroxycyclohexyl)-hydrazine (*cis*-IV), and cyclohexanone (V). On the other hand, when two or more equivalents were used, *trans*-I afforded only III and *cis*-I afforded III and V, the products and their formation ratio being closely similar to those from the same treatment of DL-2-aminocyclohexanols (VI). This close similarity, which seemed unacceptable on the stereochemical basis, was explained by presuming that the reaction occurred through degradation to the nitrosated VI. The explanation was experimentally supported by the observation that the 1-nitrosated I blocked with a carbonyl compound, *trans*-II or *cis*-IV, was converted to *trans*-VI·HCl or *cis*-VI·HCl, respectively, by acidic hydrolysis.

There have been several reports dealing with the action of nitrous acid on simple alkyl[2] and aryl hydrazines,[3] but, to our knowledge, an analogous study on 2-hydroxyalkyl hydrazines has not been reported. On the other hand, the deamination reactions of DL-2-aminocyclohexanols (VI) by means of nitrous acid were examined by McCasland[4] from a stereochemical standpoint. He clearly revealed that the reactions were governed by conformations of VI to yield III from the *trans* isomer (*trans*-VI) and III and V from the *cis* isomer (*cis*-VI), as outlined in Chart I.

In this context it was of interest to examine the reaction of the diastereomeric DL-2-hydroxycyclohexylhydrazines (I) with nitrous acid. Thus, *trans*- and *cis*-I were treated with sodium nitrite in 10% aqueous acetic acid in the present study. Authentic samples of hitherto unknown compounds used for identifications of products were synthesized by methods described below. In the reaction of *trans*-I, use of one equivalent of sodium nitrite gave rise to DL-*trans*-2-cyclopentylmethylene-1-nitroso-1-(2-hydroxycyclohexyl)hydrazine (*trans*-II) and cyclopentanecarboxaldehyde (III), while use of two or more equivalents gave only III (Chart I).

On the other hand, in the case of *cis*-I, use of one equivalent of sodium nitrite gave rise to DL-*cis*-2-cyclopentylmethylene-1-nitroso-1-(2-hydroxycyclohexyl)-hydrazine (*cis*-II), DL-*cis*-2-cyclohexylidene-1-nitroso-1-(2-hydroxycyclohexyl)hydrazine (*cis*-IV), cyclopentanecarboxaldehyde (III), and cyclohexanone (V), while use of two or more equivalents afforded III and V (see Chart I). With respect to products formed, the diazotization of VI was closely similar to the reaction of I with two or more equivalents of nitrous acid. It is quite acceptable that *trans*-I gave only III on elimination of the hydrazino group, because of the preferred diequatorial conformation in *trans*-I. But in the reaction of *cis*-I where the hydrazino group, because it is bulkier, might preferentially exist in an equatorial position, the predominance of V over III in a ratio of about 4:1 seemed incomprehensible, for such a steric situation would favor the reverse predominance. This suggests the hypothesis that reaction of I is initiated by the loss of one nitrogen to give the nitrosated VI which is further deaminated to give the end products, the deamination reactions of I and VI proceeding by a common path.

To test this hypothesis, the mononitrosated compounds blocked with a carbonyl compound, *trans*-II and *cis*-IV, were submitted to hydrolysis in 20% ethanolic hydrochloric acid solution. The experiments resulted in the formation of DL-*trans*-2-aminocyclohexanol hydrochloride (*trans*-VI·HCl) and its *cis* isomer (*cis*-VI·HCl), respectively, splitting off the carbonyl compound, III or V (see Chart II). This presented evidence for the proposed hypothesis.

The preceding discussion also serves to explain the results from I on treatment with one equivalent of nitrous acid. *trans*-I consumed two moles of nitrous acid per mole to afford cyclopentanecarboxaldehyde (III). The remaining *trans*-I was converted to *trans*-II by condensation with product III, followed by nitrosation, or vice versa. The absence of *trans*-VI in the reaction mixture is explained by the fact that its precursor, 1-nitrosated *trans*-I, is stabilized by condensation with III to give *trans*-II. As stated above, when the 1-nitrosated *trans*-I was regenerated from *trans*-II by hydrolysis, it was converted immediately to *trans*-VI. The analogous explanation is applied to the formation of products from *cis*-I on the same treatment.

Many years ago Thiele[2] proposed two possible pathways, A and B, which are outlined in Chart III for the reaction of an alkyl hydrazine with nitrous acid with elimination of the hydrazino group. In either case, the reaction leads to the alkyl nitrosamine. More recently Clusius[3b] by the use of N^{15} has confirmed the intramolecular nature of the nitroso migration in the case of phenylhydrazine. In accordance with pathway B proposed by Thiele, this work might picture the nitrosation process of a 2-hydroxyalkyl hydrazine to the 2-hydroxyalkyl nitrosamine as well as the case of an alkyl hydrazine. But the reaction course of a 2-hydroxyalkyl hydrazine, as indicated above, probably involves the temporary condensation with carbonyl compounds which are formed in the final reaction. This may be a feature differing from the case of a simple alkyl hydrazine.

Authentic compounds used for the identification of the reaction products, II and IV, were prepared as follows. The condensation of *trans*-I with cyclopentanecarboxaldehyde (III) afforded DL-*trans*-2-cyclopentylmethylene-1-(2-hydroxycyclohexyl)hydrazine which, then, was nitrosated with sodium nitrite in aqueous acetic acid furnishing *trans*-II. *cis*-II, *trans*-

(1) Studies in Stereochemistry. XXXII.

(2) J. Thiele, *Ann.*, **376**, 239 (1910).

(3) (a) K. Clusius and H. R. Weisser, *Helv. Chim. Acta*, **35**, 1548 (1952); (b) K. Clusius and K. Schwarzenbach, *ibid.*, **42**, 739 (1959).

(4) G. E. McCasland, *J. Am. Chem. Soc.*, **73**, 2293 (1951).

CHART I

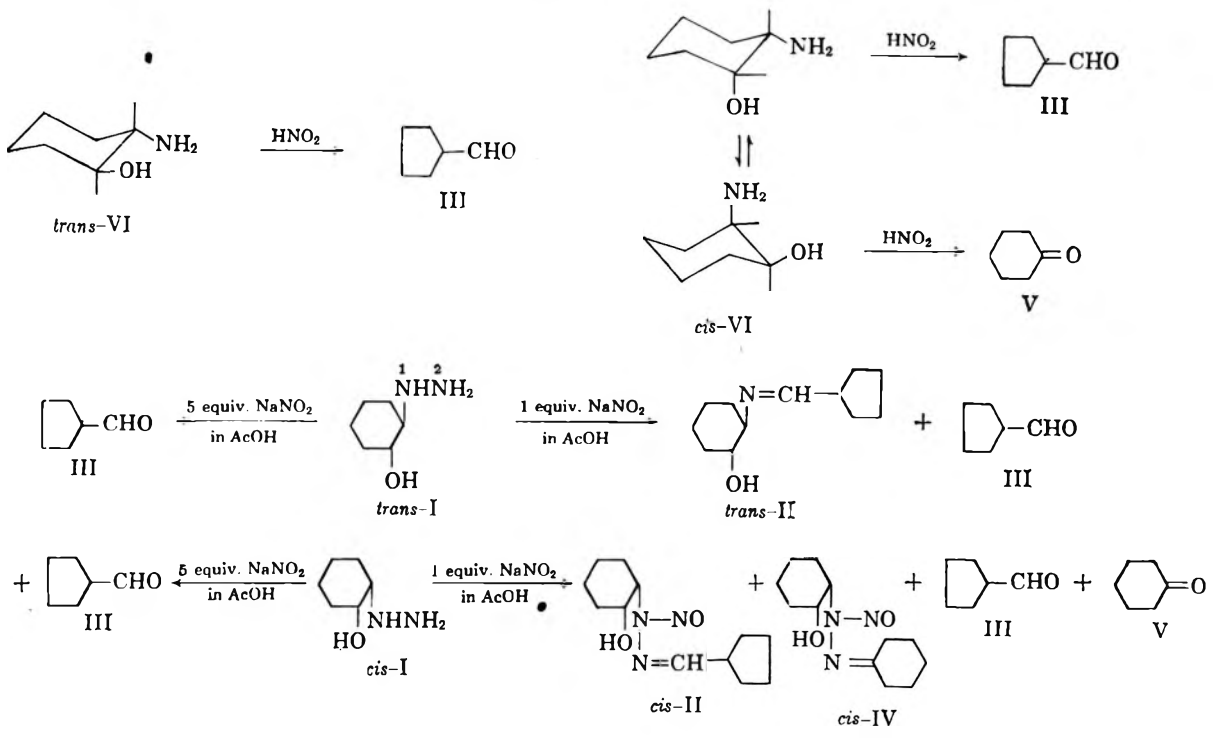


CHART II

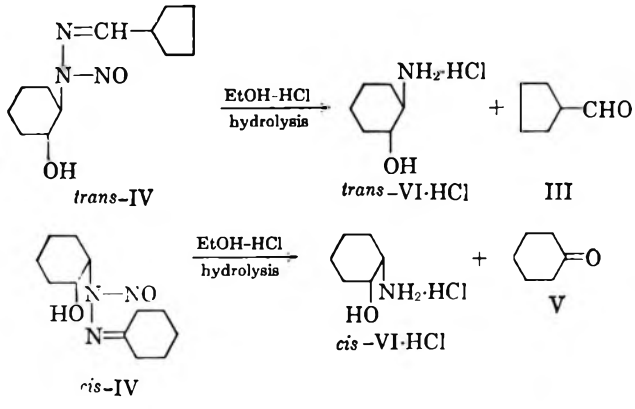


CHART III

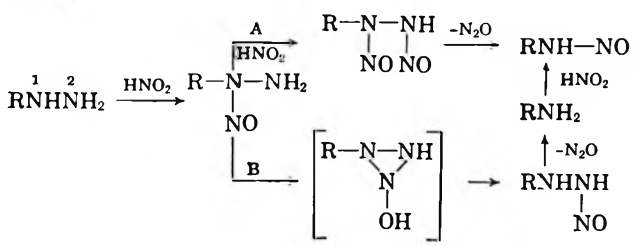
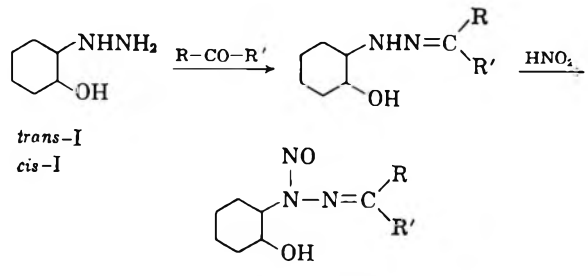


CHART IV



IV, and *cis*-IV were also prepared in the similar way (see Chart IV).

Experimental[5]

DL-*trans*-**2-Cyclopentylmethylene-1-nitroso-1-(2-hydroxycyclohexyl)hydrazine** (*trans*-II).—An ethanolic solution (2 ml.) of *trans*-I (1.03 g.) and cyclopentanecarboxaldehyde (III, 0.85 g.) was refluxed for 4 hr. and evaporated to dryness. To the residue was added ethanol and it was evaporated. The treatment was repeated until the aldehyde (III) was not detected in the distillate by the 2,4-dinitrophenylhydrazone formation test. The residue, an oil, was washed with ether to yield 1.60 g. (96%). To a 10% aqueous acetic acid solution (10 ml.) containing 1.2 g. (5.7 mmoles) of the oil was added dropwise 5.7 ml. of 1 *N* aqueous sodium nitrite (5.7 mmoles) at 5–10° and the charge was allowed to stand for 30 min. with stirring. The resulting precipitate was filtered and recrystallized from benzene as colorless needles, m.p. 70–71° dec., 0.94 g. (69%) yield.

Anal. Calcd. for $C_{12}H_{21}N_3O_2$: C, 60.22; H, 8.85; N, 17.56 Found: C, 59.91; H, 8.96; N, 17.70.

DL-*trans*-**2-Cyclohexylidene-1-nitroso-1-(2-hydroxycyclohexyl)hydrazine** (*trans*-IV).—An ethanolic solution (2 ml.) of *trans*-I (5.71 g.) and cyclohexanone (V, 4.30 g.) was refluxed for 3 hr. Evaporation of ethanol left crystals, m.p. 56–58° dec., 5.50 g. (60%) yield, which were hygroscopic and slowly decomposed in contact with air. Nitrosation of the crystals was carried out just like the preparation of *trans*-II, furnishing *trans*-IV, 86% yield, colorless needles, m.p. 119–119.5° dec. after recrystallization from methanol.

Anal. Calcd. for $C_{12}H_{21}N_3O_2$: C, 60.22; H, 8.85; N, 17.56. Found: C, 59.91; H, 8.75; N, 17.33.

DL-*cis*-**2-Cyclopentylmethylene-1-nitroso-1-(2-hydroxycyclohexyl)hydrazine** (*cis*-II).—Condensation of *cis*-I with III followed by nitrosation was carried out like the preparation of *trans*-II. The condensation product, DL-*cis*-2-cyclopentylmethylene-1-(2-hydroxycyclohexyl)hydrazine crystallized to yield 82.4% as colorless needles, m.p. 109–110° dec. after recrystallization from methanol.

Anal. Calcd. for $C_{12}H_{22}N_2O$: C, 68.53; H, 10.54; N, 13.32. Found: C, 68.34; H, 10.48; N, 13.41.

Nitrosation of the condensation product, followed by recrystallization from ethanol, gave colorless needles, m.p. 90–90.5° dec., 87% yield. It was recommended that, prior to

(5) All melting points are uncorrected.

nitrosation, a small volume of 2% aqueous hydrochloric acid be added to the acetic acid solution to dissolve the condensation product completely.

Anal. Calcd. for $C_{12}H_{21}N_3O_2$: C, 60.22; H, 8.85; N, 17.56. Found: C, 60.39; H, 8.80; N, 17.74.

DL-*cis*-**2-Cyclohexylidene-1-nitroso-1-(2-hydroxycyclohexyl)-hydrazine** (*cis*-**IV**).—Condensation of *cis*-I with V followed by nitrosation was carried out exactly like the preparation of *trans*-II. The condensation product, DL-*cis*-2-cyclohexylidene-1-(2-hydroxycyclohexyl)hydrazine, was recrystallized from benzene, m.p. 102–104° dec., 90% yield.

Anal. Calcd. for $C_{12}H_{22}N_2O$: C, 68.53; H, 10.54; N, 13.32. Found: C, 68.44; H, 10.48; N, 13.24.

The nitrosated product, *cis*-IV, was recrystallized from ethanol as colorless plates, m.p. 120–121° dec., 83% yield.

Anal. Calcd. for $C_{12}H_{21}N_3O_2$: C, 60.22; H, 8.85; N, 17.56. Found: C, 59.81; H, 9.04; N, 17.56.

Acidic Hydrolysis of *trans*-II. The Formation of DL-*trans*-**2-Aminocyclohexanol Hydrochloride** (*trans*-**VI·HCl**).—A suspension of *trans*-II (0.58 g.) in 20% ethanolic hydrochloric acid solution (2 ml.) went slowly into clear solution while standing at room temperature. After 3 hr., ethanol (10 ml.) was added to the solution, and the solution was distilled. The treatment was repeated until cyclopentanecarboxaldehyde (III) was not found in the distillate. The oily residue crystallized with ice cooling to yield 0.065 g. (20%) of colorless needles, m.p. 172–173° after recrystallization from ethanol–ether. The product was identified as *trans*-VI·HCl by a mixture melting point and infrared spectrum determinations.

Acidic Hydrolysis of *cis*-IV. The Formation of DL-*cis*-**2-Aminocyclohexanol Hydrochloride** (*cis*-**VI·HCl**).—After work-up just like the foregoing item, 1.60 g. of *cis*-IV was converted to 0.06 g. (7%) of *cis*-VI·HCl, which was recrystallized from ether–ethanol as colorless needles, m.p. 181–182°. The identification depended upon a mixture melting point and infrared spectrum determinations.

Reaction of DL-*trans*-**2-Hydroxycyclohexylhydrazine** (*trans*-**I**) **with Nitrous Acid.** (1). **The Simultaneous Formation of *trans*-II and III.**—To 11 ml. of 10% aqueous acetic acid solution containing 0.73 g. (5.6 mmoles) of *trans*-I was added dropwise 5.6 ml. of 1 *N* aqueous sodium nitrite (5.6 mmoles) at 5–10° while stirring. The solution was stirred for 30 or more minutes causing the precipitation of crystals. Filtration followed by recrystallization from benzene gave colorless needles, 0.15 g. (22.4%) yield, m.p. 70–71° dec. alone and on admixture with authentic *trans*-II. The infrared spectrum was completely superimposed on that of *trans*-II. The filtrate was neutralized with sodium carbonate, and sodium chloride was added. The solution was extracted with ether, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue was converted by the usual method to the 2,4-dinitrophenylhydrazone which was recrystallized from ethanol furnishing pale yellow scales, 0.08 g. (5%) yield, m.p. 152–154° dec. alone and on admixture with authentic III 2,4-dinitrophenylhydrazone.

(2). **The Formation of III.**—*trans*-I was treated essentially as in method 1, except 28.0 mmoles of sodium nitrite per 5.6 mmoles of the material was used. Consequently, the reaction furnished only a carbonyl compound which was converted to the 2,4-dinitrophenylhydrazone; the yield was 1.06 g. Recrystallization from ethanol gave pale yellow scales, 0.85 g. (53%) yield, m.p. 156–158° dec. alone and on admixture with authentic III 2,4-dinitrophenylhydrazone.

Reaction of DL-*cis*-**2-Hydroxycyclohexylhydrazine** (*cis*-**I**) **with Nitrous Acid.** (1). **The Simultaneous Formation of *cis*-II, III, *cis*-IV, and V.**—To 42 ml. of 10% aqueous acetic acid solution containing 3.0 g. (23 mmoles) of *cis*-I was added dropwise 23 ml. of 1 *N* aqueous sodium nitrite (23 mmoles) at 5–10° with good stirring. Stirring was continued for 30 or more minutes. An oily product which separated from the solution during the operation crystallized on standing. Filtration followed by repeated recrystallization from ethanol gave colorless plates, 0.56 g. (22%) yield, m.p. 120–121° dec. alone and on admixture with authentic *cis*-IV. Allowing the filtrate to stand for many hours caused the deposition of another crystalline product. Filtration followed by repeated recrystallization from ethanol gave colorless needles, 0.02 g. (0.7%) yield, m.p. 90–90.5° dec. alone and on admixture with authentic *cis*-II. Thereafter, the filtrate was treated as in 1 of the previous item to give a mixture of 2,4-dinitrophenylhydrazones. Fractional recrystallization gave pale yellow scales, m.p. 150–153° dec., 0.05 g. (0.71%) yield, and pale orange-yellow scales, m.p. 155–156° dec., 0.16 g. (2.4%) yield. The former and the latter scales were identical with III 2,4-dinitrophenylhydrazone and V 2,4-dinitrophenylhydrazone, respectively, by mixture melting point determinations.

(2). **The Simultaneous Formation of III and V.**—*cis*-I (11.5 mmoles) was treated with sodium nitrite (57.5 mmoles) in an aqueous acetic acid solution just like in 1 of this item. Only III and V were isolated as 2,4-dinitrophenylhydrazones from the reaction mixture to yield 0.16 g. (4.9%) and 0.61 g. (19%), respectively.

Acknowledgment.—The authors wish to acknowledge microanalysis and infrared spectrum determinations performed by the Analytical Section of this institute.

The Light-Induced Reactions of Iodine Trichloride with Cyclohexane[1]

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Iodine trichloride and cyclohexane undergo a photochemically induced reaction. The products isolated are hydrogen chloride, chlorocyclohexane, iodocyclohexane, *trans*-1,2-dichlorocyclohexane, *trans*-1-chloro-2-iodocyclohexane, and molecular iodine. A free-radical chain sequence involving the ICl_2· radical is proposed to account for the formation of hydrogen chloride, chlorocyclohexane, and iodocyclohexane. Dehydrohalogenation of the halocyclohexanes produced in the chain sequence yields cyclohexene, the intermediate required for the formation of the 1,2-dihalocyclohexanes. Molecular iodine arises from reaction of hydrogen iodide with iodine trichloride.

A number of reports dealing with the halogenation of aromatic hydrocarbons by means of iodine trichloride have appeared in the literature.[3] Products were obtained in which both chlorine and iodine had been substituted on the aromatic ring, and the nature of the products indicated that the reaction proceeded by ionic mechanisms in the absence of illumination. The present paper is concerned with the light-induced reaction of iodine trichloride with the aliphatic hydrocarbon, cyclohexane. The results of our study are best interpreted in terms of a free-radical chain reaction involving the interhalogen radical ICl_2·.

(1) This work was supported by a grant from the National Science Foundation. Support by this agency is gratefully acknowledged.

(2) This paper was taken from a portion of a thesis submitted by W. W. H. in partial fulfillment of the requirements for the Ph.D. degree from the University of Kansas, 1963.

(3) (a) E. Campaigne and J. R. Leal, *J. Am. Chem. Soc.*, **75**, 230 (1953); (b) G. Calingaert, M. E. Griffing, E. R. Kerr, A. J. Kalka, and H. D. Orloff, *ibid.*, **73**, 5224 (1951); (c) V. Arrequine, Jr., and E. B. Garcia, *Anales asoc. quim. Arg.*, **9**, 121 (1921); (d) V. Thomas and P. Depuis, *Compt. rend.*, **143**, 282 (1906); (e) H. Muller, *J. Chem. Soc.*, **15**, 41 (1862).

Results and Discussion

In a typical experiment, a stirred mixture of iodine trichloride with a large excess of cyclohexane was illuminated with a 275-watt sun lamp at 14–15° for 90 min. After a few minutes of illumination, the formation of molecular iodine and the evolution of hydrogen chloride were noted. Upon conclusion of illumination, three products—chlorocyclohexane, iodocyclohexane, and *trans*-1,2-dichlorocyclohexane—were isolated and identified by gas chromatographic retention times on two different columns and by comparison of their infrared and n.m.r. spectra with those of authentic samples. Gas chromatographic analysis of the original reaction mixture indicated the presence of a fourth organic component which decomposed when isolation by column chromatography was attempted. The gas chromatographic retention times of this fourth component on two columns were identical with the retention times of an authentic sample of *trans*-1-chloro-2-iodocyclohexane. Quantitative determination of the four organic products was made from their respective gas chromatographic peak areas. The quantities of iodine and hydrogen chloride produced were found by standard methods. The results of analyses for four separate reactions are shown in Table I.

TABLE I

DATA FROM REACTIONS BETWEEN IODINE TRICHLORIDE AND CYCLOHEXANE[a]

Run no.	ICl_3	$C_6H_{11}Cl$[b]	$C_6H_{11}I$	$C_6H_{10}Cl_2$	$C_6H_{10}ICl$	HCl	I_2
1[c]	9.91	2.77	0.59	2.41	2.52	16.44	3.20
2[d]	12.23	2.66	.81	3.40	2.92	20.48	3.91
3[d]	12.02	2.96	.75	3.50	2.80	20.88	3.87
4[d]	12.96	3.61	.78	3.81	2.88	21.65	4.58

[a] All numbers are expressed in millimoles. [b] See Experimental for accuracy of determination. [c] Organic products determined on diethylene glycol succinate column. [d] Organic products determined on E-600 column.

It is quite likely that in cyclohexane medium iodine trichloride is somewhat dissociated into iodine monochloride and molecular chlorine,[4] and the possibility that this dissociation plays a role in the formation of the products noted above must be considered. When this possibility is taken into account, two alternative paths offer themselves for the light-induced reaction of iodine trichloride with cyclohexane. One of these mechanistic pathways (A) involves iodine trichloride as the source of the halogens, and the other path (B) requires the dissociation of the trichloride into iodine monochloride and chlorine molecules (eq. 1–18).

It is to be noted that the chain sequences for both paths A and B lead to the same stoichiometry.

$$2C_6H_{12} + ICl_3 \xrightarrow{h\nu} C_6H_{11}Cl + C_6H_{11}I + 2HCl \qquad (19)$$

It is only a comparison of the relative quantities of products formed in the secondary reactions with those predicted from paths A and B that the more likely mechanism can be determined. This comparison can be justifiably made since the iodine trichloride was completely utilized in the reaction and accounted for adequately in the products formed, as is shown by the data of Table II. Although we cannot completely eliminate

(4) R. D. Whitaker and G. B. Fozzard, *Virginia J. Sci.*, **14**, 6 (1963).

Mechanistic Path A

Initiation

$$ICl_3 \xrightarrow{h\nu} ICl_2\cdot + Cl\cdot \qquad (1)$$

Chain sequence

$$C_6H_{12} + Cl\cdot \longrightarrow C_6H_{11}\cdot + HCl \qquad (2)$$

$$C_6H_{11}\cdot + ICl_3 \longrightarrow C_6H_{11}Cl + ICl_2\cdot \qquad (3)$$

$$ICl_2\cdot + C_6H_{12} \longrightarrow C_6H_{11}\cdot + ICl + HCl \qquad (4)$$

$$C_6H_{11}\cdot + ICl \longrightarrow C_6H_{11}I + Cl\cdot \qquad (5)$$

Secondary reactions

$$C_6H_{11}I \xrightarrow{HCl} C_6H_{10} + HI \qquad (6)$$

$$C_6H_{11}Cl \xrightarrow{HCl} C_6H_{10} + HCl \qquad (7)$$

$$3HI + ICl_3 \longrightarrow 2I_2 + 3HCl \qquad (8)$$

$$2C_6H_{10} + ICl_3 \longrightarrow C_6H_{10}Cl_2 + C_6H_{10}ICl \qquad (9)$$

Mechanistic Path B

$$ICl_3 \rightleftharpoons ICl + Cl_2 \qquad (10)$$

Initiation

$$ICl \xrightarrow{h\nu} I\cdot + Cl\cdot \qquad (11)$$

$$Cl_2 \xrightarrow{h\nu} 2Cl\cdot \qquad (12)$$

Chain sequence

$$C_6H_{12} + Cl\cdot \longrightarrow C_6H_{11}\cdot + HCl \qquad (13)$$

$$C_6H_{11}\cdot + ICl \longrightarrow C_6H_{11}I + Cl\cdot \qquad (14)$$

$$C_6H_{11}\cdot + Cl_2 \longrightarrow C_6H_{11}Cl + Cl\cdot \qquad (15)$$

Secondary reactions

$$C_6H_{11}I \xrightarrow{HCl} C_6H_{10} + HI \qquad (6)$$

$$C_6H_{11}Cl \xrightarrow{HCl} C_6H_{10} + HCl \qquad (7)$$

$$HI + ICl \longrightarrow I_2 + HCl \qquad (16)$$

$$C_6H_{10} + Cl_2 \longrightarrow C_6H_{10}Cl_2 \qquad (17)$$

$$C_6H_{10} + ICl \longrightarrow C_6H_{10}ICl \qquad (18)$$

the possibility that both paths may be operative, our data indicate strongly that path A must be by far the predominant one. Our arguments for this conclusion follow.

First let us compare the quantities of hydrogen iodide required to produce the experimentally determined amount of iodine in terms of mechanistic paths A and B. Using the data from run number 3 in Table I, we find for mechanism A that 5.8 mmoles of hydrogen iodide would be required according to eq. 8 to produce the observed 3.87 mmoles of iodine, whereas for mechanism B, according to eq. 16, only 3.87 mmoles of hydrogen iodide would be required. The total amount of cyclohexyl iodide (and cyclohexyl chloride) initially formed must be equal to the sum of the quantity of hydrogen iodide calculated and that of cyclohexyl iodide found experimentally. For mechanism A this sum is 6.55 mmoles and for mechanism B 4.62 mmoles. The total quantity of olefin that could be produced must be equal to the sum of the total amount of each cyclohexyl iodide and cyclohexyl chloride initially produced minus the amounts of these substances observed experimentally. For path A the *total* olefin *potentially available* turns out to be 9.39 mmoles and for path B 5.53 mmoles. Since a total of 6.30 mmoles of olefin are re-

TABLE II

MASS BALANCE CALCULATIONS

Run no.	Chlorine, g.-atoms		Iodine, g.-atoms	
	Calcd.[a]	Found[b]	Calcd.[c]	Found[d]
1	29.73	26.55	9.91	9.51
2	36.69	32.86	12.23	11.55
3	36.06	33.64	12.02	11.29
4	38.88	35.76	12.96	12.82

[a] Calculation based on 3 g.-atoms of chloride/molecule of ICl_3. [b] Summation of yields of chlorine-containing compounds, with the number of atoms of chlorine in each type of molecule taken into account. [c] Equal to the amount of iodine trichloride introduced. [d] Summation of yields of iodine-containing compounds, with the number of atoms of iodine in each type of molecule taken into account.

quired for the formation of the dihalides actually found (run 3, Table I), path A can give rise to a sufficient quantity of olefin, whereas path B obviously cannot.

Next let us examine the quantity of hydrogen chloride found with the amounts expected from paths A and B. In both mechanisms there are three sources of this gas; these are (a) the free-radical chain sequence summarized in eq. 19; (b) the reaction of hydrogen iodide with iodine trichloride (eq. 8) or with iodine monochloride (eq. 16); and (c) the dehydrohalogenation of cyclohexyl chloride (eq. 7). In the previous paragraph it was shown that 6.55 mmoles each of cyclohexyl chloride and iodide would be formed initially through mechanism A in run 3. This corresponds to the evolution of 13.10 mmoles of hydrogen chloride. On the basis of the amount of iodine observed in run 3, reaction of hydrogen iodide with iodine trichloride would yield another 5.80 mmoles of hydrogen chloride. From the amount of cyclohexyl chloride found experimentally and that expected (6.55 mmoles) another 3.59 mmoles of hydrogen chloride would arise. Thus, the total quantity of hydrogen chloride which could be formed by path A is 22.49 mmoles. Similar calculations for path B with the data of run 3 yield 14.77 mmoles as the expected quantity of hydrogen chloride. Experimentally, 20.88 mmoles of this gas were observed. Here again, it is apparent that path A is more consistent with the data than is path B.

The above calculations show unequivocally that mechanistic path B cannot supply sufficient olefin to account for the quantities of dihalocyclohexanes formed nor does it account for the amount of hydrogen chloride which was observed experimentally. On the other hand, in terms of the quantities of products isolated path A offers a reasonable mechanism. However, our data do not completely eliminate the possibility that the reactions shown in mechanism B occur to a small extent. Similar calculations to those described for run 3, with the data of runs 1, 2, and 4 (see Table I), lead to the same conclusions. Finally, it should be emphasized that pathway A requires the generation of a new inorganic free radical, namely $ICl_2\cdot$.

Experimental

Chemicals.—Iodine trichloride was prepared according to the method of Booth and Morris.[5]

Anal. Calcd. for ICl_3: I, 54.39; Cl, 45.61. Found: I, 53.88; Cl, 45.61.

The compound can be kept for several weeks in a high state of purity if maintained under a chlorine atmosphere at temperatures below 10°. Freshly prepared iodine trichloride was used where any doubt existed concerning the purity of any sample at hand.

Iodine monochloride was made by direct union of the elements in a 1:1 molar ratio as described by Cornog and Karges.[6] The liquid product was gradually cooled until about 50% had solidified and then the remaining liquid was decanted and discarded. The solid was liquefied and the cooling and decantation process was repeated. The solid obtained was placed in a tightly stoppered flask, liquefied, and stored in a refrigerator. The crystals which formed on storage were used as needed.

Spectroquality grade cyclohexane was purchased from Matheson, Coleman and Bell Chemical Co. Gas chromatographic analysis showed the purity of the compound to be greater than 99%. The material was stored under an inert atmosphere in the presence of a desiccant and used without further purification.

Cyclohexene of "chromatoquality" was obtained from Matheson, Coleman and Bell Chemical Co. and used without purification. The material came packed under an inert atmosphere and had a reported purity of 99+ mole %.

Cyclohexyl chloride was made by the photochemical chlorination of cyclohexane. The compound was distilled from the reaction mixture and then redistilled through a 60-cm. Vigreux column, the fraction boiling at 140–141° being collected. Gas chromatographic analysis showed the compound to be pure.

Cyclohexyl iodide was prepared according to the method described by Vogel.[7]

trans-1,2-Dichlorocyclohexane was prepared in the following manner. Chlorine was bubbled slowly into a solution of cyclohexene in carbon tetrachloride in the presence of ultraviolet light. Distillation of the reaction mixture yielded the crude dichloro compound which was purified by redistillation; b.p. 88–89° (30 mm.). The infrared spectrum of the compound was identical with that published by Stevens and Grummitt[8] for *trans*-1,2-dichlorocyclohexane.

trans-1-Chloro-2-iodocyclohexane was obtained as follows. Iodine monochloride dissolved in glacial acetic acid and cyclohexene in the same solvent were brought together in a 1:1 molar ratio.[9] The crude product separated as a heavy white oil and had to be distilled three times before high purity was obtained; b.p. 117–118° (14 mm.). Prior to use, the compound was stored in a refrigerator in order that decomposition be retarded.

Cyclohexyl bromide was prepared and purified by the method of Vogel.[10]

Oil-pumped dry nitrogen was employed without further purification to supply an inert atmosphere where needed.

Analytical Methods.—The organic products of reaction between iodine trichloride and cyclohexane were determined quantitatively by gas chromatography. The column found to be most suitable was composed of a polyglycol, E-600, obtained from the Dow Chemical Co., Freeport, Tex. Another substrate which was employed was diethylene glycol succinate. These substrates were put on acid-washed, 30–60-mesh Chromsorb support, obtained from the Johns Manville Co. The columns contained 10% by weight of the substrate. The E-600 column was 4 ft. in length and the succinate column 10 ft. long. The chromatograph employed was a Model A-90-P Aerograph. For the E-600 column a temperature between 80 and 90° was found to be suitable, and for the succinate column a temperature from 100 to 120° was used. Constant amounts of solution were injected by means of a Hamilton 10-μl. syringe. In all cases, at least three chromatograms of the reaction solution were taken, and the peak areas for each of the products were averaged.

In order to obtain quantitative data, an internal standard, cyclohexyl bromide, was employed. The addition of a known quantity of this compound to the reaction mixture after illumination permits one to determine the absolute quantities of the products present without knowledge of the volume of the reaction mixture. To do this, a reference solution which gave a chromatogram closely resembling that of the reaction mixture was prepared. This solution contained a known amount of the internal standard and of each of the products. Analysis of unknown reaction mixtures was immediately preceded and followed by similar analysis of the reference solution. The quantities of products in the reac-

(5) H. S. Booth and W. C. Morris, *Inorg. Syn.*, **1**, 167 (1939).

(6) J. Cornog and R. A. Karges, *ibid.*, **1**, 165 (1939).

(7) A. I. Vogel, "Practical Organic Chemistry," 3rd Ed., Longmans, Green and Co. Ltd., London, 1959, p. 284.

(8) H. C. Stevens and O. Grummitt, *J. Am. Chem. Soc.*, **74**, 4876 (1952).

(9) M. L. Brunel, *Ann. chim. phys.*, [8]**6**, 230 (1905).

(10) Ref. 7, p. 277.

tion mixture were determined by comparison of their peak areas with those of the compounds in the reference solution and with the use of the following equation.

$$\text{Moles } P_{reac} = \frac{\text{moles } (IS)_{reac}}{\text{area } (IS)_{reac}} \times \text{area } P_{reac} \left[\frac{\text{moles } P_{ref}}{\text{area } P_{ref}} \times \frac{\text{area } (IS)_{ref}}{\text{moles } (IS)_{ref}} \right]$$

where P_{reac} is the product sought, P_{ref} the product in the reference solution, $(IS)_{reac}$ the internal standard in the reaction solution, and $(IS)_{ref}$ the internal standard in the reference solution. The expression within the brackets constitutes a correction factor for the area of P_{reac} as compared to that of the internal standard; this correction factor usually had a value close to unity.

Separation of the organic products produced in the reaction was partially achieved by column chromatography on neutral Woelm alumina of varying water content. By this method, chlorocyclohexane, iodocyclohexane, and *trans*-1,2-dichlorocyclohexane were isolated and identified unequivocally by the identity of their infrared and n.m.r. spectra with those of the authentic samples. A fourth component in the reaction mixture, the presence of which was indicated by gas chromatographic analysis, was seen on the alumina columns, but attempts to elute it were unsuccessful since the compound decomposed. The fourth component had identical retention times on the two gas chromatographic columns noted above as an authentic sample of *trans*-1-chloro-2-iodocyclohexane prepared as described previously.[9]

Quantitative determination of the iodine formed was made on a Cary Model 14 spectrophotometer. Solutions containing known varying amounts of resublimed iodine dissolved in cyclohexane were prepared and their absorbance at 520 mμ measured. A plot of absorbance *vs.* concentration gave a straight line, and this plot was used as a calibration curve for the spectrophotometric determination of iodine in the reaction solution. New calibrations were made at suitable intervals to take into account minor changes that might have occurred in the instrument.

Hydrogen chloride produced in a reaction was swept into a known volume of standardized sodium hydroxide solution by means of dry nitrogen. Aliquots of the resulting solution were titrated with standardized hydrochloric acid to a phenolphthalein end point, and from the amount of base which has been consumed the quantity of hydrogen chloride was determined.

Reaction between Iodine Trichloride and Cyclohexane.—A 200-ml., three-necked standard taper round-bottomed flask was equipped with a condenser, a ground-glass Teflon blade stirrer, and a nitrogen inlet tube. A standard taper joint connected the condenser to a gas absorption tower. The entire apparatus was made moisture-free by flaming it while a rapid stream of dry nitrogen was passed through. The apparatus was cooled and then was so adjusted that the flask was submerged in a constant temperature water bath. Water from the bath maintained at 14–15° was circulated through the condenser. Approximately 90 ml. of pure cyclohexane was added to the flask and the stirrer put into operation. The nitrogen inlet tube was extended below the surface of the liquid, and the gas was permitted to flow at such a rate that the cyclohexane was not swept through the condenser. One hundred milliliters of standard sodium hydroxide solution was added to the gas absorption tower.

A carefully dried 25-ml. erlenmeyer flask fitted with a ground-glass stopper was weighed on a triple beam balance and then cold iodine trichloride was added under a stream of nitrogen to give the approximate weight of this reagent desired. The flask was tightly stoppered and weighed on an analytical balance. The bottom was then chilled in a mixture of Dry Ice and Cellosolve, and the iodine trichloride added to the stirred, cooled cyclohexane by raising the nitrogen inlet tube and quickly inverting the erlenmeyer flask. The flask was stoppered immediately, permitted to come to room temperature, and weighed. The nitrogen inlet tube was replaced and the gas flow adjusted to about 5 bubbles per min. at the absorption tower. A 275-watt ultraviolet sun lamp was placed at the outside of the water bath within 2 in. of the reaction mixture, immediately following the addition of iodine trichloride. The reaction mixture, originally red-orange in color, darkened shortly after the light was turned on and within a few minutes the violet color of iodine became evident. The reaction was allowed to proceed for 90 min., after which time the light was removed and the nitrogen flow gradually increased for a period of 2 hr. until it approximated 20 bubbles per min.

The absorption tower was then removed, stirring discontinued, and the reaction flask taken from the constant temperature bath. The nitrogen flow was stopped, and the condenser and gas inlet tube were rinsed with cyclohexane, the rinsings being added to the reaction mixture. The contents of the reaction flask were transferred quantitatively into a dry 100-ml. volumetric flask; the reaction flask was rinsed repeatedly with small amounts of cyclohexane, the washings added to the volumetric flask, and the solution brought up to volume with cyclohexane.

One milliliter of the solution was removed by means of a pipet, added to a dry 25-ml. volumetric flask, and diluted to volume with cyclohexane. A suitable aliquot (2–4 ml.) was removed, added to a dry 10-ml. volumetric flask, and diluted to volume with cyclohexane. The absorbance of this solution was measured at 520 mμ and from a previously prepared Beer's law plot of concentration *vs.* absorbance, the concentration of iodine was determined.

The other 99 ml. of reaction solution was transferred quantitatively to a 125-ml. erlenmeyer flask, and cyclohexane was removed on a "Roto-vac" apparatus. The "distillate" from this operation was condensed in a cold trap cooled by means of a Dry Ice–Cellosolve mixture. Concentration was continued until the solution remaining yielded suitable peaks for the products on the gas chromatograph.

Synthesis of Sultones from Hexachlorobicyclo[2.2.1]heptenes and -heptadienes

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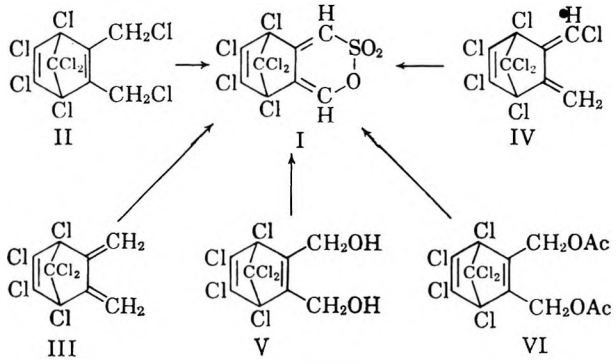
1,2,3,4,7,7-Hexachloro-5-(hydroxymethylene)-6-(sulfomethylene)bicyclo[2.2.1]hept-2-ene sultone is produced by reaction of oleum with any of the following: 2,3-bis(chloromethyl)-1,4,5,6,7,7-hexachlorobicyclo[2.2.1]-heptadiene, 5-(chloromethylene)-6-methylene-1,2,3,4,7,7-hexachlorobicyclo[2.2.1]hept-2-ene, 5,6-bis(methylene)-1,2,3,4,7,7-hexachlorobicyclo[2.2.1]hept-2-ene, 2,3-bis(hydroxymethyl)-1,4,5,6,7,7-hexachlorobicyclo[2.2.1]heptadiene, or 2,3-bis(acetoxymethyl)-1,4,5,6,7,7-hexachlorobicyclo[2.2.1]heptadiene. The reaction of oleum with 1,2,3,4,7,7-hexachlorobicyclo[2.2.1]heptadiene yields 1,2,3,4,7,7-hexachloro-3-hydroxy-5-sulfotricyclo[2.2.1.0^{2,6}]-heptane sultone. The reaction of oleum with 5-methylene-1,2,3,4,7,7-hexachlorobicyclo[2.2.1]hept-2-ene yields, *via* a skeletal rearrangement, 1,2,3,5,6,6-hexachloro-5-hydroxy-4-(sulfomethyl)bicyclo[2.2.1]hept-2-ene sultone. Spectroscopic and chemical evidence is presented for these structures.

The Diels–Alder reaction of hexachlorocyclopentadiene with 1,4-disubstituted 2-butynes has given access to a series of new 5,6-disubstituted 1,2,3,4,7,7-hexachlorobicyclo[2.2.1]hept-2-enes and -heptadienes (II–VI).[1] In the course of an investigation of the chemistry and pesticidal utility of this series, it has been found that compounds II–VI undergo reaction with fuming sulfuric acid to yield a novel dienic sultone, 1,2,3,4,7,7-hexachloro-5-(hydroxymethylene)-6-(sulfomethylene)-bicyclo[2.2.1]hept-2-ene sultone (I).

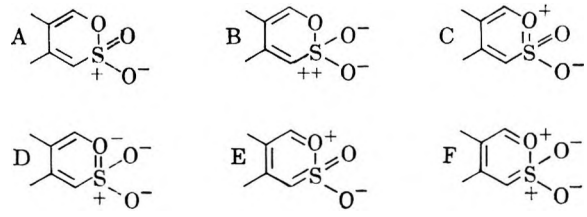


The structure of I is established by its elemental analysis, molecular weight, absence of acidic hydrogen, and spectral properties. An infrared absorption band at 6.24 μ is characteristic of the –CCl=CCl– structure as found in hexachlorobicyclo[2.2.1]heptenes.[2] Infrared bands at 6.11 and 5.93 μ indicate the presence of two other C=C bonds, probably conjugated. Bands at 7.26 (shoulder at 7.42) and 8.61 μ are found reasonably near the positions (7.44 and 8.65 μ) reported for the –SO_2–O– structure in a dienic δ-sultone by Helferich, *et al.*[3] The nuclear magnetic resonance spectrum showed an AB pattern, with two close doublets (J = 1.2 c.p.s.) of equal intensity at 6.70 and 7.03 p.p.m.[4]

The reaction of oleum with 5,6-bis(methylene)-1,2,3,4,7,7-hexachlorobicyclo[2.2.1]hept-2-ene (III) to yield I involves stoichiometrically an oxidative dehydrogenation. The evolution of sulfur dioxide was noted during the reaction, indicating that the oleum was functioning as an oxidant.

Although oleum containing 20% sulfur trioxide was found to be the most satisfactory reagent (from the standpoint of yield and ease of handling) for preparing sultone I, it was found possible to prepare the same product by the reaction of liquid sulfur trioxide (commercial, stabilized sulfuric anhydride) with 2,3-bis-(chloromethyl)-1,4,5,6,7,7-hexachlorobicyclo[2.2.1]hep-tadiene (II).

The ready formation of the dienic δ-sultone ring system from a variety of starting materials (particularly from III by dehydrogenation) and its stability to oleum suggested the possibility of this ring system possessing a considerable degree of resonance stabilization, perhaps approaching aromatic character. Canonical resonance forms such as C–F would permit the positive charge localized on the sulfur atom in A and B to be



distributed in part to the ring oxygen atom. Analogous resonance forms involving the 3d-orbitals of sulfur have been adduced to explain the conjugative effects of the *p*-methylsulfonyl group in anilines and phenols,[5a] and the stabilization of carbanions by sulfonyl groups.[5b]

However, examination of the n.m.r. spectrum of I indicated that the diene–sultone ring system represents, at most, a borderline case of aromaticity. Regardless of which of the two observed absorption peaks is assigned to the proton adjacent to the ring oxygen in I, it is evident that this proton falls roughly midway between a typical nonaromatic cyclic vinyl ether α-hydrogen (examples: dihydropyran, δ = 6.37; 2,6-dimethyl-γ-pyrone, δ = 6.03)[6] and an aromatic vinyl ether (example: furan, δ = 7.42[6]).

Although a substantial number of dienic δ-sultones have been described,[7] no previous examples were found having a hydrogen atom rather than an alkyl group on the oxygen-substituted (δ) carbon. Only one route to dienic δ-sultones has hitherto been described, namely the cyclization of β-branched α,β- or β,γ-unsaturated

(1) P. E. Hoch and J. M. Clegg, *J. Am. Chem. Soc.*, **81**, 5413 (1959).

(2) E. T. McBee, D. K. Smith, and H. E. Ungnade, *ibid.*, **77**, 559 (1955).

(3) B. Helferich, R. Dhein, K. Geist, H. Junger, and D. Wiehle, *Ann.*, **646**, 32 (1961).

(4) δ relative to tetramethylsilane. The spectrum was run in deuteriochloroform, by courtesy of Varian Associates Instrument Division, using a Model A-60 high resolution spectrometer.

(5) (a) C. C. Price and S. Oae, "Sulfur Bonding," Ronald Press Co., New York, N. Y., 1962, pp. 71, 123; (b) W. A. Pryor, "Mechanisms of Sulfur Reactions," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p. 33.

(6) "High Resolution N.M.R. Spectra Catalog," Varian Associates, Palo Alto, Calif., 1962 Spectra No. 111, 166, and 50.

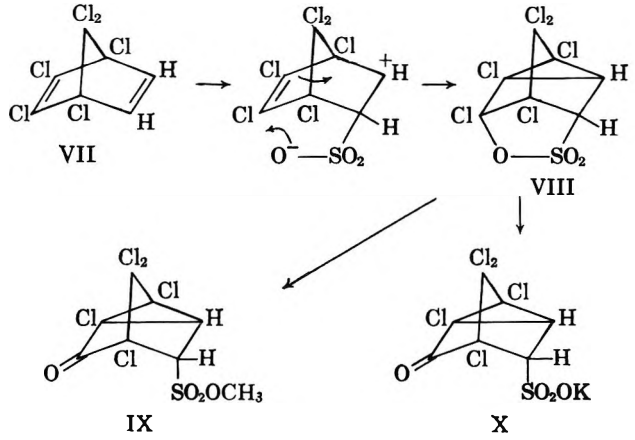
(7) W. Treibs, *Ber.*, **70**, 85 (1937); T. Morel and P. E. Verkade, *Rec. trav. chim.*, **67**, 539 (1948); **68**, 619 (1949); **70**, 35 (1951); reviewed and tabulated by A. Mustafa, *Chem. Rev.*, **54**, 195 (1954).

ketones (or corresponding ketols) by concentrated sulfuric acid in the presence of acetic anhydride. The reactions found in the present investigation, therefore, represent several new routes to the dienic δ-sultone structure.

In view of these unexpected findings concerning the reaction of oleum with 5,6-disubstituted hexachlorobicyclo[2.2.1]heptenes or -heptadienes, it was of interest to investigate the reaction of oleum with related compounds having only one side chain or lacking a side chain.

The reaction of oleum with 1,2,3,4,7,7-hexachlorobicyclo[2.2.1]heptadiene (VII)[8] yielded a nonacidic crystalline product of the empirical formula $C_7H_2Cl_6O_3S$ to which the structure VIII is assigned on the basis of the following evidence. The infrared spectrum of this compound showed no trace of absorption in the C=C region; a band appeared at 9.56 μ which coincides with the cyclopropane ring absorption reported for *trans*-1,2-dichlorocyclopropane.[9] Treatment of VIII with sodium carbonate in methanol caused release of one molar equivalent of chloride ion per mole of sultone and yielded a neutral water-insoluble crystalline product (IX) of empirical formula $C_8H_5Cl_5O_4S$; treatment of VIII with potassium hydroxide in methanol yielded one molar equivalent of chloride ion, a small amount of ester IX, and a larger amount of a salt X having the correct analysis for $C_7HCl_5O_4KS \cdot H_2O$. Both IX and X showed strong infrared absorption at 5.5 μ, characteristic of a transannular carbonyl bridge.[2,10]

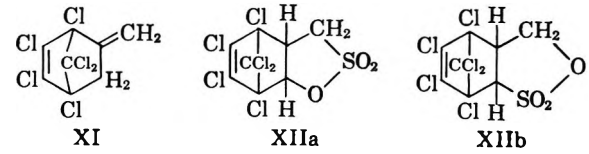
The formation of VIII may be viewed as proceeding *via* a carbonium ion in which the norbornene → norcarane rearrangement occurs.



VII VIII IX X

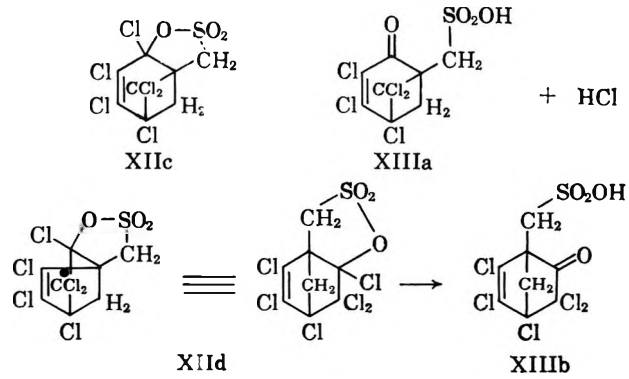
The reaction of 5-methylene-1,2,3,4,7,7-hexachlorobicyclo[2.2.1]hept-2-ene[11] (XI) with oleum yielded a crystalline product of the empirical formula $C_8H_4Cl_6O_3S$ (XII), evidently a sultone in view of its elemental analysis, nonacidic character, and hydrolytic properties. The infrared spectrum of XII exhibited only one band in the carbon-to-carbon double bond region, at 6.21 μ, characteristic of the –CCl=CCl– group in chlorine-containing bicyclo[2.2.1]heptenes,[2] thus eliminating possible structures analogous to VIII. Hydrolysis of XII in aqueous tetrahydrofuran resulted in opening of the sultone ring with the release of one equivalent of hydrochloric acid and with the formation of a ketonic sulfonic acid, $C_8H_5Cl_5O_4S$ (XIII, isolated as the dihydrate and as the barium salt).

This behavior on hydrolysis eliminates structures XIIa and XIIb for the sultone $C_8H_4Cl_6O_3S$.



XI XIIa XIIb

Two sterically feasible structures, XIIc and XIId, both of which would involve skeletal rearrangements in their formation from XI, may be hypothesized to account for the presence of the –CCl–O– group and the formation of the keto group on hydrolysis.



XIIc XIIIa + HCl

XIId XIIIb

A priori, structure XIIc appeared less probable than XIId, since no examples of carbonium ion rearrangements from the bicyclo[2.2.1]hept-2-ene skeleton to the bicyclo[3.1.1]hept-2-ene skeleton were found in the literature, whereas skeletal rearrangements of the type required to form XIId have been shown to occur in the norbornene series.[12]

Both ultraviolet and infrared evidence favor structure XIIIb for the ketonic hydrolysis product and thus favor structure XIId for the sultone.[13] The ultraviolet spectrum of the ketonic hydrolysis product (as the acid) in ether shows a strong maximum at 235–240 mμ (ε ~7000)[14] comparable to $\lambda_{max}^{cyclohexane}$ 236–237 mμ (ε 9200) reported for the unconjugated isomer of octachlorocyclohexenone.[15]

The hypothetical conjugated structure XIIIa would be expected to have λ_{max} of at least 267 mμ by com-

(8) M. Kleiman (to Velsicol Chemical Corp.), U. S. Patent 2,736,730 (1956); *Chem. Abstr.*, **50**, 10,780*h* (1956).

(9) V. A. Slabey, *J. Am. Chem. Soc.*, **76**, 3604 (1954).

(10) P. Yates and P. Eaton, *Tetrahedron*, **12**, 13 (1961).

(11) W. K. Johnson and V. Mark, *J. Org. Chem.*, **26**, 4105 (1961).

(12) J. D. Roberts, C. C. Lee, and W. H. Saunders, Jr., *J. Am. Chem. Soc.*, **77**, 3034 (1955); S. Winstein and M. Shatavsky, *Chem. Ind.* (London), 56 (1956).

(13) While the possibility of a skeletal rearrangement from XIIc to XIIIb during the hydrolytic ring opening has not rigorously been excluded, it seems quite improbable that such a rearrangement would take place under the hydrolytic conditions while not occurring under the conditions of the formation of the sultone in oleum. It is possible to postulate an intermediate carbonium ion common to both the ring-forming and ring-opening reactions, such an ion possibly being a resonance hybrid of "norpinene" and "norbornene" canonical forms. However, since this ion fails to react in the "norpinene" form with water to yield the hypothetical conjugated ketone XIIIa, where the resonance stabilization of the conjugated structure would seem to favor this path, it is difficult to see why the intermediate carbonium ion should undergo sultone ring closure in the "norpinene" form where no evident energy relationship would favor such a path.

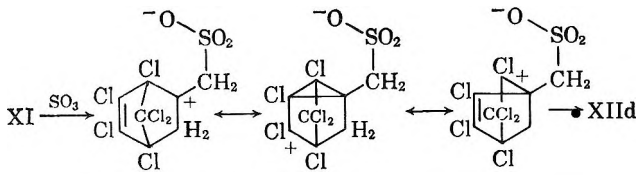
(14) It should be further noted that the ketonic hydrolysis product (XIIIb) exhibits a weak broad band at 312 mμ (ε 350) which may be attributed to the $n \rightarrow \pi^*$ transition of the carbonyl group. This broad band is comparable to the resolved $n \rightarrow \pi^*$ quadruplet [287 mμ (ε 162), 296.5 (242), 307.5 (277), 319.5 (177)] reported for bicyclo[2.2.1]hept-5-en-2-one by A. Moscowitz, K. Mislow, M. A. W. Glass, and C. Djerassi [*J. Am. Chem. Soc.*, **84**, 1945 (1962)].

(15) L. Denivelle and R. Fort, *Bull. soc. chim. France*, 459 (1958).

parison with the reported spectrum of the conjugated isomer of octachloro-2-cyclohexenone. The four-membered ring would in fact be expected to raise the λ_{max} of the hypothetical XIIIa, as can be seen by comparison of the spectrum of verbenone (253 mμ)[16] with that of isophorone (234 mμ).[17]

The carbonyl band of the ketonic hydrolysis product occurs at 5.60 μ, identical with the position reported for 1,2,3,4,7,7-hexachlorobicyclo[2.2.1]hept-2-en-5-one[11] and substantially identical with the position reported for the unconjugated isomer of octachlorocyclohexenone.[15] On the other hand, the carbonyl absorption of the less-favored hypothetical structure XIIIa would be expected to occur in the vicinity of 5.73, the value reported for 1,3,4,4,5,5,6,6-octachloro-2-cyclohexenone.[18] The presence of the four-membered ring in XIIIa would be expected to have little influence on the position of the carbonyl absorption, as can be seen from a comparison of verbenone, $\lambda_{C=O}$ 5.93 μ[16] to isophorone, $\lambda_{C=O}$ 5.95 μ.[17]

The formation of XIId from XI may be explained on the basis of a carbonium ion rearrangement as shown.



The redistribution of the positive charge to the former bridgehead carbon makes possible a facile ring closure to form the γ-sultone XIId.

Experimental

1,2,3,4,7,7-Hexachloro-5-(hydroxymethylene)-6-(sulfomethylene)bicyclo[2.2.1]hept-2-ene Sultone (I). A. From 2,3-Bis(chloromethyl)-1,4,5,6,7,7-hexachlorobicyclo[2.2.1]heptadiene (II).—Twenty grams of 2,3-bis(chloromethyl)-1,4,5,6,7,7-hexachlorobicyclo[2.2.1]heptadiene[1] and 50 ml. of oleum (20% sulfur trioxide) were heated at 72–76° for 30 min. with stirring. The dark homogeneous solution then was cooled and poured cautiously with stirring into ice–water. The sticky precipitate was extracted with benzene. The benzene extracts were washed with water, dried over magnesium sulfate, filtered, and evaporated to dryness to obtain 19 g. of tan solid, m.p. 127–129.5°.

Recrystallization from carbon disulfide yielded 17 g. (84%) of colorless crystals, m.p. 129–130°. The product is insoluble in water, slightly soluble in cold heptane, moderately soluble in hot heptane, and soluble in cold benzene; λ_{max}^{Nujol} 3.27 (w), 5.93 (m), 6.11 (w), 6.24 (m), 7.26 (s, only partly due to Nujol), 7.42 (shoulder), 7.97 (w), 8.32 (s), 8.50 (w), 8.61 (m), 8.86 (shoulder), 8.93 (s), 9.11 (w), 9.62 (w), 9.80 (m), 10.34 (w), 10.89 (m), 11.51 (m), 11.83 (m), 12.10 (m), 12.53 (w), 12.86 (m), 14.50 (s), 14.65 (s), and 15.11 μ (m). The compound is neutral to congo red indicator in aqueous ethanolic solution.

Anal. Calcd. for $C_9H_2Cl_6SO_3$: C, 26.80; H, 0.50; Cl, 52.9; S, 7.94; mol. wt., 405. Found: C, 26.84; H, 0.55; Cl, 52.8; S, 7.99; mol. wt., 388 (± 10%, ebullioscopic in benzene).

In a modification of the above procedure, 20 g. of 2,3-bis(chloromethyl)-1,4,5,6,7,7-hexachlorobicyclo[2.2.1]heptadiene was added in portions to 50 ml. of liquid sulfur trioxide (Stabilized Sulfan, Allied Chemical Corp.), maintaining the temperature below 50°. After 10 min., the reaction mixture was worked up as above to obtain 6.4 g. (32%) of I.

B. From 5-(Chloromethylene)-6-methylene-1,2,3,4,7,7-hexachlorobicyclo[2.2.1]hept-2-ene (IV).—Five grams of 5-(chloromethylene)-6-methylene-1,2,3,4,7,7-hexachlorobicyclo[2.2.1]-hept-2-ene[1] was added with stirring to 12.5 ml. of oleum (20% sulfur trioxide). The organic liquid quickly dissolved and the temperature rose to about 40°. In 15 min., the reaction mixture set to a semisolid dark sludge. It then was heated to 80° over a period of 30 min., then cooled, and added to ice–water; the organic precipitate was extracted with chloroform, and the chloroform was evaporated. The residual solid was recrystallized from hot heptane to obtain 5 g. of crystalline product, m.p. 129.5–131°, which was shown by infrared and mixture melting point to be identical with the product of method A.

C. From 5,6-Bis(methylene)-1,2,3,4,7,7-hexachlorobicyclo[2.2.1]hept-2-ene (III).—To 50 ml. of oleum (20% sulfur trioxide) was added 10 g. of 5,6-bis(methylene)-1,2,3,4,7,7-hexachlorobicyclo[2.2.1]hept-2-ene.[1] An exotherm to about 40° resulted, the characteristic odor of sulfur dioxide became evident, and within 30 min. the organic solid had almost completely dissolved. The dark solution was filtered through a sintered-glass funnel and then cautiously added to ice–water with stirring. The resultant gummy precipitate was taken up in benzene, washed with water, and evaporated to dryness. The yellowish residual solid (which appeared to be contaminated with sulfur), after three recrystallizations from heptane, yielded 4 g. of colorless needles melting at 128–129°. The identity of this product with that of method A was established by mixture melting point and infrared spectrum.

D. From 2,3-Bis(hydroxymethyl)-1,4,5,6,7,7-hexachlorobicyclo[2.2.1]heptadiene (V).—To 50 ml. of oleum (20% sulfur trioxide) was added 10 g. of 2,3-bis(hydroxymethyl)-1,4,5,6,7,7-hexachlorobicyclo[2.2.1]heptadiene,[1] with stirring. The solution rapidly darkened as the solid was added, and the temperature rose to 50°. After several hours, the solution was poured cautiously into ice–water, the resultant milky suspension was extracted with chloroform, and the chloroform extract was washed with water. Upon stripping the chloroform, a semisolid mass was obtained. This product was treated in warm heptane with Fuller's earth and charcoal, isolated by chilling, and recrystallized again from heptane to obtain colorless crystals, m.p. 129.5–130.5°. The infrared spectrum and mixture melting point established this product to be identical with the product of method A.

E. From 2,3-Bis(acetoxymethyl)-1,4,5,6,7,7-hexachlorobicyclo[2.2.1]heptadiene[1] (VI).—Two grams of the diacetate[1] and 5 ml. of oleum (20% sulfur trioxide) were heated on the steam bath 3 hr., cooled, and poured into ice–water; the organic product was extracted with chloroform and the chloroform washed with water. Upon evaporation of the chloroform, an oil remained which crystallized on standing. This was taken up in hot heptane, and on chilling the solution deposited 1.5 g. of crystals, m.p. 112–119°. The infrared spectrum of this product showed that it consisted of a mixture of the sultone (I) with about an equal amount of one or more contaminants exhibiting an –OH group (2.92 μ) and a carbonyl group (5.76 μ).

1,2,3,4,7,7-Hexachloro-3-hydroxy-5-sulfotricyclo[2.2.1.0^{2,6}]heptane Sultone (VIII).—Ten grams of 1,2,3,4,7,7-hexachlorobicyclo[2.2.1]heptadiene (VII)[8] and 20 ml. of oleum (20% sulfur trioxide) were stirred and heated, the temperature being raised to 80° over 15 min. The reaction mixture partially solidified. It was cooled and added to ice–water; the precipitated solids were removed by filtration and washed with water. The crude product was dissolved in warm heptane; the solution was filtered with Fuller's earth and charcoal, and chilled to obtain 6 g. of colorless needles, m.p. 173.5–174°; λ_{max}^{Nujol} 7.50 (w), 8.07 (s), 8.30 (m), 8.60 (m), 8.80 (w), 9.05 (s), 9.11 (s), 9.56 (m), 10.17 (m), 10.27 (s), 10.71 (m), 11.44 (m), 11.87 (s), 12.16 (s), 12.6 (m), 13.26 (vs), 14.13 (m), and 15.00 μ (m). The compound is neutral to congo red indicator in aqueous ethanolic solution.

Anal. Calcd. for $C_7H_2Cl_6O_3S$: C, 22.19; H, 0.53; Cl, 56.15; S, 8.46; mol. wt., 379. Found: C, 22.29; H, 0.66; Cl, 56.4; S, 8.46; mol. wt., 357 (± 10%, ebullioscopic in tetrahydrofuran).

Methyl 1,2,4,7,7-Pentachloro-3-ketotricyclo[2.2.1.0^{2,6}]heptane-5-sulfonate (IX).—A mixture of 10 g. of the sultone (VIII), 6 g. of anhydrous sodium carbonate, and 75 ml. of methanol was agitated for 30 min. with water-bath cooling. The mixture became thicker as solids came out of solution. The solids were removed by filtration and washed with water to remove inorganic salts. Volhard titration of the methanol filtrate and water washings showed 19.7 mequiv. of chloride to be present (theory, 26.4 mequiv.).

The water-insoluble solids were dried quickly *in vacuo* and recrystallized twice from benzene–heptane mixture to obtain 3 g.

(16) C. H. Whitham, University of Birmingham, private communication.
(17) R. L. Erskine and E. S. Waight, *J. Chem. Soc.*, 3425 (1960).
(18) L. Denivelle and R. Fort, *Bull. soc. chim. France*, 392 (1959).

of colorless needles, m.p. 171–171.5°; λ_{max}^{Nujol} 5.40 (s), 7.37 (s), 8.14 (w), 8.46 (s), 9.53 (mw), 10.17 (s), 10.34 (w), 11.08 (w), 11.39 (m), 11.70 (w), 12.16 (m), 12.64 (m), 13.07 (m), and 13.66 μ (w).

Anal. Calcd. for $C_5H_7Cl_5O_3S$: C, 25.5; H, 1.86; Cl, 47.2; S, 8.50. Found: C, 25.8; H, 1.81; Cl, 47.2; S, 8.43.

Potassium 1,2,4,7,7-Pentachloro-3-ketotricyclo[2.2.1.0^{2,6}]heptane-5-sulfonate (X).—By employing potassium hydroxide in place of sodium carbonate in the above reaction, 1.2–1.3 equiv. of chloride ion per mole was released. The methyl ester (IX) was obtained in varying but minor amounts, the principal products being methanol-soluble salts. From the methanol filtrate on successive partial evaporations, a series of three water-soluble crystalline crops were obtained which, on the basis of infrared spectra, were primarily the same compound. The first and last crops contained a tenacious unsaturated impurity (band at 6.1 μ), but the second crop was substantially free of carbon-to-carbon double bond absorption. All crops showed strong C=O absorption at 5.52 μ. The second crop was used for elemental analysis.

Anal. Calcd. for $C_7HCl_5O_4KS\cdot H_2O$: C, 20.23; H, 0.73; Cl, 42.7; S, 7.72. Found: C, 20.46; H, 1.03; Cl, 41.5; S, 7.72.

1,2,3,5,6,6-Hexachloro-5-hydroxy-4-(sulfomethyl)bicyclo[2.2.1]hept-2-ene Sultone (XII).—To 300 ml. of oleum (20% sulfur trioxide) was added 100 g. of 5-methylene-1,2,3,4,7,7-hexachlorobicyclo[2.2.1]hept-2-ene[11] with stirring and water-bath cooling to hold the temperature below 50°. After the mixture had been stirred for 30 min., during which time it became a thick crystal slurry, it was added to ice–water. The precipitated solid was extracted with methylene chloride, washed with water, dried over magnesium sulfate, and filtered, and about an equal amount of carbon tetrachloride was added. Partial evaporation yielded 83 g. of crystalline solid, m.p. 185–187.5°.

Recrystallization from methylene chloride–carbon tetrachloride yielded colorless needles, m.p. 192.5°; λ_{max}^{Nujol} 3.31 (w), 6.21 (m), 7.00 (w), 7.20 (s, partly Nujol), 7.59 (w), 7.94 (m), 8.12 (m), 8.24 (m), 8.48 (s), 8.80 (w), 8.97 (w), 9.27 (m), 9.43 (s), 9.54 (s), 9.83 (w), 9.98 (w), 10.35 (m), 10.76 (ms), 11.2 (sh), 11.33 (s), 11.77 (m), 12.28 (m), 12.51 (m), 13.20 (m), 14.12 (m), 14.82 (w), and 15.22 μ (w). The compound is neutral to congo red in aqueous ethanolic solution.

Anal. Calcd. for $C_8H_4Cl_6O_3S$: C, 24.35; H, 1.27; Cl, 54.0; S, 8.11; mol. wt., 393. Found: C, 24.35; H, 1.36; Cl, 54.1; S, 7.98; mol. wt., 423 (± 10%; ebullioscopic in benzene).

1,2,3,6,6-Pentachloro-4-(sulfomethyl)bicyclo[2.2.1]hept-2-en-5-one (XIII) and Barium Salt.—A solution of 3.93 g. (10 mmoles) of the sultone XII in 90 ml. of tetrahydrofuran and 10 ml. of water was refluxed for 27 hr. An aliquot was found to contain 7.3 mequiv. of chloride by Volhard titration. A blank experiment wherein 1 *N* hydrochloric acid in 1:9 water–tetrahydrofuran solution was refluxed for a similar period showed that one-quarter of the hydrochloric acid was consumed by reaction with the tetrahydrofuran; therefore, taking into consideration this loss of hydrogen chloride, approximately 1 equiv. of hydrogen chloride per mole of XII had been evolved. Potentiometric titration of a second aliquot with 0.1 *N* sodium hydroxide gave an unsharp end point in the vicinity of pH 5 (the fading end point attributable to the instability of XIII sodium salt toward aqueous base) indicating the formation of 2 equiv. of strong acid per mole of XII.

The reaction mixture was evaporated to obtain a gray solid, m.p. 159.5–164°, which was recrystallized from benzene–ether and dried in air to obtain 2 g. of grayish white crystals, m.p. 163–165°; λ_{max}^{Nujol} 5.61 (C=O) and 6.28 μ (C=C); λ_{max}^{ether} 235 mμ (ϵ ~7000, on side of intense band < 220 mμ), 312 mμ (ϵ 350). The compound is soluble in water, giving a solution acidic to congo red indicator.

Anal. Calcd. for $C_8H_5Cl_5O_4S\cdot 2H_2O$: C, 23.41; H, 2.21; Cl, 43.19; S, 7.81. Found: C, 23.76; H, 2.41; Cl, 43.3; S, 8.20.

To obtain a more precise analysis, XIII was converted to its barium salt by digesting it in aqueous solution with an equimolar amount of barium carbonate on the steam bath until effervescence ceased (2.5 hr.), the mixture was filtered while hot, the filtrate was concentrated and cooled, and the resultant precipitate was filtered out and dried in air to obtain tan nodular crystals, λ_{max}^{Nujol} 5.60 (C=O) and 6.26 μ (C=C).

Anal. Calcd. for $C_{16}H_8BaCl_{10}O_8S_2\cdot H_2O$: C, 21.29; H, 1.12; Ba, 15.2; Cl, 39.31; H_2O, 1.99; S, 7.10. Found: C, 21.09; H, 1.17; Ba, 14.9; Cl, 39.30; H_2O, 1.86; S, 7.02.

The Addition of Dichlorocarbene to *cis,cis*-1,5-Cyclooctadiene

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The reaction cited in the title can be conducted very smoothly by refluxing the hydrocarbon in a suspension of sodium trichloroacetate in a mixture of tetrachloroethylene and a small amount of diethylene glycol dimethyl ether. The reaction affords two crystalline bis adducts, and X-ray analysis has shown that the major, lower melting product has the *cis* configuration.

The objective of this investigation was to develop a carbene reaction suitable for use as an experiment for beginning students. The starting materials should be readily available, the reaction time short, and the product an easily isolated solid. The reaction of tetrachloroethylene with dichlorocarbene to give hexachlorocyclopropane (m.p. 104°) meets the requirements only in part. The yield is satisfactory (74%) when the intermediate is generated from phenyl(bromodichloromethyl)mercury,[2] but the preparation of this reagent is too involved and expensive. The double bond of tetrachloroethylene is so inert that generation of dichlorocarbene from chloroform or from sodium trichloroacetate in the presence of this olefin affords hexachlorocyclopropane in yields of 0.2–10%.[3,4]

It seemed to us that the bis adduct of a nonconjugated diene should have favorable properties and that *cis,cis*-1,5-cyclooctadiene offered particular promise. The hydrocarbon is available commercially[5] and has been found to react readily with hexachlorocyclopentadiene at 100° to give a high melting bis adduct.[6] Indeed, Skatteböl[7] states in a preliminary report that the cyclodiene reacts with dibromocarbene generated from bromoform and potassium *t*-butoxide to give a liquid mono adduct and a bis adduct melting at 174–180°. Since the completion of our work, Fray[8] has reported that reaction of the diene with sodium tri-

(1) Undergraduate National Institutes of Health Fellow, CA-01696-11CY.

(2) D. Seyferth, R. J. Minasz, A. J.-H. Treiber, J. M. Burlitch, and S. R. Dowd, *J. Org. Chem.*, **28**, 1163 (1963).

(3) W. R. Moore, S. E. Krikorian, and J. E. LaPrade, *ibid.*, **28**, 1404 (1963).

(4) E. K. Fields and J. Meyerson, *ibid.*, **28**, 1915 (1963).

(5) Columbia Carbon Co., Box 975, Princeton, N. J.

(6) K. Ziegler and H. Froitzheim-Kühlhorn, *Ann.*, **589**, 157 (1954).

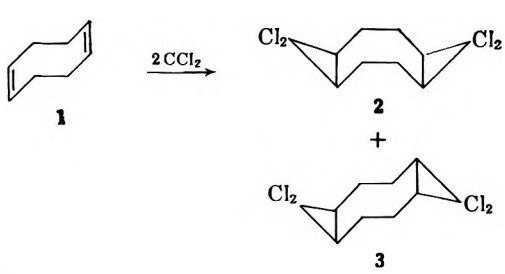
(7) L. Skatteböl, *Tetrahedron Letters*, **5**, 167 (1961).

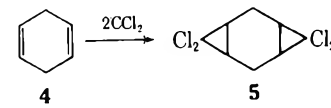
(8) G. I. Fray, *J. Chem. Soc.*, 4284 (1963).

chloroacetate in 1,2-dimethoxyethane for 16 hr. at 100–110° affords a liquid mono adduct in 59% yield along with 2% of a bis adduct, m.p. 174.5–175.5°. Neither result meets the specifications outlined.

Sodium trichloroacetate[8,9] seemed to be the precursor of choice, and we report below a simple, improved procedure for its preparation. We first tried magnetic stirring of *cis,cis*-1,5-cyclooctadiene with a suspension of sodium trichloroacetate in diglyme (diethylene glycol dimethyl ether) at a temperature maintained manually at about 120°. After a 2-hr. reaction period, the mixture was very black but tedious processing eventually afforded as the major product a bis adduct crystallizing from ethyl acetate as large needles, m.p. 176°. Recovery of the mother liquor material and repeated crystallization from toluene afforded a small amount of an isomer, m.p. 230° dec. The two substances are not separable by either thin layer or column chromatography. They often crystallize together, but can be sorted out because of a characteristic difference in crystalline form. A first idea for simplifying the procedure was to use an aprotic solvent of such a boiling point that refluxing would control the temperature in the desired range and provide stirring. Tetrachloroethylene boils at 121° and, as noted above, is very unreactive to dichlorocarbene. However, sodium trichloroacetate is insoluble in this solvent and no reaction with the diene was observed. It appeared that diglyme or an equivalent solvent is required to provide some solubility for the sodium salt, and the reaction was found to proceed materially better in a 7:10 mixture of diglyme–tetrachloroethylene than in diglyme alone. However, the solubility in this mixture is so great that the salt has to be added in small portions and the reaction mixture becomes very dark. The situation is improved greatly by the simple expedient of cutting down the amount of diglyme to a ratio 2.5:10. The salt is so sparingly soluble in this mixture that all of it can be added at the start of the experiment and it dissolves slowly as the reaction proceeds. Since boiling and carbon dioxide evolution provide adequate stirring, the mixture can be left unattended, and what little color develops is eliminated by washing the crude product with methanol. Thus, treatment of 4.4 g. of diene with the theoretical amount of sodium trichloroacetate in a 75-min. reaction period and with a very brief work-up affords 2.9 g. of the pure isomer with m.p. 176° in a yield of 29%. With twice the theoretical amount of sodium trichloroacetate, the yield rose to 62%.

Both isomers gave satisfactory analyses and were saturated to permanganate. Reduction of the more abundant isomer with lithium and *t*-butyl alcohol in tetrahydrofuran gave a product shown clearly by the n.m.r. spectrum to contain cyclopropyl hydrogens. Since the compounds presumably are *cis* and *trans* isomers, the junior author undertook to distinguish between them by X-ray analysis conducted under the guidance of Professor William N. Lipscomb and Mrs. Jean Ann Hartsuck, to whom we are greatly indebted. X-Ray data presented in the Experimental section led to the conclusion that the more abundant, lower melting isomer has the *cis* configuration. Cope, Moon, and Park[10] explored the reaction of *cis,cis*-1,5-cyclooctadiene with methylene iodide and zinc–copper couple isolated the mono adduct, and by gas chromatography detected two substances presumed to be the *cis* and *trans* bis adducts; in contrast to the present results, the substances appeared in nearly equal amounts. We applied our best dichlorocarbene procedure to 1,4-cyclohexadiene (**4**) and isolated in low yield a crystalline bis adduct **5** of unknown configuration.





Experimental

Sodium Trichloroacetate.—A cooled solution of 3.2 g. of sodium hydroxide in 12 ml. of water was poured slowly and with cooling into a 125-ml. erlenmeyer flask with side tube containing 12.8 g. of trichloroacetic acid until only about one-tenth of the alkali remained. After addition of a drop of 0.04% bromocresol green solution, further alkali was added by capillary dropper to a neutral end point. The flask was stoppered, connected to the suction pump, placed within the rings of a steam bath, and wrapped in a towel. Evacuation for 15–20 min. gave an apparently dry white cake. This was broken up with a steel spatula and the material was dried further to a constant weight of 14.5 g. Mohr titration indicated the presence of only a trace of chloride ion.

Isolation of the Two Bis Adducts.—A mixture of 5 g. of *cis,cis*-1,5-cyclooctadiene,[11] 7 ml. of diglyme, and 10 ml. of tetrachloroethylene in a 125-ml. erlenmeyer was stirred magnetically and brought to 115°, and 24 g. of sodium trichloroacetate was added in 1-g. portions over a period of 1 hr. The mixture was stirred and maintained near boiling (115–120°) during the addition and for an additional half hour. The very dark reaction mixture containing suspended sodium chloride was cooled, 90 ml. of 95% ethanol was added, and the mixture was cooled thoroughly in an ice bath and filtered by suction. The cake containing an organic solid and sodium chloride was washed with cold ethanol to remove the dark mother liquor and to give an almost colorless granular solid. This solid was distributed between ether and water, and the white solid resulting from evaporation of the washed and dried ethereal layer on crystallization from about 20 ml. of ethyl acetate afforded 3.5 g. of large, colorless needles, m.p. 175–176°, of the *cis* bis adduct, *cis*-9,9,10,10-tetrachlorotricyclo[7.1.0.^{1,8}]decane (**2**).

Anal. Calcd. for $C_{10}H_{12}Cl_4$ (274.03): C, 43.83; H, 4.42; Cl, 51.75. Found: C, 43.84; H, 4.53; Cl, 51.65.

The ethyl acetate mother liquor from the crystallization was evaporated to dryness, and the solid residue on five crystallizations from toluene afforded 0.1 g. of *trans*-9,9,10,10-tetrachlorotricyclo[7.1.0.0^{1,8}]decane (**3**), m.p. 228–230° dec. (slight gassing).

Anal. Calcd. for $C_{10}H_{12}Cl_4$ (274.03): C, 43.83; H, 4.42; Cl, 51.73. Found: C, 43.81; H, 4.42; Cl, 51.64.

Evaporation of the ethanol filtrate from the original reaction mixture gave a thick brown oil, and a solution of this material in a little ethyl acetate on standing deposited 1 g. of pale yellow

(9) W. M. Wagner, *Proc. Chem. Soc.*, 229 (1959).

(10) A. C. Cope, S. Moon, and C. H. Park, *J. Am. Chem. Soc.*, **84**, 4843 (1962).

(11) We are indebted to Professor A. C. Cope for a v.p.c. analysis conducted at Massachusetts Institute of Technology indicating that the sample used was 98.7% pure.

needles. Recrystallization gave material identical with the *cis* bis adduct.

Reaction of *cis,cis*-1,5-Cyclooctadiene with Dichlorocarbene from Chloroform.—A suspension of 10 g. of potassium *t*-butoxide in 50 ml. of dry ether was stirred magnetically in an ice bath, 2 g. of the diene was introduced, and then 5 ml. of chloroform was added dropwise in the course of 10 min. Stirring was continued for 1 hr., 50 ml. more ether was added, and the mixture was filtered by suction. After washing the filter cake thoroughly with ether, the filtrate was evaporated to dryness. Crystallization of the residual solid from ethyl acetate yielded 1.5 g. of colorless needles of nearly pure (m.p. 172–174°) *cis* bis adduct (mixture melting point determination).

***cis*-Tricyclo[7.1.0.0^{1,8}]decane.**—A solution of 2 g. of the *cis* bis adduct 2 in 20 ml. of tetrahydrofuran was stirred mechanically in a 125-ml. erlenmeyer flask mounted above an ice bath which could be raised for cooling when required to prevent boiling. Two grams of lithium wire which had been flaked with a hammer was added in portions along with enough *t*-butyl alcohol to dissolve the metal. After disappearance of all but a few small particles of lithium, the mixture was diluted with water and extracted with ether. Evaporation gave a yellow oil which was distilled at the pressure of the water pump (b.p. 135–140°). The n.m.r. spectrum in carbon tetrachloride clearly showed the presence of cyclopropyl hydrogens in a multiplet centering at τ 10.2 relative to tetramethylsilane.

Improved Procedure (L.F.F.).—A 250-ml. round-bottomed flask containing 5 ml. (4.4 g.) of *cis,cis*-1,5-cyclodecadiene, 14.5 g. (2 equiv.) of sodium trichloroacetate, 20 ml. of tetrachloroethylene, and 5 ml. of diglyme was fitted with a condenser connected to a gas bubbler containing a little tetrachloroethylene and heated over a microburner. Gas evolution continued at a steady rate for 75 min. and then stopped. Lumps of sodium trichloroacetate visible at the bottom of the flask gradually gave way completely to finely divided sodium chloride. The mixture acquired no more than a light tan color. At the end of the reaction, 75 ml. of water was added, the flask was fitted with a distillation adapter carrying a steam inlet tube, and the tetrachloroethylene was removed by distillation. The reaction product separating as a tan solid was extracted with methylene chloride; evaporation of the dried extract gave 8 g. of tan solid. The cake was covered with methanol, the lumps were crushed with a flattened stirring rod, the mixture was cooled, and the product was collected and washed free of brown mother liquor. The nearly colorless solid (3.3 g., m.p. 174–176°) consisting almost entirely of the *cis* bis adduct on crystallization from ethyl acetate (15 ml.) gave 2.9 g. (27%) of large needles of pure material, m.p. 175–176°.

In another run in which the amount of sodium trichloroacetate was increased to double the theoretical amount, gas evolution stopped after 1 hr. and 50 min. Evaporation of the dried extract gave 15.4 g. of tan product which, when washed with methanol, afforded 7.1 g. of material, m.p. 173–175°. Concentration of the methanol washings and recrystallization of the main product afforded a total of 6.6 g. (62%) of pure *cis* bis adduct, m.p. 175–176°.

7,7,8,8-Tetrachlorotricyclo[5.1.0.0^{1,6}]hexane (5).—A mixture of 3.5 ml. of 1,4-cyclohexadiene, 14.5 g. of sodium trichloroacetate, 20 ml. of tetrachloroethylene, and 5 ml. of triglyme was refluxed for 75 min., when bubbling stopped. After steam distillation for removal of solvent, further steam distillation afforded 0.53 g. of colorless solid, m.p. 169°. The substance crystallized from about 20 ml. of 95% ethanol in heavy prismatic crystals, m.p. 170–171°.

Anal. Calcd. for $C_8H_8Cl_4$ (245.97): C, 39.06; H, 3.28; Cl, 57.66. Found: C, 39.14; H, 3.39; Cl, 57.33.

X-Ray Analysis.—X-Ray photographs of a crystal of the lower melting isomer demonstrated C2h lattice symmetry, that is, a twofold axis perpendicular to a mirror plane, and hence showed that the crystal lattice is monoclinic. Measurement and calculation established the following dimensions of the unit cell: a = 14.8, b = 7.62, c = 12.1 Å.; β = 58°. Calculation from the molecular weight of 274 and the observed density of 1.49 g./ml. indicates the presence of four molecules per unit cell.

Crystals of the higher melting isomer have lattice symmetry D2h (three mutually perpendicular mirror planes) and, therefore, are orthorhombic. The units cell dimensions are a = 12.0, b = 6.11, c = 7.89 Å. On the assumption that the molecular weight is 274 and the density is the same as observed for the iso mer, calculation shows the presence of two molecules per unit cell.

The precise space group for the monoclinic crystal is C2, Cc, C2/m, or C2/c and that for the orthorhombic crystal is either Pnnm or Pnn2, but these possibilities in themselves do not distinguish between the two configurations. However, measurement of the molecular dimensions of models on the assumption of an intramolecular H–H distance of 2.4 Å. indicated that the *cis* isomer cannot preserve the symmetry of the space group Pnn2 and fit into this unit cell, whereas the *trans* isomer does fit in this space group. Furthermore, symmetry requirements show that the *cis* isomer cannot yield crystals of the Pnnm space group. Therefore, the higher melting bis adduct forming orthorhombic crystals must be the *trans* isomer.

Investigations in Heterocycles. XVI.[1] A New Synthesis of 1,2-Disubstituted 4-Thiopyrimidines *via* Enamines

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A simple one-step synthesis has been developed for the preparation of 1,2-disubstituted 4-thiopyrimidines by condensing an α,β-unsaturated amino ester (enamine) with an acyl isothiocyanate. The general structure of these compounds has been confirmed by chemical and spectral methods. The spectral properties of these compounds are described.

The recent monograph on pyrimidines by Brown[2] has outlined comprehensively the principal methods of synthesis and the chemical and physical properties of pyrimidines. It has been tacitly implied herein that, although a great variety of mercaptopyrimidines have been prepared, only the 2-mercaptopyrimidines have been synthesized directly from a 3-carbon intermediate and an appropriate condensing agent (*e.g.*, thiourea). However, the usual procedure employed to arrive at the 4-mercaptopyrimidines involves the synthesis of the 4-hydroxy- or 4-chloropyrimidines, which then are allowed to react with phosphorus pentasulfide or sodium hydrosulfide, respectively. This method is limited in that it permits substitution at position 1 only after a 4-aminopyrimidine derivative has been alkylated and the resulting alkyl 4-imino intermediate has been hydrolyzed to the corresponding 4-oxo derivative.[3] Thus, a minimum of four steps is required in the preparation of a 1-alkyl 1,4-dihydro-4-thiopyrimidine from the appro-

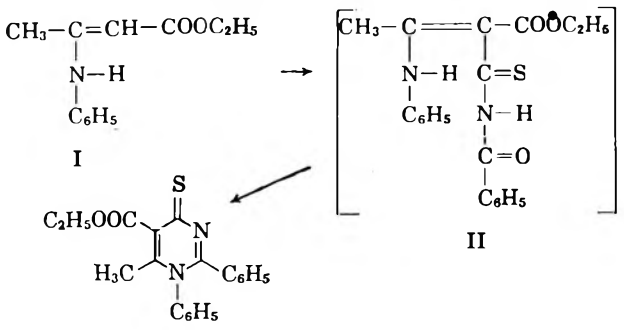
(1) Presented in part before the Organic Division at the 145th National Meeting of the American Chemical Society, New York, N. Y., Sept., 1963.

(2) D. J. Brown, "The Pyrimidines," John Wiley and Sons, Inc., New York, N. Y., 1962.

(3) D. J. Brown, E. Hoerger, and S. F. Mason, *J. Chem. Soc.*, 211 (1955); see also pp. 373–382 of ref. 2.

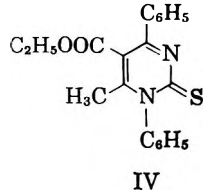
priate 3-carbon intermediate. The problem becomes even more acute if one considers the synthesis of the heretofore unknown 1,2-disubstituted 4-thiopyrimidines and especially the 1,2-diaryl substituted compounds which are unavailable by conventional routes. The synthesis of such substances serves as the subject of this report.

Behrend[4,5] found that ethyl β-aminocrotonate on condensation with phenyl isothiocyanate affords only a low yield of 6-methyl-3-phenyl-2-thiouracil along with a by-product, ethyl β-amino-α-phenylthiocarbamoylcrotonate. The identification of this ester was the first suggestion of the enamine character of ethyl β-aminocrotonate. It was with this observation in mind that we considered the condensation of ethyl β-anilinocrotonate (I) with benzoyl isothiocyanate. It was anticipated that the primary product of this condensation reaction would be ethyl β-anilino-α-benzoylthiocarbamoylcrotonate (II). However, when these intermediates were allowed to react in ethyl ether or tetrahydrofuran under mild reflux, a bright yellow copious precipitate was obtained in 60% yield. The elemental analysis of this compound indicated that the elements of water had been eliminated through condensation of the intermediates described. This substance dissolved



I II III

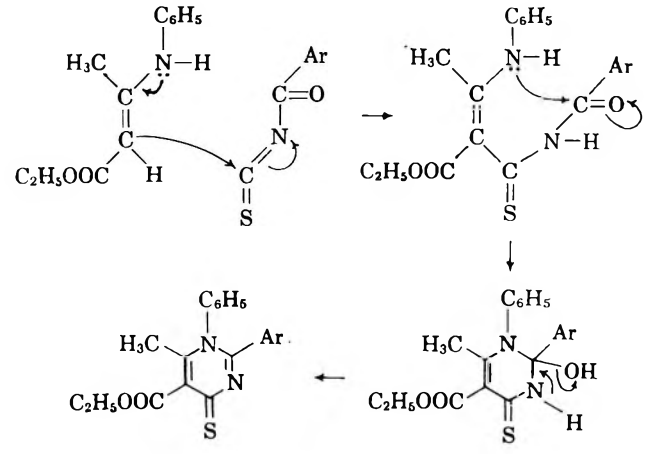
in ethyl alcohol gave maxima in the ultraviolet at 247 and 341 mμ. No bands were observed in the –NH or –OH region of the infrared, but the carbonyl region had three strong bands: 1732 cm.$^{-1}$ for the ester group, 1630 cm.$^{-1}$ for –C=N, and 1600 cm.$^{-1}$ for the phenyl group. The n.m.r. spectrum contained signals for ten aromatic protons from τ 3.12 to 2.67. The singlet at τ 8.08 corresponded to the methyl group linked to unsaturated carbon, and the triplet at τ 8.63 and the quartet at τ 5.67 are characteristic for carbethoxy protons. These data support the assignment of structure III to this compound. The alternative structure IV was not considered feasible since it required an amide carbonyl interaction with the carbon bearing the vinyl proton, a reaction which is not favored for the elimination of water under the mild reaction conditions described.



IV

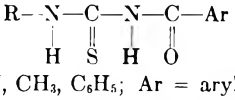
(4) R. Behrend, F. Meyer, and Y. Buchholz, *Ann.*, **314**, 200 (1901).
(5) R. Behrend and P. Hesse, *ibid.*, **329**, 341 (1903).

This reaction has been applied to a variety of α,β-unsaturated amino esters and acyl isothiocyanates, and the results of this work are recorded in Table I. Several interesting factors are worthy of note. The reaction seems to be quite general, although higher yields of 4-thiopyrimidines were obtained if the acyl isothiocyanate were substituted with an electron-withdrawing group. On the other hand, the condensation with *o*-methoxybenzoyl isothiocyanate gave a very poor yield of product and a number of different by-products were formed. These facts then suggest the following mechanism which



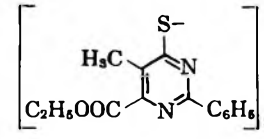
requires an electron-deficient carbonyl to facilitate the ring closure and subsequent dehydration. It was also observed that the isothiocyanate derivatives of aliphatic acids gave good yields of product. Variations in the structure of the crotonic ester did not significantly affect the course of the reaction. Ethyl β-methylaminocrotonate and ethyl β-aminocrotonate in general similarly gave good yields of the corresponding pyrimidines.

It was also observed that, in all cases, a small amount (2–5%) of the acylthiourea derivative was formed. This could usually be avoided by using freshly distilled crotonic acid ester.



R = H, CH_3, C_6H_5; Ar = aryl group

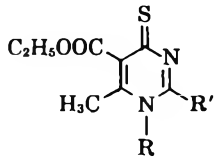
Recently, Goerdeler and Pohland[6] have reported that ethyl β-amino-α-benzoylthiocarbamoylcrotonate can be converted to the corresponding 4-thiopyrimidine in a 25% ammonium hydroxide solution. We have studied this also, but have found that the ring closure is easily accomplished merely by carrying out the reaction in refluxing tetrahydrofuran. Condensation of ethyl β-aminocrotonate with acyl isothiocyanates in refluxing tetrahydrofuran in the absence of base also affords the desired product. However, allowing III, dissolved in ammonium hydroxide solution, to stand at room temperature for 2 days gave rise to a colorless substance which was determined to have the following dimeric structure.



(6) J. Goerdeler and H. W. Pohland, *Chem. Ber.*, **96**, 526 (1963).

TABLE I

4-THIOPYRIMIDINES

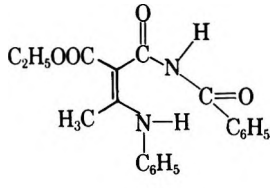


Compound	R	R′	M.p., °C.	Yield, %	Empirical formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
1	H	C_6H_5	130	42	$C_{14}H_{14}N_2O_2S$	61.30	5.14	10.21	61.04	5.15	10.60
2	H	*p*-Br-C_6H_4	174–176	45	$C_{14}H_{13}BrN_2O_2S$	47.63	3.71	7.94	47.35	3.71	7.90
3	H	$C_6H_5CH_2$	162–164	57	$C_{15}H_{16}N_2O_2S$	62.48	5.59	9.72	62.69	5.59	9.75
4	CH_3	CH_3	164–165	65	$C_{10}H_{14}N_2O_2S$	53.14	6.24	12.38	53.47	6.16	12.01
5	CH_3	C_6H_5	152	50	$C_{15}H_{16}N_2O_2S$	62.48	5.59	9.72	62.58	5.53	9.55
6	CH_3	*p*-Br-C_6H_4	230	47	$C_{15}H_{15}BrN_2O_2S$	49.09	4.12	7.63	49.18	4.12	7.32
7	C_6H_5	CH_3	207–209	70	$C_{15}H_{16}N_2O_2S$	62.48	5.59	9.72	62.60	5.58	9.42
8	C_6H_5	$ClCH_2$	130	73	$C_{15}H_{15}ClN_2O_2S$	55.95	4.70	8.70	55.97	4.81	8.53
9	C_6H_5	$C_6H_5CH_2$	182–183	65	$C_{21}H_{20}N_2O_2S$	69.15	5.53	7.69	69.05	5.50	7.46
10	C_6H_5	$C_6H_5C_3H_4$[a]	229–230	48	$C_{22}H_{22}N_2O_2S$	70.83	5.69	7.18	71.19	5.54	7.02
11	C_6H_5	C_6H_5	215	60	$C_{20}H_{18}N_2O_2S$	68.57	5.14	8.00	68.60	5.26	7.95
12	C_6H_5	*p*-Br-C_6H_4	190	45	$C_{20}H_{17}BrN_2O_2S$	55.99	3.99	6.53	60.01	3.89	6.27
13	C_6H_5	2,4-$Cl_2C_4H_3$	183–184	75	$C_{20}H_{16}Cl_2N_2O_2S \cdot C_2H_5OH$	56.89	4.73	6.03	57.04	4.73	6.03
14	C_6H_5	*o*-$(OCH_3)C_6H_4$	184–185	15	$C_{21}H_{20}N_2O_3S$	66.28	5.31	7.36	66.12	5.20	7.14
15	C_6H_5	3,4,5-$(OCH_3)_3C_6H_2$	232–233	12	$C_{23}H_{24}N_2O_5S$	62.64	5.71	6.35	62.26	5.49	6.26
16	C_6H_5	*p*-$NO_2C_6H_4$	250 dec.	77	$C_{20}H_{17}N_3O_4S$	60.81	4.34	10.64	60.72	4.30	10.25
17	C_6H_5	*m*-$NO_2C_6H_4$	240 dec.	65	$C_{20}H_{17}N_3O_4S$	60.81	4.34	10.64	60.92	4.52	10.67
18	C_6H_5	2-C_5H_4N	226–227	40	$C_{19}H_{17}N_3O_2S$	65.01	4.88	11.97	64.90	4.74	11.61

[a] Cyclopropyl.

In this case the stronger base ammonia replaces the anilino group and the resulting 4-mercaptopyrimidine can undergo air oxidation to give the disulfide.

Finally, ethyl β-anilinocrotonate was allowed to react in refluxing tetrahydrofuran with benzoyl isocyanate. Surprisingly, even after long periods of reflux, only ethyl β-anilino-α-benzoylcarbamoyl crotonate (VI) could be isolated. The absence of a vinyl proton signal in the n.m.r. served to confirm the structural assignment. Attempted ring closure in higher boiling sol-

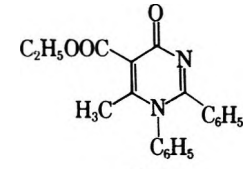


VI

vents, *e.g.*, toluene, xylene, or in the presence of dehydrating agents (*e.g.*, carbodiimide), was to no avail. Heating VI for a short time at a temperature slightly above its melting point yielded only N-benzoyl-N′-phenylurea. Condensation of I with *p*-nitrobenzoyl isocyanate also gave only the carbamoyl derivative. It, therefore, appears that the greater electronegativity of the carbamoyl oxygen as compared to sulfur[7] is instrumental in overcoming the tendency for cyclization followed by dehydration. The synthesis of ethyl 6-methyl-4-oxo-1,2-diphenylpyrimidine carboxylate (VII) was achieved through mercuric acetate in acetic acid oxidation of III. In addition to the 1735-cm.$^{-1}$ absorption band for the carbethoxy group, VIII also gave a strong band at 1648 cm.$^{-1}$, which is characteristic of the 1-substituted pyrimidin-4-ones.[8]

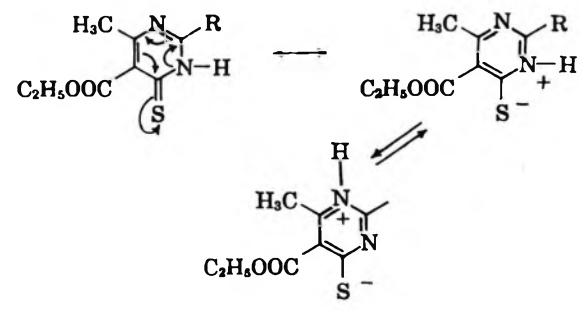
(7) L. Pauling, "Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1951, p. 59.

(8) E. D. Bergmann, S. Cohen, and I. Shakak, *J. Chem. Soc.* 3278 (1959).



VII

Spectral Data Interpretation.—The ultraviolet absorption data for the compounds prepared are listed in Table II. Several correlations can be derived therefrom. Substitution of the 2-position with an aromatic group is responsible for the absorption band at 250 to 260 mμ, since with 2-alkyl substituted derivatives this absorption maximum is shifted to approximately 230 mμ. It would appear that the 260-mμ absorption is due to the resonance contribution of the 2-phenyl group in conjugation with the 4-thione grouping through the C=N. It was also observed that the 1-unsubstituted compounds (1, 2, and 3 in Tables I and II) contain an additional absorption maximum at 305–310 mμ. Since this band is absent from the N-methyl and N-phenyl derivatives, it seems reasonable to assume that it arises mainly from this type resonance contribution.



Moreover, this indicates the difficulty of assigning a predominant tautomeric form to the -N–H compounds.

TABLE II

1,2-DISUBSTITUTED PYRIMIDINES

Compound no.[a]	λ_{max}, mμ	ε
1	240	14,540
	308	13,770
	352	4780
2	267	15,730
	308	13,940
	356	4790
3	300	12,950
	345	5920
4	228	5680
	337	21,270
5	250	10,310
	340	20,650
6	259	12,370
	340	19,190
7	228	6350
	337	22,740
8	234	11,810
	326	15,040
9	234	7920
	339	21,990
10	249	11,810
	338	25,820
11	248	8890
	341	23,420
12	254	11,670
	341	25,100
13	230	16,560
	340	24,690
14		
15	230	17,980
	340	24,940
16	262	13,350
	340	20,350
17	243	17,860
	342	22,520
18	340	10,990
	272 (shoulder)	6470
	341	24,040

[a] See Table I.

Furthermore, the absence of absorption bands at the 2600-cm.$^{-1}$ region of the infrared and the presence of only –N–H signals in the n.m.r. precluded the presence of appreciable amounts of a 4-thiol tautomer in this series of heterocycles.

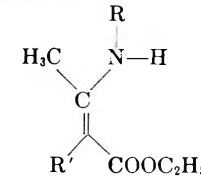
Finally, all of the 4-thiopyrimidines exhibited a maximum at 345–350 mμ, regardless of the substituents in the 1- or 2-position. This absorption maximum was found to be conspicuously absent in the spectrum of VIII. Thus, this long wave-length absorption can be attributed to the influence of the sulfur with its expanded valence shell on the resonating pyrimidine system.

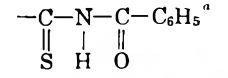
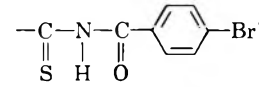
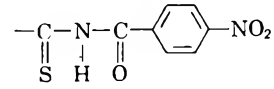
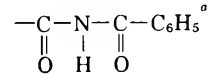
The infrared absorption spectra of these substances have already been discussed in connection with the structure proof of III. However, the ester group for the 1-unsubstituted compounds in Nujol mull absorbs at 1710 cm.$^{-1}$, whereas the 1-substituted compounds give a strong band at 1735 cm.$^{-1}$ in Nujol mull. When the infrared absorption of the former compounds was determined in chloroform, the ester absorption was shifted to 1732 cm.$^{-1}$. Thus, the shift to higher wave lengths in Nujol mull for the –N–H containing compounds can be associated with hydrogen bonding effects.

Infrared and n.m.r. spectroscopy were very useful in determining the stereochemical relationship of ethyl

TABLE III

INFRARED ABSORPTION IN THE CARBONYL REGION



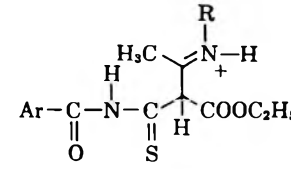
R	R′	ν, cm.$^{-1}$
H	H	1665 (s), 1624 (vs)
C_6H_5	H	1655 (s), 1620 (vs), 1600 (s)
H		1698 (s), 1665 (vs), 1618 (s)
H		1695 (s), 1665 (vs), 1615 (s)
H		1700 (s), 1672 (vs), 1610 (s)
C_6H_5		1713 (s), 1657 (vs), 1620 (s)

[a] In Nujol mull.

α-benzoylthiocarbamoyl-β-aminocrotonate and related compounds. The principal absorption bands in the carbonyl region of the infrared for these substances are listed in Table III.

The 1665-cm.$^{-1}$ band for ethyl β-aminocrotonate is assigned to the ester grouping and, in the β-anilino derivative, the carbethoxy group absorbs at 1655 cm.$^{-1}$. This shift to a lower wave length has been ascribed to intramolecular hydrogen bonding effect, thus suggesting a *cis* relationship between the amino and the ester groups. This was supported by the chemical shifts observed in the n.m.r.[9] In addition, ethyl β-diethylaminocrotonate[9] gives two carbonyl bands, 1677 (strong) and 1655 cm.$^{-1}$ (very weak), in the infrared. This consists of a mixture of *cis* and *trans* isomers, with *trans* predominating as evidenced by the strength of the absorption bands.

The *cis* stereochemical relationship (*i.e.*, the *cis* orientation of the amino and ester groups) holds for the aroylthiocarbamoyl and carbamoyl derivatives, since the ester group absorption is found at 1665–1672 cm.$^{-1}$, when the amino group is unsubstituted, and at 1657 cm.$^{-1}$ with the β-anilino derivative. However, this stereochemical assignment has little if any influence on the ring closure reaction since the driving force for this reaction appears to be the unshared pair of electrons of the amino group, thus leading to a transition state in which free rotation about the α-carbon is possible.



(9) C. F. Huebner, L. Dorfman, M. M. Robison, E. Donoghue, W. G. Pierson, and P. Strachan, *J. Org. Chem.*, **28**, 3134 (1963).

Experimental

The n.m.r. spectra were run in deuteriochloroform solutions at 60 Mc. using trimethylsilane as an internal standard. The infrared spectra were obtained from Nujol mulls or chloroform using a Perkin-Elmer Model 21 grating spectrophotometer. The ultraviolet absorption spectra were obtained from ethyl alcohol solutions using a Beckman recording spectrophotometer, Model DK. The melting points are corrected.

All acyl isothiocyanates were prepared by allowing equimolar amounts of acid chloride and lead isothiocyanate to react in benzene solution under mild reflux for 1 hr. The lead salts then were removed by filtration, and the filtrate was concentrated to an oily residue which then was purified by vacuum distillation. As outlined by Assony[10] acid chlorides as a rule react with isothiocyanate salts to form the isothiocyanate derivatives rather than the thiocyanate. Infrared absorption spectroscopy supported this, since the acyl isothiocyanates prepared exhibited a broad strong band at 2000–2050 cm.$^{-1}$, typical of the isothiocyanate group, whereas the thiocyanate group shows a sharp medium band at 2150 cm.$^{-1}$.

General Method for the Preparation of Thiocarbamoyl Derivatives. Ethyl β-Amino-α-benzoylthiocarbamoylcrotonate.—Ethyl β-aminocrotonate (5.5 g., 0.043 mole) dissolved in 50 ml. of ethyl ether was treated with vigorous stirring at 5–10° with 7.0 g. (0.043 mole) of benzoyl isothiocyanate. An immediate reaction occurred resulting in the formation of a copious orange precipitate, m.p. 115°. This was found to be identical with the compound prepared by Goerdeler and Pohland.[11]

Anal. Calcd. for $C_{14}H_{16}N_2O_3S$. N, 9.58; S, 10.97. Found: N, 9.32; S, 10.62.

Ethyl β-amino-α-(*p*-bromobenzoylthiocarbamoyl)crotonate had m.p. 106°.

Anal. Calcd. for $C_{14}H_{15}BrN_2O_3S$: C, 45.45; H, 4.06; N, 7.50. Found: C, 45.71; H, 4.07; N, 7.31.

Ethyl β-amino-α-(*p*-nitrobenzoylthiocarbamoyl)crotonate had m.p. 112°.

Anal. Calcd. for $C_{14}H_{15}N_3O_5S$: C, 49.80; H, 4.47; N, 12.45. Found: C, 49.72; H, 4.36; N, 12.29.

The above described esters could be recrystallized from glacial acetic acid.

Conversion of Crotonate Derivatives to Pyrimidines. Ethyl 4-Mercapto-6-methyl-2-phenyl-5-pyrimidinecarboxylate.—Ethyl β-amino-α-benzoylthiocarbamoylcrotonate (5.0 g., 0.017 mole) was dissolved in 25 ml. of ethyl alcohol and refluxed on the steam bath for 6 hr. The color of the solution turned from orange to bright yellow. The solvent then was removed *in vacuo*, and the resulting bright yellow residue was crystallized from ethyl alcohol to give the product, m.p. 140°.

Anal. Calcd. for $C_{14}H_{14}N_2O_2S$: C, 61.30; H, 5.14; N, 10.21. Found: C, 61.14; H, 5.15; N, 10.23.

This compound could be obtained also by allowing ethyl β-aminocrotonate to react with benzoyl isothiocyanate in refluxing tetrahydrofuran for 2 hr. After chilling the reaction mixture overnight, the yellow precipitate was collected on a filter and crystallized from ethyl alcohol. The yield of product was usually higher by this direct method.

Bis(6-methyl-2-phenyl-5-carbethoxypyrimidyl) Disulfide (V).—Six grams (0.017 mole) of ethyl 4-mercapto-6-methyl-2-phenyl-5-pyrimidinecarboxylate was dissolved in 100 ml. of 28% ammonium hydroxide solution. The solution was allowed to stand at room temperature for 24 hr. A white precipitate formed which was collected and recrystallized from methylene chloride–ethyl alcohol (1:1). The white crystalline substance melted at 174–175°. Molecular weight determination by osmometry gave a value of 548. Thus, a dimeric compound (molecular weight of 546.7) was indicated; it showed $\lambda_{max}^{C_2H_5OH}$ 273 mμ (ε 59,568).

Anal. Calcd. for $C_{28}H_{26}N_4O_4S_2$: C, 61.59; H, 4.80; N, 10.26; S, 11.77. Found: C, 61.73; H, 4.96; N, 10.05; S, 11.49.

Goerdeler and Pohland have reported a melting point of 137° for their bis compound. We are at a loss to explain this discrepancy; however, these investigators did not determine the molecular weight of their substance.

General Method for Preparation of 1,2-Disubstituted Pyrimidines. Ethyl 6-Methyl-1,2-diphenyl-4-thiono-5-pyrimidinecarboxylate (III).—Ethyl β-anilinocrotonate (4.01 g.) dissolved in 25 ml. of ethyl ether was allowed to react at room temperature with stirring for 2 hr. with 3.6 g. of benzoyl isothiocyanate. A copious yellow orange precipitate formed which was collected on a filter and washed with a small amount of ether. The weight of this substance, m.p. 210°, was 2.0 g. Work-up of the mother liquors gave an additional 1.8 g. of product plus a small amount (0.3 g.) of N-benzoyl-N′-phenylthiourea, m.p. 148–150°, lit.[12] m.p. 150°.

Ethyl β-Anilino-α-benzoylcarbamoylcrotonate (VI).—Ethyl β-anilinocrotonate (10 g., 0.05 mole) was dissolved in 25 ml. of ethyl ether and then treated at 5–10° with 7.4 g. (0.05 mole) of benzoyl isocyanate. An immediate reaction occurred and a white precipitate was formed. This was collected and crystallized from ethyl alcohol to give 4.0 g. of white crystals, m.p. 120°. In the n.m.r. spectrum, the absence of a signal at τ 3–4 characteristic of a vinyl proton confirmed the structural assignment.

Anal. Calcd. for $C_{20}H_{20}N_2O_4$: C, 68.25; H, 5.68; N, 7.97. Found: C, 68.23; H, 5.75; N, 7.94.

Several attempts were made to convert VII to the corresponding pyrimidine. Compound VII was refluxed in benzene with carbodiimide or in toluene or xylene, but only starting material was recovered. Compound VII also was heated at its melting point for 10 min. Under these conditions only N-benzoyl-N′-phenylurea, m.p. 209° (lit.[13] m.p. 210°), was identified.

Ethyl β-methylamino-2-(benzoylcarbamoyl)crotonate was crystallized from ethyl alcohol to give 60% yield of product, m.p. 134–135°.

Anal. Calcd. for $C_{15}H_{18}N_2O_4$: C, 62.12; H, 6.26; N, 9.66. Found: C, 62.23; H, 6.40; N, 9.63.

Ethyl β-anilino-2-(*p*-nitrobenzoylcarbamoyl)crotonate was crystallized from ethyl alcohol to afford a 45% yield of product, m.p. 157–159°.

Anal. Calcd. for $C_{20}H_{19}N_3O_6$: C, 60.61; H, 4.82; N, 10.59. Found: C, 61.00; H, 4.77; N, 10.87.

Ethyl 6-Methyl-1,2-diphenyl-4-oxopyrimidinecarboxylate (VII).—Compound III (2.7 g.) dissolved in 100 ml. of glacial acetic acid was treated with 2.7 g. of mercuric acetate. The resulting pale yellow solution was heated at reflux temperature for 5 hr. The dark brown mixture was filtered, and the filtrate was concentrated *in vacuo* on the steam bath. A yellow oil was obtained which was triturated with ether. The white solid which formed was collected and triturated with chloroform. The chloroform extract was concentrated *in vacuo* to afford a powder which was crystallized from isopropyl alcohol–ether (1:2). The product was obtained as tiny white crystals, m.p. 155–157°, in 34% yield; $\lambda_{max}^{C_2H_5OH}$ 244 mμ (ε 22,230), 274 shoulder (8100); infrared absorption 1735 (ester), 1648 cm.$^{-1}$ (–C=O of ring system).

Anal. Calcd. for $C_{20}H_{18}N_2O_3$: C, 71.92; H, 5.43; N, 8.39. Found: C, 71.52; H, 5.41; N, 8.45.

(10) J. J. Assony in M. Kharasch, "Organic Sulfur Compounds," Vol. I, Pergamon Press, London, 1961, pp. 325–338.

(11) J. Goerdeler and H. W. Pohland, *Chem. Ber.*, **94**, 2950 (1961).

(12) H. J. Wheeler and J. Sanders, *J. Am. Chem. Soc.*, **22**, 375 (1900).

(13) O. C. Billeter, *Ber.*, **36**, 3220 (1909).

The Hydration of Unsaturated Steroids by the Brown Hydroboration Reaction. I. Monounsaturated Steroids

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A wide variety of monounsaturated steroids was subjected to hydration by the Brown method (involving hydroboration and subsequent oxidation with alkaline hydrogen peroxide), in order to investigate the scope and steric course of the reaction. The hydroboration step was carried out either by means of lithium aluminum hydride and boron trifluoride *in situ* or alternatively by passing in diborane gas. It was found that nearly all of the unsaturated steroids studied could be hydrated successfully by this method, the only exceptions noted being the highly hindered Δ^7-, $\Delta^{9(11)}$-5β-, and $\Delta^{8(14)}$-ethylenes. The hydration in all cases proceeded by over-all *cis* addition of the elements of water, predominantly from the less hindered side (usually the α side) of the molecule. In the case of steroids containing 1,2-disubstituted double bonds, approximately equal amounts of both possible positionally isomeric alcohols were obtained, while steroidal trisubstituted ethylenes gave only the secondary alcohols (anti-Markownikoff addition). The hydroboration of certain 1,2-disubstituted steroidal ethylenes with bis-3-methyl-2-butylborane (disiamylborane) was also investigated, and it was found that in the case of 5α-cholest-1-ene this reagent resulted in the formation of only 5α-cholestan-2α-ol.

An excellent method for the hydration of olefins has been discovered by H. C. Brown and co-workers,[2] involving hydroboration of the double bond and subsequent oxidation of the resulting alkylborane with alkaline hydrogen peroxide. Most of the examples studied by Brown involved acyclic or simple cyclic olefins. It was of interest to investigate this hydration method in the steroid series, since the results were expected to provide valuable information regarding the scope and steric course of this important reaction. Consequently, a variety of unsaturated steroids, both hydrocarbons and compounds incorporating various functional groups, were subjected to hydration by the Brown method.[3a-d] The results obtained with monounsaturated steroids are described in the present paper, and those obtained with steroidal conjugated dienes in the following paper.[3e] No steroid had been hydrated by this method when we started our studies in 1958. Subsequently other workers have subjected various steroids to the hydration reaction, as will be mentioned later where relevant.

Nearly all of the unsaturated steroids investigated could be hydrated successfully by the hydroboration procedure, and this represents a useful, generally stereospecific, method of synthesis of hydroxy steroids from steroidal olefins. The only exceptions noted were the highly hindered Δ^7-, $\Delta^{9(11)}$-5β-, and $\Delta^{8(14)}$-ethylenes. As found in other series,[2] the hydration in all cases proceeded by over-all *cis* addition of the elements of water, predominantly from the less hindered side (usually the α side) of the molecule. In the case of steroids containing 1,2-disubstituted double bonds, approximately equal amounts of both possible positionally isomeric alcohols were usually obtained, while steroidal trisubstituted ethylenes gave the secondary alcohols (anti-Markownikoff addition) as the only products isolated. These results parallel those obtained with 1,2-disubstituted and trisubstituted ethylenes in the acyclic and simple cyclic series.

Methods.—The hydroboration experiments were carried out either by adding an ethereal solution of lithium aluminum hydride to a solution of the steroidal olefin and boron trifluoride etherate in ether or tetrahydrofuran (method a)[3a,4] or alternatively by passing diborane gas (generated by adding a solution of sodium borohydride in diglyme to boron trifluoride etherate in diglyme)[5] through a solution of the olefin in tetrahydrofuran (method b).[6] Method a possesses the advantage that the necessity of generating diborane separately is avoided, and, unlike the earlier Brown *in situ* procedures,[7] the high-boiling diglyme is not employed.[8] Moreover, in a number of cases when method b resulted in the recovery of comparatively large amounts of starting materials (despite the use of a considerable excess of diborane), a more complete conversion was achieved by use of method a. Method a, however, generally cannot be used with ketals or with esters,[9] and in these cases method b was the method of choice. In addition to these two methods of hydroboration, some experiments were performed with bis-3-methyl-2-butylborane (disiamylborane), as described at the end of this paper.

In no case was the hydroboration product investigated (*e.g.*, whether it consisted of the mono-, di-, or trialkylborane),[2] the total material always being oxidized directly with alkaline hydrogen peroxide. This oxidation step was generally carried out by addition of 10% aqueous sodium hydroxide to a solution of the alkylborane in tetrahydrofuran, followed by 30% aqueous hydrogen peroxide at 0°. In some early experiments, however, the reaction was performed by addition of 30% aqueous hydrogen peroxide to a solution containing the alkylborane and potassium hydroxide in ethanol, followed by boiling under reflux.

(1) Taken in part from a Ph.D. thesis submitted by M. Nussim to the Hebrew University, Jerusalem, April, 1961.

(2) See H. C. Brown, "Hydroboration," W. A. Benjamin, Inc., New York, N. Y., 1962, and references cited there.

(3) For preliminary communications, see (a) S. Wolfe, M. Nussim, Y. Mazur, and F. Sondheimer, *J. Org. Chem.*, **24**, 1034 (1959); (b) Y. Mazur, M. Nussim, and F. Sondheimer, *Proc. Chem. Soc.*, 314 (1959); (c) M. Nussim and F. Sondheimer, *Chem. Ind.* (London), 100 (1960); (d) F. Sondheimer and M. Nussim, *J. Org. Chem.*, **26**, 630 (1961); (e) M. Nussim, Y. Mazur, and F. Sondheimer, *ibid.*, **29**, 1131 (1964).

(4) F. Sondheimer and S. Wolfe, *Can. J. Chem.*, **37**, 1870 (1959). The lithium aluminum hydride was added to the boron trifluoride, rather than vice versa, to ensure a steady evolution of diborane [see I. Shapiro, H. G. Weiss, M. Schmich, S. Skolnik, and G. B. L. Smith, *J. Am. Chem. Soc.*, **74**, 901 (1952)].

(5) H. C. Brown and P. A. Tierney, *ibid.*, **80**, 1552 (1958).

(6) *Inter alia*, see H. C. Brown and G. Zweifel, *ibid.*, **83**, 2544 (1961).

(7) (a) H. C. Brown and B. C. Subba Rao, *ibid.*, **81**, 6423 (1959); (b) 6428 (1959).

(8) For other methods for avoiding the necessity of generating diborane separately or of using diglyme, see H. C. Brown, K. J. Murray, L. J. Murray, J. A. Snover, and G. Zweifel, *ibid.*, **82**, 4233 (1960).

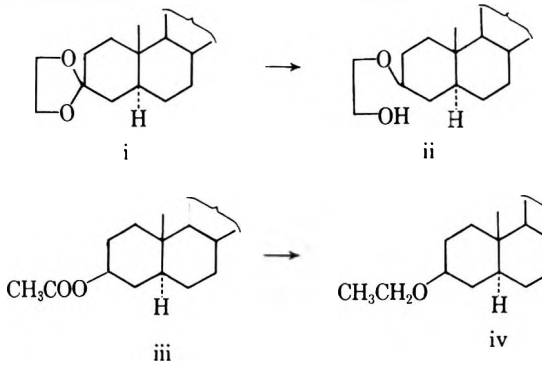
The two oxidation procedures are equally convenient. However the first-mentioned one, unlike the second, caused only slow hydrolysis of 3β-acetoxy steroids, and, therefore, is the method of choice when saponification of esters is to be avoided.

The alcohols obtained by the hydroboration–oxidation sequence were usually isolated by chromatography on alumina. The yields, given to the nearest 5%, are those of materials actually obtained in reasonably pure form. No complete analytical study of the product composition was made in any case, and small amounts of by-products may well have been formed but were not detected.

1,2-Disubstituted Ethylenes.[3d]—All the possible types of steroidal 1,2-disubstituted ethylenes containing the double bond in the normal 5α steroid nucleus, except for ring D ethylenes, were subjected to the hydration reaction. Approximately equal amounts of both possible positionally isomeric alcohols were obtained in all the cases studied, except when bis-3-methyl-2-butylborane was used (following). Attack appeared to occur invariably at the less hindered α side of the steroid nucleus, giving rise to the α alcohols. A clear-cut chromatographic separation between the two isomeric alcohols formed in each case usually could be effected, since one of the products contains an equatorial hydroxyl group and the other an axial hydroxyl group.

5α-Cholest-1-ene (I) on hydration by method a yielded 35% of 5α-cholestan-1α-ol (IIa)[11] and 40% of 5α-cholestan-2α-ol (Va)[12]; 20% of unchanged starting material was recovered. 5α-Cholest-2-ene (IV) either by method a or b afforded 35% of 5α-cholestan-2α-ol (Va) (identical with the previously described compound) and 45% of 5α-cholestan-3α-ol (VIIIa),[13] as well as 10% of unchanged starting material.[14]

(9) This was established by blank experiments. Thus, 3-cycloethylenedioxy-5α-cholestane (i) on being subjected to the reaction conditions of method a yielded 90% of the hydroxy ether (ii).[10] 5α-Cholestan-3β-yl acetate under these conditions was reduced to 3β-ethoxy-5α-cholestane (iv)[10] in 20% yield.



(10) For similar reductions of ketals and esters with lithium aluminum hydride–boron trifluoride and lithium aluminum hydride–aluminum trichloride combinations, see (a) G. R. Pettit and W. J. Bowyer, *J. Org. Chem.*, **25**, 84 (1960); (b) G. R. Pettit and T. R. Kasturi, *ibid.*, **26**, 4553 (1961); (c) E. L. Eliel, V. G. Badding, and M. N. Rerick, *J. Am. Chem. Soc.*, **84**, 2371 (1962).

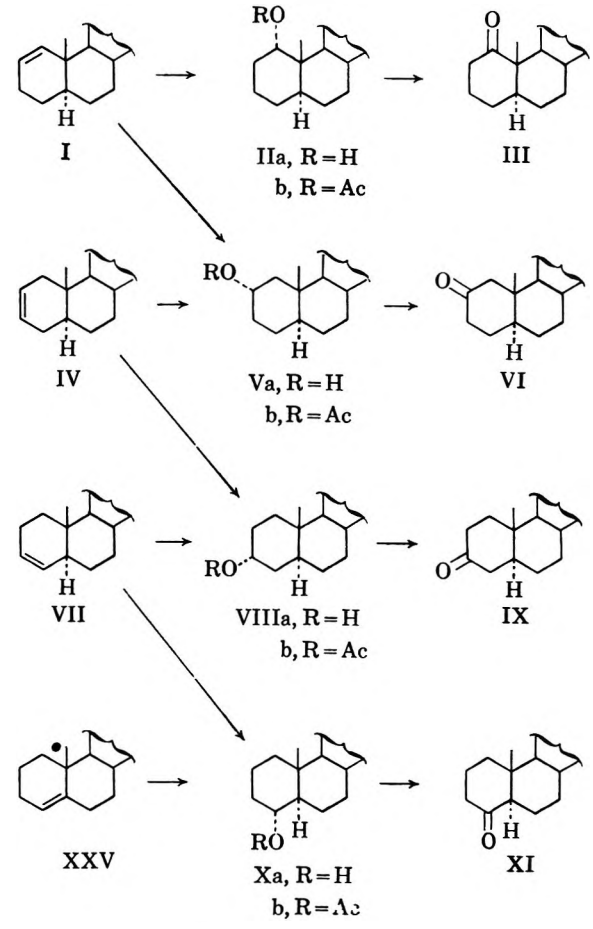
(11) *Inter alia*, P. Striebel and C. Tamm, *Helv. Chim. Acta*, **37**, 1094 (1954).

(12) *Inter alia*, A. Fürst and P. A. Plattner, *ibid.*, **32**, 275 (1949).

(13) *Inter alia*, C. W. Shoppee, *J. Chem. Soc.*, 1138 (1946).

(14) These results[3d] are in agreement with the recent findings of Cross, *et al.*,[15] that the hydration of 17α-methyl-5α-androst-2-en-17β-ol by method b yields 30% of the corresponding 2α-ol and 35% of the 3α-ol. They also agree in essence with the results obtained by Hassner and Pillar[16] from the hydration of Δ²-cholestene by method b; these workers showed that this reaction in addition to the predominantly formed α-ols gives rise to appreciable amounts of the β-ols.

CHART I



5α-Cholest-3-ene (VII) by method a yielded 40% of 5α-cholestan-3α-ol (VIIIa) (identical with the compound obtained before) and 45% of 5α-cholestan-4α-ol (Xa).[17] The structures assigned to the 1α-ol IIa, the 2α-ol Va, the 3α-ol VIIIa, and the 4α-ol Xa follow from the good agreement of the physical properties of the alcohols, as well as of the corresponding acetates IIb, Vb, VIIIb, and Xb, with those reported,[11,12,13,17] while oxidation with chromium trioxide in acetic acid led to 5α-cholestan-1-one (III),[11] 5α-cholestan-2-one (VI),[12] 5α-cholestan-3-one (IX) (identical with an authentic sample), and 5α-cholestan-4-one (XI),[17] respectively. (See Chart I.)

5α-Cholest-6-en-3β-ol (XII) on hydration by method a gave a 55% yield of a mixture apparently consisting of about equal amounts of 5α-cholestane-3β,6α-diol (XIIIa)[18a] and 5α-cholestane-3β,7α-diol (XVa).[17c,18b] The hydration of XII is assumed to have proceeded from the α side, since this appears to be the less hindered side of the molecule.[19] Unfortunately neither the mixture of diols XIIIa and XVa nor the corresponding diacetates XIIIb and XVb could be separated by

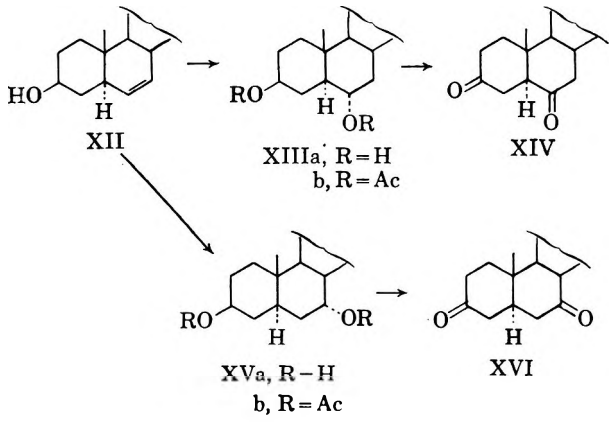
(15) A. D. Cross, J. A. Edwards, and A. Bowers, *J. Med. Chem.*, **5**, 406 (1962); A. D. Cross, J. A. Edwards, J. C. Orr, B. Berköz, L. Cervantes, M. C. Calzada, and A. Bowers, *ibid.*, **6**, 162 (1963).

(16) A. Hassner and C. Pillar, *J. Org. Chem.*, **27**, 2914 (1962).

(17) *Inter alia*, (a) R. Tschesche and A. Hagedorn, *Ber.*, **68**, 2247 (1935); (b) L. Ruzicka, P. A. Plattner, and M. Furrer, *Helv. Chim. Acta*, **27**, 727 (1944); (c) D. H. R. Barton and W. J. Rosenfelder, *J. Chem. Soc.*, 1048 (1951).

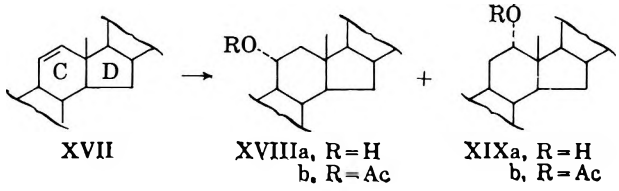
(18) *Inter alia*, (a) P. A. Plattner and W. Lang, *Helv. Chim. Acta*, **27**, 1872 (1944); (b) O. Wintersteiner and M. Moore, *J. Am. Chem. Soc.*, **65**, 1503 (1943).

(19) See D. R. James, R. W. Rees, and C. W. Shoppee, *J. Chem. Soc.*, 1370 (1955).



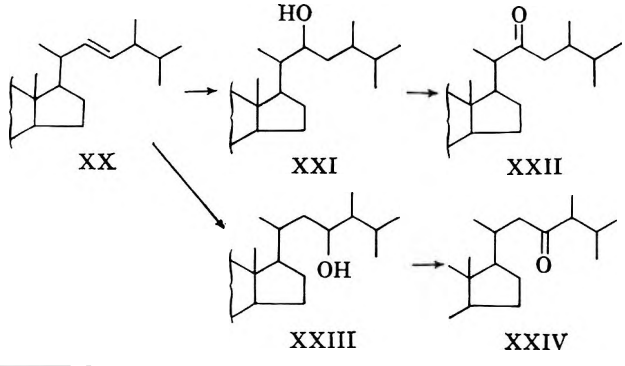
chromatography or by crystallization. Oxidation of the mixed diols XIIIa and XVa with chromium trioxide in acetic acid gave *ca.* a 1:1 mixture of 5α-cholestane-3,6-dione (XIV)[20] and 5α-cholestane-3,7-dione (XVI),[20a] as evidenced by thin layer chromatography (comparison with authentic samples). Small quantities of the pure 3,6-dione XIV as well as of the 3,7-dione XVI could be isolated by fractional crystallization.

5α-25D-Spirost-11-en-3β-ol acetate (XVII) on hydration by method b, followed by saponification and chromatography, afforded 40% of 5α-25D-spirostane-3β,11α-diol (XVIIIa) and 40% of 5α-25D-spirostane-3β,12α-diol (12-epirockogenin) (XIXa), in addition to 10% of unchanged Δ^{11} compound. The 3β,11α-diol



XVIIIa and the 3β,12α-diol XIXa, as well as the derived diacetates XVIIIb and XIXb, agreed well in physical properties with those reported,[21] and were identified by direct comparison with authentic samples.

One example of the hydration of a steroid containing a 1,2-disubstituted double bond in the side chain was investigated. 5α-Ergost-22-en-3β-ol (XX) by method a was converted in 70% yield to what appears to be a mixture of 5α-ergostane-3β,22ξ-diol (XXI) and 5α-ergostane-3β,23ξ-diol (XXIII). This mixture could

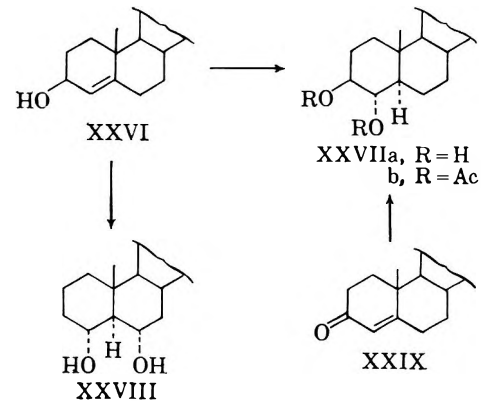


not be resolved by chromatography on alumina, but an apparently pure substance, either XXI or XXIII, was separated by repeated crystallization. That the diols obtained by hydration of XX were positional isomers rather than stereoisomers was shown by the fact that oxidation with chromium trioxide again gave a mixture, presumably of 5α-ergostane-3,22-dione (XXII) and 5α-ergostane-3,23-dione (XXIV).

Trisubstituted Ethylenes.[3a,c]—All the possible types of steroidal trisubstituted ethylenes containing the double bond in the normal 5α steroid nucleus were investigated.

Cholest-4-ene (XXV) on hydration by method a gave 60% of 5α-cholestan-4α-ol (Xa) [identical with that obtained from 5α-cholest-3-ene (VII)], besides 25% of unchanged starting material. By use of method b, the yield of 5α-cholestan-4α-ol (Xa) was only 30%, and 60% of starting material was recovered, despite the fact that a considerable excess of diborane was employed.

Cholest-4-en-3β-ol (XXVI) on hydroboration by a modification of method a, involving addition of ethereal boron trifluoride to a solution of the steroid and lithium aluminum hydride in ether (inverse addition),[4] followed by peroxide oxidation and acetylation, yielded 60% of 5α-cholestane-3β,4α-diol diacetate (XXVIIb). The properties of this diacetate, as well as of the corresponding diol XXVIIa obtained by saponification, agreed well with those reported.[22] Very similar results were obtained when XXVI was hydrated by method b.



However cholest-4-en-3β-ol (XXVI) on hydration by the unmodified method a furnished 50% of 5α-cholestane-4α,6α-diol (XXVIII) as sole crystalline product. This diol is obtained in about the same yield by the hydration of cholesta-3,5-diene (see following paper[*]), and the latter diene is clearly formed first in the conversion of XXVI to XXVIII through dehydration by means of the boron trifluoride prior to addition of the lithium aluminum hydride.

Cholest-4-en-3-one (XXIX) by either method a or b yielded, after acetylation, *ca.* 60% of 5α-cholestane-3β,4α-diol diacetate (XXVIIb), identical with that obtained from the Δ^4-3β-ol XXVI.[23] This reaction involves reduction of the 3-ketone group as well as hydration of the Δ^4 double bond.

(20) *Inter alia*, (a) D. H. R. Barton and J. D. Cox, *J. Chem. Soc.*, 783 (1948); (b) P. A. Plattner, A. Fürst, F. Koller, and H. H. Kuhn, *Helv. Chim. Acta*, **37**, 258 (1954).

(21) *Inter alia*, (a) C. Djerassi, E. Batres, M. Velasco, and G. Rosenkranz *J. Am. Chem. Soc.*, **74**, 1712 (1952); (b) R. Hirschmann, C. S. Snoddy, and N. L. Wendler, *ibid.*, **74**, 2693 (1952).

(22) L. F. Fieser and R. Stevenson, *ibid.*, **76**, 1728 (1954).

(23) The conversion of both cholest-4-en-3β-ol (XXVI) and cholest-4-en-3-one (XXIX) to 5α-cholestane-3β,4α-diol (XXVIIa) by method b has been carried out independently by L. Caglioti and G. Cainelli, *Atti accad. nazl. Lincei Rend. Classe sci. fis. mat. e nat.*, [8]**29**, 555 (1960).

With cholest-5-ene derivatives, it was found that the direction of attack of the double bond depends on the nature of the substituent at C-3. Cholest-5-ene (XXX) by method a produced 75% of 5α-cholestan-6α-ol (XXXIa), besides 20% of unchanged starting material. By method b the yield of the 6α-ol XXXIa was only 40%, 45% of the Δ^5-ene XXX being recovered. In neither case could any isomeric alcohol be detected. The resulting 5α-cholestan-6α-ol (XXXIa) and the corresponding acetate XXXIb possessed physical properties in good agreement with those reported.[24,25]

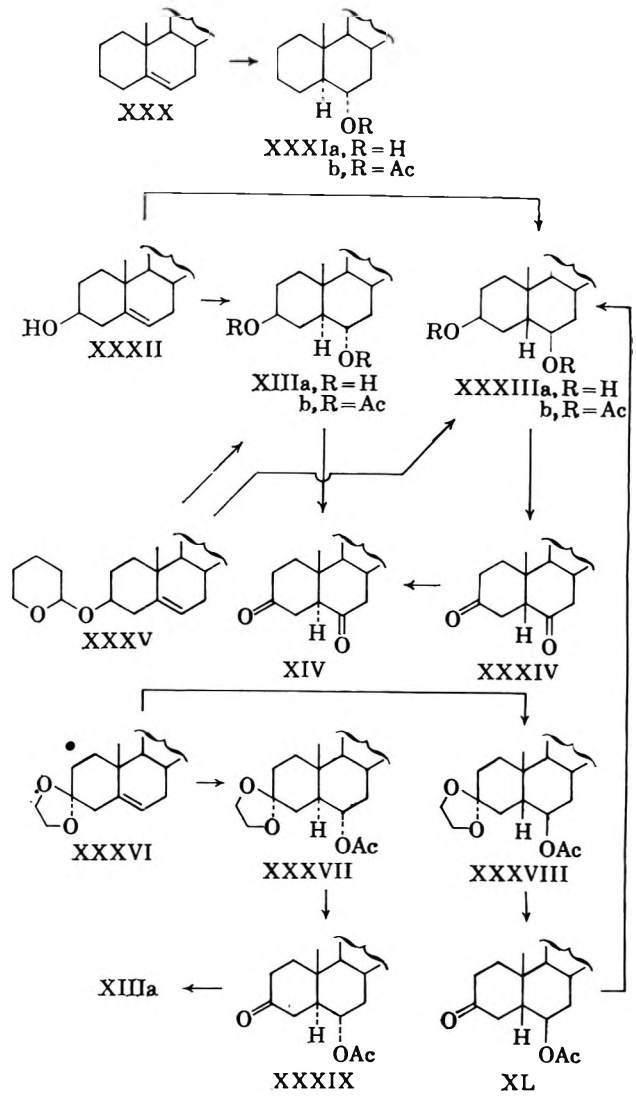
On the other hand, cholesterol (XXXII) on hydration by method a or b yielded, after acetylation, 70% of 5α-cholestane-3β,6α-diol diacetate (XIIIb), as well as *ca.* 20% of 5β-cholestane-3β,6β-diol diacetate (XXXIIIb) (besides 10% of unchanged cholesteryl acetate).[26] Saponification of the diacetates XIIIb and XXXIIIb led to the corresponding diols XIIIa and XXXIIIa, respectively. The structures assigned to these substances follow from the good correspondence of the physical properties with those reported.[18a,29] Moreover oxidation of the diols XIIIa and XXXIIIa with chromium trioxide in acetic acid led to 5α-cholestane-3,6-dione (XIV)[20] and 5β-cholestane-3,6-dione (XXXIV),[29] respectively. The latter diketone could be epimerized to the former by adsorption on basic alumina. (See Chart II.)

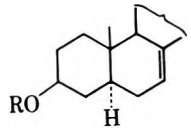
Cholesterol 3-(2′-tetrahydropyranyl) ether (XXXV) on hydration by method a, followed by acid treatment and acetylation, produced 45% of the 3β,6α-diacetate XIIIb and 35% of the 3β,6β-diacetate XXXIIIb, identical with the substances obtained previously.

3-Cycloethylenedioxycholest-5-ene (XXXVI) on hydration by method b and subsequent acetylation gave 95% of an apparently pure substance, which in view of further transformations must be *ca.* a 1:2 mixture of 3-cycloethylenedioxy-5α-cholestan-6α-ol acetate (XXXVII) and 3-cycloethylenedioxy-5β-cholestan-6β-ol acetate (XXXVIII).[30] Removal of ketal groupings by means of boiling aqueous acetic acid led to a mixture which by chromatography now could be separated, affording both 6α-acetoxy-5α-cholestan-3-one (XXXIX) and 6β-acetoxy-5β-cholestan-3-one (XL) in 30% and 60% yields (based on the Δ^5-ketal XXXVI), respectively. The structures of the 6-acetoxy-3-ketones XXXIX and XL follow from the fact that lithium aluminum hydride reduction yielded 5α-cholestane-3β,6α-diol (XIIIa) and 5β-cholestane-3β,6β-diol (XXXIIIa), respectively. Both of these diols, as well as the derived diacetates XIIIb and XXXIIIb, proved to be identical with the corresponding substances derived from cholesterol. Moreover the physical properties of the 6β-acetoxy 3-ketone XL agreed well with those reported.[31] The fact that lithium aluminum hydride reduction of the keto group in this acetoxy ketone XL led to the axial 3β-ol was unexpected and must be due to the presence of the 6β-acetoxy group, since the corresponding reduction of 5β-cholestan-3-one leads mainly to the equatorial 3α-ol.[32] The finding that hydroboration of the ketal XXXVI proceeds mainly from the β side is understandable in view of the presence of an axial 3α-oxygen substituent in this substance.

Attempted hydration of 5α-cholest-7-en-3β-ol (XLIa) by method a led to an 80% recovery of starting material, as well as 20% of an unidentified oil. Method b gave back starting material quantitatively. Similar results were obtained with 5α-ergosten-7-en-3β-ol (type XLIa) using method a, and with 5α-25D-spirost-

CHART II





(24) *Inter alia*, R. Tschesche, *Ber.*, **65**, 1842 (1932).

(25) *Inter alia*, C. W. Shoppee, *et al.*, *J. Chem. Soc.*, 3361 (1952).

(26) W. J. Wechter [*Chem. Ind.* (London), 294 (1959)] independently has performed the reaction with cholesterol, using method b, and obtained results similar to ours. Moreover the hydroboration of certain Δ^5-3β-acetoxy steroids[27] and Δ^5-3β-dimethylamino steroids[28] have been described; the products were oxidized directly with sodium dichromate or chromium trioxide, whereby the corresponding 5α-6-keto compounds were obtained.

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

(28) R. Pappo, *J. Am. Chem. Soc.*, **81**, 1010 (1959).

(29) V. Prelog and E. Tagmann, *Helv. Chim. Acta*, **27**, 1880 (1944).

(30) The hydration of 3,20-biscycloethylenedioxypregn-5-ene (type XXXVI) through hydroboration has been described by Bagli, *et al.*[27] The steric course of addition was not determined, the product being oxidized at C-6 and then treated with sodium methoxide, whereby the 5α-6-ketone was obtained.

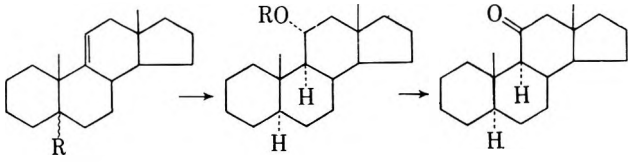
(31) D. N. Jones, J. E. Lewis, C. W. Shoppee, and G. H. R. Summers, *J. Chem. Soc.*, 2876 (1955).

(32) C. W. Shoppee and G. H. R. Summers, *ibid.*, 687 (1950).

7-en-3β-ol acetate (type XLIb) using method b. This lack of reactivity of Δ^7 steroids is not surprising, since this type of ethylene is known to be inert; *e.g.*, it cannot be hydrogenated without prior rearrangement.[33a]

We turn now to the hydration of $\Delta^{9(11)}$ steroids. It has been reported by Wechter[26] that 3,20-biscycloethylenedioxy-5β-pregn-9(11)-ene (XLVb) is inert to hydroboration. We have found similarly that 5β-androst-9(11)-ene (XLIIb)[34] on attempted hydration by method a or b was recovered completely unchanged. This lack of reactivity must be due to the A/B-*cis* junction in compounds XLIIb and XLVb, resulting in hindrance of the $\Delta^{9(11)}$ double bond from the α as well as from the β side. On the other hand, 5α-$\Delta^{9(11)}$ steroids are not appreciably hindered from the α side, and such compounds in fact have been found by us to undergo smooth hydration to give the expected 11α-hydroxy steroids with the normal (α) hydrogen configuration at C-9. This represents a useful new method for introducing an 11-oxygen group into steroids.

5α-Androst-9(11)-ene (XLIIa)[34] on hydration by method a gave over 90% of 5α-androstan-11α-ol (XLIIIa). The structure of this product, which could not be crystallized, follows from the facts that it could be acetylated to XLIIIb on treatment with acetic



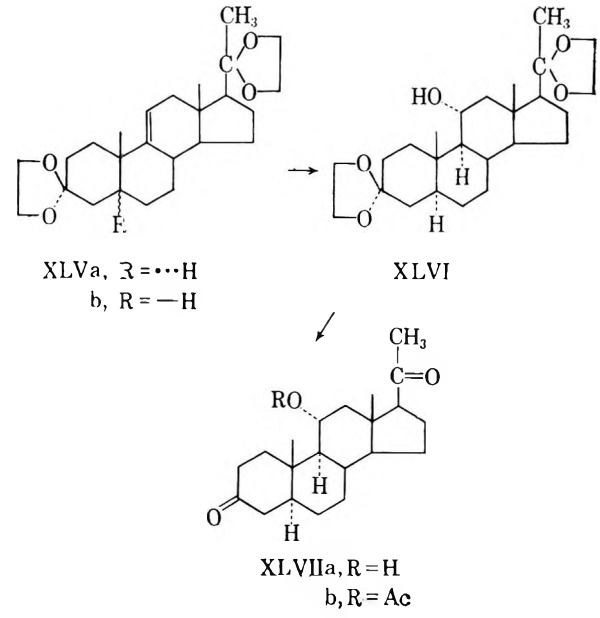
XLIIa, R = ···H
b, R = —H

XLIIIa, R = H
b, R = Ac

XLIV

anhydride in pyridine, and that oxidation with chromium trioxide in acetic acid led to 5α-androstan-11-one-(XLIV), identical with an authentic sample.[35] Hydration of XLIIa by method b furnished the 11α-ol XLIIIa in only 55% yield, and 40% of starting material was recovered.

XLVa, 3,20-biscycloethylenedioxy-5α-pregn-9(11)-ene,[34] which is the 5α isomer of the 5β compound XLVb that had been found to be unreactive,[26] on hydration by method b yielded 60% of 3,20-biscycloethylenedioxy-5α-pregnan-11α-ol (XLVI) besides 30% of unchanged starting material. The structure of the amorphous 11α-hydroxy bisketal XLVI is based on the fact that removal of the ketal groupings with aqueous sulfuric acid led in 90% yield to 11α-hydroxy-5α-pregnane-3,20-dione (XLVIIa). The physical properties of this latter substance, as well as of the derived acetate XLVIIb, agreed well with those reported,[36] and oxidation of the hydroxydione XLVIIa with chromium trioxide in acetic acid led to 5α-pregnane-3,11,20-trione,[37] identified by direct comparison with an authentic sample.

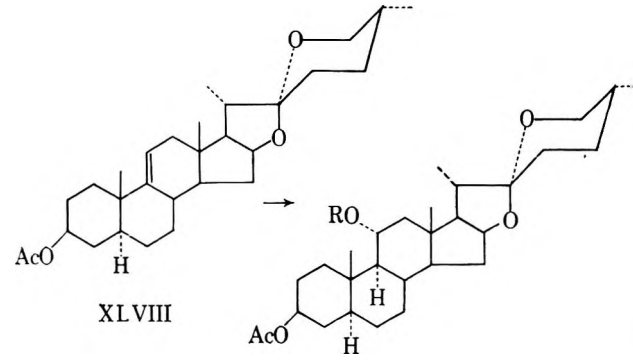


XLVa, R = ···H
b, R = —H

XLVI

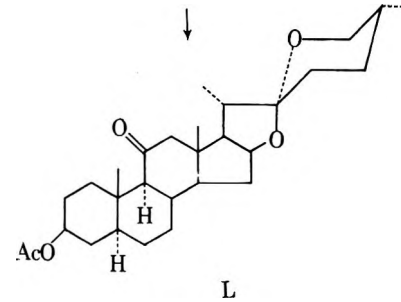
XLVIIa, R = H
b, R = Ac

A practical example of the utility of the hydration of 5α-$\Delta^{9(11)}$ steroids is the hydration of 5α-25D-spirost-9(11)-en-3β-ol acetate (XLVIII),[38] which by method b and subsequent acetylation gave 60% of 5α-25D-spirostane-3β,11α-diol diacetate (ILb), as well as 30% of recovered starting material. The physical properties



XLVIII

ILa, R = H
b, R = Ac



L

of the diacetate ILb, as well as of the corresponding 3β,11α-diol obtained by saponification, agreed well with those reported,[21a] and these substances proved to be identical with the corresponding ones (XVIIIb and XVIIIa) obtained by the previously mentioned

(33) See L. F. Fieser and M. Fieser, "Steroids," 3rd Ed., Reinhold Publishing Corp., New York, N. Y., 1959: (a) p. 260; (b) pp. 667-671.

(34) The preparation of this previously unknown compound is described in Experimental.

(35) F. Sondheimer, E. Batres, and G. Rosenkranz, *J. Org. Chem.*, **22**, 1090 (1957).

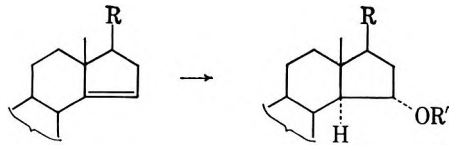
(36) *Inter alia*, O. Mancera, J. Romo, F. Sondheimer, G. Rosenkranz, and C. Djerassi, *ibid.*, **17**, 1066 (1952).

(37) *Inter alia*, (a) M. Steiger and T. Reichstein, *Helv. Chim. Acta*, **21**, 161 (1938); (b) C. Djerassi, O. Mancera, J. Romo, and G. Rosenkranz, *J. Am. Chem. Soc.*, **75**, 3505 (1953).

(38) Prepared from hecogenin acetate by selenium dioxide dehydrogenation [A. Bowers, E. Denot, M. B. Sanchez, F. Neumann, and C. Djerassi, *J. Chem. Soc.*, 1859 (1961)], and subsequent removal of the 12-ketone group by Wolff–Kishner reduction [C. Djerassi, H. Martinez, and G. Rosenkranz, *J. Org. Chem.*, **16**, 1278 (1951)], as well as *via* the ethylenethioketal [(R. Hirschmann, C. S. Snoddy, and N. L. Wendler, *J. Am. Chem. Soc.*, **75**, 3252 (1953)].

hydration of 5α-25D-spirost-11-en-3β-ol acetate (XVII). In another experiment the total hydration product derived from the $\Delta^{9(11)}$-ethylene XLVIII was oxidized with chromium trioxide in acetic acid, whereby 50% of 3β-acetoxy-5α-25D-spirostan-11-one (L) (identical with an authentic sample)[21a] besides 35% of recovered starting material was obtained. This last experiment demonstrates that a 3β-acetoxy grouping can be kept intact in the hydration reaction when method b is used. The $\Delta^{9(11)}$ compound XLVIII is readily prepared in two or three steps from hecogenin acetate,[38] and its conversion to the 11-ketone L by the present method constitutes a short and convenient way for shifting the 12-carbonyl group to the 11-position, a transformation of importance for the production of hormones of the cortisone type.[33b]

5α-Cholest-14-en-3β-ol (LIa) on hydration by method a yielded 75% of 5α-cholestane-3β,15α-diol (LIIa), converted by acetylation to the diacetate LIIb. That hydration of the Δ^{14}-ene LIa, like catalytic hydrogena-



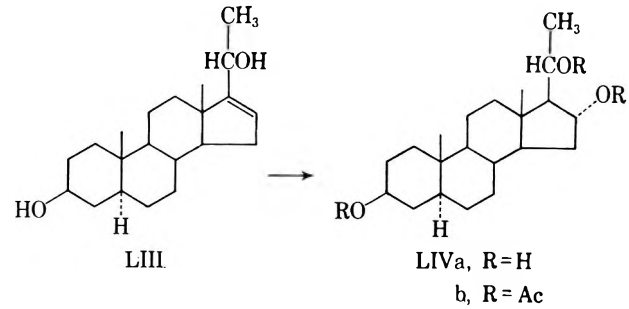
LIa, R = C_8H_{17}
b, R = OH

LIIa, R = C_8H_{17}, R′ = H
b, R = C_8H_{17}, R′ = Ac
c, R = OH, R′ = H

tion,[33a] has proceeded from the α side to produce the 3β,15α-diol LIIa follows from the fact that the physical properties of the diacetate LIIb agreed reasonably well with those of a substance considered most probable to possess this structure,[39] as well as from a consideration of molecular rotation ([M]D) differences. Thus, the shift in [M]D on passing from 5α-cholestan-3β-ol to the diol LIIa is +184, in accord with the positive value (*ca.* +100) observed for the shift in passing from a pregnan-20-one to the corresponding 15α-ol, and not with the negative value (*ca.* −100) for passing to the 15β-ol.[40]

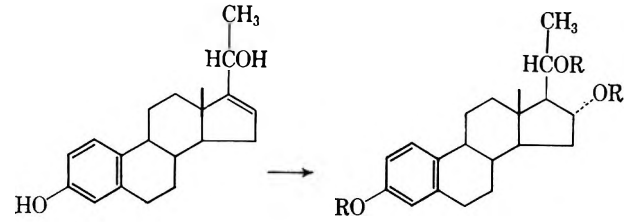
Similarly, hydration of 5α-androst-14-ene-3β,17β-diol (LIb) by method a gave 70% of 5α-androstane-3β,15α,17β-triol (LIIc). The shift in [M]D on passing from 5α-androstane-3β,17β-diol to this triol is +133, again confirming the 15α configuration of the new hydroxyl group.[43]

5α-Pregn-16-ene-3β,20α-diol (LIII)[34] was hydrated by method a, whereby 5α-pregnane-3β,16α,20α-triol (LIVa)[44] was obtained in 80% yield. This represents a convenient synthetic route to this urinary constit-



LIII

LIVa, R = H
b, R = Ac

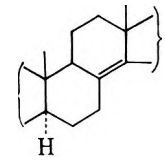


LV

LVIa, R = H
b, R = Ac

uent.[44b] The physical properties of the triol LIVa, as well as those of its triacetate LIVb, agreed reasonably well with those reported.[44] In similar fashion, 19-norpregna-1,3,5(10),16-tetraene-3,20α-diol (LV)[34] on hydration by method a was converted in 90% yield to a triol, by analogy assigned the structure of 19-norpregna-1,3,5(10)-triene-3,16α,20α-triol (LVIa); acetylation gave the corresponding 3,16,20-triacetate LVIb.

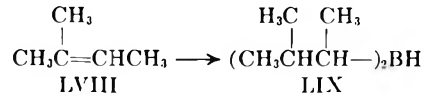
Tetrasubstituted Ethylenes.—The only steroidal tetrasubstituted ethylene investigated was 5α-cholest-8(14)-en-3β-ol (LVII), which on attempted hydration either by method a or b was recovered completely



LVII

unchanged. This result was not unexpected in view of the known lack of reactivity of steroidal $\Delta^{8(14)}$-ethylenes, *e.g.*, towards catalytic hydrogenation.[33a]

Hydroboration with Bis(3-methyl-2-butyl)borane (Disiamylborane) (LIX).[3d]—It has been shown by Brown and Zweifel[2,45] that the hydroboration of simple olefins with the bulky bis(3-methyl-2-butyl)borane (disiamylborane) [LIX, obtained by hydroboration of 2-methyl-2-butene (LVIII)] results in greater steric



LVIII LIX

control than if diborane is used. Since the previously described hydration experiments with steroidal 1,2-disubstituted ethylenes had given rise to comparable amounts of both possible positionally isomeric alcohols, it was decided to investigate with certain of these ethylenes whether use of disiamylborane would change the ratio of the products.

(39) D. H. R. Barton and G. F. Laws, *J. Chem. Soc.*, 52 (1954); W. Klyne and W. M. Stokes, *ibid.*, 1979 (1954). Unfortunately no sample was available for direct comparison.

(40) These values are based on the fact that the shift in [M]D on passing from progesterone and desoxycorticosterone to the corresponding 15α-hydroxy derivative is +117[41] and +92,[42] respectively, while the shift associated with passage to the corresponding 15β derivative is −108[41] and −95,[42] respectively.

(41) J. Fried, R. W. Thoma, D. Perlman, J. E. Herz, and A. Borman, *Recent Progr. Hormone Res.*, **11**, 149 (1955).

(42) C. Meystre, E. Vischer, and A. Wettstein, *Helv. Chim. Acta*, **38**, 381 (1955); for reassignment of configuration, see A. Wettstein, *Experientia*, **11**, 465 (1955).

(43) The corresponding shift in passing from testosterone to 15α-hydroxytestosterone is +100 [A. Gubler and C. Tamm, *Helv. Chim. Acta*, **41**, 301 (1958)].

(44) (a) H. Hirschmann and F. B. Hirschmann, *J. Biol. Chem.*, **184**, 259 (1950); (b) S. Lieberman, B. Praetz, P. Humphries, and K. Dobriner, *ibid.*, **204**, 491 (1953).

(45) H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, **82**, 3222, 3223 (1960); **83**, 1241, 2544 (1961).

Disiamylborane (LIX) was prepared by hydroboration of 2-methyl-2-butene (LVIII)[46] through addition of ethereal lithium aluminum hydride to an ether solution of the ethylene LVIII and boron trifluoride,[3a,4] as well as through addition of boron trifluoride etherate to a solution of the ethylene LVIII and sodium borohydride in diglyme.[45] 5α-Cholest-1-ene (I) was allowed to react with this reagent, prepared by either method, and the product was oxidized with alkaline hydrogen peroxide in the usual way. Chromatography then yielded 75% of 5α-cholestan-2α-ol (Va), the less hindered isomer, and no detectable amount of 5α-cholestan-1α-ol (IIa). On the other hand, no significant change from the previous results was observed when 5α-cholest-2-ene (IV) and 5α-cholest-3-ene (VII) were hydrated under these conditions, the former giving 35% of 5α-cholestan-2α-ol (Va) and 45% of 5α-cholestan-3α-ol (VIIIa), while the latter gave 45% of 5α-cholestan-3α-ol (VIIIa) and 35% of 5α-cholestan-4α-ol (Xa). These results are in keeping with the fact that the two possible sites of attack in the Δ^1 compound differ sterically to a greater extent than in the Δ^2 or the Δ^3 compound.

Experimental[48]

Hydroboration Procedures. i. **Method a.**—The following is a typical example of the use of method a. Boron trifluoride etherate (5 g., 35.2 mmoles) was added to a solution of 1 g. of the steroidal olefin in 40 cc. of dry ether (or tetrahydrofuran where indicated). A solution of 0.6 g. (15.8 mmoles) of lithium aluminum hydride in 30 cc. of ether was then added dropwise during 1 hr. under nitrogen with stirring and continuous cooling in ice–water. The ice bath was removed and the mixture was stirred for 1 hr. Water was added carefully, and the organic layer, after being washed with sodium bicarbonate solution and water, was dried over sodium sulfate and evaporated.

ii. **Method b.**—The following is a typical example of the use of method b. Diborane was generated by adding a solution of 0.6 g. (15.9 mmoles) of sodium borohydride in 30 cc. of diglyme to a solution of 5 g. (35.2 mmoles) of boron trifluoride etherate in 20 cc. of diglyme, in the type of apparatus described by Brown and Subba Rao.[7b] The gas was passed into a solution of 1 g. of the steroidal olefin in 40 cc. of dry tetrahydrofuran during *ca.* 1 hr. by means of a slow stream of nitrogen. After an additional hour at room temperature, *ca.* 5 cc. of water was added to destroy excess diborane, and the mixture was oxidized directly.

Oxidation of Organoboranes.—Unless stated otherwise, all oxidations were carried out by the following procedure. Aqueous sodium hydroxide (20 cc. of a 10% solution) was added to a solution of the organoborane (derived from 1 g. of olefin) in 40 cc. of tetrahydrofuran. The solution was then cooled in ice–water, and 15 cc. of 30% aqueous hydrogen peroxide was added dropwise with stirring and continued cooling. The mixture was stirred for 1 hr. at 0° and diluted with water and ether; the organic layer was washed with sodium bisulfite solution and water. The extract was then dried over sodium sulfate and evaporated.

Blank Experiments (Carried Out by Dr. E. Levy). a. 3-Cycloethylenedioxy-5α-cholestane (i).—This ketal (2.15 g., 5 mmoles) was subjected to the reaction conditions of method a, and the product was chromatographed on 100 g. of Alcoa activated alumina (grade F-20). Elution with benzene–ether (1:1) gave 1.95 g. (90%) of 3β-(β-hydroxyethoxy)-5α-cholestane (ii), m.p. 144–147°. Crystallization from hexane yielded 1.60 g., m.p. 148–149°, $[\alpha]_D$ +20°; strong hydroxyl band in the infrared (potassium bromide).

Anal. Calcd. for $C_{29}H_{52}O_2$: C, 80.49; H, 12.11. Found C, 80.80; H, 11.98.

b. 5α-Cholestan-3β-yl Acetate (iii).—Cholestanyl acetate (4.3 g.) was subjected to the reaction conditions of method a, and the product was chromatographed on 200 g. of Alcoa activated alumina (grade F-20). Elution with pentane–benzene (4:1) and crystallization from ether–methanol yielded 0.83 g. (20%) of 3β-ethoxy-5α-cholestane (iv), m.p. 80–81°, identified by direct comparison with an authentic sample (m.p. 81–82°).[10b] Elution with benzene–ether (9:1) yielded 2.82 g. (73%) of 5α-cholestan-3β-ol, m.p. 140–142°.

Hydration of 5α-Cholest-1-ene (I).—5α-Cholest-1-ene (I) was prepared according to Henbest and Wilson[49]; after regeneration from the dibromide, it showed m.p. 69–70°, $[\alpha]_D$ +14°. Hydration of 1 g. of this olefin was carried out by method a, and the product was chromatographed on 35 g. of alumina. Elution with pentane gave 210 mg. (21%) of unchanged starting material. Elution with pentane–benzene (1:1) yielded 345 mg. (33%) of 5α-cholestan-1α-ol (IIa), m.p. 97–100°, which after crystallization from acetone–methanol showed m.p. 103–104°, $[\alpha]_D$ +36°; lit.[11] m.p. 102–103°, $[\alpha]_D$ +35°. The corresponding acetate IIb was obtained as a colorless oil, $[\alpha]_D$ +40°; lit.[11] $[\alpha]_D$ +39°, oil; lit.[49] m.p. 73–75°, $[\alpha]_D$ +43°. Elution with benzene gave 395 mg. (38%) of 5α-cholestan-2α-ol (Va), m.p. 175–178°, which after crystallization from methanol showed m.p. 181–182°, $[\alpha]_D$ +28°; lit.[12] m.p. 181°, $[\alpha]_D$ +27°. The corresponding acetate Vb on crystallization from methanol exhibited m.p. 89–91°, $[\alpha]_D$ 0°; lit.[12] m.p. 90°, $[\alpha]_D$ −1°.

Oxidation of the 1α-ol IIa (60 mg.) with chromium trioxide in acetic acid for 1 hr. at room temperature, followed by crystallization from methanol, gave 41 mg. of 5α-cholestan-1-one (III), m.p. 86–88°, $[\alpha]_D$ +114°; lit.[49] m.p. 87–89°, $[\alpha]_D$ +114°. Similar oxidation of the 2α-ol Va (100 mg.) and crystallization from methanol led to 70 mg. of 5α-cholestan-2-one (VI), m.p. 129–130°, $[\alpha]_D$ +50°; lit.[12] m.p. 130°, $[\alpha]_D$ +51°. The corresponding oxime on crystallization from methanol exhibited m.p. 197–198°, $[\alpha]_D$ +12°; lit.[12] m.p. 200°, $[\alpha]_D$ +14°.

Hydration of 5α-Cholest-2-ene (IV).—5α-Cholest-2-ene (IV) was prepared according to Fieser and Dominguez[50]; after regeneration from the dibromide, it showed m.p. 74–75°, $[\alpha]_D$ +67°. Hydration of 1 g. of this olefin by method a, followed by chromatography on 30 g. of alumina, yielded three different substances. The first, eluted with pentane, proved to be unchanged starting material (120 mg., 12%). The second, eluted with pentane–benzene (1:1), was 5α-cholestan-3α-ol (VIIIa) (450 mg., 43%), m.p. 185–187°, which after crystallization from methanol showed m.p. 187–188°, $[\alpha]_D$ +24°, no precipitate with digitonin; lit.[13] m.p. 186–187°, $[\alpha]_D$ +26°. The corresponding acetate VIIIb after crystallization from methanol exhibited m.p. 97–98°, $[\alpha]_D$ +28°; lit.[13] m.p. 94–95°, $[\alpha]_D$ +30°. The third substance, eluted with benzene, was 5α-cholestan-2α-ol (Va) (350 mg., 33%), m.p. 176–180°, which on crystallization from methanol showed m.p. 181–183°; it was identical with the previously described sample derived from 5α-cholest-1-ene (I).

Oxidation of the 3α-ol VIIIa (100 mg.) with chromium trioxide in acetic acid and crystallization of the product from methanol gave 60 mg. of 5α-cholestan-3-one (IX), m.p. 127–128°, $[\alpha]_D$ +41°. This ketone was identified by direct comparison with an authentic sample (m.p. 128–129°, $[\alpha]_D$ +42°).

Hydration of the Δ^2-ene IV by method b gave almost identical results.

5α-Cholest-3-ene (VII).—This olefin previously has been prepared from cholest-4-en-3-one by Wolff–Kishner reduction.[51]

(46) This olefin was obtained from *t*-amyl alcohol by dehydration with aqueous sulfuric acid to give a mixture consisting of 87% of 2-methyl-2-butene and 13% of 2-methyl-1-butene.[47] The latter olefin was then removed through hydroboration of part of this mixture with sodium borohydride–boron trifluoride to give mainly disiamylborane (LIX), followed by addition of the rest of the olefin mixture, whereby the 2-methyl-1-butene component was attacked preferentially (see second reference in ref. 45).

(47) F. C. Whitmore, C. S. Rowland, S. N. Wrenn, and G. W. Kilmer, *J. Am. Chem. Soc.*, **64**, 2970 (1942).

(48) Melting points are uncorrected. All chromatograms were carried out with Merck "acid-washed" alumina unless otherwise stated. Rotations were determined at room temperature in chloroform solution, unless specified otherwise. Ultraviolet spectra were measured in 95% ethanol solution on a Unicam Model S.P. 500 spectrophotometer. Infrared spectra were determined in chloroform solution (except those marked "KBr", which were measured as potassium bromide pellets) with a Perkin-Elmer Infracord recording spectrophotometer with sodium chloride optics. Analyses were carried out in our microanalytical department under the direction first of Mr. Erich Meier and recently of Mr. Raoul Heller. All acetylations were performed by means of acetic anhydride in pyridine at room temperature for 16 hr.

(49) H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 3289 (1956).

(50) L. F. Fieser and X. A. Dominguez, *J. Am. Chem. Soc.*, **75**, 1704 (1953).

(51) G. Lardelli and O. Jeger, *Helv. Chim. Acta*, **32**, 1817 (1949).

We have carried out this reduction under the Huang-Minlon conditions.[52] Careful chromatography of the product on alumina followed by repeated crystallization from ether–methanol yielded 25% of 5α-cholest-3-ene (VII), m.p. 71–72°, [α]D +55°; lit.[17c] m.p. 72–72.5°, [α]D +57°. The melting point was depressed on admixture with 5α-cholest-2-ene (IV), as well as with cholest-4-ene (XXV). Hydrogenation in acetic acid over platinum smoothly gave 5α-cholestane, m.p. 78–79°, identical with an authentic sample (m.p. 79–80°) by mixture melting point determination and infrared comparison.

Hydration of 5α-Cholest-3-ene (VII).—Hydration of 1 g. of the Δ³-ene VII was carried out by method a, and the product was chromatographed on 30 g. of alumina. Elution with pentane–benzene (1:1) furnished 400 mg. (38%) of 5α-cholestan-3α-ol (VIIIa), m.p. 187–188°, [α]D +24°, identical with the previously described sample derived from 5α-cholest-2-ene (IV). Elution with pentane–benzene (1:4) afforded 460 mg. (44%) of 5α-cholestan-4α-ol (Xa), m.p. 182–185°, which after crystallization from ether–methanol showed m.p. 188–189°, [α]D +3°; lit.[17a] m.p. 189°, [α]D +4°. The corresponding acetate Xb after crystallization from methanol exhibited m.p. 110–112°, [α]D +15°; lit.[17b] m.p. 112.5–113°, [α]D +16°.

Oxidation of the 4α-ol Xa (100 mg.) with chromium trioxide in acetic acid, followed by crystallization from methanol, led to 65 mg. of 5α-cholestan-4-one (XI), m.p. 99–100°, [α]D +30°; lit.[17b] m.p. 99–99.5°, [α]D +30°.

Hydration of 5α-cholest-6-en-3β-ol (XII) (Experiment Carried Out by Dr. E. Levy).—5α-Cholest-6-en-3β-ol (XII) was prepared by the hydroboration of 7-dehydrocholesterol, as described in the following paper.[3e] Hydration of 250 mg. of this olefin was carried out by method a, and the product was chromatographed on 15 g. of Alcoa activated alumina (grade F-20). Elution with ether–chloroform (1:1) yielded 150 mg. (57%) of a crystalline material, m.p. 130–135°, [α]D +24°. The value of the optical rotation suggests this to be *ca.* a 1:1 mixture of 5α-cholestane-3β,6α-diol (XIIIa) (lit.[18a] m.p. 216–217°, [α]D +38°) and of the 3β,7α-diol XVa (lit.[18b] m.p. 152–153°, [α]D +8°; lit.[17c] m.p. 149–150°, [α]D +12°). Recrystallization or rechromatography of this diol mixture did not lead to a pure substance nor could the corresponding diacetates XIIIb and XVb be separated.

The diol mixture (150 mg.) was oxidized with 150 mg. of chromium trioxide in 40 cc. of 90% acetic acid for 16 hr. at room temperature. Isolation with ether led to a crystalline residue, which was chromatographed on 10 g. of Alcoa activated alumina (grade F-20). Elution with pentane–ether (1:1) gave 110 mg. of *ca.* a 1:1 mixture of 5α-cholestane-3,6-dione (XIV) and 5α-cholestane-3,7-dione (XVI), as evidenced by the fact that thin layer chromatography (development with 2,4-dinitrophenylhydrazine solution) revealed two substances to be present in about equal amounts, which were shown to be the diketones XIV and XVI through chromatographic comparison with the respective authentic samples.[20] Several crystallizations of the diketone mixture from ether–pentane gave 24 mg. of the 3,7-dione XVI, m.p. 187–188°, while repeated crystallizations of the mother liquors from methanol afforded 12 mg. of the 3,6-dione XIV, m.p. 171–172°. The two diketones were identified by direct comparison with the authentic samples (m.p. 189–190° and 172–173°, respectively).

5α-25D-Spirost-11-en-3β-ol Acetate (XVII).—Hecogenin acetate was successively brominated to 3β-acetoxy-11α,23ξ-dibromo-5α-25D-spirostan-12-one, reduced with lithium aluminum hydride to 11α,23ξ-dibromo-5α-25D-spirostane-3β,12ξ-diol, and acetylated to the corresponding 3,12-diacetate, as described by Cornforth, *et al.*[53] A solution of the last-mentioned diacetate (1.7 g.) in 60 cc. of glacial acetic acid was heated to boiling, 15 g. of zinc powder was added in several portions, and the mixture was then boiled under reflux for 4 hr. The mixture was filtered, evaporated under reduced pressure, and diluted with water. Extraction with ether led to 1.2 g. of product, m.p. 195–200°, negative Beilstein test, which was chromatographed on 30 g. of alumina. Elution with pentane–benzene (1:1), followed by crystallization from acetone, yielded 0.82 g. of 5α-25D-spirost-11-en-3β-ol acetate (XVII), m.p. 207–210°, [α]D −45°; lit.[54] m.p. 206–210°, [α]D −44°.[55]

Anal. Calcd. for $C_{29}H_{44}O_4$: C, 76.27; H, 9.71. Found: C, 76.37; H, 9.77.

Hydration of 5α-25D-Spirost-11-en-3β-ol Acetate (XVII).—The Δ¹¹-ene XVII (500 mg.) was hydrated by method b and then saponified through 2-hr. boiling with 60 cc. of 3% methanolic potassium hydroxide. The product was chromatographed on 20 g. of alumina. Elution with benzene–ether (9:1) afforded 45 mg. (10%) of unchanged 5α-25D-spirost-11-en-3β-ol, which after crystallization from acetone showed m.p. 198–200°, [α]D −38°; lit.[54] m.p. 193–195°, α]D −36°. Elution with ether gave 200 mg. (42%) of 5α-25D-spirostane-3β,11α-diol (XVIIIa), m.p. 213–216°, which after crystallization from acetone exhibited m.p. 216–218°, [α]D −68°; lit.[21a] m.p. 217–218°, [α]D −69°. The corresponding diacetate XVIIIb showed m.p. 175–177°, [α]D −86°; lit.[21a] m.p. 175–177°, [α]D −84°. Both XVIIIa and XVIIIb were identified by direct comparison with the respective authentic samples.

Elution with ether–chloroform (4:1) yielded 195 mg. (41%) of 5α-25D-spirostane-3β,12α-diol (12-epirockogenin) (XIXa), m.p. 208–212°, which after crystallization from methanol showed m.p. 214–217°, [α]D −30° (acetone); lit.[21b] m.p. 216–220°, [α]D −32° (acetone). The corresponding diacetate XIXb exhibited m.p. 153–155°, [α]D −12° (acetone); lit.[21b] m.p. 156–159°, [α]D −15° (acetone). Both XIXa and XIXb were identified by direct comparison with the respective authentic samples derived from hecogenin.

5α-Ergost-22-en-3β-ol (XX).—Ergosterol was converted to ergosta-4,6,22-trien-3-one (isoergosterone) in *ca.* 65% yield by the two-step method described by Shepherd, *et al.*[56] The reduction of this trienone to ergosta-4,22-dien-3-one by means of lithium in liquid ammonia and alcohol has been reported by Johnson, *et al.*,[57] as well as by Daglish, *et al.*[58] We have found this reduction (carried out in the absence of alcohol) to give mainly the unconjugated ergosta-5,22-dien-3-one, which then can be conjugated, as described in the sequel.[59]

A solution of 5 g. of ergosta-4,6,22-trien-3-one in 200 cc. of dry ether was added to a stirred solution of 1 g. of lithium in 400 cc. of liquid ammonia. After a further 15-min. stirring, ammonium chloride was added until the blue color disappeared, and the ammonia then was evaporated. Ether and water were added to the residue; the organic layer was washed with dilute hydrochloric acid and water, then dried, and evaporated. The resulting material (4.75 g.) consisted mainly of ergosta-5,22-dien-3-one, as shown by the spectral properties [λ_{max} 242 mμ (ε 1,500), indicative of *ca.* 10% of Δ⁴-3-one; strong infrared band at 1710 (Δ⁵-3-one) and weak band at 1670 cm.$^{-1}$ (Δ⁴-3-one)]. This material was dissolved in 50 cc. of methanol containing 0.2 cc. of 10% aqueous potassium hydroxide, and the solution was boiled for 5 min. Dilution with water and extraction with ether afforded 4.65 g. of a product which possessed only a strong band at 1670 cm.$^{-1}$ in the carbonyl region of the infrared. Crystallization from ethanol yielded 3.95 g. (79% based on isoergosterone) of ergosta-4,22-dien-3-one, m.p. 129–131°, [α]D +44°, λ_{max} 242 mμ (ε 16,500); lit.[56] m.p. 127–131°, [α]D +43°, λ_{max} 242 mμ (ε 16,600).

Ergosta-4,22-dien-3-one (3.6 g.) in 150 cc. of dry ether was reduced with 0.7 g. of lithium in 300 cc. of liquid ammonia, and the excess lithium was then destroyed with ammonium chloride, exactly as described before for the reduction of ergosta-4,6,22-trien-3-one. Isolation with ether afforded 3.45 g. of a mixture of 5α-ergost-22-en-3-one and 5α-ergost-22-en-3β-ol (hydroxyl band

(52) Huang-Minlon, *J. Am. Chem. Soc.*, **71**, 3301 (1949). This investigator has reported that reduction of cholest-4-en-3-one under these conditions yielded 61% of a hydrocarbon, m.p. 77–78°, [α]D +64°, considered to be cholest-4-ene. The course of the reduction of 25D-spirost-4-en-3-one under the Huang-Minlon conditions has been studied by C. Djerassi and J. Fishman [*J. Am. Chem. Soc.*, **77**, 4291 (1955)], who showed that the 5α-Δ³-ene was the major product.

(53) J. W. Cornforth, J. M. Osbond, and G. H. Phillips, *J. Chem. Soc.*, 907 (1954).

(54) J. Elks, G. H. Phillips, D. A. H. Taylor, and L. J. Wyman, *ibid.*, 1739 (1954).

(55) It has been reported by Cornforth, *et al.*, in ref. 53 that, when this zinc reduction was carried out for 1 hr. on the steam bath, the product was the 23-bromo derivative of the olefin XVII. However, Elks, *et al.*,[54] have shown that treatment of 12α,23ξ-dibromo-5α-25D-spirostane-3β,11β-diol 3-acetate with zinc in boiling acetic acid for 3.5 hr. resulted in the olefin XVII, the 23-bromo group being reduced.

(56) D. A. Shepherd, R. A. Donia, J. A. Campbell, B. A. Johnson, R. P. Holysz, G. Slomp, J. E. Stafford, R. L. Pedersen, and A. C. Ott, *J. Am. Chem. Soc.*, **77**, 1212 (1955).

(57) F. Johnson, G. T. Newbold, and F. S. Spring, *J. Chem. Soc.*, 1302 (1954).

(58) A. F. Daglish, J. Green, and V. D. Poole, *ibid.*, 2627 (1954).

(59) Since completion of this part of the work, R. E. Schaub and M. J. Weiss [*Chem. Ind.* (London), 2003 (1961)] have reported the analogous reduction of 17β-hydroxyandrosta-4,6-dien-3-one to 17β-hydroxyandrost-5-en-3-one under conditions similar to those used by ourselves.

and comparatively weak carbonyl band at 1710 cm.$^{-1}$ in the infrared).[60] This mixture was then reduced through 2-hr. boiling with 0.7 g. of lithium aluminum hydride in 300 cc. of dry tetrahydrofuran. Isolation with ether, followed by crystallization from chloroform–methanol, yielded 2.65 g. (73% based on the $\Delta^{4,22}$-dien-3-one) of 5α-ergost-22-en-3β-ol (XX), m.p. 155–156°, $[\alpha]_D$ −9°; lit.[61a] m.p. 152°, $[\alpha]_D$ −9°; lit.[61b] m.p. 154–156°, $[\alpha]_D$ −11°. The corresponding acetate after crystallization from methanol showed m.p. 155–156°, $[\alpha]_D$ −20°; lit.[61a] m.p. 155.5°, $[\alpha]_D$ −17°; lit.[61c] m.p. 157°, $[\alpha]_D$ −19°.

Anal. Calcd. for $C_{30}H_{50}O_2$: C, 81.39; H, 11.38. Found: C, 81.30; H, 11.15.

Hydration of 5α-Ergost-22-en-3β-ol (XX).—This olefin (1 g. in 80 cc. of tetrahydrofuran) was hydrated by method a, and the product was chromatographed on 40 g. of alumina. Elution with benzene–ether (1:1) yielded 720 mg. (69%) of a crystalline material, m.p. 184–190°, which appears to be a mixture of 5α-ergostane-3β,22ξ-diol (XXI) and 5α-ergostane-3β,23ξ-diol (XXIII). This mixture could not be separated by further chromatography; however, several crystallizations from aqueous acetone afforded an apparently pure substance, m.p. 199–201°, $[\alpha]_D$ −6°, which seems to be a hydrate of either XXI or XXIII.

Anal. Calcd. for $C_{28}H_{50}O_2 \cdot H_2O$: C, 77.00; H, 12.00. Found: C, 77.17; H, 12.03.

Oxidation of the mixture of diols with chromium trioxide in acetic acid led to a mixture of the 3,22-dione XXII and the 3,23-dione XXIV, m.p. 123–128°, which also could not be separated by chromatography.

Hydration of Cholest-4-ene (XXV).—Cholest-4-ene (XXV) was prepared from cholest-4-en-3-one by conversion to the ethylenethioketal by the method of Fieser[62] and subsequent Raney nickel desulfurization,[63] as well as by direct reduction of the Δ^4-3-one with lithium aluminum hydride and aluminum chloride.[64] The olefin, after purification *via* the corresponding dibromide as described by Bladon, *et al.*,[65] showed m.p. 83–84°, $[\alpha]_D$ +75°.

Cholest-4-ene (1 g.) was hydrated by method a. The oxidation was carried out by dissolving the organoborane in 100 cc. of 10% ethanolic potassium hydroxide, and 30 cc. of 30% aqueous hydrogen peroxide was then added during 5 min. without external cooling. The solution was boiled under reflux for 15 min., and the product was then isolated with ether as usual. Chromatography on 30 g. of alumina and elution with pentane gave 255 mg. (25%) of unchanged starting material. Elution with pentane–benzene (1:4), followed by crystallization from ether–methanol, produced 615 mg. (59%) of 5α-cholestan-4α-ol (Xa), m.p. 187–188°, $[\alpha]_D$ +3°. This substance proved to be identical with the one described previously, derived from 5α-cholest-3-ene (VII).

By use of method b and subsequent oxidation, as described directly preceding, 500 mg. of cholest-4-ene yielded 155 mg. (30%) of 5α-cholestan-4α-ol (Xa) and 305 mg. (61%) of unchanged starting material.

Hydration of Cholest-4-en-3β-ol (XXVI). a. Inverse Addition.—Cholest-4-en-3β-ol (XXVI) (m.p. 130–132°, $[\alpha]_D$ +44°) was prepared by the reduction of cholest-4-en-3-one with lithium tri-*t*-butoxy aluminum hydride.[66] A solution of 500 mg. of this unsaturated alcohol in 20 cc. of ether was added to a solution of 300 mg. of lithium aluminum hydride in 30 cc. of ether. Boron trifluoride etherate (2.5 g.) in 20 cc. of ether was then added dropwise during 10 min., with stirring and ice cooling. The mixture was stirred for 1 hr. at room temperature, and the organoborane was then isolated and oxidized in the usual manner. The product was acetylated and then chromatographed on 15 g. of alumina. Elution with pentane–benzene (2:1) furnished 385 mg. (61%) of 5α-cholestane-3β,4α-diol diacetate (XXVIIb), m.p. 159–161°, which on crystallization from methanol showed m.p. 161–162°, $[\alpha]_D$ +32°; lit.[22] m.p. 161.5–162.5°, $[\alpha]_D$ +30°. Saponification with boiling 3% methanolic potassium hydroxide for 1 hr. and crystallization from ether–methanol yielded the free diol XXVIIa, m.p. 236–238°, $[\alpha]_D$ +20°; lit.[22] m.p. 236–237°, $[\alpha]_D$ +20°.

Hydration of cholest-4-en-3β-ol by method b yielded the diacetate XXVIIb in 55% yield.

b. **Normal Addition.**—Cholest-4-en-3β-ol (500 mg.) was hydrated by the unmodified method a, and the product was chromatographed on 15 g. of alumina. The only crystalline product isolated (260 mg., 50%) was 5α-cholestane-4α,6α-diol (XXVIII), m.p. 186–190°, which after crystallization from acetone showed m.p. 193–195°, $[\alpha]_D$ +20°. It was identical with the diol obtained by the hydration of cholesta-3,5-diene (see following paper[3e]).

Hydration of Cholest-4-en-3-one (XXIX).—Hydration of 1 g. of cholest-4-en-3-one by method a, acetylation of the product, and chromatography on 30 g. of alumina led to 760 mg. (60%) of 5α-cholestane-3β,4α-diol diacetate (XXVIIb), m.p. 160–161°, identified with the previously described substance obtained from cholest-4-en-3β-ol (inverse addition). None of the diacetate of the 4α,6α-diol XXVIII could be detected. The yield of the 3β,4α-diacetoxy compound XXVIIb was 56% when the hydration of cholest-4-en-3-one was carried out by method b.

Hydration of Cholest-5-ene (XXX).—Cholest-5-ene (XXX) (m.p. 93–94°, $[\alpha]_D$ −56°) was prepared by the reduction of cholesteryl chloride with sodium in liquid ammonia, according to Ireland, *et al.*[67] This olefin (1 g.) was hydrated by method a, the oxidation being carried out as described for the hydration of cholest-4-ene (XXV). The product was chromatographed on 30 g. of alumina. Elution with pentane yielded 210 mg. (21%) of unchanged starting material. Elution with benzene then produced 765 mg. (73%) of 5α-cholestan-6α-ol (XXXIa), m.p. 124–126°, which after crystallization from ether–methanol showed m.p. 128–129°, $[\alpha]_D$ +35°; lit.[24] m.p. 128–129°, $[\alpha]_D$ +35°. The corresponding acetate XXXIb after crystallization from ethyl acetate–ethanol exhibited m.p. 94–96°, $[\alpha]_D$ +69°; lit.[24] m.p. 95°, $[\alpha]_D$ +69°. No isomeric alcohol could be detected from the hydration reaction.

Hydration of cholest-5-ene (500 mg.) by method b, followed by chromatography, yielded 230 mg. (46%) of unchanged starting material and 205 mg. (39%) of 5α-cholestan-6α-ol. No isomeric alcohol could again be detected.

Hydration of Cholesterol (XXXII).—Cholesterol (1 g.) was hydrated by method a, the oxidation begin carried out as described for the hydration of cholest-4-ene (XXV). The product was acetylated and then chromatographed on 40 g. of alumina. Elution with pentane–benzene (9:1) yielded 100 mg. (9%) of unchanged cholesteryl acetate, m.p. 113–114°. Elution with pentane–benzene (1:1) gave 855 mg. (68%) of 5α-cholestane-3β,6α-diol diacetate (XIIIb), m.p. 100–102°, which after crystallization from methanol showed m.p. 106–107°, $[\alpha]_D$ +41°; lit.[18a] m.p. 107–108°, $[\alpha]_D$ +39°.

Anal. Calcd. for $C_{31}H_{52}O_4$: C, 76.18; H, 10.72. Found: C, 75.90; H, 10.54.

Elution with benzene furnished 235 mg. (19%) of 5β-cholestane-3β,6β-diol diacetate (XXXIIIb), m.p. 129–133°, which on crystallization from methanol exhibited m.p. 136–138°, $[\alpha]_D$ +16°; lit.[29] m.p. 137–139°, $[\alpha]_D$ +13°.

Anal. Calcd. for $C_{31}H_{52}O_4$: C, 76.18; H, 10.72. Found: C, 76.00; H, 10.61.

Hydration of cholesterol by method b and subsequent acetylation yielded 70% of the 3β,6α-diacetate XIIIb and 16% of the 3β,6β-diacetate XXXIIIb.

Saponification of 200 mg. of the 3β,6α-diacetate XIIIb through 2-hr. boiling with 3% methanolic potassium hydroxide, followed by crystallization from ether–methanol, led to 130 mg. of 5α-cholestane-3β,6α-diol (XIIIa), m.p. 215–217°, $[\alpha]_D$ +38°; lit.[18a] m.p. 213–215°, $[\alpha]_D$ +38°. Oxidation of 100 mg. of this diol with chromium trioxide in acetic acid for 18 hr. at room temperature and subsequent crystallization from methanol afforded 65 mg. of 5α-cholestane-3,6-dione (XIV), m.p. 171–173°, $[\alpha]_D$ +8°, identical with the previously described sample obtained from 5α-cholest-6-en-3β-ol acetate (XII); lit.[20b] m.p. 171–172°, $[\alpha]_D$ +8°.

Similarly, saponification of 100 mg. of the 3β,6β-diol diacetate XXXIIIb and crystallization from ether–methanol yielded 75 mg. of the free 3β,6β-diol XXXIIIa, m.p. 197–199°, $[\alpha]_D$ +23°;

(60) The lithium ammonia reduction of ergosta-4,22-dien-3-one to 5α-ergost-22-en-3-one has been reported previously by D. H. R. Barton, D. A. J. Ives, and B. R. Thomas, *J. Chem. Soc.*, 903 (1954).

(61) (a) D. H. R. Barton, J. D. Cox, and N. Y. Holness, *J. Chem. Soc.*, 1771 (1949); (b) D. H. R. Barton and C. H. Robinson, *ibid.*, 3045 (1954); (c) R. Budziarek, F. Johnson, and F. S. Spring, *ibid.*, 534 (1953).

(62) L. Fieser, *J. Am. Chem. Soc.*, **76**, 1945 (1954).

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(64) J. Broome, B. R. Brown, A. Roberts, and A. M. S. White, *J. Chem. Soc.*, 1406 (1960).

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lit.[29] m.p. 198–200°, $[\alpha]_D$ +24°. Oxidation of 50 mg. of this diol with chromium trioxide in acetic acid and crystallization from methanol furnished 25 mg. of 5β-cholestane-3,6-dione (XXXIV), m.p. 178–180°, $[\alpha]_D$ −72°; lit.[29] m.p. 170–174°, $[\alpha]_D$ −57°; lit.[68] m.p. 175–179°, $[\alpha]_D$ −79°, −82°.

5β-Cholestane-3,6-dione (10 mg.), dissolved in 2 cc. of benzene, was adsorbed on a column of 2 g. of Alcoa activated alumina (grade F-20) and allowed to stand overnight. Elution with benzene and crystallization from methanol yielded 7 mg. of 5α-cholestane-3,6-dione, m.p. 168–170°, $[\alpha]_D$ +7°, identified by direct comparison with the previously described sample.

Hydration of Cholesterol 3-(2′-Tetrahydropyranyl) Ether (XXXV).—The ether XXXV (m.p. 154–156°, $[\alpha]_D$ −24°) was prepared from cholesterol, 2,3-dihydropyran, and phosphorus oxychloride, as described by Greenhalgh, *et al.*[69] This ether (1 g.) was hydrated by method a, the oxidation being carried out as described for the hydration of cholest-4-ene (XXV). The product, dissolved in 95% ethanol containing *p*-toluenesulfonic acid, was boiled for 1 hr. Acetylation, followed by chromatography on 40 g. of alumina, yielded 470 mg. (45%) of the 3β,6α-diacetate XIIIb, m.p. 101–103°, and 350 mg. (34%) of the 3β, 6β-diacetate XXXIIIb, m.p. 131–134°. Each of these substances was identical with the corresponding one obtained from the direct hydration of cholesterol. In addition, 95 mg. of an oil was obtained which was not investigated further.

Hydration of 3-Cycloethylenedioxycholest-5-ene (XXXVI).—The ketal XXXVI (m.p. 134–135.5°) was prepared from cholest-4-en-3-one and ethylene glycol, as described by Antonucci, *et al.*[70] This ketal (1.7 g.) was hydrated by method b, the oxidation being carried out as described for the hydration of cholest-4-ene (XXV). The product was acetylated and then chromatographed on 60 g. of alumina. Elution with benzene afforded 1.82 g. (94%) of *ca.* a 1:2 mixture of 3-cycloethylenedioxy-5α-cholestan-6α-ol acetate (XXXVII) and 3-cycloethylenedioxy-5β-cholestan-6β-ol acetate (XXXVIII), m.p. 116–119°; crystallization from methanol gave a sample, m.p. 123–125° (unchanged by further crystallization), $[\alpha]_D$ +21°.

Anal. Calcd. for $C_{31}H_{52}O_4$: C, 76.18; H, 10.72. Found: C, 75.93; H, 10.79.

A solution of 1.78 g. of the mixed acetoxy ketals XXXVII and XXXVIII in 50 cc. of 90% acetic acid was boiled under reflux for 15 hr. The solution was diluted with water; the product was isolated with ether and chromatographed on 50 g. of alumina. Elution with benzene furnished 510 mg. (30% over-all from XXXVI), of 6α-acetoxy-5α-cholestan-3-one (XXXIX), m.p. 126–128°, which after crystallization from ether–methanol showed m.p. 132–133°, $[\alpha]_D$ +62°.

Anal. Calcd. for $C_{29}H_{48}O_3$: C, 78.32; H, 10.88. Found: C, 78.37; H, 10.81.

Elution with benzene–ether (9:1) yielded 1.05 g. (61% over-all from XXXVI) of 6β-acetoxy-5β-cholestan-3-one (XL), m.p. 105–108°, which after crystallization from ether–methanol exhibited m.p. 112–114°, $[\alpha]_D$ +22°; lit.[31] m.p. 113–115°, $[\alpha]_D$ +20°.

Anal. Calcd. for $C_{29}H_{48}O_3$: C, 78.32; H, 10.88. Found: C, 78.57; H, 10.94.

Reduction of 100 mg. of the 6α-acetoxy-3-one XXXIX with 200 mg. of lithium aluminum hydride in 20 cc. of ether (1-hr. reflux), followed by crystallization from ether–methanol, led to 5α-cholestane-3β,6α-diol (XIIIa), m.p. 212–214°. The corresponding diacetate XIIIb showed m.p. 105–107°, $[\alpha]_D$ +40°. Both these substances were identical with the corresponding ones obtained by the hydration of cholesterol.

Reduction of 150 mg. of the 6β-acetoxy-3-one XL with 300 mg. of lithium aluminum hydride in 30 cc. of ether (1-hr. reflux), followed by crystallization from ether–methanol, yielded 5β-cholestane-3β,6β-diol (XXXIIIa), m.p. 196–197°, $[\alpha]_D$ +23°. The corresponding diacetate XXXIIIb showed m.p. 135–137°, $[\alpha]_D$ +14°. Both of these compounds were found to be identical with the corresponding ones obtained by the hydration of cholesterol.

5α-Androst-9(11)-ene (XLIIa).—5α-Androstan-11-one (XLIV) was prepared according to Sondheimer, *et al.*[35] This ketone (1.2 g.) was reduced with 1 g. of lithium aluminum hydride in 50 cc. of dry tetrahydrofuran (6-hr. boiling). Isolation with ether and crystallization from pentane yielded 1.05 g. (87%) of 5α-androstan-11β-ol, m.p. 92–93°, $[\alpha]_D$ +19°, no carbonyl band in the infrared.

Anal. Calcd. for $C_{19}H_{32}O$: C, 82.54; H, 11.66. Found: C, 82.81; H, 11.51.

5α-Androstan-11β-ol (1.0 g.) dissolved in 10 cc. of dry pyridine was dehydrated by addition of 3 cc. of freshly distilled phosphorus oxychloride at 0°. The mixture was allowed to stand overnight at room temperature and the product was then isolated with ether. Chromatography on 30 g. of alumina, elution with pentane, and crystallization from ether–methanol gave 0.65 g. (70%) of 5α-androst-9(11)-ene (XLIIa), m.p. 41–42°. The analytical sample showed m.p. 43–44°, $[\alpha]_D$ +15°.

Anal. Calcd. for $C_{19}H_{30}$: C, 88.30; H, 11.70. Found: C, 88.08; H, 11.70.

Hydration of 5α-Androst-9(11)-ene (XLIIa).—5α-Androst-9-(11)-ene (250 mg.) was hydrated by method a, and the product was chromatographed on 10 g. of alumina. Elution with benzene yielded 245 mg. (92%) of 5α-androstan-11α-ol (XLIIIa) as a colorless oil which could not be crystallized. Acetylation led to the 11α-acetate XLIIIb (strong infrared bands at 1726 and 1243 cm.$^{-1}$), which also was not crystalline. Oxidation of the 11α-ol XLIIIa (100 mg.) with chromium trioxide in acetic acid for 16 hr. at room temperature afforded 62 mg. of 5α-androstan-11-one (XLIV), m.p. 47–49°, $[\alpha]_D$ +64°, which was identified by direct comparison with an authentic sample (lit.[35] m.p. 49–50°, $[\alpha]_D$ +65°).

Hydration of 5α-androst-9(11)-ene (100 mg.) by method b, followed by chromatography, gave 41 mg. (41%) of unchanged starting material as well as 58 mg. (54%) of 5α-androstan-11α-ol.

5β-Androst-9(11)-ene (XLIIb).—This olefin was obtained from 5β-androstan-11-one[35] (1 g.) by reduction with lithium aluminum hydride and subsequent dehydration with phosphorus oxychloride, exactly as described in the 5α-series. Chromatography of the product on 30 g. of alumina and elution with pentane gave 0.68 g. (72% over-all) of 5β-androst-9(11)-ene, m.p. 66–68°. Crystallization from ether led to the analytical specimen, m.p. 69–70°, $[\alpha]_D$ +32°.

Anal. Calcd. for $C_{19}H_{30}$: C, 88.30; H, 11.70. Found: C, 88.23; H, 11.65.

Attempted hydration of 5β-androst-9(11)-ene by method a or b led to the recovery of unchanged starting material in over 95% yield.

3,20-Biscycloethylenedioxy-5α-pregn-9(11)-ene (XLVa).—A solution of 10 g. of pregn-4-ene-3,11,20-trione (11-ketoprogesterone) in 500 cc. of dioxane was shaken in hydrogen over 1.4 g. of a 10% palladium–charcoal catalyst for 24 hr. at room temperature and a pressure of 45 p.s.i.[71] The mixture was then heated, the catalyst was removed, and the filtrate was evaporated. Crystallization from ethyl acetate yielded 7.0 g. (70%) of 5α-pregnane-3,11,20-trione, m.p. 209–212°, $[\alpha]_D$ +135° (ethanol), no selective absorption in the ultraviolet; lit.[37b] m.p. 211–213°, $[\alpha]_D$ +129° (ethanol).

5α-Pregnane-3,11,20-trione (6 g.) in 150 cc. of benzene containing 14 cc. of ethylene glycol was slowly distilled until 30 cc. were removed, in order to remove moisture. *p*-Toluenesulfonic acid (300 mg.) was added and the mixture was boiled for 15 hr., water being removed during this time by means of a Dean–Stark tube. Aqueous sodium bicarbonate was then added, and the organic layer was washed with water, dried, and evaporated. Crystallization from ethyl acetate yielded 6.35 g. (84%) of 3,20-biscycloethylenedioxy-5α-pregnan-11-one, m.p. 210–212°. The analytical sample showed m.p. 213–214°, $[\alpha]_D$ +47°.

Anal. Calcd. for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15. Found: C, 71.70; H, 9.05.

The keto diketal (2.5 g.) was reduced with 2.5 g. of lithium aluminum hydride in 150 cc. of tetrahydrofuran (15-hr. reflux). The excess reagent was decomposed by the addition of ethyl acetate, followed by a saturated sodium sulfate solution. Solid sodium sulfate was then added, the mixture was filtered, and the filtrate was evaporated. Crystallization from isopropyl alcohol yielded 2.05 g. (82%) of 3,20-biscycloethylenedioxy-5α-pregnan-11β-ol, m.p. 164–166°. Further crystallization gave the analytical sample, m.p. 167–169°, $[\alpha]_D$ +38°.

Anal. Calcd. for $C_{25}H_{40}O_5$: C, 71.39; H, 9.59. Found: C, 71.81; H, 9.61.

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The hydroxy diketal (1.8 g.) dissolved in 20 cc. of dry pyridine was dehydrated by addition of 5 cc. of freshly distilled phosphorus oxychloride at 0°. The mixture was set aside overnight at room temperature, and the product was then isolated with ether. Crystallization from ether–methanol afforded 1.45 g. (84%) of 3,20-biscycloethylenedioxy-5α-pregn-9(11)-ene (XLVa), m.p. 155–157°. A further purified sample showed m.p. 161–162°, $[\alpha]_D$ +33°.

Anal. Calcd. for $C_{25}H_{38}O_4$: C, 74.59; H, 9.52. Found: C, 74.39; H, 9.57.

Hydration of 3,20-Biscycloethylenedioxy-5α-pregn-9(11)-ene (XLVa).—The unsaturated diketal XLVa (500 mg.) was hydrated by method b, and the product was chromatographed on 15 g. of alumina. Elution with pentane–benzene (1:1) furnished 160 mg. (32%) of unchanged starting material. Elution with benzene–ether (4:1) yielded 325 mg. (62%) of 3,20-biscycloethylenedioxy-5α-pregnan-11α-ol (XLVI) as an amorphous substance which could not be crystallized. The product dissolved in 12 cc. of acetone was boiled under reflux for 1 hr. with 4 cc. of water containing 1 drop of concentrated sulfuric acid. The solution was evaporated to small volume and diluted with water. Isolation with ether and crystallization from acetone–hexane yielded 225 mg. (88%) of 11α-hydroxy-5α-pregnane-3,20-dione (XLVIIa), m.p. 193–195°, $[\alpha]_D$ +84°; lit.[36] m.p. 193–195°, $[\alpha]_D$ +83°.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.47; H, 9.71.

The corresponding acetate XLVIIb after crystallization from acetone–hexane showed m.p. 175–177°, $[\alpha]_D$ +64°; lit.[36] m.p. 177–179°, $[\alpha]_D$ +66°.

Oxidation of the hydroxydione XLVIIa with chromium trioxide in acetic acid (16 hr. at room temperature) and crystallization from ethyl acetate yielded 5α-pregnane-3,11,20-trione, m.p. 210–213°; the melting point was undepressed on admixture with the previously described sample (m.p. 209–212°) obtained by the hydrogenation of 11-ketoprogesterone, and the infrared spectra were identical.

Hydration of 5α,25D-Spirost-9(11)-en-3β-ol Acetate (XLVIII). This olefin (500 mg., m.p. 205–206°, $[\alpha]_D$ −64°)[38] was hydrated by method b. The product was acetylated and then chromatographed on 15 g. of alumina. Elution with pentane–benzene (1:1) yielded 155 mg. (31%) of unchanged starting material. Elution with benzene furnished 335 mg. (59%) of 5α,25D-spirostane-3β,11α-diol diacetate (IIb), m.p. 167–169°, which after crystallization from acetone–hexane showed m.p. 173–175°, $[\alpha]_D$ −82°; lit.[21a] m.p. 175–177°, $[\alpha]_D$ −84°. The corresponding free diol, obtained by 1-hr. boiling with 3% methanolic potassium hydroxide, after crystallization from acetone exhibited m.p. 217–219°, $[\alpha]_D$ −68°; lit.[21a] m.p. 217–218°, $[\alpha]_D$ −69°. The diacetate IIb and the corresponding diol proved to be identical with the corresponding substances (XVIIIb and XVIIIa) obtained by the hydration of 5α-25D-spirost-11-en-3β-ol acetate (XVII).

In another experiment, 250 mg. of the $\Delta^{9(11)}$-ene XLVIII was hydrated by method b, as before, and the total product was then oxidized with 150 mg. of chromium trioxide in 50 cc. of 95% acetic acid for 16 hr. at room temperature. Isolation with ether yielded material, which was chromatographed on 20 g. of alumina. Elution with pentane–benzene (3:7) furnished 90 mg. (36%) of unchanged starting material. Elution with benzene then gave 126 mg. (49%) of 3β-acetoxy-5α-25D-spirostan-11-one (L), m.p. 216–218°, which after crystallization from acetone exhibited m.p. 223–225°, $[\alpha]_D$ −37°; lit.[21a] m.p. 222–223°, $[\alpha]_D$ −32°; lit.[72] m.p. 223–227°, $[\alpha]_D$ −41°. The substance was identified by direct comparison with an authentic specimen.

5α-Cholest-14-en-3β-ol (LIa). This substance was obtained by isomerization of 5α-cholest-7-en-3β-ol (XLIa) under conditions based on those described by Cornforth, *et al.*,[73] involving the passage of a stream of hydrogen chloride through a chloroform solution of the Δ^7 compound at −30° for 2 hr. The chloroform solution was then poured into 3% sodium bicarbonate solution and ether was added. After 30 min. shaking, the organic layer was separated, washed with water, dried, and evaporated. Chromatography on alumina, elution with benzene, and crystallization from methanol gave 55% of the Δ^{14} compound LIa, m.p. 129–131°, $[\alpha]_D$ +36°; lit.[74] m.p. 130–131°, $[\alpha]_D$ +34°.

Hydration of 5α-Cholest-14-en-3β-ol (LIa).—The Δ^{14} compound LIa (200 mg.) was hydrated by method a, and the product was chromatographed on 6 g. of alumina. Elution with benzene–ether (1:1) gave 155 mg. (74%) of 5α-cholestane-3β,15α-diol (LIIa), which after crystallization from acetone showed m.p. 191–193°, $[\alpha]_D$ +60°; the substance appears to contain one molecule of acetone of crystallization.

Anal. Calcd. for $C_{27}H_{48}O_2 \cdot C_3H_6O$: C, 77.86; H, 11.76. Found: C, 77.70; H, 11.88.

The corresponding diacetate LIIb after crystallization from ether–methanol exhibited m.p. 144–146°, $[\alpha]_D$ +45°; for a substance believed to have this structure, lit.[39] m.p. 145–147 $[\alpha]_D$ +50°.

Hydration of 5α-Androst-14-ene-3β,17β-diol (LIb).—This olefin, obtained in 80% yield from 3β-acetoxy-5α-androst-14-en-17-one[75] by reduction with lithium aluminum hydride in boiling ether, showed m.p. 141–143°, $[\alpha]_D$ +35°; by St. André, *et al.*, who carried out this reduction in *ca.* 50% yield with sodium borohydride, lit.[75a] m.p. 140–141°, $[\alpha]_D$ +36°. The Δ^{14}-ene LIb (100 mg. in 25 cc. of tetrahydrofuran) was hydrated by method a, and the product was chromatographed on 3 g. of alumina. Elution with chloroform–methanol (9:1) yielded 73 mg. (69%) of 5α-androstane-3β,15α,17β-triol (LIIc), m.p. 255–262°, which after crystallization from choloroform–methanol exhibited m.p. 263–265°, $[\alpha_D]$ +49° (pyridine).

5α-Pregn-16-ene-3β,20α-diol (LIII).—This substance was prepared by the lithium aluminum hydride reduction of 3β-acetoxy-5α-pregn-16-en-20-one (a degradation product of tigogenin)[76]; it has been shown that this type of reduction of Δ^{16}-20-ones leads to the Δ^{16}-20α-ols.[77] A solution of 1 g. of the Δ^{16}-20-one and 0.5 g. of lithium aluminum hydride in 100 cc. of ether was boiled under reflux for 30 min. Ethyl acetate was added to destroy excess reagent and then dilute sulfuric acid. Isolation with ether and crystallization from acetone yielded 0.75 g. (84%) of 5α-pregn-16-ene-3β,20α-diol (LIII), m.p. 178–180°. The analytical sample exhibited m.p. 181–182°, $[\alpha]_D$ −14°, no high-intensity absorption in the ultraviolet.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 79.06; H, 10.80.

The 20α stereochemistry in LIII was confirmed by hydrogenation in ethyl acetate over a 10% palladium–charcoal catalyst. Crystallization from acetone then yielded 5α-pregnane-3β,20α-diol, m.p. 217–218°, $[\alpha]_D$ +25°; for this diol, lit.[78] m.p. 218–219°, $[\alpha]_D$ +23°; for 5α-pregnane-3β,20β-diol, lit.[79] m.p. 194.5–195.5, $[\alpha]_D$ +4°.

Hydration of 5α-Pregn-16-ene-3β,20α-diol (LIII).—The Δ^{16} compound LIII (0.5 g. in 40 cc. of tetrahydrofuran) was hydrated by method a, and the product was chromatographed on 15 g. of alumina. Crystallization from acetone yielded 0.42 g. (80%) of 5α-pregnane-3β,16α,20α-triol (LIVa), m.p. 255–258°, $[\alpha]_D$ −5° (ethanol); lit.[44a] m.p. 251–253°; lit.[45b] m.p. 254–256°.

Anal. Calcd. for $C_{21}H_{36}O_3$: C, 74.95; H, 10.78. Found: C, 74.65; H, 10.78.

The corresponding triacetate LIVb after crystallization from ether–methanol showed m.p. 174–176°, $[\alpha]_D$ −50° (ethanol); lit.[44a] m.p. 177–179°, $[\alpha]_D$ −58° (ethanol); lit.[44b] m.p. 177–180°, $[\alpha]_D$ +(?)5±° (ethanol).

19-Norpregna-1,3,5(10),16-tetraene-3,20α-diol (LV).—3-Hydroxy-19-norpregna-1,3,5(10),16-tetraen-20-one[80] (2 g.) was reduced through 2-hr. boiling with 1 g. of lithium aluminum hydride in 150 cc. of tetrahydrofuran. Ethyl acetate was added, followed by dilute sulfuric acid. Isolation with ethyl acetate and crystallization from acetone furnished 1.52 g. (76%) of 19-norpregna-1,3,5(10),16-tetraene-3,20α-diol (LV),[81] m.p. 201–202°, $[\alpha]_D$ +82° (ethanol), λ_{max}^{EtOH} 280 mμ (ε 2400).

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Anal. Calcd. for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78. Found: C, 80.17; H, 8.70.

Hydration of 19-Norpregna-1,3,5(10),16-tetraene-3,20α-diol (LV).—The diol LV (0.5 g. in 40 cc. of tetrahydrofuran) was hydrated by method a, and the product was chromatographed on 15 g. of alumina. Elution with chloroform–methanol (4:1) furnished 0.47 g. (89%) of 19-norpregna-1,3,5(10)-triene-3,16α,-20α-triol (LVIa), m.p. 202–204°, which after crystallization from acetone–hexane showed m.p. 206–208°, $[\alpha]D$ +49° (ethanol). The corresponding triacetate LVIb after crystallization from ether exhibited m.p. 178–180°, $[\alpha]D$ −20°.

Anal. Calcd. for $C_{26}H_{31}O_6$: C, 70.56; H, 7.74. Found: C 70.39; H, 7.84.

2-Methyl-2-butene (LVIII).—Dehydration of *t*-amyl alcohol with 15% aqueous sulfuric acid according to Whitmore, *et al.*,[47] afforded in 85% yield a mixture consisting of 87% of 2-methyl-2-butene and 13% of 2-methyl-1-butene (determined by gas–liquid chromatography). A solution of 14 g. (0.2 mole) of this olefin mixture and 3 g. (0.079 mole) of sodium borohydride in 50 cc. of diglyme was cooled in an ice bath and 15 g. (0.106 mole) of boron trifluoride etherate was added during 30 min., with stirring and continued cooling. The reaction mixture was allowed to stand for 1 hr. at 0°, and a further 35 g. (0.5 mole) of the olefin mixture was then added during 5 min., with stirring and cooling. The reaction was allowed to proceed for 2 hr. at room temperature, and the remaining olefin was then distilled through a column. The resulting 2-methyl-2-butene (23.5 g.) showed b.p. 38–38.5° and, on gas–liquid chromatographic analysis, proved to be uncontaminated with 2-methyl-1-butene.

Hydroboration of 5α-Cholest-1-ene (I) with Disiamylborane.—A solution of 0.50 g. (13.2 mmoles) of lithium aluminum hydride in 30 cc. of dry ether was added dropwise during 20 min. to a stirred solution containing 2.47 g. (35.3 mmoles) of 2-methyl-2-butene and 2.50 g. (17.6 mmoles) of boron trifluoride etherate in 40 cc. of ether, with ice cooling under nitrogen. After an additional hour at 0°, a solution of 0.50 g. (1.35 mmoles) of 5α-cholest-1-ene[49] in 30 cc. of ether was added during 5 min. at 0°, and the mixture was allowed to stand for 4 hr. without further cooling. It was then treated with a saturated sodium sulfate solution and solid sodium sulfate, and then filtered and evaporated. The residue was oxidized in tetrahydrofuran with alkaline hydrogen peroxide, in the usual way. Chromatography on 15 g. of alumina led to 0.39 g. (74%) of cholestan-2α-ol, m.p. 178–180°, $[\alpha]D$ +27°, identical with a previously obtained sample; no cholestan-1α-ol could be detected.

Essentially identical results were obtained when the hydroboration of 5α-cholest-1-ene was carried out with disiamylborane prepared from 2-methyl-2-butene by reaction with sodium borohydride and boron trifluoride etherate in diglyme at 0°, according to Brown and Zweifel.[45]

Hydroboration of 5α-Cholest-2-ene (IV) with Disiamylborane.—5α-Cholest-2-ene[50] (500 mg.) was allowed to react with disiamylborane (prepared from 2-methyl-2-butene, lithium aluminum hydride, and boron trifluoride in ether) exactly as described previously for the Δ^1 isomer, and the product was oxidized with alkaline hydrogen peroxide in the usual way. Chromatography on 15 g. of alumina then yielded 229 mg. (44%) of 5α-cholestan-3α-ol, m.p. 185–187°, and 185 mg. (35%) of 5α-cholestan-2α-ol, m.p. 180–181°. Each of these alcohols was identical with a previously obtained sample.

Hydroboration of 5α-Cholest-3-ene (VII) with Disiamylborane.—The experiment was carried out with 170 mg. of 5α-cholest-3-ene exactly as described before for the Δ^1 and Δ^2 olefins. Chromatography on alumina then yielded 79 mg. (44%) of 5α-cholestan-3α-ol, m.p. 186–188°, and 63 mg. (35%) of 5α-cholestan-4α-ol, m.p. 187–189°. Each of these alcohols was identical with a previously obtained sample.

The Hydration of Unsaturated Steroids by the Brown Hydroboration Reaction. II.[1] Steroidal Conjugated Dienes

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The hydration of a number of steroidal conjugated dienes, through hydroboration and subsequent oxidation with alkaline hydrogen peroxide, was studied. Both cholesta-3,5-diene (I) and cholesta-4,6-diene (II) gave rise to 5α-cholestane-4α,6α-diol (IIIa), the structure of which was established by various transformations as well as through its formation by hydration of 6α-acetoxycholest-4-ene (V). Attempted hydration of 7-dehydrocholesterol (XIa) unexpectedly yielded 5α-cholest-6-en-3β-ol (XIIa), this substance presumably being formed by hydrolysis with rearrangement of the intermediate Δ^7-6α-borane XV. Hydration of several steroidal $\Delta^{7,9(11)}$-dienes (XVIa,b) was found to result only in attack of the $\Delta^{9(11)}$ double bond, and yielded the Δ^7-11α-ols XVIIa in high yield.

In the preceding paper[1] the hydration of a number of monounsaturated steroids was reported, through hydroboration and subsequent oxidation with alkaline hydrogen peroxide. We now describe the results obtained when steroidal conjugated dienes were subjected to the hydration reaction. Acyclic and simple cyclic dienes previously had been hydrated by this method, whereby unsaturated monools as well as saturated diols were formed.[3a]

As previously,[1] the hydroboration was carried out by adding an ethereal solution of lithium aluminum hydride to an ethereal solution of the diene and boron trifluoride (method a) or alternatively by passing diborane gas through a solution of the diene in tetrahydrofuran (method b). An excess of reagent was always used, and the preferential hydroboration of one of the two double bonds was not studied. Unless otherwise stated, the product, without further investigation, was oxidized directly in tetrahydrofuran solution through addition of 10% aqueous sodium hydroxide, followed by 30% aqueous hydrogen peroxide. The resulting alcohols were then isolated by chromatography on alumina, either directly or after acetylation.

Cholesta-3,5-diene (I), a heteroannular diene, on hydration by method a or b, gave rise to *ca.* 45%[4] of the hitherto unknown 5α-cholestane-4α,6α-diol (IIIa) as sole crystalline material isolated. The structure and stereochemistry assigned to this diol follow from the following facts. Acetylation with acetic anhydride in pyridine at room temperature afforded a *di-*

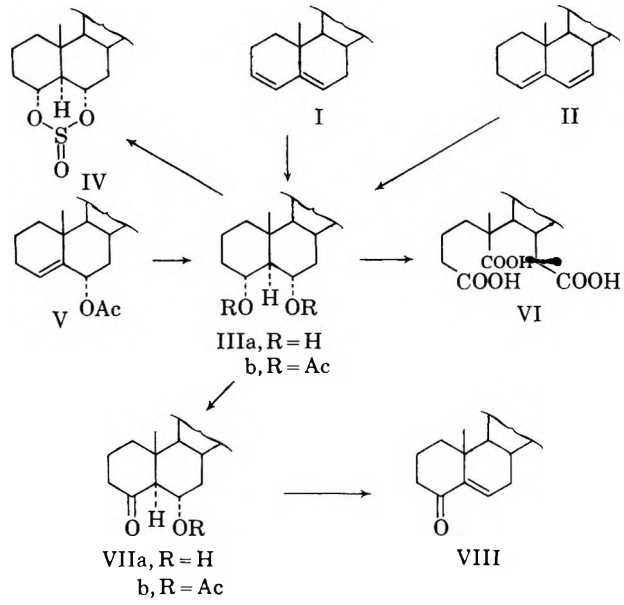
(1) Part I, M. Nussim, Y. Mazur, and F. Sondheimer *J. Org. Chem.*, **29**, 1120 (1964).

(2) Taken in part from a Ph.D. thesis presented by M. Nussim to the Hebrew University, Jerusalem, April, 1961.

(3) For a survey, see H. C. Brown, "Hydroboration," W. A. Benjamin, Inc., New York, N. Y., 1962: (a) Chapter 15; (b) Chapter 7.

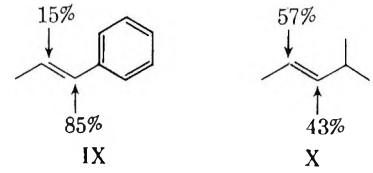
(4) Yields are given to the nearest 5%.

acetate (IIIb), indicating the presence of two secondary hydroxyl groups. The same diol was obtained from cholesta-4,6-diene (II) (following), and the hydroxyl groups must, therefore, be at C-4 and C-6. The diol IIIa readily yielded the cyclic sulfite IV on treatment with thionyl chloride and pyridine, indicating a *cis* relationship of the hydroxyl groups.[5] It was suspected that the hydroxyl groups are α oriented in view of the usual predominant attack of diborane from the α side of steroidal Δ^3 and Δ^5 double bonds[1]; confirmation was provided by a separate experiment, involving the hydration of 6α-acetoxycholest-4-ene (V) by method b, whereby the same diol IIIa was obtained (60% yield) after saponification. The 5α configuration assigned to IIIa follows from the usual over-all *cis* addition of water by the hydration reaction.[1,3]



The oxidation of the 4α,6α-diol IIIa under various conditions was studied, whereby further confirmation of structure was obtained. Oxidation with chromium trioxide in acetic acid gave rise to the amorphous triacid VI, presumably formed *via* 5α-cholestane-4,6-dione. The structure of VI is based on the fact that it required almost exactly 3 molar equiv. of sodium hydroxide for neutralization. On the other hand, oxidation of the 4α,6α-diol IIIa with chromium trioxide in pyridine[6] yielded 6α-hydroxy-5α-cholestan-4-one (VIIa) as sole crystalline material. The corresponding acetate VIIb on treatment with potassium bisulfate at 170° underwent β elimination to give the known cholest-5-en-4-one (VIII), identified by direct comparison with an authentic sample.[7] This transformation shows the ketol obtained by the chromium trioxide–pyridine oxidation of IIIa to possess the 6α-hydroxy-4-one structure VIIa rather than the alternative 4α-hydroxy-6-one structure.

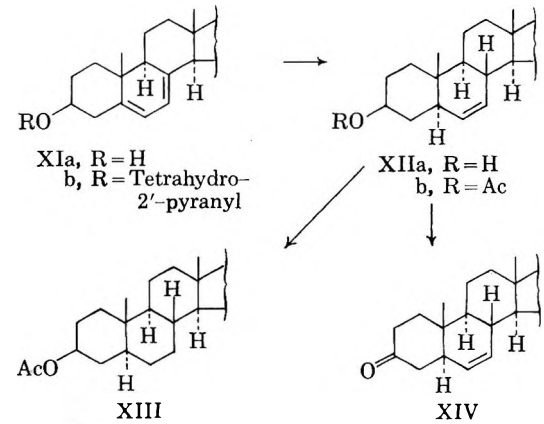
It has been observed previously that ethylenes conjugated with a phenyl group[3b] or with another double bond[3a] on hydroboration undergo addition of the boron atom to the carbon atom α to the conjugating group to a considerably greater extent than ethylenes with the same degree of substitution in which the conjugating group is absent. For instance, *trans*-1-phenylpropene (IX) is attacked at the α-position to the extent of 85%, while the nonconjugated *trans*-4-methyl-2-pentene (X) is attacked at the corresponding position



to the extent of only 43%.[3b,8] An explanation for this behavior of conjugated ethylenes in terms of electronic factors has been given.[3a,b] The result obtained on hydroboration of cholesta-3,5-diene (I) is completely in accord with the previously observed behavior of conjugated ethylenes. The disubstituted Δ^3 double bond is presumably attacked first, the presence of the conjugated Δ^5 bond causing boron to add predominantly at the 4-position; the equatorial α configuration is that expected from steric factors. The trisubstituted Δ^5 double bond is then attacked at C-6 in the usual anti-Markownikoff manner, addition again occurring from the less hindered α side.

The next diene investigated was cholesta-4,6-diene (II). This substance on hydration by method a yielded 35% of 5α-cholestane-4α,6α-diol (IIIa), identical with that obtained by the hydration of the $\Delta^{3,5}$-diene I. In addition *ca.* 10% of a more polar hydroxy compound was isolated, which was not further investigated. The conversion of cholesta-4,6-diene (II) to the 4α,6α-diol IIIa presumably involves attack first of the disubstituted Δ^6 double bond, the presence of the conjugated Δ^4 bond causing boron to add predominantly at the 6-position; the trisubstituted Δ^4 bond is then attacked in the expected anti-Markownikoff manner, both additions again occurring from the less hindered α side.

7-Dehydrocholesterol (cholesta-5,7-dien-3β-ol) (XIa)[9] by method a unexpectedly yielded 20% of 5α-cholest-6-en-3β-ol (XIIa) as the only crystalline substance to be



(5) *Inter alia*, see P. A. Plattner, A. Segré, and O. Ernst, *Helv. Chim. Acta*, **30**, 1432 (1947); P. B. D. de la Mare, W. Klyne, D. J. Millen, J. G. Pritchard, and D. Watson, *J. Chem. Soc.*, 1813 (1956).

(6) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 422 (1953).

(7) *Inter alia*, A. Butenandt and G. Rothenstroth Bauer, *Ber.*, **77**, 397 (1944).

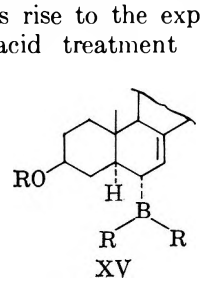
(8) For a similar result with the *p*-methoxy derivative of IX (anethole), see E. L. Allred, J. Sonnenberg, and S. Winstein, *J. Org. Chem.*, **25**, 26 (1960).

(9) Kindly provided by Dr. B. A. Hems, Glaxo Ltd., Greenford, Middlesex, England

isolated.[10] That the product was a cholestenol followed from the elemental composition of the corresponding acetate XIIb, and the fact that the latter substance on catalytic hydrogenation smoothly furnished cholestanyl acetate (XIII) by uptake of 1 molar equiv. of hydrogen. The Δ^6 formulation XIIa was indicated on the basis of the good agreement of the physical properties of the alcohol XIIa, the acetate XIIb, and the ketone XIV (obtained by oxidation of XIIa with chromium trioxide in pyridine)[11] with those reported[12]; subsequently these three substances were identified by direct comparison with the respective authentic samples.

The formation of 5α-cholest-6-en-3β-ol (XIIa) presumably takes place prior to the alkaline hydrogen peroxide oxidation, and in fact about the same yield of this olefin was obtained when the oxidation step was omitted. Since this represents a useful synthetic route to the Δ^6-ene XIIa, the reaction was studied in more detail. It was found that the yield was improved when 7-dehydrocholesterol 3-(2′-tetrahydropyranyl) ether (XIb) was subjected to the lithium aluminum hydride–boron trifluoride reaction, whereby 5α-cholest-6-en-3β-ol acetate (XIIb) was obtained in 35% yield after acetylation of the product. None of the Δ^6 compound was obtained when 7-dehydrocholesterol was treated with lithium aluminum hydride and aluminum chloride[13] in ether.

The mechanism of the reaction leading from 7-dehydrocholesterol to 5α-cholest-6-en-3β-ol was not studied by us. However, it has been shown very recently by Caglioti, Cainelli, and Maina[14] that hydroboration of 7-dehydrocholesterol by passing in diborane gas gives rise to the expected Δ^7-6α-borane XV, which on acid treatment (acetic anhydride–



XV

acetic acid in boiling diglyme) undergoes hydrolysis with rearrangement to yield 5α-cholest-6-en-3β-ol in 35% over-all yield. The apparent direct formation of the Δ^6 compound from 7-dehydrocholesterol in our hands is, therefore, presumably due to the prior formation of the borane XV by means of the lithium aluminum hydride–boron trifluoride combination, hydrolysis with rearrangement occurring subsequently through the action of the fluoroboric acid which is generated from the excess boron trifluoride when water is added at the end of the reaction. It is known that allylic organoboranes are readily susceptible to hydrolysis.[15] This explanation also accounts for the apparent paradox that 5α-cholest-6-en-3β-ol had been formed in the presence of excess of lithium aluminum hydride–boron trifluoride, despite the fact that this combination is known to react readily with this olefin.[1]

Finally the hydration of several $\Delta^{7,9(11)}$-dienes was studied. Hydration of 5α,25D-spirosta-7,9(11)-dien-3β-ol acetate (XVIb) by method b, followed by acetylation, yielded 70% of a substance subsequently shown to be the previously unknown 5α,25D-spirost-7-ene-3β,11α-diol diacetate (XVIIb). In addition, *ca.* 10% of 5α,25D-spirost-7-en-3β-ol acetate (XVIII) was isolated, identified by direct comparison with an authentic sample.[16] This substance most probably had been present as an impurity in the starting $\Delta^{7,9(11)}$-diene XVIb (which had been prepared from the Δ^7-ene XVIII by mercuric acetate dehydrogenation according to Ruyle, *et al.*[17]), and, as found previously,[1] did not undergo hydroboration. It has been noted previously that $\Delta^{7,9(11)}$-dienes prepared by the mercuric acetate dehydrogenation of Δ^7-enes are contaminated with the latter.[17]

The formation of the 11α-acetoxy-Δ^7 compound XVIIb is in keeping with expectation, since Δ^7 steroids are unreactive and $\Delta^{9(11)}$ steroids yield the 11α-hydroxy derivatives in the hydroboration reaction.[1] The structure XVIIb follows from the following observations. Saponification led to the free diol XVIIa, which, though unaffected on treatment with manganese dioxide,[18] yielded the known 5α,25D-spirost-8-ene-3,7,11-trione (XIX)[19] on oxidation with chromium trioxide in pyridine.[6] These results indicated the presence of a β,γ-unsaturated alcohol grouping in XVIIa. Oxidation of the latter substance by the Oppenauer method resulted merely in attack at C-3 to give the hydroxy ketone XX, but oxidation of XVIIa with chromium trioxide in acetone–sulfuric acid[20] affected both hydroxyl groups and gave a mixture of the unconjugated Δ^7-3,11-dione XXI and the conjugated Δ^8-3,11-dione XXII. Isomerization of this mixture with sodium hydroxide at room temperature then yielded the pure Δ^8-3,11-dione XXII, the physical properties of which were in good agreement with those reported.[21] Final proof of the location of the new oxygen group was provided by reduction of Δ^8-3,11-dione XXII with lithium in ammonia containing methanol,[22] giving 5α,25D-spirostane-3β,11α-diol (XXIII), identified by direct comparison with an authentic sample.[19,22] The fact that the 11-hydroxyl group in the hydration product XVIIa is α oriented follows

(10) For preliminary communication, see Y. Mazur, M. Nussim, and F. Sondheimer, *Proc. Chem. Soc.*, 314 (1959).

(11) F. Sondheimer, Y. Klibansky, Y. M. Y. Haddad, G. H. R. Summers, and W. Klyne, *J. Chem. Soc.*, 767 (1961).

(12) *Inter alia*, (a) D. H. R. Barton and W. J. Rosenfelder, *ibid.*, 2459 (1949); (b) O. Wintersteiner and M. Moore, *J. Am. Chem. Soc.*, **72**, 1923 (1950).

(13) See E. L. Eliel, *et al.*, *ibid.*, **82**, 1362, 1367 (1960); **84**, 2356, 2371, 2377 (1962).

(14) L. Caglioti, G. Cainelli, and G. Maina, *Tetrahedron*, **19**, 1057 (1963).

(15) B. M. Mikhailov and F. B. Tutorskaya, *Doklady Akad. Nauk SSSR*, **123**, 479 (1958) [*Chem. Abstr.*, **53**, 6990 (1959)]; D. Devaprabhakara and P. D. Gardner, *J. Am. Chem. Soc.*, **85**, 1458 (1963).

(16) *Inter alia*, G. Rosenkranz, J. Romo, E. Batres, and C. Djerassi, *J. Org. Chem.*, **16**, 298 (1951); W. V. Ruyle, E. M. Chamberlin, J. M. Chemerda, G. E. Sita, L. M. Aliminosa, and R. L. Erickson, *J. Am. Chem. Soc.*, **74**, 5929 (1952).

(17) W. V. Ruyle, T. A. Jacob, J. M. Chemerda, E. M. Chamberlin, D. W. Rosenburg, G. E. Sita, R. L. Erickson, L. M. Aliminosa, and M. Tishler, *ibid.*, **76**, 2604 (1953).

(18) See 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); F. Sondheimer, C. Amendolla, and G. Rosenkranz, *J. Am. Chem. Soc.*, **75**, 5930 (1953).

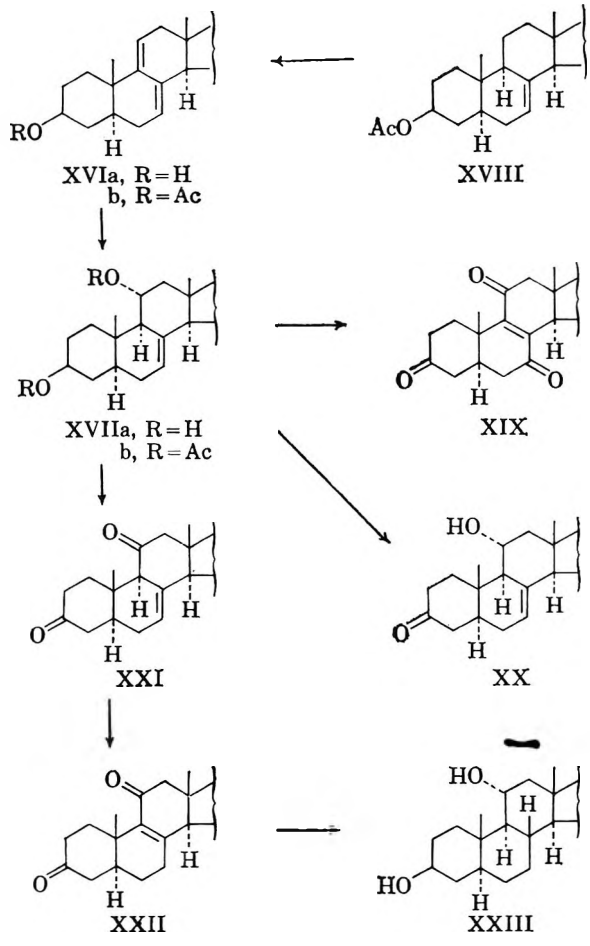
(19) C. Djerassi, E. Batres, M. Velasco, and G. Rosenkranz, *ibid.*, **74**, 1712 (1952).

(20) *Inter alia*, K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946); P. Bladon, J. M. Fabian, H. B. Henbest, H. P. Koch, and G. W. Wood, *ibid.*, 2402 (1951); R. G. Curtis, I. M. Heilbron, E. R. H. Jones, and G. F. Woods, *ibid.*, 457 (1953).

(21) A. J. Lemin and C. Djerassi, *J. Am. Chem. Soc.*, **76**, 5672 (1954).

(22) See F. Sondheimer, O. Mancera, G. Rosenkranz, and C. Djerassi, *ibid.*, **75**, 1282 (1953).

CHART I



from its ready acetylation with acetic anhydride in pyridine, while the 9α configuration is based on the usual over-all *cis* addition of water by the hydration reaction. (See Chart I.)

5α-Cholesta-7,9(11)-dien-3β-ol (type XVIa) on hydration by method a behaved similarly to the $\Delta^{7,9(11)}$-diene in the spirostane series. After acetylation, 60% of 5α-cholest-7-ene-3β,11α-diol diacetate (type XVIIb) was isolated, which on saponification yielded the corresponding diol (type XVIIa). The structures of these substances are based on analogy with the results obtained in the spirostane series. In addition, 10% of 5α-cholest-7-en-3β-ol acetate (type XVIII) was obtained, this substance (as the alcohol) presumably again having been present as an impurity in the $\Delta^{7,9(11)}$-diene.

In the same way, 5α-ergosta-7,9(11)-dien-3β-ol (type XVIa) by method a and subsequent acetylation led to 70% of 5α-ergost-7-ene-3β,11α-diol diacetate (type XVIIb, saponifiable to the corresponding diol XVIIa), as well as to *ca.* 10% of 5α-ergost-7-en-3β-ol acetate (type XVIII).

Experimental[23]

Hydration of Cholesta-3,5-diene (I).—Cholesta-3,5-diene (I) [m.p. 79–80°, $[\alpha]_D$ −123°; λ_{max} 228, 235, and 243 mμ (ϵ 19,000, 20,200, and 12,600)] was prepared from cholest-4-en-3-one by lithium aluminum hydride reduction to a mixture of cholest-4-en-3β-ol and cholest-4-en-3α-ol,[24] followed by dehydration with boiling ethanolic hydrochloric acid.[25] The diene I (1 g.) was hydrated by method a, and the product was chromatographed on 30 g. of alumina. Elution with ether and crystallization from acetone yielded 535 mg. (49%) of 5α-cholestane-4α,6α-diol (IIIa), m.p. 188–190°, as only crystalline material. The analytical sample showed m.p. 194–196°, $[\alpha]_D$ +21°.

Anal. Calcd. for $C_{27}H_{48}O_2$: C, 80.14; H, 11.96. Found: C, 80.38; H, 11.97.

Acetylation of the diol IIIa, followed by crystallization from acetone, led to the diacetate IIIb, m.p. 98–100°, $[\alpha]_D$ +65°.

Anal. Calcd. for $C_{31}H_{52}O_4$: C, 76.18; H, 10.72; $COCH_3$ (2), 17.62. Found: C, 76.22; H, 10.85; $COCH_3$, 17.97.

Hydration of cholesta-3,5-diene by method b gave the 4α,6-diol IIIa, m.p. 187–189°, in 42% yield.

5α-Cholestane-4α,6α-diol Cyclic Sulfite (IV).—Dry pyridine (0.5 cc.) and then thionyl chloride (0.4 cc.) were added to an ice-cold solution of 80 mg. of the 4α,6α-diol IIIa in 5 cc. of dry chloroform. The solution was allowed to stand for 40 hr., and ice was then added. The product was isolated with ether and chromatographed on 3 g. of alumina. Elution with pentane–benzene (4:1) yielded 78 mg. of the cyclic sulfite IV, m.p. 98–100°, which on crystallization from methanol showed m.p. 103–104°, $[\alpha]_D$ +25°, no hydroxyl bands in the infrared.

Anal. Calcd. for $C_{27}H_{46}O_3S$: C, 71.96; H, 10.29; S, 7.10. Found: C, 71.75; H, 10.25; S, 6.75.

The cyclic nature of the sulfite IV was confirmed by the fact that it was recovered unchanged on treatment with acetic anhydride in pyridine at room temperature.

Oxidation of 5α-Cholestane-4α,6α-diol (IIIa). a. With Chromium Trioxide in Acetic Acid.—A solution containing 100 mg. of the diol IIIa and 100 mg. of chromium trioxide in 20 cc. of 95% acetic acid was allowed to stand at room temperature for 16 hr. Isolation with ether and separation into neutral and acidic products gave rise to 85 mg. of an acidic amorphous material (after evaporation of acetic acid) which appears to be the crude triacid VI. Titration of 13.3 mg. of this substance in 20 cc. of ethanol against 0.01 *N* aqueous sodium hydroxide required 8.6 cc. for neutralization; the theoretical amount needed for the triacid VI is 8.55 cc.

b. With Chromium Trioxide in Pyridine.—A solution of 200 mg. of the 4α,6α-diol IIIa in 5 cc. of pyridine was added to a mixture of 260 mg. of chromium trioxide and 2 cc. of pyridine, and the mixture was shaken for 4 days. Saturated aqueous sodium sulfite was added, and shaking was continued for 4 hr. Water was then added, and the product was isolated with ether. Crystallization from methanol afforded 32 mg. of 6α-hydroxy-5α-cholestan-4-one (VIIa), m.p. 128–130°, infrared bands at 1703 cm.$^{-1}$ (4-one) and hydroxyl band.

Anal. Calcd. for $C_{27}H_{46}O_2$: C, 80.54; H, 11.52; active H (1), 0.25. Found: C, 80.35; H, 11.45; active H, 0.26.

Acetylation of the hydroxy ketone VIIa led to 6α-acetoxy-5α-cholestan-4-one (VIIb), which on crystallization from methanol showed m.p. 156–158°, $[\alpha]_D$ +81°; infrared bands at 1721 and 1236 (acetate) and 1706 cm.$^{-1}$ (4-one), no hydroxyl band.

Converstion of 6α-Acetoxy-5α-cholestan-4-one (VIIb) to Cholest-5-en-4-one (VIII).—The acetoxy ketone VIIb (10 mg.) and freshly fused anhydrous potassium bisulfate (100 mg.) were finely ground together and then heated at 170° under reduced pressure (*ca.* 2 mm.) for 30 min. The mixture was cooled, water was added, and the product was isolated with ether. Chromatography on 2 g. of alumina and crystallization from acetone yielded 4 mg. of cholest-5-en-4-one (VIII), m.p. 108–110°, λ_{max} 240 mμ (ϵ 7400); lit.[7] m.p. 111–112°, λ_{max} 241 mμ (ϵ 7200). The substance proved to be identical with an authentic sample (prepared from 2-bromo-5α-cholestan-3-one, according to Butenandt, *et al.*[7]) through infrared comparison and nondepression of the melting point on admixture.

Hydration of 6α-Acetoxycholest-4-ene (V).—6α-Acetoxycholest-4-ene (V) was prepared from cholest-5-ene as described by Jones, *et al.*[26] The acetate V (250 mg.) was hydrated by method b; the product was saponified by means of boiling methanolic potassium hydroxide and then chromatographed on 8 g. of alumina.

(23) For general experimental conditions, as well as details of methods a and b, see the preceding paper.[1]

(24) *Inter alia*, see W. G. Dauben, R. A. Micheli, and J. F. Eastham, *J. Am. Chem. Soc.*, **74**, 3852 (1952).

(25) See (a) R. Schoenheimer and E. A. Evans, *J. Biol. Chem.*, **114**, 567 (1936); (b) J. C. Eck, R. L. Van Peursem, and E. W. Hollingsworth, *J. Am. Chem. Soc.*, **61**, 171 (1939).

(26) D. N. Jones, J. R. Lewis, C. W. Shoppee, and G. H. R. Summers *J. Chem. Soc.*, 2876 (1955).

Benzene eluted 55 mg. (24%) of unchanged cholest-4-en-6α-ol, m.p. 136–138°, while ether eluted 145 mg. (61%) of 5α-cholestane-4α,6α-diol (IIIa), m.p. 186–188°. Crystallization of this diol from acetone yielded a sample, m.p. 193–196°, $[\alpha]_D$ +23°, which was identical with the diol obtained from cholesta-3,5-diene through infrared comparison and nondepression of the melting point on admixture.

Cholesta-4,6-diene (II).—Cholest-5-en-7-one was prepared in three steps from cholesteryl acetate, essentially as described by Nickon and Bagli.[27] The unsaturated ketone (2.5 g.) was reduced with 1 g. of lithium aluminum hydride in 200 cc. of ether (2-hr. boiling), and the total reduction product, consisting mainly of cholest-5-en-7β-ol,[28] was dehydrated directly with boiling alcoholic hydrochloric acid as described by Eck, *et al.*[25b,29] The product was isolated with ether and chromatographed on 500 g. of Alcoa activated alumina (grade F-20). Elution with pentane and crystallization from acetone yielded 1.55 g. of cholesta-4,6-diene (II), m.p. 91–92°, $[\alpha]_D$ +7°, λ_{max} 230, 238, and 245 mμ (ε 21,500, 25,800, and 14,500); lit.[27] m.p. 92–92.5°, $[\alpha]_D$ +13° (lit.[30] $[\alpha]_D$ +9°), λ_{max} 230, 238, and 246 mμ (ε 22,300, 26,100, and 15,200).

Hydration of Cholesta-4,6-diene (II).—Cholesta-4,6-diene (500 mg.) was hydrated by method a, and the product was chromatographed on 15 g. of alumina. Elution with ether furnished 195 mg. (36%) of 5α-cholestane-4α,6α-diol (IIIa), m.p. 184–188°, which after crystallization from acetone showed m.p. 192–194°, $[\alpha]_D$ +20°; it was identical with the diol obtained from cholesta-3,5-diene by infrared comparison and nondepression of the melting point on admixture. Elution with chloroform yielded 55 mg. of crystalline material, m.p. 115–120°, which was not further investigated.

Conversion of 7-Dehydrocholesterol (XIa) to 5α-Cholest-6-en-3β-ol (XIIa).—7-Dehydrocholesterol (XIa)[9] (1 g.) was hydrated by method a, and the product was chromatographed on 30 g. of alumina. The only crystalline material was eluted with benzene. Crystallization from ether–methanol yielded 205 mg. (20%) of 5α-cholest-6-en-3β-ol (XIIa), m.p. 116–117°, $[\alpha]_D$ −86°; lit.[12a] m.p. 114–115°, $[\alpha]_D$ −92°; lit.[12b] m.p. 114–119°, $[\alpha]_D$ −81°. Essentially identical results were obtained when the alkaline hydrogen peroxide step was omitted.

Acetylation of XIIa led to the acetate XIIb, which after crystallization from methanol showed m.p. 104–105°, $[\alpha]_D$ −88°; lit.[12a] m.p. 103.5–104.5°, $[\alpha]_D$ −89°; lit.[12b] m.p. 104–106°, $[\alpha]_D$ −88°.

Anal. Calcd. for $C_{29}H_{48}O_2$: C, 81.25; H, 11.29. Found: C, 81.22; H, 11.40.

Full hydrogenation of the acetate XIIb in acetic acid over a platinum catalyst resulted in the uptake of 1.02 molar equiv. of hydrogen and yielded 5α-cholestan-3β-yl acetate (XIIII), m.p. and m.m.p. 109–110°.

Oxidation of the alcohol XIIa with chromium trioxide in pyridine (see Sondheimer, *et al.*[11]), followed by crystallization from methanol, yielded 5α-cholest-6-en-3-one (XIV), m.p. 120–121°, $[\alpha]_D$ −73°; lit.[11] m.p. 121–122°, $[\alpha]_D$ −75°.

Subsequent to the appearance of the preliminary communication describing this work,[10] authentic samples of the alcohol XIIa, the acetate XIIb, and the ketone XIV became available, and identity with the respective compounds derived from 7-dehydrocholesterol was established by infrared comparison and mixture melting point determination.

Conversion of 7-Dehydrocholesterol 3-(2′-Tetrahydropyranyl) Ether (XIb) to 5α-Cholest-6-en-3β-ol Acetate (XIIb).—The ether XIb was prepared in 90% yield from 7-dehydrocholesterol,[9] 2,3-dihydropyran, and phosphorus oxychloride in chloroform, as described for cholesterol by Greenhalgh, *et al.*[31] After crystallization from acetone it showed m.p. 139–141°, $[\alpha]_D$ −58°; λ_{max} 272, 282, and 293 mμ (ε 11,400, 11,900, and 6,700).

Anal. Calcd. for $C_{32}H_{52}O_2$: C, 81.99; H, 11.18. Found: C, 81.65; H, 11.09.

Boron trifluoride etherate (20 g.) was added to a solution of 2 g. of the ether XIb in 80 cc. of ether, the solution was cooled in ice–water, and a solution of 1.2 g. of lithium aluminum hydride in 60 cc. of ether was then added dropwise during 1 hr., with stirring and continued ice–water cooling, under nitrogen. The ice bath was removed, and the mixture was stirred for 1 hr. at room temperature. Water (50 cc.) was added, and the mixture was stirred for a further 10 min. to complete cleavage of the ether. Ether and more water were added; the ether solution was washed with water, dilute sulfuric acid, sodium bicarbonate solution, and water, and was then dried and evaporated. The residue was acetylated directly and was then chromatographed on 60 g. of alumina. Elution with pentane–benzene (9:1), followed by crystallization from methanol, yielded 650 mg. (36%) of 5α-cholest-6-en-3β-ol acetate (XIIb), m.p. 102–104°. Further crystallization gave a sample, m.p. 104–105°, $[\alpha]_D$ −89°, identical with the compound obtained by the hydroboration of free 7-dehydrocholesterol.

Hydration of 5α,25D-Spirosta-7,9(11)-dien-3β-ol Acetate (XVIb).—This diene [m.p. 208–212°, $[\alpha]_D$ −15°; λ_{max} 236, 242, and 251 mμ (ε 13,500, 14,400, and 9500)] was prepared by dehydrogenation of 5α,25D-spirost-7-en-3β-ol acetate (XVIII)[16] with mercuric acetate, as described by Ruyle, *et al.*[17] The diene (1 g.) was hydrated by method b; the product was acetylated and then chromatographed on 35 g. of alumina. Elution with pentane–benzene (1:3) yielded 80 mg. (8%) of 5α,25D-spirost-7-en-3β-ol acetate (XVIII), m.p. 228–231°, identified by direct comparison with an authentic sample.[6] Elution with benzene furnished 790 mg. (70%) of 5α,25D-spirost-7-en-3β,11α-diol diacetate (XVIIb), m.p. 183–185°, which after crystallization from acetone–methanol exhibited m.p. 187–188°, $[\alpha]_D$ −96°. The compound gave a yellow color with tetranitromethane, and a positive Fieser selenium dioxide test (in keeping with the 5α-Δ⁷ formulation).[32]

Anal. Calcd. for $C_{31}H_{46}O_6$: C, 72.34; H, 9.01. Found: C, 72.46; H, 9.13.

Saponification of the diacetate XVIIb with methanolic potassium hydroxide (1-hr. boiling), followed by crystallization from acetone, afforded 5α,25D-spirost-7-ene-3β,11α-diol (XVIIa), m.p. 190–192°, $[\alpha]_D$ −86°.

Oxidation of 5α,25D-Spirost-7-ene-3β,11α-diol (XVIIa). a. With Chromium Trioxide in Pyridine.—A solution of 100 mg. of the diol XVIIa in 2 cc. of pyridine was added to 130 mg. of chromium trioxide in 1.5 cc. of pyridine, and the mixture was shaken for 48 hr. Methanol was added, the solvents were evaporated under reduced pressure, and the residue was extracted with hot benzene. Evaporation of the solvent, followed by crystallization from methylene chloride–acetone afforded 32 mg. of the yellow 5α,25D-spirost-8-ene-3,7,11-trione (XIX), m.p. 238–242°, $[\alpha]_D$ 0°, λ_{max} 268 mμ (ε 8900); lit.[19] m.p. 243–245°, $[\alpha]_D$ −3°, λ_{max} 268 mμ (ε 8900).

b. With Aluminum Isopropoxide.—A solution of 50 mg. of the diol XVIIa in 5 cc. of toluene and 1 cc. of cyclohexanone was distilled until *ca.* 1 cc. had passed over, in order to remove moisture. Aluminum isopropoxide (100 mg.) was then added, and the solution was boiled under reflux for 1 hr. Ether and water were added, and the organic layer was washed with dilute hydrochloric acid and water. Steam distillation, followed by extraction with ether and crystallization from acetone, furnished 28 mg. of 11α-hydroxy-5α-25D-spirost-7-en-3-one (XX), m.p. 258–262° dec., $[\alpha]_D$ −68°, infrared bands (potassium bromide) at 1710 cm.⁻¹ (3-one) and free hydroxyl band. The compound was unchanged on treatment with sodium hydroxide, showing the absence of the Δ⁷-11-one grouping.

Anal. Calcd. for $C_{27}H_{40}O$: C, 75.66; H, 9.41. Found: C, 75.38; H, 9.31.

c. With Chromium Trioxide in Acetone–Sulfuric Acid.—An 8 *N* chromium trioxide solution in aqueous sulfuric acid[20] was added dropwise to a solution of 50 mg. of the diol XVIIa in 10 cc. of acetone until the orange color persisted. After being shaken at room temperature for 5 min., the mixture was diluted with water and extracted with ether. The resulting product, consisting of a mixture of the unconjugated Δ⁷-3,11-dione XXI and the conjugated Δ⁸-3,11-dione XXII, showed a strong infrared band at 1705 (3-one and Δ⁷-11-one) as well as a weak band at 1675 cm.⁻¹ (Δ⁸-11-one), but no hydroxyl band. This material was isomerized through being allowed to stand for 10 min. in 10 cc. of methanol with 3 drops of 10% aqueous sodium hydroxide. Water was then added, and the product was isolated with ether. Crystallization from acetone yielded 5α,25D-spirost-8-ene-3,11-dione (XXII), m.p. 209–212°, λ_{max} 253 mμ (ε 9200), infrared bands

(27) A. Nickon and J. F. Bagli, *J. Am. Chem. Soc.*, **83**, 1498 (1961).

(28) See ref. 27; L. F. Fieser, M. Fieser, and R. N. Chakravarti, *ibid.*, **71**, 2226 (1949).

(29) J. C. Eck and E. W. Hollingsworth, *ibid.*, **63**, 107 (1941).

(30) C. W. Shoppee, G. H. R. Summers, and R. J. W. Williams, *J. Chem. Soc.*, 1893 (1956); G. J. Kent and E. S. Wallis, *J. Org. Chem.*, **24**, 1235 (1959).

(31) C. W. Greenhalgh, H. B. Henbest, and E. R. H. Jones, *J. Chem. Soc.*, 1190 (1951).

(32) See L. F. Fieser, *J. Am. Chem. Soc.*, **75**, 4395 (1953).

(potassium bromide) at 1712 (3-one) and 1675 cm.$^{-1}$ (Δ^8-11-one), no hydroxyl band; lit.[21] m.p. 210–212°, λ_{max} 253 mμ (ϵ 9300).

Lithium–Ammonia Reduction of 5α,25D-Spirost-8-ene-3,11-dione (XXII).—A solution of 30 mg. of the diketone XXII in 10 cc. of ether was added to a stirred solution of 1 cc. of methanol in 30 cc. of liquid ammonia. Lithium (60 mg.) was added in small pieces, and the mixture was stirred for 10 min. Ammonium chloride (1 g.) was then added, the ammonia was allowed to evaporate, water was added to the residue, and the product was isolated with chloroform. Chromatography on 2 g. of alumina and crystallization from methanol yielded 9 mg. of 5α,25D-spirostane-3β,11α-diol (XXIII), m.p. 216–218°. This compound was identical with an authentic sample (m.p. 217–219°)[19,22] through infrared comparison and nondepression of the m.p. on admixture.

Hydration of 5α-Cholesta-7,9(11)-dien-3β-ol (XVIa).—5α-Cholesta-7,9(11)-dien-3β-ol [m.p. 110–112°, $[\alpha]_D$ +40°; λ_{max} 235, 243, and 251 mμ (ϵ 13,500, 15,600, and 10,100)] was prepared by dehydrogenation of 5α-cholest-7-en-3β-ol with mercuric acetate, as described by Fieser and Herz.[33] The diene (500 mg.) was hydrated by method a; the product was acetylated and then chromatographed on 20 g. of alumina. Elution with pentane–benzene (9:1) yielded 55 mg. (10%) of 5α-cholest-7-en-3β-ol acetate (XVIII), m.p. 116–118°, identified by direct comparison with an authentic sample. Elution with pentane–benzene (1:1) afforded 375 mg. (59%) of 5α-cholest-7-ene-3β,11α-diol diacetate (XVIIb), m.p. 146–148°, which after crystallization from ether–methanol showed m.p. 150–151°, $[\alpha]_D$ −20°. The compound gave a yellow color with tetranitromethane and a positive Fieser selenium dioxide test.[32]

Anal. Calcd. for $C_{31}H_{50}O_4$: C, 76.50; H, 10.36. Found: C, 76.17; H, 10.39.

(33) L. F. Fieser and J. E. Herz, *J. Am. Chem. Soc.*, **75**, 121 (1953).

Saponification of the diacetate XVIIb with methanolic potassium hydroxide (1-hr. boiling), followed by crystallization from ether–methanol, yielded 5α-cholest-7-ene-3β,11α-diol (XVIIa), m.p. 161–162°, $[\alpha]_D$ +3°.

Hydration of 5α-Ergosta-7,9(11)-dien-3β-ol (XVIa).—5α-Ergosta-7,9(11)-dien-3β-ol [m.p. 142–144°, $[\alpha]_D$ +32°; λ_{max} 236, 243, and 252 mμ (ϵ 13,200, 14,900, and 9600)] was prepared by dehydrogenation of 5α-ergost-7-en-3β-ol with mercuric acetate, as described by Fieser and Herz[33] for 5α-cholest-7-en-3β-ol. The diene (500 mg.) was hydrated by method a; the product was acetylated and then chromatographed on 20 g. of alumina. Elution with pentane–benzene (4:1) furnished 65 mg. (12%) of 5α-ergost-7-en-3β-ol acetate (XVIII), m.p. 155–157°, identified by direct comparison with an authentic sample. Elution with pentane–benzene (4:1) yielded 425 mg. (68%) of 5α-ergost-7-ene-3β,11α-diol diacetate (XVIIb), m.p. 137–140°, which after crystallization from ether–methanol showed m.p. 143–145°, $[\alpha]_D$ −17°. The substance gave a yellow color with tetranitromethane and a positive Fieser selenium dioxide test.[32]

Saponification of the diacetate XVIIb through 1-hr. boiling with methanolic potassium hydroxide and subsequent crystallization from ether–methanol led to 5α-ergost-7-ene-3β,11α-diol (XVIIa), m.p. 171–173°, $[\alpha]_D$ +2°.

Anal. Calcd. for $C_{28}H_{48}O_2$: C, 80.71; H, 11.61. Found: C, 80.35; H, 11.56.

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Nuclear Magnetic Resonance Studies on Steroids. III.[1] Steroidal Epoxides and Episulfides

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Proton magnetic resonance spectra of steroidal epoxides and episulfides were investigated to evaluate chemical shifts of the angular methyls and of the epoxidic or episulfidic protons due to the orientation of α and β isomers. The epoxidic or episulfidic proton signal of α isomers is generally found at a higher field than that of β isomers, and their patterns are characteristic of the locations and configurations. Even though the coupling constants obtained from those signals by first-order approximation were considerably smaller than the values calculated from the Karplus equation with the dihedral angles measured in Dreiding models, they allowed the estimation of a $\cos^2$ dependence of the coupling constants on dihedral angles in the epoxide or episulfide systems. A revised Karplus equation is proposed for the 1,2-epoxycyclohexane system. Furthermore, the relationship between the magnitudes of the coupling constants and electronegativities is discussed briefly.

In regard to the proton magnetic resonance (n.m.r.) spectra of steroidal epoxides, Zürcher[2] has reported the chemical shift of the 19-methyl group in several compounds. More recently, Cross[3] has published the n.m.r. spectra of many steroidal 5,6-epoxides, with a discussion on the signal of the epoxidic and 19-methyl protons. On the other hand, the n.m.r. spectra of ethylene oxide, ethylene sulfide,[4] and their monosubstituted derivatives[5–7] have been reported in detail.

This paper presents the n.m.r. spectra of 33 steroidal epoxides and episulfides, and the relationships of the angular methyl and epoxidic (episulfidic) proton signals to the location and configuration of the epoxy (epithio) group. Further, correlation of the coupling constant of the epoxidic (episulfidic) proton with the dihedral angle is discussed in connection with the electronegativities of the participating atoms.

Results and Discussion

Table I lists the n.m.r. spectral data obtained, and Fig. 1 shows typical examples of the signal patterns of epoxidic and episulfidic protons.

Recent studies have shown that geminal and vicinal proton spin-coupling constants are of the opposite sign in various systems.[6,8] In a series of ethylene oxides, geminal couplings (J_{gem}) and vicinal couplings (J_{trans}

(1) Part II: K. Tori and K. Kuriyama, *Chem. Ind.* (London), 1525 (1963).

(2) R. F. Zürcher, *Helv. Chim. Acta*, **44**, 1380 (1961).

(3) A. D. Cross, *J. Am. Chem. Soc.*, **84**, 3206 (1962).

(4) F. S. Mortimer, *J. Mol. Spectry.*, **5**, 199 (1960).

(5) H. S. Gutowsky, M. Karplus, and D. M. Grant, *J. Chem. Phys.*, **31**, 1278 (1959); C. A. Reilly and J. D. Swalen, *ibid.*, **32**, 1378 (1960); **34**, 980 (1961); J. I. Musher, *Mol. Phys.*, **4**, 311 (1961).

(6) C. A. Reilly and J. D. Swalen, *J. Chem. Phys.*, **35**, 1522 (1961).

(7) J. I. Musher and R. G. Gordon, *ibid.*, **36**, 3097 (1962).

(8) For example, R. Freeman, K. A. McLauchlan, J. I. Musher, and K. G. R. Pachler, *Mol. Phys.*, **5**, 322 (1962); R. R. Fraser, *Can. J. Chem.*, **40**, 1483 (1962).

and J_{cis}) between epoxidic protons appear to be of the same signs; whereas in the same series geminal couplings of a methylene group attached to an epoxy ring and vicinal couplings (J_{vic}) between the methylene and the epoxidic protons are of opposite signs, and J_{vic} has the same sign as that of J_{trans}.[5-7] This is clearly demonstrated in the spectrum of epichlorohydrin.[6] However, in spectra of steroidal epoxides (episulfides), it is difficult to assign the signals of methylene groups attached to the epoxy (epithio) ring. Therefore, analyses of the epoxidic (episulfidic) proton signals in the present work were carried out mainly by first-order approximation. Thus, the coupling constants shown in Table I are given without signs. All of these are J_{cis} and J_{vic}, and there are no J_{gem} and J_{trans} in these systems.

Signal Shifts of the Angular Methyl Groups Due to an Epoxy or Epithio Group.—In the n.m.r. spectra of steroids, it is well-known that the substituent effect of various functional groups on the position of the angular methyl signal shows additivity.[2,9] This substituent effect, or the additivity value, is given by the shift in the angular methyl signal due to introduction of a functional group to the steroidal nucleus. The additivity value is fairly large when the substituent is in a 1,3-diaxial relationship to the angular methyl group, and the value for a polar substituent at a β-position of the methyl group is relatively large.[1,2,9-12] However, the additivity in steroids having a functional group that causes alterations in the relative positions of the angular methyls to it is difficult to realize, because of the mutual interactions with other substituents and of the change in ring conformation.[3,11,13]

On the assumption that the additivity rule would hold in the steroids examined, substituent effects due to epoxy (epithio) groups on the angular methyl signals were obtained as shown in Table II, by using the reference compounds listed in Table I. In order to obtain the values for 5β,6β-,[14] 9β,11β-, and 14β,15β-epoxy (epithio) groups in Table II, 5α-H, 9α-H, and 14α-H steroids were respectively used as reference compounds in accordance with Zürcher's view.[2] Zürcher used 9α-H and 14α-H steroids as references for 9β,11β- and 14β,15β-epoxides, respectively.[2] This treatment is believed to be reasonable because the 1,2-epoxycyclohexane ring takes a half-chair form like the cyclohexene ring, as has been demonstrated by Ottar[15] with the electron diffraction method.

Table II gives the following conclusions: (i) in general, an epithio group gives larger shifts than does the corresponding epoxy group; (ii) in the effects of 2,3-epoxy (epithio) and 11,12-epoxy group on the 19-methyl, β isomers show larger values than do α isomers; (iii) a large shift is effected even by an α isomer when the substituent is located at a β,γ-position of the angular methyl group [for example, the 5α,6α-epoxy (epithio) group to the 19-methyl and the 11α,12α-epoxy (epithio) group to the 18-methyl group].

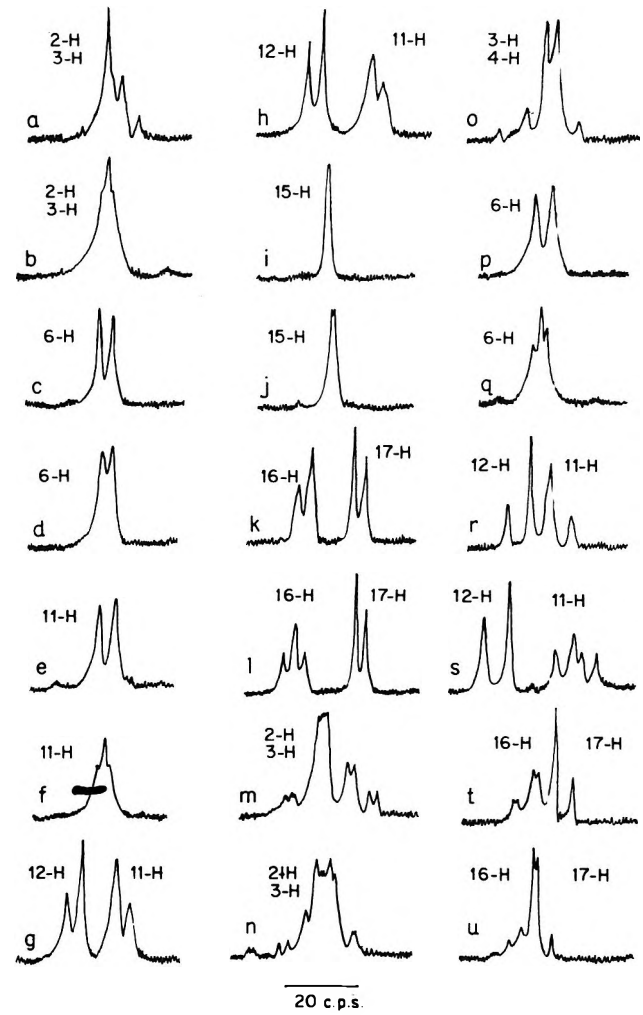

Fig. 1.—Signal pattern of epoxidic or episulfidic protons, at 60 Mc./sec., in 10–15% solutions, in chloroform at room temperature: a, 2α,3α-epoxide; b, 2β,3β-epoxide; c, 5α,6α-epoxide; d, 5β,6β-epoxide; e, 9α,11α-epoxide; f, 9β,11β-epoxide; g, 11α,12α-epoxide; h, 11β,12β-epoxide; i, 14α,15α-epoxide; j, 14β,15β-epoxide; k, 16α,17α-epoxide; l, 16β,17β-epoxide; m, 2α,3α-episulfide; n, 2β,3β-episulfide; o, 3β,4β-episulfide; p, 5α,6α-episulfide; q, 5β,6β-episulfide; r, 11α,12α-episulfide; s, 11β,12β-episulfide; t, 16α,17α-episulfide; and u, 16β,17β-episulfide.

In facts i and ii, the size of the substituent and its spatial proximity to the angular methyl group can be considered as a major contributing factor. However, for fact iii, the inductive effect may also contribute to the shift.[11] In Table II, the shift value of the 9β,11β-epoxy group obtained from IX and XXXVIII is large when compared with the value obtained by Zürcher,[2] who examined methyl 3β-acetoxy-9β,11β-epoxy-5β-etianate. Examination of Dreiding models shows that this difference can result from the Δ^4-3-ketone grouping in IX which causes the 19-methyl group to come closer to the 9β,11β-epoxy group. Similarly, the large shift value for the 16α,17α-epoxy group, obtained in the cases of XV and XVII, may be due to the change in spatial relation between the 18-methyl group and the 17-methyl ketone with an introduction of the epoxy group into the D ring.

As seen from the results in Table II, it is difficult to differentiate the isomers only from the shift of angular

(9) J. N. Shoolery and M. T. Rogers, *J. Am. Chem. Soc.*, **80**, 5121 (1958); J. S. G. Cox, E. O. Bishop, and R. E. Richards, *J. Chem. Soc.*, 5118 (1960); J. C. Jacquesy, J. M. Lehn, and J. Levisalles, *Bull. soc. chim. France*, 2444 (1961).

(10) G. Slomp and B. R. McGarvey, *J. Am. Chem. Soc.*, **81**, 2200 (1959).

(11) Y. Kawazoe, Y. Sato, M. Nutsume, H. Hasegawa, T. Okamoto, and K. Tsuda, *Chem. Pharm. Bull.* (Tokyo), **10**, 338 (1962).

(12) K. Tori and E. Kondo, *Tetrahedron Letters*, **No. 10**, 645 (1963).

(13) K. Tori and T. Komeno, to be published.

(14) In this case Cross[3] has used 5β-H steroids as the references, contrary to Zürcher's view.[2]

(15) B. Ottar, *Acta Chem. Scand.*, **1**, 283 (1947).

TABLE I

N.M.R. DATA OF STEROIDAL EPOXIDES, EPISULFIDES, AND REFERENCE COMPOUNDS[a]

No.	Compound	Chemical shift (τ)[b] 19-H	18-H	O⟨H or S⟨H	Coupling constant, J (c.p.s.)
	Steroidal epoxide				
I	2α,3α-Epoxy-5α-cholestane[c]	9.23	9.35	~6.85 (center)	
II	2α,3α-Epoxy-5α-androstan-17β-ol acetate[d]	9.24	9.24	~6.85 (center)	
III	2β,3β-Epoxy-5α-cholestane[c]	9.15	9.36	~6.87 (center)	
IV	5α,6α-Epoxy-5α-cholestan-3β-ol[e]	8.84	9.38	7.11	$J_{6,7}$ = 3.8
V	5α,6α-Epoxy-5α-androstane-3,17-dione 3,17-bisethylene ketal	8.92	9.21	7.18	$J_{6,7}$ = 3.5
VI	5β,6β-Epoxy-5β-cholestan-3β-ol acetate[e]	8.98	9.35	6.93	$J_{6,7}$ = 2.5
VII	5β,6β-Epoxy-5β-androstane-3,17-dione 3,17-bisethylene ketal	9.00	9.18	6.93	$J_{6,7}$ = 2.5
VIII	Methyl 3α-acetoxy-9α,11α-epoxy-5β-cholanate[f]	8.87	9.26	6.85	$J_{11,12}$ = 4.5
IX	9β,11β-Epoxy-17α-hydroxy-21-acetoxypregn-4-ene-3,20-dione[g]	8.60	9.17	6.54	$J_{11,12}$ = 1.5
X	Methyl 3α-acetoxy-11α,12α-epoxy-5β-cholanate[h]	9.00	9.23	7.09 (11-H) 6.88 (12-H)	$J_{11,12}$ = 4.0 $J_{9,11}$ ~0
XI	Methyl 3α-carbethoxy-11α,12α-epoxy-5β-cholanate	9.00	9.23	7.10 (11-H) 6.89 (12-H)	$J_{11,12}$ = 4.0 $J_{9,11}$ ~0
XII	11β,12β-Epoxy-5α-pregnane-3β,20β-diol diacetate[i]	9.00	9.28	6.91 (11-H) 6.63 (12-H)	$J_{11,12}$ = 3.8 $J_{9,11}$ ~1.5
XIII	3β-Acetoxy-14α,15α-epoxy-5β,14α-card-20(22)-enolide[j]	9.00	9.22	6.46	$J_{15,16}$ ~0.3
XIV	3β-Acetoxy-14β,15β-epoxy-5β,14β-card-20(22)-enolide[j]	8.98	9.06	6.50	$J_{15,16}$ ~0.7
XV	16α,17α-Epoxypregn-4-ene-3,20-dione[k]	8.80 (8.81)[s]	8.93	6.28	$J_{15,16}$ ~0
XVI	2β,3α-Diacetoxy-16α,17α-epoxy-5β-pregnan-20-one[l]	9.00	8.98	6.33	$J_{15,16}$ ~0
XVII	3β-Acetoxy-16α,17α-epoxy-5α-pregnan-20-one[m]	9.17	8.98	6.34	$J_{15,16}$ ~0
XVIII	16α,17α-Epoxyandrostan-3β-ol acetate[n]	9.17	9.28	6.68 (16-H) 6.91 (17-H)	$J_{16,17}$ = 3.0 $J_{15,16}$ ~0
XIX	16β,17β-Epoxyandrostan-3β-ol acetate[q]	9.19	9.19	6.54 (16-H) 6.84 (17-H)	$J_{16,17}$ = 3.0 $J_{15,16}$ = 2.7
	Steroidal episulfide				
XX	2α,3α-Epithio-5α-cholestane[o]	9.20	9.36	6.72 6.95 (2- or 3-H)	$J_{2,3}$ = 7.0
XXI	2β,3β-Epithio-5α-cholestane[o]	9.09	9.36	~6.78 (center)	
XXII	2β,3β-Epithio-5α-androstan-17β-ol acetate[p]	9.10	9.24	~6.77 (center)	
XXIII	3β,4β-Epithio-5α-androstan-17β-ol acetate[p]	9.02	9.24	6.81 6.91 (3- or 4-H)	$J_{3,4}$ = 6.5
XXIV	5α,6α-Epithio-5α-cholestan-3β-ol acetate[q]	8.80	9.39	6.95	$J_{6,7}$ = 5.0
XXV	5α,6α-Epithio-5α-cholestan-3β-ol[q]	8.81	9.39	6.95	$J_{6,7}$ = 5.0
XXVI	5β,6β-Epithio-5β-cholestan-3β-ol[p]	8.85	9.36	6.72	$J_{6,7}$ = 2.0
XXVII	11α,12α-Epithio-5α-pregnane-3β,20β-diol diacetate[r]	9.08	9.09	7.10 (11-H) 6.93 (12-H)	$J_{11,12}$ = 7.0 $J_{9,11}$ ~0
XXVIII	Methyl 3-oxo-11β,12β-epithio-5β-cholanate[r]	8.83	9.17	7.03 (11-H) 6.68 (12-H)	$J_{11,12}$ = 7.0 $J_{9,11}$ = 5.0
XXIX	Methyl 3α-acetoxy-11β,12β-epithio-5β-cholanate[r]	8.92	9.21	7.10 (11-H) 6.73 (12-H)	$J_{11,12}$ = 7.0 $J_{9,11}$ = 5.0
XXX	11β,12β-Epithio-5β-cholane-3α,24-diol diacetate[r]	8.91	9.21	7.10 (11-H) 6.73 (12-H)	$J_{11,12}$ = 7.0 $J_{9,11}$ = 5.0
XXXI	16α,17α-Epithio-5α-androstan-3β-ol acetate[n]	9.17	9.11	6.83 (16-H) 6.98 (17-H)	$J_{16,17}$ = 4.8 $J_{15,16}$ = 1.5
XXXII	16β,17β-Epithio-5α-androstan-3β-ol acetate[n]	9.19	9.19	6.77 (16-H) 6.83 (17-H)	$J_{16,17}$ = 5.2 $J_{15,16}$ = 3.4
XXXIII	16β,17β-Epithioandrost-4-en-3-one[n]	8.82	9.12	6.75 (16-H) 6.82 (17-H)	$J_{16,17}$ = 5.5 $J_{15,16}$ = 3.4
	Reference compound				
XXXIV	5α-Cholestane	9.22	9.35		
XXXV	5α-Cholestan-3β-ol	9.20	9.36		
XXXVI	5α-Cholestan-3β-ol acetate	9.18	9.35		
XXXVII	Methyl 3α-acetoxy-5β-cholanate	9.07	9.35		
XXXVIII	17α-Hydroxy-21-acetoxypregn-4-ene-3,20-dione	8.82[t]	9.28[t]		
XXXIX	5α-Pregnane-3β,20β-diol diacetate	9.17	9.37		
XL	3β-Acetoxy-5β,14α-card-20(22)-enolide[j]	9.01	9.37		
XLI	Pregn-4-ene-3,20-dione	8.81 (8.808)[s] (8.79)[u]	9.32 (9.31)[u]		
XLII	Methyl 3-oxo-5β-cholanate	8.98	9.31		
XLIII	3β-Acetoxy-5α-pregnan-20-one	9.17 (9.177)[s]	9.40		

[a] Chloroform solution [10–15% (w./v.)] at room temperature. [b] Signal positions of the side chain of cholestane derivatives are always τ 9.09 and 9.18, and that of the COOMe group of cholanate derivatives is always τ 6.33 ~ 6.34. [c] A. Fürst and P. A. Plattner, *Helv. Chim. Acta*, **32**, 275 (1949). [d] J. Fajkos and F. Šorm, *Collection Czech. Chem. Commun.*, **24**, 3115 (1959). [e] T. Westphalen, *Ber.*, **48**, 1064 (1915); J. Hattori, *Yakugaku Zasshi*, **60**, 334 (1940); P. A. Plattner, T. Petrzilka, and W. Lang, *Helv. Chim. Acta*, **27**,

513 (1944). [j] E. Seebeck and T. Reichstein, *ibid.*, **26**, 536 (1943). [g] J. Fried and E. F. Sabo, *J. Am. Chem. Soc.*, **79**, 1130 (1957). [h] J. Press and T. Reichstein, *Helv. Chim. Acta*, **25**, 878 (1942); A. Fürst and R. Scotoni, Jr., *ibid.*, **36**, 1410 (1953). [i] R. K. Callow and V. H. T. James, *J. Chem. Soc.*, 4744 (1956). [j] P. Hofer, H. Linde, and K. Meyer, *Helv. Chim. Acta*, **45**, 1041 (1962); H. Ishii, T. Tozyo, and D. Satoh, *Chem. Pharm. Bull.* (Tokyo), **10**, 645 (1962), kindly supplied by Dr. Ishii. [k] O. Mancera, H. J. Ringold, C. Djerassi, G. Rosenkranz, and F. Sondheimer, *J. Am. Chem. Soc.*, **75**, 1286 (1953). [l] Derived from "Yonogenin"; *cf.* K. Takeda, T. Okanishi, and A. Simaoka, *Chem. Pharm. Bull.* (Tokyo), **6**, 532 (1958). [m] B. Camerino, C. G. Alberti, and A. Vercellone, *Gazz. chim. ital.*, **83**, 795 (1953). [n] J. Fajkos, *Collection Czech. Chem. Commun.*, **20**, 312 (1955). [o] D. A. Lightner and C. Djerassi, *Chem. Ind.* (London), 1236 (1962); K. Takeda and T. Komeno, *ibid.*, 1793 (1962). [p] K. Takeda and T. Komeno, to be published. [q] T. Komeno, *Chem. Pharm. Bull.* (Tokyo), **8**, 672 (1960). [r] K. Takeda, T. Komeno, and J. Kawanami, *ibid.*, **8**, 621 (1960). [s] Ref. 2. [t] Ref. 12. [u] Ref. 11.

Table II

Substituent Effect Due to an Epoxy or an Epithio Group on the Position of the Angular Methyl Signals[a]

Substituent	Site of substituent	α 19-H	α 18-H	β 19-H	β 18-H
	2, 3	+0.01	0.00	−0.07	+0.01
	3, 4			(−0.042)[b]	
	5, 6	−0.26	+0.02	−0.20	0.00
		(−0.25)[c]		(−0.042)[c,d]	
Epoxy group	8, 9	(−0.100)[b]			
	9, 11	−0.20	−0.09	−0.22	−0.11
		(−0.200)[b]		(−0.125)[b,c]	
	11, 12	−0.07	−0.12	−0.17	−0.09
		(−0.067)[b]		(−0.192)[b]	
	14, 15	−0.01	−0.15	−0.03	−0.31
		(−0.017)[b]		(−0.100)[b]	
	16, 17	−0.01	−0.42		
Epithio group	2, 3	−0.02	+0.01	−0.13	+0.01
	5, 6	−0.385	+0.035	−0.35	0.00
	11, 12	−0.09	−0.28	−0.15	−0.14

[a] Values are given in p.p.m.; plus sign represents upfield shift. [b] Zürcher's value.[2] [c] Cross' value.[3] [d] This discrepancy is due to the use of 5β-H steroids as references.[3,14] The same value as ours can be obtained if 5α-H steroids were used as references. [e] See text.

Table III

Difference in Signal Positions of Epoxidic or Episulfidic Protons between α and β Isomer, $\Delta\tau_{\alpha,\beta}$ (p.p.m.)

Substituent	Site of proton	$\Delta\tau_{\alpha,\beta}$	Compound to be compared
	2, 3	−0.02 (center)	I, III
	6	0.18	IV, VI
Epoxy group	6	0.25	V, VII
	15	−0.04	XIII, XIV
	16	0.14	XVIII, XIX
	17	0.07	
	2, 3	0.06 (center)	XX, XXI
Epithio group	6	0.23	XXV, XXVI
	16	0.06	XXXI, XXXII
	17	0.05	

methyl signals, even though some of the α isomers can be distinguished from the β isomers.

Signal of Epoxidic or Episulfidic Proton.—Signal peaks of epoxidic (episulfidic) protons in the steroids examined appear at around τ 6.5–7.1, and at about τ 6.3 when the epoxy (epithio) group is conjugated with a carbonyl group, as shown in Table I. These chemical shifts of the epoxidic proton are close to those observed in simple monosubstituted ethylene oxides.[5-7] It should be noted that the epoxidic proton resonates at a considerably higher field than does an ordinary proton attached to an oxygen-bearing carbon atom. This fact can be explained by a possible small ring-current effect in three-membered rings, analogous to the case of the cyclopropyl ring.[16]

It is a known fact that an axial proton in a cyclohexane ring is more shielded than its equatorial counterpart.[17] In the present case of steroidal epoxides (episulfides), however, an epoxidic (episulfidic) proton in a 1,2-epoxycyclohexane (1,2-epithiocyclohexane) ring, regardless of α or β configuration, forms almost the same angle to the cyclohexane ring and is equatorial-like. However, as seen from Table I, the signal of an epoxidic (episulfidic) proton of α isomers generally appears at a higher field than that of β isomers. This difference in signal shift ($\Delta\tau_{\alpha,\beta}$) is listed in Table III. Although this fact is of considerable interest, a satisfactory explanation for this difference is not apparent at present.

The signal pattern of the epoxidic (episulfidic) proton, as shown in Fig. 1, has a characteristic form with regard to the location and configuration of the epoxy (epithio) group. It is not surprising that this signal pattern is always the same, so long as other substituents are not introduced into the same ring bearing the epoxy (epithio) group. For example, the episulfidic protons in XXVIII, XXIX, and XXX (11β,12β-episulfides) show the same signal pattern shown in Fig. 1 (s). Therefore, by comparing the signal pattern of an epoxidic (episulfidic) proton in a steroid with the patterns shown in Fig. 1, one can determine the location and configuration of this epoxy (epithio) group.[18]

Coupling Constant of Epoxidic or Episulfidic Proton.—In recent years, n.m.r. studies of ethylene oxide and and its monosubstituted derivatives[4-7] showed that this system is of an essentially different type from olefins, and its coupling constants are consistent with the Karplus correlation[19] because J_{cis} should be larger than J_{trans}.[4-7] For further confirmation of this view, systematic experiments on disubstituted ethylene oxides and epoxy groups in ring systems are required. Recently, Cross[3] has obtained the J_{vic} value between the epoxidic proton on the C-6 atom and the two protons on the C-7 atom in many steroidal 5,6-epoxides and has compared the observed values with those calculated by applying the Karplus equation (1)[19] to the dihedral angles measured in Dreiding models. However, J_{trans} and J_{cis} can not be obtained from these compounds. Thus,

$$\begin{cases} J = k_1 \cos^2\theta - c: & 0° \leq \theta \leq 90° \\ J = k_2 \cos^2\theta - c: & 90° \leq \theta \leq 180° \end{cases} \quad (1)$$

(16) J. D. Graham and M. T. Rogers, *J. Am. Chem. Soc.*, **84**, 2249 (1962); K. B. Wiberg and B. T. Nist, *ibid.*, **83**, 1226 (1961).

(17) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Inc., New York, N. Y., 1959, p. 115.

(18) In the cases of XV, XVI, and XVII, the signal patterns of the epoxidic protons appear, as a singlet, different from that of XVIII shown in Fig. 1 (k), because another substituent (17β-acetyl group) is introduced into the epoxy ring. The location and configuration of an epoxy (epithio) group, of course, can not be estimated in such cases as above.

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

TABLE IV

COUPLING CONSTANTS IN THREE-MEMBERED RING SYSTEMS

Substance	Coupling constants, J (c.p.s.) J_{cis}	J_{trans}	J_{gem}	$J_{C^{13}-H}$	Ref.
Cyclopropane	7.5			161	21
Substituted cyclopropanes[a]	8.67	5.71	−6.65		20
Ethylene oxide	4.45	3.1		175.8	4
Propylene oxide	4.5	2.5	5.5		7
Monosubstituted ethylene oxides[a]	4.3	2.3	5.7		5, 6
1,2-Epoxycyclohexane deriv.[a]	3.9				This work
1,2-Epoxycyclopentane deriv.[a]	3.0				This work
Ethylene sulfide	7.15	5.65		170.5	4
Propylene sulfide	6.3	5.4	$\lesssim$0.4		7
1,2-Epithiocyclohexane deriv.[a]	6.9				This work
1,2-Epithiocyclopentane deriv.[a]	5.6				This work
Ethylene imine	6.3	3.8		168.1	4

[a] Coupling constants are shown in mean values, as data for a series of derivatives are cited in the reference.

J = coupling constant in a >CH–CH< fragment

k_1, k_2, c = constants ($k_1 = 8.5, k_2 = 9.5, c = 0.28$ c.p.s.)

θ = dihedral angle between a respective pair of protons

it is not yet clear whether the Karplus correlations hold in the ethylene oxide system over the whole range of the dihedral angle. On the other hand, Hutton and Schaefer[20] have concluded from studies on the spectra of cyclopropane derivatives that J_{cis} is larger than J_{trans} and that both couplings are in good agreement with those calculated from the Karplus equation. Furthermore, the nonolefinic type of this coupling is supported by the fact that introduction of an electronegative substituent into the ring influences the coupling constants only a little,[20] although it is well-known that the cyclopropane ring has a π-character.

As can be seen from Table I, the magnitudes of J_{cis} (about 3.0 ~ 4.5 c.p.s., corresponding to dihedral angle 0°) between the epoxidic protons of various steroidal epoxides are in good agreement with those of ethylene oxide systems.[4-7] Similarly, good agreement with that of the ethylene sulfide system[4,7] is obtained in the case of steroidal episulfides (about 5.0 ~ 7.0 c.p.s.). These facts confirmed the previous conclusion that J_{cis} is larger than J_{trans}.

The coupling constants in three-membered ring systems are summarized in Table IV. Table IV shows that the magnitudes of J_{cis} and J_{trans} increase in the following order, ethylene oxide < ethylene sulfide $\lesssim$ ethylene imine < cyclopropane system, whereas $J_{C^{13}-H}$ determined by C^{13} satellites decreases in the above order.[4,21] Microwave studies showed that the H–C–H angles and accordingly the H–C–C–H dihedral angles in both ethylene oxide and ethylene sulfide are equal within a fraction of a degree, and also that the C–C bond lengths are almost equal.[22] The data on ethylene imine are not very different from those in the above two

(20) H. M. Hutton and T. Schaefer, *Can. J. Chem.*, **41**, 684 (1963).
(21) N. Muller and D. Pritchard, *J. Chem. Phys.*, **31**, 768 (1959).
(22) G. L. Cunningham, A. W. Boyd, R. J. Myers, W. D. Guinn, and W. I. LeVan, *ibid.*, **19**, 676 (1951).

TABLE V

CALCULATED AND OBSERVED COUPLING CONSTANTS FOR STEROIDAL EPOXIDIC AND EPISULFIDIC PROTONS, J (C.P.S.)

Site of substituent	Proton (H)	Dihedral angle[a]	Epoxidic proton J_{calcd}[b]	Epoxidic proton J_{obsd}	Episulfidic proton J_{calcd}[c]	Episulfidic proton J_{obsd}
5α, 6α	6β–7α	92°	0.3	~0	0.1	~0
		(94 ± 4°)[d]	(0.28–0.1)[d]	(~0)[d]		
	6β–7β	28°	6.4	3.8, 3.5	4.0	5.0
		(28 ± 4°)[d]	(5.8–6.8)[d]	(3.3–4.1)[d]		
5β, 6β	6α–7α	72°	0.5	~0	0.5	~0
		(75 ± 4°)[d]	(0.03–0.62)[d]	(~0)[d]		
	6α–7β	48°	3.5	2.5	2.3	2.0
		(49 ± 4°)[d]	(2.8–4.0)[d]	(2.1–2.7)[d]		
9α, 11α	11β–12α	98°	0.1	~0	0.1	
	11β–12β	22°	7.0	4.5	4.4	
9β, 11β	11α–12α	58°	2.1	~1.5	1.4	
	11α–12β	62°	1.6	~1.5	1.2	
11α, 12α	11β–9α	90°	0.3	~0	0.0	~0
11β, 12β	11α–9α	50°	3.2	~1.5	2.1	5.0
14α, 15α	15β–16α	74°	0.4	~0		
	15β–16β	46°	3.8	~0.3		
14β, 15β	15α–16α	38°	5.0	~0.7		
	15α–16β	82°	0.1	~0		
16α, 17α	16β–15α	62°	1.6	~0		~0
	16β–15β	58°	2.1	~0		1.5
16β, 17β	16α–15α	15°	7.6	2.7		3.4
	16α–15β	105°	0.4	~0		~0

[a] These values were measured in Dreiding models (accuracy about ±2°). [b] Calculated from Karplus equation 1.[19] [c] Calculated from a revised Karplus equation (2) for 1,2-epoxycyclohexane ring system proposed in the present work. [d] Cross' value.[3]

systems.[23] Therefore, as has already been pointed out, molecular geometry does not appear to contribute to the coupling constants in these systems.[4,7] Recent studies indicated that coupling constants in vinyl systems decrease with the increase in electronegativities of substituents.[24] This is also the case with the $-CH_2-CHX-$ fragment, although the effect of electronegativity of the substituent X on the coupling constant is much weaker.[25] Further, it has been shown that $J_{C^{13}-H}$ increases when an electronegative atom is bonded to the carbon.[26] The variation in the coupling constants in three-membered ring systems is, therefore, attributable to the electronegativity of the third atom of these ring systems, as already quoted by Williamson.[25] This consideration also gives a clear explanation for the difference in J_{vic} values of epoxides and episulfides from theoretical values, as quoted later. Table IV also shows that the coupling constants are somewhat smaller in a 1,2-epoxycyclopentane ring system (an epoxide on the steroidal D-ring) than those in a 1,2-epoxycyclohexane ring system. This point is discussed later.

In order to examine the applicability of the Karplus correlation[19] to J_{vic} between the epoxidic (episulfidic) proton and the proton on the adjacent carbon atom, we compared the observed J_{vic} values with those calculated from the Karplus equation 1 by using the dihedral angles between the respective pair of protons directly measured in Dreiding models, as shown in Table V. The dihedral angles obtained for the epoxides were adopted for the episulfides, because there may be no significant difference in C–C bond lengths and bond

(23) T. E. Turner, V. C. Fiova, and W. M. Kendrick, *ibid.*, **23**, 1966 (1955).
(24) For example, T. Schaefer, *Can. J. Chem.*, **40**, 1 (1962).
(25) K. L. Williamson, *J. Am. Chem. Soc.*, **85**, 516 (1963).
(26) J. N. Shoolery, *J. Chem. Phys.*, **31**, 1427 (1959); E. R. Malinowski, *J. Am. Chem. Soc.*, **83**, 4479 (1961).

angles between epoxy and epithio groups as shown by the microwave studies mentioned above.[22] Figure 2 shows the plots of J_{vic} against dihedral angles together with the curve calculated from the Karplus equation 1. As clearly seen from Fig. 2, although the coupling constant of the epoxides has considerably smaller values than the calculated values, the J_{vic} is apparently a function of the dihedral angle. In the case of episulfides, this discrepancy is not so pronounced as in the case of the epoxides. As already mentioned, these discrepancies from the Karplus curve can be explained by the electronegativities of oxygen and sulfur atoms. The discrepancy is even larger when an epoxy or epithio ring is attached to the D-ring, that is, in the case of the 1,2-epoxy- or 1,2-epithiocyclopentane ring system. This fact was also seen in J_{cis} in Table IV. In the rigid ring system, the magnitudes of these couplings appear to be affected by the ring size also. Probably, these are due to the distortion of the normal bond angles of the epoxy (epithio) ring induced by the rigid ring system.

In the theoretically derived Karplus equation (1),[19] the values for the coefficients, k_1, k_2, and c, can be replaced by other values which vary with the nature of substituents on the >CH–CH< fragment and of the environments around it.[25,27] Several sets of the coefficients have been proposed from the experimental results for several systems.[27] From the results in Table V, we have deduced an approximate k_1 value for the 1,2-epoxycyclohexane ring system. Because there should be some difference in contribution of electronegativity of the oxygen atom, J_{cis} can not be discussed on the same basis as J_{vic}. The following revised Karplus equation (2) is proposed for the system.

$$J = 5.1 \cos^2 \theta \qquad 0° \leq \theta \leq 90° \qquad (2)$$

Calculated values of J_{vic} from this equation are also shown in Table V, and the calculated curve is shown in Fig. 2 by the broken line. Although the k_2 value is believed to be small as compared with that in the Karplus equation 1, the twin equation (2) for the dihedral angle 90–180° can not be obtained from the steroidal epoxides employed in the present study. Similarly, more experimental data will be required to derive revised Karplus equations for 1,2-epoxycyclopentane or epithio ring systems.

Experimental

The spectra were taken with a Varian A-60 analytical n.m.r. spectrometer system on 10–15% (wt./v.) solutions of the samples in purified chloroform containing 1% tetramethylsilane as an internal standard. All the chemical shifts are expressed in τ-units, and coupling constants are in c.p.s. The calibration of the spectrometer was checked by using the signal peaks of pure *p*-anisaldehyde in 4.0% (wt./v.) solution in carbon tetrachloride.[28] Accuracy limits are about τ ±0.02 for chemical shifts and about ±0.3 c.p.s. for coupling constants. All the samples employed (see Table I) were synthesized by authentic methods in this laboratory.

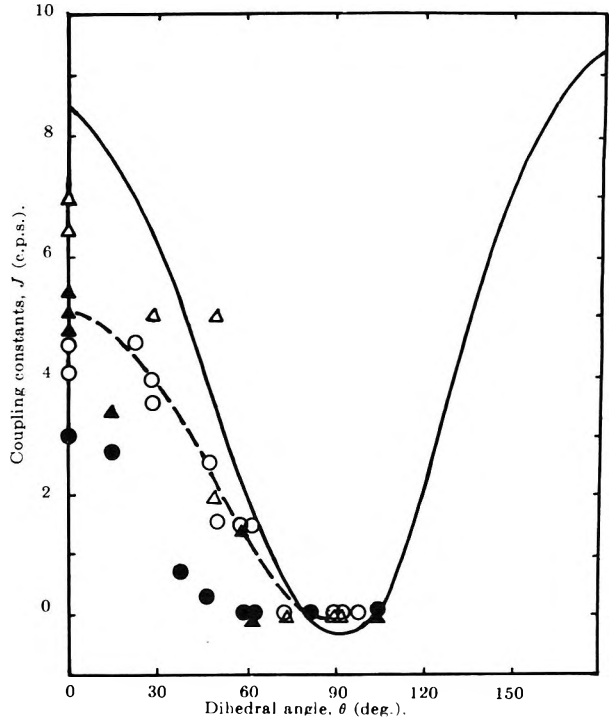

Fig. 2.—Plots of the coupling constants of steroidal epoxidic and episulfidic protons against the dihedral angles measured in Dreiding models: ○, observed in 1,2-epoxycyclohexane ring system; △, observed in 1,2-epithiocyclohexane ring system; observed in 1,2-epoxycyclopentane ring system; ▲, observed in 1,2-epithiocyclopentane ring system; ———, calculated curve from the Karplus equation (1); – – – –, calculated curve from the revised Karplus equation (2) for 1,2-epoxycyclohexane ring system proposed in the present work.

Acknowledgment.—We are greatly indebted to Dr. H. Ishii for supplying us with the compounds (XIII, XIV, and XL), and also to Dr. K. Takeda, Director of this laboratory, and Dr. H. Minato for their helpful advice on this work.

(27) K. L. Williamson and W. S. Johnson, *J. Am. Chem. Soc.*, **83**, 4623 (1961); R. J. Abraham and J. S. E. Holker, *J. Chem. Soc.*, 806 (1963).
(28) G. V. D. Tiers and D. R. Hotchkiss, *J. Phys. Chem.*, **66**, 560 (1962).

The Synthesis and Stereochemistry of Isomeric 16-Hydroxy-17(20)-pregnenes

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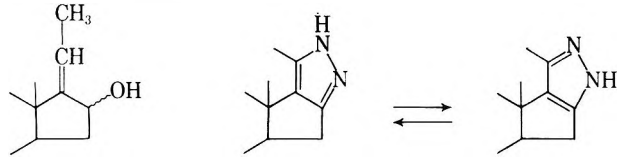
The hydrazine reduction of 16α,17-epoxypregnenolone (**5**) afforded a pyrazole (**9**) and two isomeric allylic alcohols, 5,17(20)-(*cis*)-pregnadiene-3β,16α-diol (**8**) and 5,17(20)-(*trans*)-pregnadiene-3β,16α-diol (**7**). The acid-catalyzed equilibration of 5,16-pregnadiene-3β,20(α or β)-diol also afforded two isomeric allylic alcohols, compound **7**, identical with the product of the hydrazine reaction, and 5,17(20)-(*trans*)-pregnadiene-3β,16β-diol (**6**). Assignments of structure were made on the basis of the methods of preparations, conversions of the isomers to identical products, n.m.r. spectra of the compounds, and molecular rotations.

Several years ago we observed that the Kishner reduction–elimination of the steroidal 16α,17-epoxy-20-keto system afforded two isomeric unsaturated alcohols together with a steroidal pyrazole.[1] The stereochemistry of the isomeric alcohols remained in question until recently. The investigation of the prototropic equilibration of the steroidal allylic Δ^{16}-20-hydroxy system also afforded two isomeric alcohols, one of which was identical with one of the alcohols obtained in the previously mentioned Kishner reduction–elimination. The three alcohols represented three of four possible isomeric 5,17(20)-pregnadiene-3β,16-diols having the partial structure **1**, while the pyrazole isolated in the hydrazine reduction had the partial structure **2**.

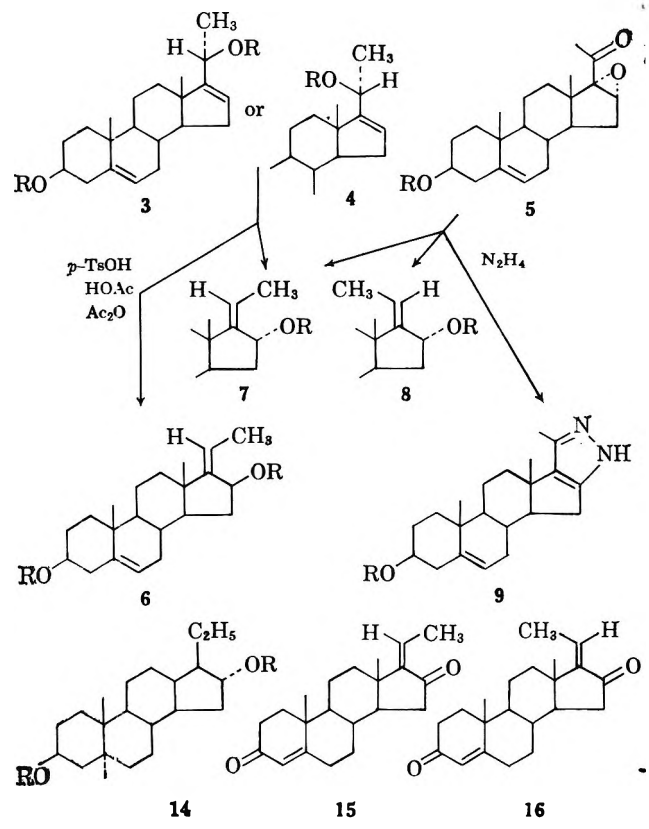


1 **2**

These structural assignments are supported by the recent work of Wharton and Bohlen[2] wherein α,β-epoxy ketones also were shown to react with hydrazine to afford allylic alcohols.[3,4]

The Hydrazine Reduction of 16α,17-Epoxypregnenolone (5).—The Kishner reduction–elimination of 16α,17-epoxypregnenolone (**5**), under Huang-Minlon conditions,[5] yielded 3β-hydroxyandrost-5-ena-[16,17-*c*]-5′-methylpyrazole (**9a**), and a mixture of difficultly separable 5,17(20)-pregnadiene-3β,16-diols (**7a** and **8a**). The steroidal pyrazole (**9a**) was readily identified by its analysis, its infrared and ultraviolet spectra [λ_{max} 225 mμ (ϵ 6100)],[6] and by analogy with previous reactions of α,β-epoxy ketones with hydrazine.[7]

CHART I



Series a, R = H
Series b, R = Ac

The isomeric 5,17(20)-pregnadiene-3β,16-diols (**7a** and **8a**), which also could be made more simply by heating 16α,17-epoxypregnenolone (**5a**) with hydrazine hydrate under reflux, could be separated with difficulty into pure 5,17(20)-(*trans*)-pregnadiene-3β,16α-diol (**7a**), m.p. 219–222°, and 5,17(20)-(*cis*)-pregnadiene-3β,16α-diol (**8a**), m.p. 190–191.5°, by careful chromatography on silica gel, followed by fractional crystallization of the intermediate fractions. The evidence for these assignments of structure is presented later in this paper. From reactions run either at the high or low temperature, the *cis* isomer (**8a**) was isolated in slightly higher yield than the *trans* compound (**7a**).

The course of this reaction can be most readily rationalized as another example of the Kishner reduction–elimination reaction, which has been investigated most competently by Leonard and Gelfand.[8] The partial stereoselectivity of the reaction also can be rationalized

(1) R. M. Dodson, U. S. Patent 2,937,168 (May 17, 1960).

(2) P. S. Wharton and D. H. Bohlen, *J. Org. Chem.*, **26**, 3615 (1961).

(3) Since this work was completed, a communication has appeared describing the hydrazine reduction of the same 16α,17-epoxy 20-ketone described herein. However, only a single alcohol was isolated and the stereochemistry was not assigned. See Huang-Minlon and Chung-Tungshun, *Tetrahedron Letters*, **No. 19**, 666 (1961).

(4) The formation of both isomers is shown by C. Djerassi, "Steroid Reactions," Holden-Day, Inc., San Francisco, Calif., 1963, p. 256. No physical properties or evidence for the assigned configurations are given. NOTE ADDED IN PROOF.—Two recent publications describing the hydrazine reduction of 16,17-epoxy 20-ketones have appeared since the submission of this manuscript: R. Sciaky and F. Facciano, *Gazz. chim. ital.*, **93**, 1028 (1963); and C. Beard, J. M. Wilson, H. Budzikiewicz, and C. Djerassi, *J. Am. Chem. Soc.*, **86**, 269 (1964).

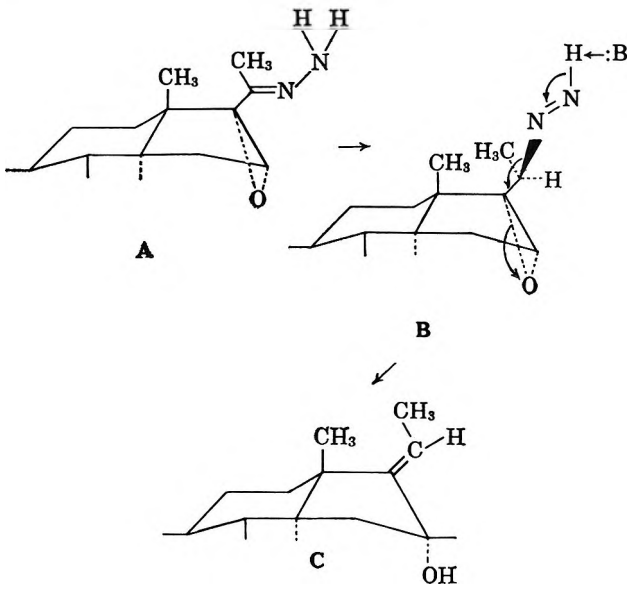
(5) Huang-Minlon, *ibid.*, **68**, 2487 (1946).

(6) 3,4,5-Trimethylpyrazole has λ_{max}^{EtOH} 223 mμ (ϵ 4900). D. Dal Monte Casoni, A. Mangini, and P. Passerini, *Boll. sci. fac. chim. ind. Bolongna*, **12**, 147 (1954). For the infrared spectrum of 3,4,5-trimethylpyrazole see v. R. Hüttel, H. Wagner, and P. Jochum, *Ann. Chem.*, **593**, 179 (1955).

(7) R. C. Elderfield, "Heterocyclic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1957, Vol. 5, Chapter 2 (T. L. Jacobs), p. 68.

(8) N. J. Leonard and S. Gelfand, *J. Am. Chem. Soc.*, **77**, 3272 (1955). For other examples of the Kishner reduction–elimination reaction, see the many references in this paper.

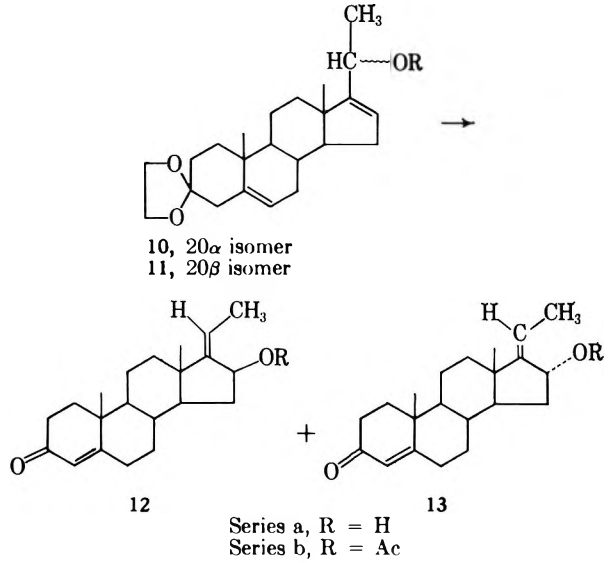
on the basis of the mechanisms contained in that paper. Thus, if it is assumed that the preferred conformation of the 20-hydrazone (**A**) is similar to that of the 20-ketone in pregnan-20-one[9] or in 3β-acetoxy-17α-bromo-5α-pregnan-20-one,[9] then protonation at C-20, either of the hydrazone, or of a negative ion obtained from it, should occur preferentially from the α side and result in the formation of **B**. *trans* elimination from **B** should lead to the formation of 5,17(20)-(*cis*)-pregnadiene-3β,16α-diol (**C**, **8a**).



The Acid Equilibration of 20-Hydroxy-16-pregnenes.—In an attempt to synthesize the other isomeric 16-hydroxy-17(20)-pregnenes and in an attempt to determine the relative stability of the various isomeric endocyclic (Δ^{16}-20-ols) and exocyclic ($\Delta^{17(20)}$-16-ols) allylic alcohols, the acid-catalyzed isomerization of the 20-hydroxy-16-pregnenes was studied. Initially, we had intended to study the equilibration in acid of *pure* 20α- and 20β-hydroxy-Δ^{16}-pregnenes. However, in the preparation of these starting materials we observed[10] a marked tendency for the epimeric 20-hydroxy-5,16-pregnadienes to form molecular complexes. Indeed, because of the extreme difficulty encountered in separating these epimers, the following rearrangement studies were made: (a) in the 3-hydroxy-Δ^5 series, rearrangements were run on the pure 20β-hydroxy compound (**4a**) and on a 1:1 mixture of 20α- and 20β-hydroxy compounds (**3a** and **4a**); (b) in the 3-ethylene ketal-Δ^5 series, rearrangements were run on the pure 20α-hydroxy ketal (**10a**) and on a 1:1 mixture of 20α- and 20β-hydroxy ketals (**10a** and **11a**). This potentially complicating factor proved to be of no consequence as to the position of the equilibrium. Thus the stereochemistry at C-20 did not appear to alter the position of the *exo–endo* equilibrium nor the ratio of the geometric isomers in the products under the reaction conditions employed. The equilibrations were run at room temperature in acetic acid–acetic anhydride medium in the presence of 0.01 to 0.02 *N* *p*-toluenesulfonic acid for at least 24 hr.[11] The resulting mixture of products resisted several attempts at precise quantitation by thin layer, vapor phase, or paper chromatographic techniques. Nevertheless, sufficient resolution was attained by column chromatography to indicate quite clearly that the position of the equilibrium lay well in the direction of the *exo*-unsaturated compound.

The mixture resulting from the previously described acid-catalyzed equilibration of 5,16-pregnadiene-3β,20β-diol[12] was partly resolved by chromatography on alumina. The major components, isolated in a ratio of about 3:1, were 3β,16β- and 3β,16α-diacetoxy-5,17(20)-(*trans*)-pregnadiene (**6b** and **7b**), respectively, accompanied by a small amount of the unrearranged epimeric 20β- and/or 20α-acetoxy-Δ^{16}-pregnenes (**3b** and **4b**). As far as we could determine the same ratio of products resulted from the equilibration of a 1:1 mixture of the C-20 epimers[10] as from the 20β-diol. Equilibration of the corresponding diacetates gave the same ratio of products.

In the 3-ethylene ketal[10] series, the results of equilibration were strictly analogous to the 3-hydroxy compounds. Thus the pure 20α-hydroxy compound, which was the more readily purified of this pair of epimers, gave the same ratio of products as resulted from a 1:1 mixture of C-20 epimers, namely the analogous 3-keto-Δ^4 structures **12** and **13**. In this series also, the 16β isomer was the preponderant product.



Stereochemistry of the 5,17(20)-Pregnadiene-3,16-diols.—The assignment of configuration of the hydroxyl group as well as the geometry about the 17(20) double bond in each of the isomeric products was based largely on n.m.r. spectral evidence. Various chemical transformations as well as an analysis of the molecular rotations of the compounds provided additional evidence for the assignments given. As seen in Table I the two 17(20)-(*trans*)-diols (**6** and **7**) and their diacetates exhibited the expected molecular rotatory contributions for 16β and 16α substitution. The single

(9) N. L. Allinger and M. A. DeRooge, *J. Am. Chem. Soc.*, **83**, 4256 (1961); C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, p. 128.

(10) W. R. Benn, *J. Org. Chem.*, **28**, 3557 (1963).

(11) This system was chosen to avoid competing etherification, dehydration, or rearrangement to a ketone. In preliminary experiments, attempts to study the equilibrium of the alcohols rather than their esters, *e.g.*, treatment with perchloric acid in acetone, led to polymeric products.

(12) R. E. Marker, D. L. Turner, R. B. Wagner, P. R. Ulshafer, H. M. Crooks, Jr., and E. L. Wittle, *J. Am. Chem. Soc.*, **63**, 779 (1941).

TABLE I

ROTATIONAL VALUES

Isomer	Configuration 16-OR	Configuration $\Delta^{17(20)}$	$[\alpha]_D$	M_D	ΔM_D (16-OR) Obsd.[a]	ΔM_D (16-OR) Lit.[b]	ΔM_D (OAc-OH) Obsd.	ΔM_D (OAc-OH) Lit.[b]	ΔM_D (*cis-trans*)[c]
6a	β-OH	*trans*	−32	−101	121	38			
6b	β-OAc	*trans*	−17	−68	175	102	54	64	
7a	α-OH	*trans*	−73	−231	−9	−59			
7b	α-OAc	*trans*	−116	−465	−222	−298	−213	−239	
8a	α-OH	*cis*	−89	−282					−51
8b	α-OAc	*cis*	−89.5	−359			−56	−239	106
15	=O	*trans*	−61	−191	−542	−490			
16	=O	*cis*	−30	−94					97

[a] The observed values of ΔM_D are calculated from reported molecular rotational values for the 16-desoxy analogs believed to have the more stable *trans* configuration at the 17(20) double bond. This assignment is most reasonable in light of the several methods reported for the preparation of the reference compounds: L. Ruzicka, M. W. Goldberg, E. Hardegger, *Helv. Chim. Acta*, **22**, 1294 (1939); **25**, 1297 (1942); and R. Fischer, G. Lardelli, and O. Jeger, *ibid.*, **33**, 1335 (1950). [b] Literature values are taken from L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p. 179, and from W. Klyne, "The Chemistry of the Steroids," Methuen and Co. Ltd., London, 1957, p. 55. [c] Hogg and co-workers report positive values for ΔM_D (*cis-trans*) in a series of $\Delta^{17(20)}$-C_{21} compounds; J. A. Hogg, *et al.*, *J. Am. Chem. Soc.*, **77**, 4436 (1955).

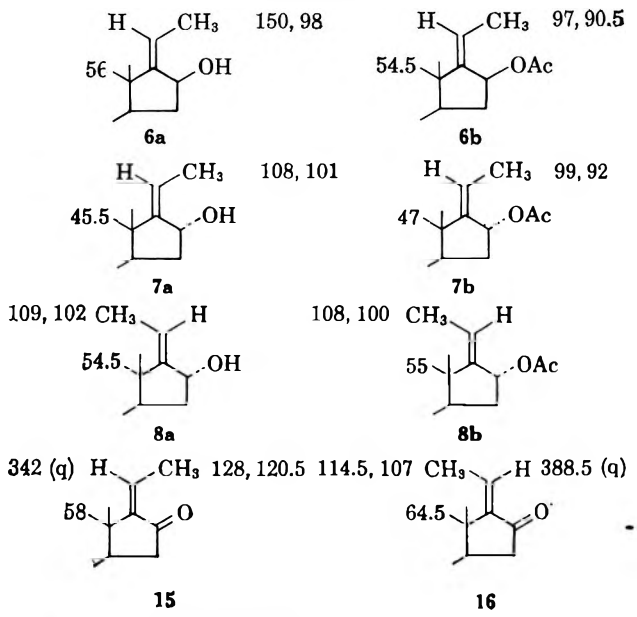
cis compound (**8**) showed a molecular rotatory contribution for the acetylation of a 16α-hydroxy group different from those previously recorded. This may reflect distortion in the *cis* isomer that is not present in the other two compounds.

Tsuda and co-workers[13a] and Tweit, Dodson, and Muir[13b] have observed that a β-hydroxy or β-acyloxy substituent at C-14[13a] or C-15 causes a marked downfield shift in the position of the C-18 methyl resonance in the n.m.r. spectrum of pregnane derivatives, whereas the corresponding α isomer results in a much smaller displacement. We have observed a similar downfield shift in the position of the C-18 methyl resonance in two of the three diols and their diacetates relative to the position of this absorption in the third isomer (Table II). This might suggest that these two isomers had the β configuration at C-16 and the remaining isomer the α configuration. However, an explanation that is more in agreement with the other data is that in one of the two isomers (**6**) the downfield shift results from the deshielding effect of a β-oxygen function at C-16, while in the second compound (**8**) a corresponding shift of the *same magnitude* is produced by interaction between the C-18 angular methyl group and the C-21 methyl group of a *cis*-oriented ethylidene side chain, a situation that is precluded by the geometry of a *trans* conformation.[14]

In further support of the assignments shown, a comparison of the n.m.r. spectra of the 16-acetylated diols with their respective alcohols reveals a long-range effect on the position of the doublet produced by the C-21 methyl proton resonance in two of the isomers and not in the third. As can be seen from molecular models, a *trans*-oriented $\Delta^{17(20)}$-pregnene forces the C-21 methyl group into close proximity to a substituent at C-16. Thus in the two isomers assigned the *trans* structure (**6** and **7**), replacement of the proton of the hydroxyl function with an electron-withdrawing acetyl group results in less deshielding of the protons of the C-21 methyl group by the electrons of the C-16 oxygen,

TABLE II[a]

C-18 AND C-21 METHYL PROTON RESONANCE FREQUENCIES OF ISOMERIC 5,17(20)-PREGNADIENE-3β,16-DIOLS AND THEIR DERIVATIVES



[a] N.m.r. spectra were determined in deuteriochloroform using a Varian Associates A-60 spectrometer operating at 60 Mc.p.s. The numbers adjacent to the protons at C-18, C-20, and C-21 indicate their resonance frequencies expressed in cycles per second in the direction of decreasing field strength relative to an internal tetramethylsilane standard.

i.e., an upfield shift in the C-21 absorption upon acetylation. Tsuda[13a] also has observed an upfield shift in the position of angular methyl resonance upon acetylation of a hydroxyl function so situated as to permit a spatial interaction of the two groups. In the *cis* isomer (**8**) the C-21 methyl group is physically remote from the long-range influence of functionality at C-16 and thus there is essentially no change in the position of this band upon acetylation.

The configurations of the two isomeric 16-hydroxy-4,17(20)-pregnadiene-3-ones (**12** and **13**) isolated from the acid-catalyzed equilibration of the 3-ethylene ketals (**10** or **11**) were assigned using the same line of reasoning. Thus the major product was assigned the 16β-$\Delta^{17(20)}$-*trans* structure, and the minor component the 16α-$\Delta^{17(20)}$-*trans* configuration.

(13) (a) Y. Kawazoe, Y. Sato, M. Natsume, H. Hasegawa, T. Okamoto, and K. Tsuda, *Chem. Pharm. Bull.* (Tokyo), **10**, 338 (1962); (b) R. C. Tweit, R. M. Dodson, and R. D. Muir, *J. Org. Chem.*, **27**, 3654 (1962).

(14) The principle of additivity of effects would predict a downfield shift of about 20 c.p.s. for the missing 16β-*cis* isomer. *Cf.* J. N. Shoolery and M. T. Rogers, *J. Am. Chem. Soc.*, **80**, 5121 (1958). NOTE ADDED IN PROOF.—B. J. Magerlein, *et al.*, *J. Org. Chem.*, **28**, 3474 (1963), recently have observed the same deshielding influence on the C-18 protons by *cis*-$\Delta^{17(20)}$-21-hydroxy compounds relative to the *trans* isomers.

The products of reduction and oxidation of the diols **6**, **7**, and **8** showed properties in agreement with those expected on the basis of the structural assignments given. Thus isomers **7** and **8** and their respective diacetates are shown to differ only in geometry about the 17(20) double bond by virtue of their reduction in the presence of palladium on carbon to a common saturated 5α-pregnane-3β,16α-diol (**14**). Reduction of the third isomer assigned the 16β-*trans* configuration (**6**) gave a mixture of a hydrogenolysis product together with what appears to be, on the basis of spectral evidence, a 16-keto-17ξ-ethyl derivative resulting from isomerization of the double bond through the enol intermediate.[15]

The allylic 16-hydroxy-$\Delta^{17(20)}$ system was very unreactive toward selective oxidation by either manganese dioxide or dichlorodicyanobenzoquinone. Room temperature treatment resulted in recovery of considerable starting material. Use of elevated temperatures resulted in appreciable oxidation of the 3-hydroxyl group to a 3-keto-4,6-diene system as evidenced by the appearance of a band in the ultraviolet spectrum at 283 mμ. In light of these observations the experiments were not pursued.[16]

Oxidation under Oppenauer conditions proceeded smoothly; however, there invariably was an appreciable amount of isomerization of the resulting dienedione about the 17(20) double bond even under these mild conditions. Nevertheless, the predominant isomer in each case was that expected on the basis of the previous assignment of geometry about the 17(20) double bond.

The n.m.r. spectra of the two isomeric 4,17(20)-pregnadiene-3,16-diones afforded an unequivocal assignment of the configuration of the ethylidene side chain. The substituent at C-20 adjacent to the carbonyl function at C-16 is subject to the magnetic anisotropic influence of that group resulting in a deshielding or downfield shift. Thus the spectrum for one isomer assigned the *trans* configuration (**15**) displayed a doublet for the C-21 methyl proton centered 13.5 c.p.s. downfield from the corresponding absorption of the other isomer, assigned the *cis* structure (**16**). The spectrum for the latter compound exhibited a quartet for the C-20 vinyl proton centered 46.5 c.p.s. downfield relative to the first.[17] The comparable deshielding of the C-18 methyl protons by the C-21 methyl group in the *cis* compounds (**8a** and **16**) when compared with the *trans* compounds (**7a** and **15**) also should be noted.

Discussion

The question of the relative stability of a double bond exocyclic or endocyclic to a five-membered ring has been discussed by several authors.[18] Turner's[18c] studies on the heats of hydrogenation of the isomeric *exo–endo* pairs of five-, six-, and seven-membered ring compounds showed that in each case the *endo* isomer was the more stable member of the pair. Dreiding and Hartman[19] have observed that either 2-methylenecyclopentanol or 1-cyclopentenyl methanol in the presence of 1% sulfuric acid at reflux temperature underwent rearrangement to 2-methylcyclopentanone. However, from these experiments no conclusions could be drawn concerning the relative stability of the isomers.

The steroidal Δ^{16}-20-acetoxy system offers one advantage in the study of *exo–endo* equilibria involving a five-membered ring in that each of the isomeric olefins are trisubstituted. However, the rigidity of the steroid nucleus (the *trans* C:D ring juncture), the steric effects of the neighboring ring, and the C-18 angular methyl group impose such limiting features on this system that generalization to other systems would of necessity be limited.

From the lack of stereospecificity of this anionotropic rearrangement, it is reasonable to conclude that thermodynamic equilibrium has been approached among the products formed. Thus, in this system (1) only the *trans*-olefin was isolated; (2) the trisubstituted exocyclic [$\Delta^{17(20)}$] double bond was favored over the trisubstituted endocyclic [$\Delta^{16,17}$] double bond; and (3) the more stable 16β-acetoxy isomer was favored over the less stable 16α-acetoxy compound. That the 16β configuration is more stable than the 16α in certain 16-substituted steroids possessing an exocyclic double bond at C-17 can be seen from the work of Fajkos,[20] Bowers,[21] and others.

Experimental[22]

The Reaction of 16,17-Epoxypregnenolone with Hydrazine. Method A. 5,17(20)-(*trans*)-Pregnadiene-3β,16α-diol (7α).—A solution of 10.0 g. of 3β-hydroxy-16α,17-oxido-5-pregnen-20-one in 200 ml. of hydrazine hydrate (85%) was brought slowly to reflux temperature over 0.75 hr. and allowed to reflux for 15 min. The reaction mixture was cooled and the grey precipitate separated by filtration and washed thoroughly with water. The dried solids were dissolved in a 5% ethyl acetate–benzene solution and placed on a column of 400 g. of silica gel. From the early fractions eluted by 20% ethyl acetate–benzene there crystallized prisms melting 213–218°. Recrystallization from ethyl acetate afforded the 16α-*trans* isomer (**7a**) as blades melting 219–222°, $[\alpha]_D$ −73°.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.70; H, 10.07 (MT).

5,17(20)-(*cis*)-Pregnadiene-3β,16α-diol (8a).—From later fractions of the previous chromatogram the major product was eluted with 20% ethyl acetate–benzene and crystallized to give the 16α-*cis* isomer (**8a**) as needles having m.p. 185–190°. An analytical sample was obtained by recrystallization from ethyl acetate, m.p. 190–191.5°, $[\alpha]_D$ −89°.[23]

(15) *Cf.* R. Delaby and J. Dumoulin, *Bull. soc. chim. France*, **39**, 1578 (1926), for analogous isomerization of allylic alcohols to ketones on palladium catalysts.

(16) P. N. Rao, *J. Org. Chem.*, **26**, 2149 (1961). See, however, ref. 4.

(17) Other recent examples of the use of n.m.r. spectroscopy in distinguishing between isomeric ethylidenes adjacent to a five-membered ring carbonyl are reported by G. Albers-Schönberg and H. Schmid, *Helv. Chim. Acta*, **44**, 1447 (1961), in the elucidation of the structures of plumericin and isoplumericin, and by K. S. Brown, Jr., and S. M. Kupchan, *J. Am. Chem. Soc.*, **84**, 4590 (1962), working with derivatives of cyclobuxine. *Cf.* also L. M. Jackman and R. H. Wiley, *J. Chem. Soc.*, 2881 (1960).

(18) (a) H. C. Brown, J. H. Brewster, and H. Shechter, *J. Am. Chem. Soc.*, **76**, 467 (1954); H. C. Brown, *J. Org. Chem.*, **22**, 439 (1957). (b) B. R. Fleck, *ibid.*, **22**, 439 (1957), and references cited therein. (c) R. B. Turner and R. H. Garner, *J. Am. Chem. Soc.*, **80**, 1424 (1958).

(19) A. S. Dreiding and J. A. Hartman, *ibid.*, **78**, 1216 (1956).

(20) J. Fajkos, *J. Chem. Soc.*, 3966 (1959), and references cited therein.

(21) A. Bowers, P. G. Holton, E. Necoechea, and F. A. Kincl [*ibid.*, 4057 (1961)] have shown that 16α-methyl-4-androstene-3,17-dione is converted by acid or alkali completely to the 16β-methyl isomer.

(22) Melting points were taken on a Fisher melting point apparatus. Rotations were taken in chloroform at about 1% concentration at 26 ± 2° and the ultraviolet spectra were determined in methanol. Analyses marked by MT were carried out by Micro-Tech Laboratories, Skokie, Ill. All other spectra and analytical results were carried out under the direction of Dr. R. T. Dillon of the Analytical Department of G. D. Searle and Co. We wish to acknowledge the assistance of Dr. E. G. Daskalakis and his associates for some of the chromatographic separations.

(23) In their communication Huang-Minlon and Chung-Tungshun[3] describe a single 16-hydroxy-$\Delta^{17(20)}$ compound from the hydrazine reaction, m.p. 182–183°, $[\alpha]^{27}D$ −89° (ethanol), and its diacetate, m.p. 158–160°, $[\alpha]^{27}D$ −67° (ethanol). These physical constants are more nearly in agreement with our *cis* compound (**8**), isolated as the major product, than with the *trans* isomer.

The diol fraction was eluted with 20% ethyl acetate in benzene as a pair of incompletely resolved bands. The total yield of diol material was 51% with the *cis* isomer (**8a**) somewhat predominant over the *trans* (**7a**).

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 80.09; H, 9.97.

5,17(20)-(*trans*)-Pregnadiene-3β,16α-diol Diacetate (7b).—The diacetate was prepared by treatment of the diol **7a** with acetic anhydride in pyridine at room temperature overnight. It crystallized as prisms from methanol, m.p. 149–151.5°, $[\alpha]_D$ −116°.

Anal. Calcd. for $C_{25}H_{36}O_4$: C, 74.96; H, 9.06. Found: C, 74.82; H, 8.93.

5,17(20)-(*cis*)-Pregnadiene-3β,16α-diol Diacetate (8b).—The diacetate was prepared in the same manner as described for the *trans* isomer. It crystallized from methanol as plates, m.p. 163–165°, $[\alpha]_D$ −89.5°.[23]

Anal. Calcd. for $C_{25}H_{36}O_4$: C, 74.96; H, 9.06. Found: C, 75.15; H, 8.76.

The Reaction of 16,17-Epoxypregnenolone with Hydrazine. Method B.—The first reaction in this series was run under the usual conditions for the Huang-Minlon modification of the Wolff–Kishner reduction.[5] From the reaction of 2.00 g. of 16,17-epoxypregnenolone with 2.00 g. of potassium hydroxide and 2.0 ml. of hydrazine hydrate (85%) in 20 ml. of diethylene glycol (195° for 5.5 hr.) was isolated, by chromatography on silica gel, 140 mg. of 5,17(20)-(*trans*)-pregnadiene-3β,16α-diol (**7a**), m.p. 217.5–218.5°, and 277 mg. of 5,17(20)-(*cis*)-pregnadiene-3β,16α-diol (**8a**), m.p. 190–191.5°, $[\alpha]_D$ −88°.

3β-Hydroxyandrost-5-ena-[16,17-*c*]-5′-methylpyrazole (9a).—9a was obtained from the preceding reaction on elution of the chromatographic column with ethyl acetate. Crystallization of the material so obtained from acetone–cyclohexane yielded 92 mg. of the steroid pyrazole, m.p. 305–307° dec., with rapid heating; $[\alpha]_D$ −73°; λ_{max} 225 mμ (ε 6100); λ_{max}^{KBr} 2.70, 3.02, 6.20, 7.23, 7.82, 9.19, 9.48, 9.58, and 9.82 μ; lit.[3] m.p. 302–304°; $[\alpha]^{27}_D$ −76° (chloroform) (see also ref. 1).

Anal. Calcd. for $C_{21}H_{30}N_2O$: C, 77.25; H, 9.26; N, 8.58. Found: C, 77.12, 76.89; H, 8.85, 8.96; N, 8.68, 8.86.

3β-Acetoxyandrost-5-ena-[16,17-*c*]-5′-methylpyrazole (9b).—**9b**, m.p. 268–273°, λ_{max} 225 mμ (ε 6650), was obtained by the acetylation of 9a with acetic anhydride in pyridine and crystallization of the resulting material from aqueous methanol containing a little ammonium hydroxide.

Anal. Calcd. for $C_{23}H_{32}N_2O_2$: C, 74.97; H, 8.76. Found: C, 75.04; H, 8.71.

Acid-Catalyzed Rearrangement of 5,16-Pregnadiene-3β,20-diols. 5,17(20)-(*trans*)-Pregnadiene-3β,16α-diol Diacetate (7b).—To a solution of 12.3 g. of a 1:1 molecular mixture of 5,16-pregnadiene-3β,20α- and -3β,20β-diol[10] in 180 ml. of acetic acid and 30 ml. of acetic anhydride was added 800 mg. of *p*-toluenesulfonic acid. The reaction mixture was allowed to stand under nitrogen at room temperature for 48 hr. A green color slowly developed over the reaction period. The reaction was diluted with warm water and extracted with benzene; the organic phase was washed with sodium carbonate solution, then with water, and finally dried and concentrated under vacuum to an amber gum. Crystallization from methylcyclohexane afforded 3.8 g. of light yellow crystals, m.p. 149–163°. Further recrystallization did not result in narrowing the melting range. On the basis of the infrared spectrum the material was judged to be predominantly the 16β-acetoxy *trans* isomer (**6b**) described subsequently.

The filtrates from the crystallization were chromatographed on neutral alumina. The band of material eluted by benzene was clearly not homogeneous. From the early fractions of this band there was obtained, by crystallization from methanol, prisms melting at 145–148°, amounting to about 13% of the total product. Further recrystallization afforded a pure sample of 5,17(20)-(*trans*)-pregnadiene-3β,16α-diol diacetate (**7b**) having melting point and spectra identical with the diacetate, m.p. 149–151.5°, derived from the hydrazine reaction.

Later fractions from the benzene eluted band, amounting to about 10% of the total product, crystallized poorly. However, on the basis of the infrared spectra these fractions were shown to be predominantly the 3,20-diacetoxy starting material.

5,17(20)-(*trans*)-Pregnadiene-3β,16β-diol Diacetate (6b).—A second very broad band was collected from eluates of 1 to 2% ethyl ether in benzene. From these fractions there was isolated by crystallization from methanol the pure 16β-acetoxy *trans* isomer (**6b**), m.p. 173–175.5°, $[\alpha]_D$ −17°. This material together with the solids collected by direct crystallization from the crude reaction product accounted for about 40% of the total product.

Anal. Calcd. for $C_{25}H_{36}O_4$: C, 74.96; H, 9.06. Found: C, 75.07; H, 9.02.

From the more polar eluates of the previous chromatogram there were obtained only gummy products that resisted crystallization and characterization. These fractions amounted to some 30% of the total and appeared to be mixtures of monoacetates of the previously described diols, probably resulting from partial hydrolysis of the allylic acetates during the work-up or during chromatography by traces of moisture, together with some polymeric products of the reaction.

5,17(20)-(*trans*)-Pregnadiene-3β,16β-diol (6a).—A sample of the 3β,16β-diacetate (**6b**) was hydrolyzed by refluxing with 5% methanolic potassium hydroxide for 2.5 hr. The product was crystallized from ethyl acetate–methylcyclohexane and finally from acetone to give an analytical sample, m.p. 182–188°, $[\alpha]_D$ −32°.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.80; H, 10.11.

Of the three isomeric diols described, this one proved to be the most unstable and difficult to purify. In one instance the compound crystallized as plates from methanol and had m.p. 186.5–188.5°. However, this solvent generally was avoided as it led to contamination by impurities resulting from methyl ether formation as shown by the appearance of a band at 206 c.p.s. in the n.m.r. spectrum. After having stood for a few months, this compound had a much broader melting point range. The infrared spectrum of the resulting material showed absorption in the carbonyl region, suggesting that some oxidation of the allylic hydroxyl group had occurred.

Rearrangement of a 1:1 Mixture of 5,16-Pregnadiene-3β,20α-diol and -3β,20β-diol Diacetates (3b:4b).—A solution containing 3.0 g. of a 1:1 complex of **3b:4b**,[10] m.p. 142–143°, was allowed to stand in the presence of 100 mg. of *p*-toluenesulfonic acid in 45 ml. of acetic acid and 7.5 ml. of acetic anhydride at room temperature for 60 hr. The reaction mixture was then poured into 400 ml. of water water and allowed to cool to room temperature and then extracted with ether. The organic phase was washed with sodium carbonate solution, dried, and evaporated under vacuum to give 2.93 g. of gummy solid material, $[\alpha]_D$ −51°. Vapor phase chromatography[24] indicated that the product consisted of about 60% of the 16β-*trans* isomer (**6b**) and about 30% of a mixture of the 16α-*trans* isomer (**7b**) and the 20-acetoxy-Δ^{16} starting material as a second unresolved band. A third, less polar band of variable intensity (10–20% of the total) appeared in each of the chromatographic studies and is most likely a triene resulting from pyrolytic elimination of an allylic acetoxy function occurring in the preheater of the instrument. Thin layer chromatography on silica gel did not show sufficient resolution to permit estimation of quantities. Chromatography on alumina afforded a partial separation and isolation of the two isomeric 16α- and 16β-acetoxy compounds in the same proportions as described in the preceding experiment.

A pure sample of 5,16-pregnadiene-3β,20β-diol[12] was subjected to the identical acid-catalyzed equilibration conditions with essentially the same results as were obtained from the 1:1 mixture of C-20 epimers. The predominant product isolated by column chromatography was the 16β-(*trans*)-diacetate (**6b**) together with lesser amounts of the 16α epimer (**7b**).

5-Pregnene-3β,16α-diol.[3]—A solution containing 150 mg. of 5,17(20)-(*cis*)-pregnadiene-3β,16α-diol (**8a**) in 20 ml. of ethyl alcohol was stirred in a hydrogen atmosphere in the presence of 30 mg. of 5% palladium on carbon. After a period of 50 min. 1 molar equiv. of hydrogen had been consumed and the reduction was discontinued. Removal of the catalyst by filtration, followed by evaporation of the solvent under vacuum, afforded 109 mg. of amorphous solid melting 230–245°. Crystallization from ethyl acetate gave 76 mg. of needles, m.p. 247–250°. The analytical sample had m.p. 249–250°, $[\alpha]_D$ −62°; lit.[3] m.p. 240–251°, $[\alpha]_D$ −73° (ethanol); Δν 38.5 (18-H), 61.5 (19-H) c.p.s. (CD_3COOD)).

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 79.40; H, 10.79.

5α-Pregnane-3β,16α-diol (14a). From 5,17(20)-(*cis*)-Pregnadiene-3β,16α-diol (8a).—The reduction of the 16α-(*cis*)-diene (**8a**) was carried out as in the preceding experiment but allowed

(24) A gas chromatography column packed with β-cyanoethylmethylpolysilane suspended on Chromosorb W was employed.

to continued until uptake of hydrogen ceased. After 2.25 hr. approximately 2 moles of hydrogen had been absorbed. Following removal of the catalyst, the ethanol was evaporated under vacuum and the product crystallized as fine needles from ethyl acetate in 90% yield, m.p. 259.5–260°, $[\alpha]_D$ −12.5° (0.5%).

Anal. Calcd. for $C_{21}H_{36}O_2$: C, 78.69; H, 11.32. Found: C, 78.61; H, 11.42 (MT).

From 5,17(20)-(*trans*)-Pregnadiene-3β,16α-diol (7a).—The reduction of the 16α-(*trans*)-diene (**7a**) was carried out under identical conditions as described before. After 3.75 hr. about 2 moles of hydrogen had been absorbed and the catalyst was removed, the ethanol evaporated and the product crystallized from ethyl acetate. The saturated diol (**14a**) isolated in 87% yield was shown to be identical with the product of the reduction of the previous *cis* isomer by melting point and infrared spectral identity.

5α-Pregnane-3β,16α-diol Diacetate (14b). Method A.—The diacetate was prepared from the saturated diol (**14a**) by treatment with acetic anhydride in pyridine. A sample crystallized from methanol had m.p. 152.5–153.5°; $[\alpha]_D$ −78°; ΔM_D (16-OAc–16-OH) −246, −259; Δν 37 (18-H), 49 (19-H) c.p.s.

Method B.—A solution of 5,17(20)-(*trans*)-pregnadiene-3β,16α-diol diacetate (**7b**) in ethanol was shaken in an atmosphere of hydrogen together with 5% palladium on carbon until 2 molar equiv. of hydrogen had been absorbed. The saturated diacetate was identical with that prepared by method A.

Reduction of 5,17(20)-(*trans*)-Pregnadiene-3β,16β-diol and Its Diacetate (6a and 6b).—Reduction of the diol **6a** in the presence of palladium on calcium carbonate in ethyl alcohol was very sluggish. After 5 hr. only about 0.2 molar equiv. of hydrogen had been taken up and the reduction was discontinued. The crude product was largely starting diol. However, the appearance of a band at 5.76 μ in the infrared spectrum suggested formation of a five-membered ring ketone by isomerization of the allylic 16-hydroxyl function into the keto form.

In the presence of palladium on carbon the uptake of hydrogen was more rapid. After an interval of 40 min. 1 molar equiv. had been absorbed but only impure solids were isolated. The material gave a yellow 2,4-dinitrophenylhydrazone and had a band at 5.75 μ in the infrared. When the reduction was allowed to continue for 3.75 hr. approximately 2 molar equiv. of hydrogen had been absorbed. A solid was isolated in low yield having m.p. 137–139°. This was shown to be the product resulting from hydrogenolysis of the 16-hydroxy group and reduction of both double bonds. Mixture melting point determination and a comparison of the infrared spectra with an authentic sample showed this to be 5α-pregnan-3β-ol (lit.[25a] m.p. 137–138°). The crude residue from crystallization of the product had a band in its infrared spectrum at 5.74 μ, again indicating isomerization to a ketone.

Treatment of the 5α-pregnan-3β-ol with acetic anhydride in pyridine afforded the acetate as leaflets having m.p. 113–114° (lit.[25c] m.p. 113–114°).

Reduction of 0.2 g. of the 16β-(*trans*)-diacetate (**6b**) in the presence of palladium on carbon proceeded rapidly with the uptake of 2 molar equiv. of hydrogen in 1 hr. and 10 min. The product was a mixture from which could be isolated in somewhat impure form two hydrogenolysis products. From methanol there was obtained as first crop 73 mg. of prisms having m.p. 143–152°, $[\alpha]_D$ −55°. A comparison of infrared spectra and mixture melting point determination showed this to be slightly impure 3β-acetoxy-5-pregnene (lit.[26] m.p. 151–152°, $[\alpha]_D$ −60°).

Anal. Calcd. for $C_{23}H_{36}O_2$: C, 80.18; H, 10.53. Found: C, 79.82; H, 10.66.

The second crop from the preceding reduction crystallized as leaflets from methanol, 51 mg., m.p. 109–110°. Mixture melting point determination with an authentic sample of 3β-acetoxy-5α-pregnane,[25c] m.p. 113–114°, showed no depression. The infrared spectra of the two samples were virtually identical.

Anal. Calcd. for $C_{23}H_{38}O_2$: C, 79.71; H, 11.05. Found: C, 79.78; H, 11.00.

Later crops appeared to be mixtures of these two compounds.

***trans*- and *cis*-4,17(20)-Pregnadiene-3,16-dione (15 and 16). From 5,17(20)-(*trans*)-Pregnadiene-3β,16β-diol (6a).**—A solution of 1.0 g. of the 16β-*trans* isomer (**6a**) and 1.0 g. of aluminum isopropoxide in 100 ml. of toluene and 14 ml. of cyclohexanone was maintained at reflux for 1 hr. during which time a total of 37 ml. of solvent was removed by distillation. Following this period the solution was diluted with Rochelle salt solution and steam distilled for 2 hr. Solids were collected by filtration, and dried to constant weight, 0.78 g., m.p. 172–190°. This material was taken up in benzene and placed on a column of 45 g. of alumina. Elution with 3 to 5% ethyl acetate in benzene afforded 336 mg. of crystalline solids melting at 180–190°. Recrystallization from aqueous methanol afforded an analytical sample of 4,17(20)-(*trans*)-pregnadiene-3,16-dione (**15**), m.p. 188–190°; $[\alpha]_D$ −61°; λ_{max} 241 mμ (25,000); λ_{max}^{KBr} 5.82, 5.96, 6.07, 6.17 μ; Δν 58 (18-H), 73.5 (19-H), 120.5, 128 (21-H), 331.5, 338.5, 345.5, 353 (20-H) c.p.s.

Anal. Calcd. for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.74; H, 9.41.

Further elution of the product from the column with 10% ethyl acetate–benzene yielded as a minor component 143 mg. of the *cis* isomer (**16**) as prisms from aqueous methanol, m.p. 170–171.5°; $[\alpha]_D$ −30°; ΔM_D (*cis*–*trans*) +97.5°; λ_{max} 241 mμ (ε 27,600); λ_{max}^{KBr} 5.80, 5.95, 6.06, 6.16 μ; Δν 64.5 (18-H), 74 (19-H), 107, 114.5 (21-H), 377, 384.5, 392, 399.5 (20-H) c.p.s.

Anal. Calcd. for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.48; H, 8.87.

Paper chromatography indicated that the oxidation of the 16β-(*trans*)-diol afforded the mixture of *trans*–*cis* diones in the ratio of about 4:1, respectively.

From 5,17(20)-(*cis*)-Pregnadiene-3β,16α-diol (8a).—An Oppenauer oxidation of the 16α-*cis* isomer carried out in the same fashion as described before afforded the *cis*-dienedione (**16**) and *trans*-dienedione (**15**) in a ratio of about 2:1 as determined by paper chromatography.

From 5,17(20)-(*trans*)-Pregnadiene-3β,16α-diol (7a).—This isomer upon Oppenauer oxidation gave the *trans*-dienedione (**15**) in 57% yield by direct crystallization. The filtrates were shown by paper chromatography to contain additional quantities of this product accompanied by lesser amounts of the *cis* isomer.

Acid-Catalyzed Rearrangement of the Epimeric 20-Hydroxy-5,16-pregnadiene-3-one Ethylene Ketals. 16α-Acetoxy-4,17(20)-(*trans*)-pregnadien-3-one (13b).—A solution of 5 g. of 20α-hydroxy-5,16-pregnadiene-3-one ethylene ketal[10] in 110 ml. of acetic acid and 15 ml. of acetic anhydride together with 250 mg. of *p*-toluenesulfonic acid monohydrate was allowed to stand at room temperature for 60 hr. The reaction mixture was poured into warm water and then extracted with benzene. The organic layer was washed with sodium carbonate solution, dried, and concentrated to a sirup. The ultraviolet spectrum showed a maximum at 239 mμ (ε 14,320).

The crude product was placed on a column of alumina and, using a gradient elution technique, eluted by gradually varying the solvent from pure benzene to 3% ethyl acetate–benzene. The products were not cleanly separated but were eluted as a single rather broad band. From the early fractions, eluted by 1% ethyl acetate in benzene there was obtained as long rods from methanol 16α-acetoxy-4,17(20)-(*trans*)-pregnadien-3-one (**13b**), m.p. 133–133.5°. An analytical sample had m.p. 133–134°; $[\alpha]_D$ +5°; λ_{max} 240.5 mμ (ε 17,050); Δν 49 (18-H), 72.2 (19-H), 92.2, 99 (21-H) c.p.s.

Anal. Calcd. for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.39; H, 8.96.

16β-Acetoxy-4,17(20)-(*trans*)-pregnadien-3-one (12b).—From the fractions obtained as the trailing edge of the band of eluents containing 1.5 to 2.5% ethyl acetate in benzene the major component in the reaction mixture was isolated. Crystallization of this material from methanol yielded the 16β-acetoxy-*trans* isomer (**12b**), m.p. 157–159.5°; $[\alpha]_D$ +114°; λ_{max} 241 mμ (ε 17,050); Δν 57 (18-H), 72.4 (19-H), 91.5, 98.5 (21-H) c.p.s.

Anal. Calcd. for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.45; H, 8.89.

The intermediate fractions could not be induced to crystallize. In one experiment these fractions were pooled and rechromatographed on alumina using the same gradient elution procedure as employed in the initial separation. By this operation additional quantities of the isomeric 16-hydroxy compounds **12b** and **13b** were isolated. Nevertheless, the separation was incomplete and intermediate fractions again were not crystalline. By analogy with the results obtained in the 3-acetoxy series, the

(25)(a) L. Ruzicka, M. W. Goldberg, and E. Hardegger, *Helv. Chim. Acta*, **22**, 1294 (1939); (b) Huang-Minlon, *J. Am. Chem. Soc.*, **71**, 3301 (1949); (c) D. H. R. Barton and N. J. Holness, *ibid.*, **72**, 3274 (1950).

(26) R. W. Jeanloz, *ibid.*, **72**, 2281 (1950).

presence of a small amount of Δ^{16}-20-acetoxy material may account, in part, for the difficulties encountered in obtaining crystalline material.

A similar acid-catalyzed equilibration of a 1:1 mixture of 20α- and 20β-hydroxy-Δ^{16}-3-ethylene ketals[10] afforded the same mixture of products in the same relative proportions as were isolated from the pure 20α isomer.

16α-Hydroxy-4,17(20)-(*trans*)-pregnadien-3-one (13a).—The treatment of the 16α-acetate **13b** with alcoholic potassium hydroxide at reflux for 1.5 hr. afforded the 16α-hydroxy compound (**13a**). The product crystallized as needles from ether–petroleum ether (b.p. 66–69°) and had m.p. 173.5–175.5°; $[\alpha]_D$ +104.5°; ΔM_D (16-OAc–16-OH) −311°; λ_{max} 240 mμ (ε 16,700); Δν 47.5 (18-H) 72.5 (19-H), 105, 112 (21-H) c.p.s.

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.21; H, 9.54.

16β-Hydroxy-4,17(20)-(*trans*)-pregnadien-3-one (12a).—Alkaline hydrolysis of the 16β-acetate (**12b**) afforded the 16β-hydroxy compound (**12a**) as blades from ether–petroleum ether, m.p. 172–175°; $[\alpha]_D$ +141.5°; ΔM_D (16-OAc–16-OH) −39°; λ_{max} 240.5 mμ (ε 16,850); Δν 58.4 (18-H), 72.2 (19-H) 100, 106 (21-H) c.p.s.

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.55; H, 9.70.

Preparation of Amino Acids from Trichloromethylcarbinols[1]

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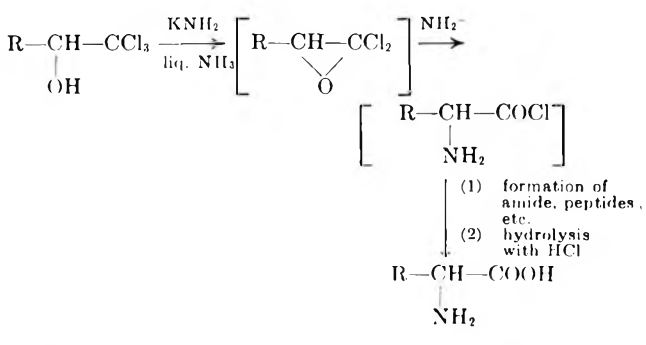
The conversion of four trichloromethylcarbinols to amino acids by treatment with potassium amide in liquid ammonia at −33° has been studied. The reaction occurs in 29 to 48% yields, and is believed to involve the formation of an intermediate epoxide followed by the opening of the epoxide ring by amide ion. The amino acids prepared were α-aminobutyric acid, valine, 2-methyl-2-aminopropionic acid, and phenylglycine. Methods of preparing alkyl and aryl trichloromethylcarbinols are reviewed and discussed.

Alkyl and aryl trichloromethylcarbinols are potentially useful intermediates for the synthesis of α-substituted carboxylic acids. It is known that phenyltrichloromethylcarbinol reacts with a concentrated aqueous potassium hydroxide solution to form α-chlorophenylacetic acid in 26% yield,[3] with methanolic potassium hydroxide to form α-methoxyphenylacetic acid in 72% yield,[4] and with ethanolic sodium ethoxide to form α-ethoxyphenylacetic acid in 33% yield.[5] The mechanism proposed for these reactions involves the intermediate formation of an epoxide and the subsequent opening of the epoxide ring by a nucleophilic reagent.[6] In the present work, amide ion was used as the nucleophilic reagent to obtain α-amino acids.



The conversion of four trichloromethylcarbinols to amino acids was studied (Table I). The R group in the above equation was ethyl, isopropyl, and phenyl. In addition, 1,1,1-trichloro-2-methyl-2-propanol (chlorobutanol) was studied. In all cases, the reaction was carried out by adding the carbinol to a solution of potassium amide in liquid ammonia at −33°. The mixture was stirred for 8 to 12 hr. the ammonia was allowed to evaporate, and the final amino acid was obtained by hydrolyzing the initially formed products with ethanolic hydrochloric acid.

Attempts were made to isolate the α-amino amide, a postulated intermediate prior to acid hydrolysis, but positive identification could not be made. It appears that a mixture of products are formed at this stage of the reaction. Thus, if the excess potassium amide is decomposed under mild conditions, *e.g.*, by the use of 95% ethanol, and the hydrolysis step with hydrochloric acid is omitted, phenylglycine is still obtained in 5 to 12% yield. When hydrolyzed with hydrochloric acid, the yield is 48%. Apparently, there are both readily hydrolyzable and difficultly hydrolyzable species in the reaction mixture. The former probably includes the amino acid amide; the latter may include the diketopiperazine, peptides, and Schiff bases. Even under what appeared to be optimum conditions, a red, viscous nonhydrolyzable oil accounted for about half of the reaction product. Infrared spectroscopy and v.p.c. showed benzaldehyde and unchanged starting materials to be two of the major components of this oil.

Optimum reaction conditions were determined with phenyltrichloromethylcarbinol. With potassium amide the reaction did occur, whereas sodamide was ineffective, presumably because of its insolubility in the liquid ammonia solvent. Even powdered potassium hydroxide slurried in liquid ammonia was almost as effective (39% yield) as the potassium amide. With no base present there was no reaction. Using potassium hydroxide as the base, attempts to carry out the reaction at 30 and at 100° in a steel hydrogenation vessel gave only 15% yields, probably because the rocking autoclave provided insufficient agitation. The reaction was also carried out at 48° in a methanolic potassium hydroxide solution saturated with ammonia, and a 34% yield of phenylglycine was obtained.

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(2) This investigation was supported in part by a Predoctoral Fellowship to L. W. F. from the Division of General Medical Studies, U. S. Public Health Service.

(3) J. Jociez, *J. Russ. Phys. Chem. Soc.*, **29**, 97 (1897); *Chem. Zentr.*, **68**, 1013 (1897).

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TABLE I

PREPARATION OF α-AMINO ACIDS FROM TRICHLOROMETHYLCARBINOLS

Amino acid (yield, g.)	Carbinol (g.)	Yield, %[a]	M.p., °C. dec.[a]	—Carbon, %— Calcd.	Found	—Hydrogen, %— Calcd.	Found	—Nitrogen, %— Calcd.	Found
α-Aminobutyric (3.0)	$C_2H_5CHOHCCl_3$ (18)	29	268[b]	46.59	46.60	8.79	8.54	13.59	13.32
Valine (3.9)	$(CH_3)_2CHCHOHCCl_3$ (19)	34[c]	292–295[d]	51.25	51.40	9.48	9.75	11.95	12.15
2-Methyl-2-aminopropionic (4.5)	$CH_3C(CH_3)OHCCl_3$ (18)	43	280[e]	46.59	46.59	8.79	8.50	13.59	13.41
Phenylglycine (7.3)	$C_6H_5CHOHCCl_3$ (22)	48	253–256[b]	63.56	63.46	6.00	6.28	9.26	9.01

[a] After amino acids were recrystallized from water. [b] N. Zelinski and G. Stadnikoff, *Ber.*, **41**, 2061 (1908). [c] Potassium amide prepared by method of P. A. McCuster and R. R. Vogt [*J. Am. Chem. Soc.*, **59**, 1307 (1937)]. [d] M. D. Slimmer [*Ber.*, **35**, 400 (1902)] report m.p. 295–299° dec. [e] N. Zelinski and G. Stadnikoff, *ibid.*, **39**, 1726 (1906).

Formation of the Trichloromethylcarbinols.—The practical utility of the reaction for preparing amino acids depends very much on the ready availability of the starting trichloromethylcarbinols. The aryl trichloromethylcarbinols are readily available by any of the following three methods. First, reaction of aromatic aldehydes with chloroform at 0° in the presence of dry potassium hydroxide usually results in about 45% yields of the carbinols.[3,7] In the case of benzaldehyde and chloroform, we have increased the yield to 75% by the use of potassium *t*-butoxide in *t*-butyl alcohol. A second general method involves the normal addition of aryl Grignard reagents to chloral, usually in about 50% yield.[8] The third procedure involves the reaction of chloral with benzene, toluene, or *p*-xylene in the presence of aluminum chloride to form the trichloromethylcarbinol, usually in about 70% yield.[9]

The synthesis of alkyl trichloromethylcarbinols is much more difficult. Acetone will undergo a condensation with chloroform, catalyzed by potassium hydroxide, in 84% yield,[10] but the yields are very low when aldehydes are condensed with chloroform. In the present work, isopropyltrichloromethylcarbinol was prepared in 18% yield from isobutyraldehyde and chloroform using potassium *t*-butoxide as the base. Most alkyl Grignard reagents on reacting with chloral undergo oxidation–reduction exclusively, with formation of an olefin and trichloroethanol. Certain Grignard reagents, such as methyl- and benzylmagnesium halides, which cannot undergo this side reaction, give the normal carbinol adduct in good yield.[8] Vinyl and substituted vinylmagnesium halides also add normally to chloral in approximately 30% yield, and the trichloromethylvinylcarbinols can be hydrogenated quantitatively over a palladium-on-carbon catalyst to the alkyl trichloromethylcarbinols. The ethyltrichloromethylcarbinol used in this work was prepared in this way.[11] Unfortunately, the substituted vinyl halides are not easily obtained in good yield.

Experimental

All melting and boiling points are corrected. Analyses are by Dr. Franz J. Kasler. The infrared spectra were determined on a Beckman IR-5.

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(8)(a) J. Jocicz, *J. Russ. Phys. Chem. Soc.*, **34**, 96 (1902); "Beilsteins Handbuch"; (b) J. Jocicz, *J. Russ. Phys. Chem. Soc.*, **36**, 8 (1904); *Bull. soc. chim. France*, **34**, 204 (1905); (c) V. W. Floutz, *J. Am. Chem. Soc.*, **65**, 2255 (1943); **71**, 2859 (1949).

(9) A. Dinesmann, *Compt. rend.*, **141**, 201 (1905).

(10) C. Weizmann, E. D. Bergmann, and M. Sulzbacher, *J. Am. Chem. Soc.*, **70**, 1189 (1948).

(11) H. Normant and J. Ficini, *Bull. soc. chim. France*, 1441 (1956); W. Reeve and L. W. Fine, *J. Am. Chem. Soc.*, **86**, 880 (1964).

General Procedure for the Reaction of Trichloromethylcarbinols with Amide Ion.—To a 1000-ml., three-necked flask, equipped with a dropping funnel and Hershberg stirrer and placed neck-deep in a large dewar flask, was added 0.6 l. of liquid ammonia. A slice of potassium was added followed by a crystal (approximately 2 mm.[3] in size) of anhydrous ferric nitrate. The solution changed from blue to pale yellow. The rest of the potassium (total of 18 g., 0.45 g.-atom) was then added at a rate such that each piece had reacted before the next was introduced. This required about 30 min. The carbinol (0.1 mole) was then added dropwise over a period of about 10 min., and the reaction mixture was stirred for an additional 12 hr.

The ammonia was allowed to evaporate and the last traces were removed using a warm-water bath. The flask was cooled in an ice bath and 100 ml. of absolute ethyl alcohol was added in one portion; this was followed by the dropwise addition of 100 ml. of concentrated hydrochloric acid over a 15-min. period. The mixture was filtered; the filtrate was refluxed for 12 hr. and then evaporated nearly to dryness on a steam bath to remove most of the hydrochloric acid. A red oil remained. Much of this dissolved when treated with 100 ml. of water. The mixture was extracted twice with 25-ml. portions of ether and the aqueous solution was made alkaline (pH approximately 11) with a saturated lithium hydroxide solution. The mixture was again extracted with ether, treated with decolorizing carbon, filtered, and neutralized to pH approximately 6 with dilute hydrochloric acid. The solution was then concentrated to a volume of approximately 20 ml. on a steam bath. A fivefold excess of anhydrous ethanol was added and the salts which immediately precipitated were filtered off. The amino acid began to precipitate after a period varying from 30 min. (for phenylglycine) to 2 weeks (for α-aminobutyric acid and α-aminoisobutyric acid).

Phenyltrichloromethylcarbinol.—Most of this was prepared by the reaction of chloroform with benzaldehyde in the presence of dry, powdered potassium hydroxide[7] according to the following procedure. In a 1000-ml., three-necked flask, equipped with a condenser, thermometer, and an efficient Hershberg stirrer, were placed 212 g. (2 moles) of redistilled benzaldehyde and 400 g. (3.3 moles) of chloroform. The solution was cooled to 0°, and 120 g. (2.1 moles) of freshly powdered potassium hydroxide pellets were spooned in, in small portions, over a 1-hr. period. After an induction period of approximately 0.5 hr., the reaction mixture rapidly became very thick and much heat was evolved. The reaction mixture was stirred for 30 min. longer, 150 ml. of cold water was added, and the mixture was poured into a mixture of ice and excess 6 *N* sulfuric acid. On distillation, 215 g. of **α-(trichloromethyl)benzyl alcohol** (47% yield) was obtained, b.p. 148–149° (17 mm.), $n^{30}D$ 1.5660. The infrared spectrum showed ν_{max} (liq. film between salt plates) 3550–3300, 3050, 2925, 1500, 1485, 1455, 1390, 1335, 1300, 1230, 1200–1170, 1090, 1060, 1030, 1010, 1000, 925, 855, 835–810, 785–770, 755–735, 710–695, and 655–640 cm.$^{-1}$.

The second method for preparing phenyltrichloromethylcarbinol used potassium *t*-butoxide as the base. To a stirred solution of 32 g. (0.3 mole) of redistilled benzaldehyde in 143 g. (1.20 moles) of chloroform was added at 0° over a 45-min. period a solution prepared from 18 g. (0.45 mole) of potassium and 300 ml. of *t*-butyl alcohol. After stirring for another 45 min., 150 ml. of dry benzene was added, and the reaction mixture was stirred for 3 hr. at 0°. The reaction mixture was poured into 300 ml. of ice–water containing sufficient sulfuric acid to acidify the mixture to congo red, and was worked up as before. Distillation gave 51 g. of product (75% yield), b.p. 148–149° (17 mm.). A 15% yield of benzaldehyde was recovered as forerun.

Isopropyltrichloromethylcarbinol.—This was prepared by the potassium *t*-butoxide procedure given above. From 22 g. (0.3

mole) of isobutyraldehyde, there was obtained 10 g. (18% yield) of 1,1,1-trichloro-3-methyl-2-butanol, b.p. 88–89° (20 mm.), $n^{25}D$ 1.4737. The physical constants are in agreement with those of Normant and Ficini[11] who prepared it by another method. The infrared spectrum showed ν_{max} (liq. film between salt plates) 3575–3350, 3000, 2900, 1495, 1405, 1380, 1305, 1250, 1180, 1150, 1110, 1055, 1020, 920, 855–800, 780–750, and 660–640 cm.$^{-1}$.

Anal. Calcd. for $C_5H_9Cl_3O$: C, 31.34; H, 4.73; Cl, 55.58. Found: C, 31.58; H, 4.92; Cl, 55.30.

Using potassium hydroxide as the base, the yield was 12% of theory.

Acknowledgment.—We are grateful to Dr. Ellis Lippincott and Dr. Francis Powell for their assistance in obtaining and interpreting the infrared spectra. The financial support provided by the National Institutes of Health is deeply appreciated.

The Thermal Decomposition of 2-Azidobenzylideneamines

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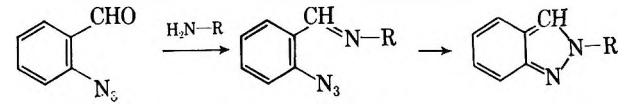
The synthesis and thermal decomposition of a series of 2-azidobenzylideneamines are described. In every case the reaction resulted in an intramolecular cyclization to yield a five-membered ring structure possessing the indazole nucleus.

Thermal- or photo-induced decompositions of biaryl azides which result in intramolecular cyclization with a loss of nitrogen are well-known. For example, Smith and co-workers[1] have reported that the decomposition of 2-azidobiphenyl produced carbazole in high yield. This reaction has been extended to vinyl azides by Smolinsky[2] who obtained 2-phenylazirine upon pyrolysis of α-azidostyrene. The decomposition of 2,2′-diazidoazobenzene has been reported by Carboni and Castle[3] to yield 1,3a,4,6a-tetraazapentalene. The decomposition of azides has been shown by several workers[4] to be capable of intramolecular cyclization at saturated centers. These products can be explained readily by a mechanism involving a univalent, uncharged nitrogen atom frequently called an azene. This intermediate also has been called nitrene, imene, and imine.

Analogous cyclization reactions proceeding presumably through the azene intermediate have also been effected by the reduction of a nitroso or nitro group. Thus, 2-nitrobenzylideneaniline[5] upon treatment with triethyl phosphite was reduced to 2-phenylindazole, and, similarly, 2-nitroso-[6] and 2-nitrobiphenyls[7] were converted to the corresponding carbazoles. The reductive cyclization of 2-nitrophenylpyridine[8] also has been reported.

In this report there are described the thermal decompositions of 2-azidobenzylideneamines in an inert solvent to yield cyclized products. The synthesis of the starting azido compounds with one exception were conveniently effected by the condensation of 2-azidobenzaldehyde with the appropriate amine. These azides are listed in Table I. The decomposition of the azide was carried out in either 1,2-dichloro- or 1,2,4-trichlorobenzene at a temperature (approximately 150°) where a smooth liberation of nitrogen was observed. In every case a high yield of the corresponding 2-substituted indazole was obtained. The



results of the thermal decompositions of 2-azidobenzylideneamines together with several azines are summarized in Table II.

The decompositions of 2-azidobenzylideneaniline (I) and 4-nitro(2-azidobenzylidene)aniline (II) yielded 2-phenylindazole[9] and 2-(4-nitrophenyl)indazole, respectively. In the case of the pyrolysis of 2,4-dinitro(2-azidobenzylidene)aniline (III) the presence of the indazole nucleus in the product, 2-(2,4-dinitrophenylamino)indazole, was substantiated by reductive cleavage to indazole.

Upon heating a solution of 2,2′-diazidobenzylideneazine (V) in either di- or trichlorobenzene, the decomposition occurred in two discrete stages. One mole of nitrogen was released at a temperature of 120–130° to yield 2-(2-azidobenzylideneamino)indazole (VI). At a temperature of 150–155°, a second mole of nitrogen was evolved and 2,2′-biindazole (VII) was produced in high yield. Both stages of the decomposition can be effected by heating V to 150° in an inert solvent producing VII in 93% yield.

A similar cyclization reaction to form the indazole nucleus was also carried out with 2-azido-2′-nitrobenzylideneazine (IV). The decomposition of IV at 150° in dichlorobenzene occurred smoothly producing a 97% yield of 2-(2-nitrobenzylideneamino)-indazole (VIII). The structural similarity of VIII and the azidoindazole (VI) mentioned earlier was established by catalytic reduction of these compounds to 2-(2-aminobenzylideneamino)indazole (IX). Further confirmation of structure IX was obtained by the conversion of the two reduction products to the identical acetamide. The possibility that a skeletal rearrange-

(1) P. A. S. Smith and B. B. Brown, *J. Am. Chem. Soc.*, **73**, 2435 (1951); P. A. S. Smith and J. H. Boyer, *ibid.*, **73**, 2626 (1951); P. A. S. Smith, B. B. Brown, R. K. Putney, and R. F. Reinisch, *ibid.*, **75**, 6335 (1953); P. A. S. Smith, J. M. Clegg, and J. H. Hall, *J. Org. Chem.*, **23**, 524 (1958).

(2) G. Smolinsky, *J. Am. Chem. Soc.*, **83**, 4483 (1961).

(3) R. A. Carboni and J. E. Castle, *ibid.*, **84**, 2453 (1962).

(4) K. H. Saunders, *J. Chem. Soc.*, 3275 (1955); D. H. R. Barton and L. R. Morgan, Jr., *ibid.*, 622 (1962); G. Smolinsky, *J. Am. Chem. Soc.*, **82**, 4717 (1960).

(5) J. I. G. Cadogan and R. J. G. Searle, *Chem. Ind.* (London), 1282 (1963).

(6) P. J. Bunyan and J. I. G. Cadogan, *J. Chem. Soc.*, 42 (1963).

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(8) R. A. Abramovitch, Y. Ahmad, and D. Newman, *Tetrahedron Letters*, 752 (1961); R. A. Abramovitch and K. A. H. Adams, *Can. J. Chem.*, **39**, 2516 (1961).

(9) A. Reissert and F. Lemmer, *Ber.*, **56B**, 356 (1926).

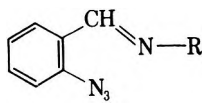
TABLE I

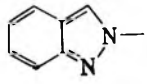
2-AZIDOBENZYLIDENEAMINES

No.	Azide	Yield, %	M.p., °C., dec.	Empirical formula	% carbon Calcd.	% carbon Found	% hydrogen Calcd.	% hydrogen Found	% nitrogen Calcd.	% nitrogen Found
I	2-Azidobenzylideneaniline	44	83	$C_{13}H_{10}N_4$	70.25	70.34	4.54	4.56	25.20	25.00
II	4-Nitro(2-azidobenzylidene)aniline	66	155	$C_{13}H_9N^5O_2$	58.43	58.49	3.40	3.54	26.21	26.20
III	2,4-Dinitro(2-azidobenzylidene)aniline	83	288	$C_{13}H_9N_7O_4$	47.72	47.80	2.77	2.39	29.97	29.90
IV	2-Azido-2′-nitrobenzylideneazine	50	148	$C_{14}H_{10}N_6O_2$	57.14	57.30	3.43	3.83	28.56	28.65
V	2,2′-Diazidobenzylideneazine	~100	160	$C_{14}H_{10}N_8$	57.92	58.13	3.48	3.40	38.60	38.60

TABLE II

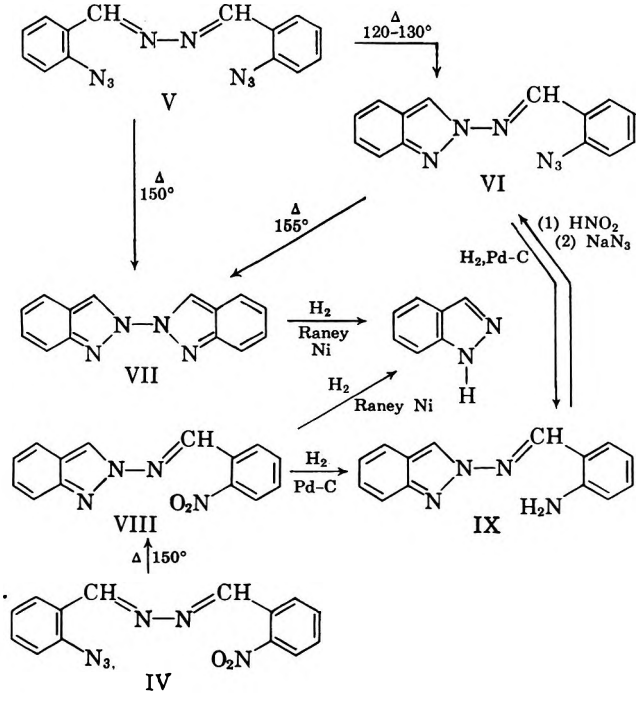
DECOMPOSITION OF 2-AZIDOBENZYLIDENEAMINES



No.	R	Dec. temp., °C.	Solvent	Product	Yield, %	M.p., °C.	Empirical formula	% carbon Calcd.	% carbon Found	% hydrogen Calcd.	% hydrogen Found	% nitrogen Calcd.	% nitrogen Found
I	C_6H_5-	150	DCB[a]	2-Phenylindazole	75	82–83[b]	$C_{13}H_{10}N_2$		[c]		[c]		[c]
II	4-$NO_2C_6H_4$-	155	TCB[d]	2-(4-Nitrophenyl)-indazole	93	225	$C_{13}H_9N_3O$	65.27	65.26	3.80	3.65	17.56	17.50
III	2,4-$(NO_2)_2C_6H_3NH$-	150	TCB	2-(2,4-Dinitrophenyl-amino)indazole	94	118	$C_{12}H_9N_5O_4$	52.18	52.19	3.03	3.21	23.41	23.55
IV	2-$NO_2C_6H_4CH{=}N$-	150	DCB	2-(2-Nitrobenzylidene-amino)indazole	97	138	$C_{14}H_{10}N_4O_2$	63.15	63.49	3.79	3.96	21.04	21.10
V	2-$N_3C_6H_4CH{=}N$-	120–130	DCB	2-(2-Azidobenzylidene-amino)indazole	79	122	$C_{14}H_{10}N_6$	64.12	64.26	3.84	3.96	32.05	32.90
V	2-$N_3C_6H_4CH{=}N$-	150	DCB	2,2′-Biindazole	93	268	$C_{14}H_{10}N_4$	71.77	71.84	4.31	4.40	23.92	23.80
VI		155	DCB	2,2′-Biindazole	90	268	$C_{14}H_{10}N_4$						

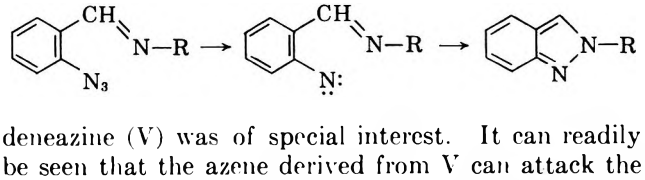
[a] 1,2-Dichlorobenzene. [b] Lit.[9] m.p. 81–82°. [c] Analyses were obtained only for new compounds. [d] 1,2,4-Trichlorobenzene.

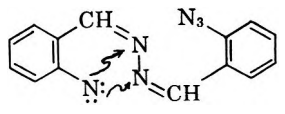
ment might have occurred during either of these reductions was conclusively ruled out by the conversion of IX back to VI. Compound VI, obtained in this manner, was identical with that obtained by the partial decomposition of V and, upon decomposition in dichlorobenzene, also yielded biindazole VII. The reduction of VII with Raney nickel yielded indazole, however, only in 40–50% yield. Apparently a significant amount was lost during the removal of the solvent.



Indazole was also obtained by the Raney nickel reduction of VIII. Thus, the above sequence of reactions indicated that the indazole nucleus was present in VI, VII, VIII, and IX. The assignment of 2,2′-biindazole for the structure of VII was based on the isolation of indazole from the catalytic reduction of VII and VIII, coupled with the establishment of the empirical formula, $C_{14}H_{10}N_4$, and the absence of the NH absorption in the infrared spectrum.

In the present study, the results of the thermal decomposition of 2-azidobenzylideneamines are explained readily by a mechanism involving an electron-deficient azene intermediate formed by the loss of nitrogen. The azene is then believed to attack the nitrogen atom of the azomethine linkage to form the 2-substituted indazoles. The pyrolysis of 2,2′-diazidobenzylideneazine (V) was of special interest. It can readily be seen that the azene derived from V can attack the the nitrogen atom of the azomethine linkage to yield either a five of a six-membered ring. The two possible





sites of attack are very similar except for the effect of the azene *vs.* the azido group. The fact that the only products isolated were those possessing the indazole nucleus indicates the high degree of preference for the

five-membered ring formation in the ring closure reactions of azenes. In view of the high yield (93%) of the biindazole obtained with V, the formation of benzotriazine (six-membered ring) occurred to only a small extent, if at all.

Decomposition reactions of 2-azidodiphenylmethane derivatives are presently being investigated to determine whether a six-membered ring closure can be effected.

Experimental[10,11]

With the exception of 2-(2-azidobenzylideneamino)indazole (VI) all azides used in this study were prepared by the condensation of 2-azidobenzaldehyde with the appropriate amines. The azides prepared in this manner are summarized in Table I. A typical example of the synthesis of azides is given below.

2-Azido-2′-nitrobenzylideneazine (IV).—A solution of 5.0 g. of 2-azidobenzaldehyde[12] in 50 ml. of ethanol was added to a solution of 5.0 g. of 2-nitrobenzylidenehydrazine[13] in 100 ml. of ethanol. A few drops of acetic acid were added, and the mixture was stirred for a few minutes. The yellow precipitate which separated was collected and dried, yielding 5.0 g. (50%) of 2-azido-2′-nitrobenzylideneazine, melting at 145–148° dec. An analytical sample was prepared by recrystallization from ethanol, yielding yellow needles, m.p. 148° dec.

2-(2-Azidobenzylideneamino)indazole (VI).—A solution of 3.5 g. of 2,2′-diazidobenzylideneazine (V) in 200 ml. of dichlorobenzene was heated to 120–130° for 2 hr. During this heating period considerable evolution of gas was observed and the solution turned dark brown. The solvent then was removed at approximately 100° under reduced pressure. The residue was recrystallized from ethanol, yielding 2.5 g. (79%) of yellow 2-(2-azidobenzylideneamino)indazole, m.p. 116–118° dec. An analytical sample, m.p. 122° dec., was prepared by dissolving the product in cold benzene, filtering, and reprecipitating by the addition of ethanol.

Thermal decompositions of all the azides were carried out under essentially the same conditions. The results are summarized in Table II. Pyrolysis of 2-(2-azidobenzylideneamino)indazole is described below as a representative example.

2,2′-Biindazole (VII).—A solution of 1.5 g. of 2-(2-azidobenzylideneamino)indazole (VI) in 150 ml. of dichlorobenzene was heated to 155° for 2 hr. The solution darkened to dark brown and gas was evolved. The solvent then was removed under reduced pressure at 100°. The residue was recrystallized from toluene, yielding 1.2 g. (90%) of 2,2′-biindazole, m.p. 260–264°. Further recrystallizations from toluene yielded an analytical sample melting at 268°.

2-(2-Aminobenzylideneamino)indazole (IX). A.—A solution of 1.7 g. of 2-(2-nitrobenzylideneamino)indazole in 250 ml. of ethanol was hydrogenated with 1.0 g. of 5% palladium on charcoal on a Parr shaker for 1 hr. at 30 p.s.i. The mixture was filtered and the solvent was removed at reduced pressure. The residue was recrystallized from ethanol, yielding 1.0 g. (66%) of yellow 2-(2-aminobenzylideneamino)indazole, m.p. 165–167°. Further recrystallizations from ethanol yielded an analytical sample melting at 167–167.5°.

Anal. Calcd. for $C_{14}H_{12}N_4$: C, 71.17; H, 5.12; N, 23.71 Found: C, 71.02; H, 5.10; N, 23.90.

B.—A suspension of 1.0 g. of 2-(2-azidobenzylideneamino)-indazole (VI) in 200 ml. of ethanol was hydrogenated at 40–50° with 1.0 g. of 5% palladium on charcoal on a Parr shaker at 50 p.s.i. for 2 hr. The mixture was filtered and the solvent was removed at reduced pressure. The residue was recrystallized from alcohol to yield 0.7 g. (78%) of 2-(2-aminobenzylideneamino)indazole melting at 165–167°. Mixture melting point with the reduction product of 2-(2-nitrobenzylideneamino)indazole showed no depression.

2-(2-Acetamidobenzylideneamino)indazole.—A mixture of 0.1 g. of 2-(2-aminobenzylideneamino)indazole (IX) and 5 ml. of acetic anhydride was heated gently for 10 min. After cooling, the mixture was poured into 50 ml. of ice-cold water. The crystals which separated were collected and dried, yielding 0.1 g. (82%) of 2-(2-acetamidobenzylideneamino)indazole, m.p. 205–212°. An analytical sample melting at 212° was prepared by recrystallizations from ethanol.

Anal. Calcd. for $C_{16}H_{14}N_4O$: C, 69.04; H, 5.07; N, 20.14. Found: C, 68.88; H, 5.14; N, 20.20.

2-(2-Azidobenzylideneamino)indazole (VI) from Amine IX.—A solution of 1.0 g. of 2-(2-aminobenzylideneamino)indazole (IX) in 75 ml. of glacial acetic acid and 25 ml. of concentrated hydrochloric acid was cooled to 0°. To the cold mixture a solution of 0.35 g. of sodium nitrite in 5 ml. of water was added. The resulting mixture was stirred for 10 min. at 0°, and 150 ml. of ice-cold water was added followed by a solution of 1.0 g. of sodium azide in 10 ml. of water. The mixture was diluted further by the addition of 150 ml. of water and then extracted with ether. The ethereal extract was washed first with water, then with 5% sodium hydroxide solution, and dried over sodium sulfate. After the removal of the solvent under reduced pressure at 30°, the solid residue was recrystallized from ethanol yielding 0.5 g. (45%) of 2-(2-azidobenzylideneamino)indazole, m.p. 117–118° dec. A mixture melting point with the partial decomposition product of 2,2-diazidobenzylideneazine (V) showed no depression.

Reductive Cleavage of 2-(2,4-Dinitrophenylamino)indazole.—A suspension of 2.0 g. of 2-(2,4-dinitrophenylamino)indazole in 200 ml. of ethanol was hydrogenated with 0.5 g. of 5% palladium on charcoal on a Parr shaker at 40 p.s.i. for 2 hr. The mixture was separated and the solvent was removed at reduced pressure. A solution of the residue in benzene was placed on an alumina packed chromatography column and eluted with a mixture of benzene and cyclohexane to yield 0.3 g. (38%) of indazole, melting at 147°; picrate, m.p. 137° (lit.[14] m.p. 148°; picrate, m.p. 136°).

Reductive Cleavage of 2,2′-Biindazole (VII).—A suspension of 1.0 g. of 2,2′-biindazole in 300 ml. of ethanol was hydrogenated with Raney nickel catalyst on a Parr shaker at 40–50° for 0.5 hr. The mixture was separated and the solvent was removed at 60–70°. The residue was recrystallized from water yielding 0.5 g. (50%) of indazole melting at 145–146°, m.m.p. 146–147°.

Reductive Cleavage of 2-(2-Nitrobenzylideneamino)indazole.—A solution of 1.5 g. of 2-(2-nitrobenzylideneamino)indazole in 250 ml. of ethanol was hydrogenated at 40–50° with Raney nickel catalyst for 0.5 hr. The mixture was worked up as above yielding 0.4 g. (60%) of indazole, m.p. 146°.

Acknowledgment.—The authors are deeply indebted to Dr. L. Schieler for his helpful interest in this work, to Professor P. A. S. Smith for his many invaluable suggestions, and to Mr. S. Hotta for infrared spectral measurements and preparative assistance.

(10) All melting points are uncorrected.

(11) Analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich.

(12) E. Bamberger and E. Demuth, *Ber.*, **34**, 1334 (1901).

(13) T. Curtius and A. Lublin, *ibid.*, **33**, 2463 (1900).

(14) E. Fischer and O. Seuffert, *ibid.*, **34**, 797 (1901).

The Conversion of Benzoylacetanilides into 2- and 4-Hydroxyquinolines

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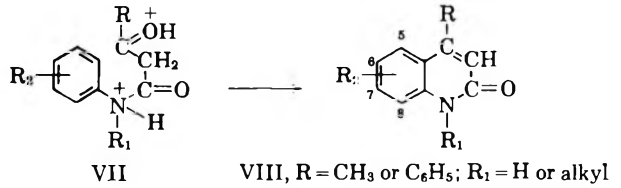
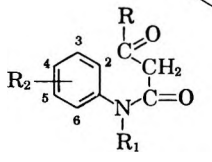
Relatively small proportions of polyphosphoric acid or anhydrous aluminum chloride convert benzoylacetanilides (II) to the corresponding 4-hydroxyquinolines (XII), while with excess of reagent the expected 2-hydroxyquinolines (IX) are furnished. A scheme to account for these results and for the action of acids on the anilide generally is discussed.

The cyclization of a substituted anilide (I) to the 2-hydroxyquinoline (VIII) is effected usually with concentrated sulfuric acid,[1-4] and it is believed generally that the product results from the ring closure of a monoprotonated entity such as V. This view of the mechanism now requires modification since it has been found that the reaction course may be altered by varying the acid–anilide ratio. A relatively small amount of acid merely hydrolyzes the anilide (I, R = C_6H_5) at 130–140° to the arylamine and acetophenone, and negligible 2-hydroxyquinoline results; utilization of a higher proportion of acid in the reaction, however, leads to the Knorr product in good yield.

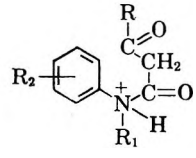


VII

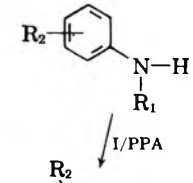
VIII, R = CH_3 or C_6H_5; R_1 = H or alkyl
IX, R = C_6H_5; R_1 = H
X, R = C_6H_5; R_1 = H; R_2 = H

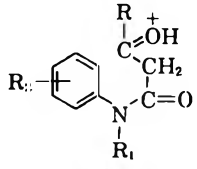


I, R = CH_3 or C_6H_5; R_1 = H or alkyl
II, R = C_6H_5; R_1 = H
III, R = C_6H_5; R_1 = H; R_2 = H
IV, R = C_6H_5; R_2 = H

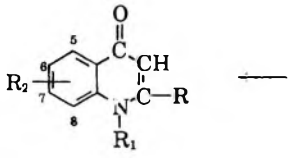


VI

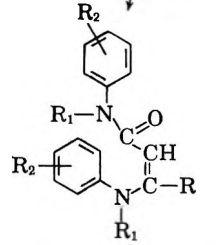




V



XI, R = CH_3 or C_6H_5; R_1 = H or alkyl
XII, R = C_6H_5; R_1 = H
XIII, R = C_6H_5; R_1 = H; R_2 = H



XV, R = CH_3 or C_6H_5; R_1 = H or alkyl
XVI, R = C_6H_5; R_1 = H; R_2 = H

It is now suggested that the anilide (I) on treatment with a limited amount of reagent is transformed to the monoprotonated form (VI), the amide function alone being affected.[5] On warming, VI is unable to cyclize, and undergoes fission at the susceptible amide link (*cf.* Duffy and Leisten[6]) producing arylamine and eventually also, acetophenone.[7] With a larger proportion of acid, the weakly basic carbonyl group in VI is likewise affected, furnishing a diprotonated anilide (VII). A subsequent electrophilic attack on the neighboring aromatic nucleus by the protonated carbonyl group in VII, the positive charge of which tends to hinder the competing ionization process at the amide bond, leads eventually to the 2-hydroxyquinoline (VIII).[8] The nature and position of the substituents in I will necessarily influence the electronic effects operating in VI and VII and consequently also the competing heterolytic and cyclization processes. It is reported,[3,9] for example, that the nitro- and chloroacetoacetanilides (I, R = CH_3; R_1 = H; R_2 = NO_2 or Cl) are appreciably decomposed to arylamine even in an excess of concentrated sulfuric acid. Moreover, cyclization to the quinoline proceeds more readily with acetoacetanilides (I, R = CH_3; R_1 = H) than with the corresponding benzoylacetanilides (II) under similar conditions (*cf.* Knorr[10]).

The acid strength of the reagent needs to be considered in the Knorr reaction: an excess of glacial acetic acid and even a mixture of concentrated sulfuric acid and glacial acetic acid were ineffective at 90° in transforming benzoylaceto-*o*-toluidide (II, R_2 = 2-CH_3) to the 2-hydroxyquinoline. The acetic acid and the acetic acidium ion[11] (in the latter solution) were incapable, presumably, unlike concentrated sulfuric acid or 74% sulfuric acid,[12] of protonating the carbonyl group in VI and forming VII.

It was recently reported[13] that, while an excess of

(1) L. Knorr, *Ann.*, **236**, 83 (1886).
(2) R. C. Elderfield, "Heterocyclic Compounds," Vol. 4, John Wiley and Sons, Inc., New York, N. Y., 1952, p. 32.
(3) J. Joubert, M.S. thesis, Witwatersrand University, 1960.
(4) C. F. Koelsch and J. W. Britain, *J. Org. Chem.*, **24**, 1551 (1959).
(5) It is now generally agreed [A. R. Katritzky and R. A. Y. Jones, *Chem. Ind.* (London), 722 (1961)] that amides are predominantly protonated at the oxygen atom. The fission process may possibly involve this form of the protonated amide; alternatively, the N-protonated form (VI) could arise from the former *via* a tautomeric change.
(6) J. A. Duffy and J. A. Leisten, *Nature*, **178**, 1242 (1956).
(7) Koelsch and Britain[4] isolated acetophenone from the reaction mixtures of N-alkylbenzoylacetanilides and concentrated sulfuric acid at 60–90°, and the ketone was assumed to arise during the subsequent working up procedures. It is possible, however, for the acetophenone to have been produced during the reaction proper.
(8) The conversion of anils into quinolines by means of concentrated sulfuric acid is believed to proceed by cyclization of the diprotonated anils [T. G. Bonner and M. Barnard, *J. Chem. Soc.*, 4181 (1958)].
(9) J. L. C. Marais and O. G. Backeberg, *ibid.*, 2207 (1950).
(10) L. Knorr, *Ann.*, **245**, 372 (1888).
(11) R. J. Gillespie and J. A. Leisten, *Quart. Rev.* (London), 40 (1954).
(12) A. L. Searles and R. J. Kelly, *J. Am. Chem. Soc.*, **77**, 6075 (1955).
(13) B. Staskun and S. S. Israelstam, *J. Org. Chem.*, **26**, 3191 (1961). In the Experimental section, the weight of anilide (II) taken for reaction with PPA (1 g.) at 140° for 20 min. to form 4-hydroxyquinoline (XII) was 1 g. and not 0.5 g. as reported.

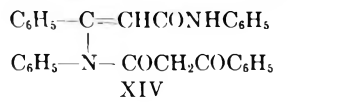
TABLE I

ACTION OF POLYPHOSPHORIC ACID ON BENZOYLACETANILIDES

Anilide[a] (1 g.)	PPA, g.	Reaction time, min.	Temp., °C.	2-Hydroxyquinoline, g.[b]	4-Hydroxyquinoline, g.[b]
III	0.5	20	140	Nil[c]	0.16 (+0.2, recovered anilide)
	+0.5, sirupy phosphoric acid			Nil	0.09
	0.8			Nil[c]	0.22–0.24
	1			Negligible[c]	0.22–0.24
		30	145–150	Negligible[c]	0.24
		40	110–120	Negligible[c]	0.20 (+0.16, recovered anilide)
		12	180	Negligible[c]	0.18
	+0.5, aniline	30	145–150	Negligible	0.1 g. (+0.2, recovered anilide)
	+0.5, ethyl benzoylacetate	20	140	Negligible[c]	0.34–0.40
	+0.5, acetophenone				0.15
	+1, benzanilide[d]				0.24
	+1, β-phenylpropionanilide[d]				0.22
	1.5			*ca.* 0.2[e]	0.15–0.18
	+1, ethyl benzoylacetate			Nil	0.34
	2	30	145–150	*ca.* 0.4[e]	0.07
	+0.5, aniline			Negligible	0.42
	2.5			0.53	0.02
	4			0.63	Negligible
	+0.5, aniline			0.15	0.15
II, R_2 = 2-CH_3	1	30	145–150	Negligible	0.14[f]
	+0.5, ethyl benzoylacetate				0.30
	+0.5, acetophenone				0.10
II, R_2 = 4-CH_3	1	30	145–150	Negligible	0.13[g]
	+0.5, ethyl benzoylacetate				0.23
II, R_2 = 4-NO_2	1	20	140	Negligible	0.10–0.14[h]
	+0.5, ethyl benzoylacetate				0.19

[a] Ref. 13. [b] Crude yields reported; the melting point of the product was taken and, after recrystallization from dilute ethanol, its identity was confirmed by melting point and mixture melting point with authentic sample.[13,22] [c] The alkali-insoluble material isolated from the reaction mixture consisted of substance B (see Experimental), m.p. 200–201°, and contained little if any 4-phenyl-2-hydroxyquinoline (X). [d] Recovered unchanged. [e] Contaminated with substance B, m.p. 200–201°. [f] XII, R_2 = 8-CH_3, m.p. 226–227°. [g] XII, R_2 = 6-CH_3, m.p. 296–297°. [h] XII, R_2 = 6-NO_2; pale yellow tiny needles from glacial acetic acid, m.p. 378–380° (copper block) (incorrectly reported[13] as 328–330°); soluble in dilute alkali to give an orange solution. The infrared spectrum was identical with that of the sample prepared from ethyl benzoylacetate, *p*-nitroaniline, and PPA.[13]

polyphosphoric acid (PPA) converts the anilide (II) to the expected 2-hydroxyquinoline (IX) in good yield, utilization of a smaller proportion of reagent furnishes the isomeric 4-hydroxyquinoline (XII). Further study has shown that the yield of 2-phenyl-4-hydroxyquinoline (XIII) from benzoylacetanilide (III) at 140° varies considerably with the PPA–anilide ratio. The optimum yield (~24%) was obtained when treating III with an equal weight of acid, while with both lesser and greater weights of the latter the production of XIII was decreased (Table I). An ω-(*p*-aminobenzoyl)acetophenone, which might have been expected as a by-product on the basis of a Fries-type rearrangement,[13] was not isolated.[14] Benzanilide (and β-phenylpropionanilide) had no significant effect on the optimum yield (Table I), thus making an entity such as XIV improbable as the precursor of XIII.[15] When mixed with ethyl benzoylacetate, however, III was transformed into XIII in increased (35–40%) yield; since acetophenone was without a similar effect, the improvement could not be attributed to the solvent action of the ester on the reactants. The anilide (III) on warming with an equal weight of sirupy phosphoric acid at 140° merely was hydrolyzed to aniline and acetophenone, while, with a larger quantity of acid, it was converted to the 2-hydroxyquinoline (X). Poor yields of XIII resulted when employing PPA diluted with sirupy phosphoric acid.

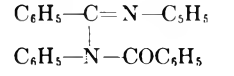


XIV

The results, collectively, make improbable a purely intramolecular reaction mechanism[13] and may be ac-

(14) A fair amount (about 10% yield) of an alkali- and acid-insoluble substance (B), m.p. 200–201°, was isolated (see Experimental).

(15) Benzanilide is not affected by PPA at 140°; at a higher temperature (180°), however excess reagent converts it to 4-aminobenzophenone while utilization of an equal weight of reagent furnishes N,N'-diphenylbenzamidine as will be reported at a later date. Formation of the latter base most likely involves self-condensation of benzanilide to an intermediate of type

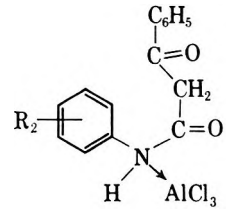


and the possibility of a similar self-condensation of III to XIV occurring, therefore, was considered and subsequently rejected.

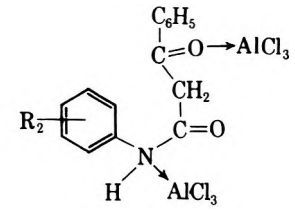
counted for as follows. With an excess of PPA, the anilide (III) is extensively diprotonated, thus allowing for its appreciable conversion to the 2-hydroxyquinoline (X). A small proportion of acid, however, forms the monoprotonated VI solely and this hydrolyzes to aniline under the reaction conditions prevailing. The latter now condenses with unchanged III to give an acrylanilide (XVI)[16] which then cyclizes to the 4-hydroxyquinoline (XIII).[17] When ethyl benzoylacetate is also present, ethyl β-phenylaminocinnamate likewise results[13] and the over-all yield of XIII is consequently increased. Support for the view that XVI is in fact formed was obtained by rearranging III with PPA in the presence of aniline when the yield of XIII relative to X was enhanced (Table I). Increased proportions of PPA, however, brought about preferential cyclization of III to X. The observation that XIII is formed on warming N-ethylbenzoylacetanilide (IV, $R_1 = C_2H_5$) with aniline in the presence of PPA is explicable in terms of the suggested acrylanilide-type intermediate (XV).

Although not isolated from the reaction mixtures of III and PPA, β-phenylamino-β-phenylacrylanilide (XVI) was prepared by warming III with aniline in the presence of a small amount of PPA.[18] Its structure was confirmed by (i) acid hydrolysis to III, (ii) thermal cyclization in liquid paraffin to 2-phenyl-4-hydroxyquinoline (XIII), and (iii) conversion to 4-phenyl-2-hydroxyquinoline (X) with 74% sulfuric acid (involving preliminary *in situ* hydrolysis of XVI to III and subsequent ring closure of the latter). On warming with an equal weight of PPA, XVI was quantitatively converted to XIII, making feasible its proposed role of precursor.[19]

The critical effect of the anilide–reagent ratio on the course of the Knorr reaction was observed also when using a Lewis-type acid, *viz.*, anhydrous aluminum chloride. The behavior of I with this reagent previously has not been reported. Treatment of II with an equimolar proportion of aluminum chloride for 1 hr. at 200° brought about its conversion to 4-hydroxyquinoline (XII) in 20–46% yields; little if any of the isomeric 2-hydroxyquinoline (IX) was formed. Arylamine (detected as a sublimate of the hydrochloride) was produced during the reaction, and it is, therefore, possible for XII to have arisen *via* an acrylanilide intermediate (XV). An alternative Fries-type process,[13] nevertheless, also merits consideration and further work to help decide the issue is in progress. A preliminary step in the reaction sequence leading to XII (and arylamine) may well be heterolysis at the amide link in an initially formed anilide–aluminum chloride complex such as XVII.



XVII



XVIII

An increased molar proportion (3:1) of aluminum chloride, however, converted II solely to the 2-hydroxyquinoline (IX), in high yield. A doubly coordinated complex such as XVIII, analogous in structure and behavior to VII, may be involved in this instance.

In the absence of reagent, II was decomposed by dry hydrogen chloride at 200° furnishing arylamine, acetophenone, a trace (3%) of 4-hydroxyquinoline (XII), and negligible 2-hydroxyquinoline (IX). It may be supposed that the hydrogen chloride converts II to VI which then rapidly decomposes to arylamine under the conditions prevailing so that negligible VII is made available for cyclization to the Knorr quinoline. During the process some XV may arise and so account for the XII obtained. The effect on anilides (I) of various acidic reagents is being studied further.

Experimental[20]

The Action of Concentrated Sulfuric Acid on Anilides (I).—Benzoylacetanilide (III, 1 g.) was warmed with the acid (0.7 g., *d* 1.84, 98%) on the water bath (about 90°) for 1 hr. with occasional stirring, and the viscous solution was treated with water. The precipitated material was removed and separated into crude alkali-soluble anilide (0.68 g.) and alkali-insoluble 4-phenyl-2-hydroxyquinoline (X, 0.05 g., colorless crystals from dilute ethanol, m.p. and m.m.p. 256–257° with authentic sample[13]) by means of dilute sodium hydroxide. Benzoylacet-*o*-toluidide (II, $R_2 = CH_3$), acetoacet-*o*-toluidide (I, $R = CH_3$; $R_1 = H$; $R_2 = 2\text{-}CH_3$; 2 g.), and the alkali-insoluble N-methylbenzoylacetanilide (IV, $R_1 = CH_3$), when similarly treated and suitably worked up, likewise yielded unchanged anilide (0.75 g., *ca.* 0.5 g., 0.75 g., respectively) and negligible Knorr product. With an increased reaction time (4.5 hr.), the yield of X was improved (0.26 g.). A smaller weight of acid (0.5 g.) was even less effective as a catalyst.

Compound III (1 g.), on warming with the acid (0.7 g.) at 130–140° for 10–15 min., was decomposed rapidly. The green viscous mixture was treated with dilute sulfuric acid, and a small amount (0.16 g.) of insoluble X was removed. The ether-extracted filtrate when made alkaline furnished aniline while the ethereal layer on evaporation yielded crude acetophenone (characterized as its 2,4-dinitrophenylhydrazone, m.p. 237°). Acetoacet-*o*-toluidide (2 g.) and N-methylbenzoylacetanilide were likewise hydrolyzed to the respective amines and ketones at 130–140°, negligible Knorr quinoline being isolated in each case.

Utilization of increased acid (2 g.) in the reaction with III (1 g.) at ±90° for 1 hr. led to enhanced conversion to X (0.30 g.); some III (0.32 g.) was recovered. Substantially higher yields (60–70%) of Knorr product were obtained from acetoacet-*o*-toluidide (2 g.), benzoylacet-*o*-toluidide, and N-methylbenzoylacetanilide under similar conditions.[21a]

Reaction of III (1 g.) with acid (2 g.) at 130–140° for 10–15 min., followed by addition of water to the mixture, deposited X (0.37 g.) and negligible unchanged III. In like manner acetoacet-*o*-toluidide (2 g.) gave 4,8-dimethyl-2-hydroxyquinoline (1.1 g., colorless crystals from dilute ethanol, m.p. 228–229°, lit.[3]

(16) The acrylanilide (XVI) has been proposed as an intermediate (not isolated) in the formation of the anil of benzoylmalonic acid dianilide from acetophenone anil and phenyl isocyanate [J. Moszew, A. Inasinski, K. Kubiczek, and J. Zawrzykraj, *Chem. Abstr.*, **55**, 15383 (1961)]; also ref. 19.

(17) It is possible also that XIII may result by cyclization of a β-phenylaminocinnamate formed from the aniline and an ester such as $C_6H_5COCH_2CO_2PO(OH)_2$ (furnished by PPA hydrolysis of III). It is suggested, however, that the predominating reaction of the latter ester would be a rapid preferential decomposition to acetophenone, and that XVI is the chief precursor.

(18) The preparation of XVI from aniline and methyl benzoylacetate has been reported by L. Knorr[10] who gives its melting point as 133°.

(19) J. Moszew (Abstracts of Congress Lectures and Scientific Papers presented at the XIXth Conference of the IUPAC, July, 1963, p. 38) has reported on the quinoline cyclization of anil-anilides of β-keto esters by H_2SO_4 and PPA which proceed according to the Conrad-Limpach scheme.

(20) Melting points are uncorrected and infrared spectra were measured on a Perkin-Elmer Infracord Model 137 spectrophotometer.

(21) (a) Treatment of benzoylaceto-*o*-toluidide (II, $R_2 = 2\text{-}CH_3$, 1 g.) with a relatively larger amount of acid (3 ml.) at 90° for 1 hr. gave the 2-hydroxyquinoline in poor yield (0.25 g.). It is supposed that some of the product remains in aqueous solution as the soluble sulfonated base (*cf.* J. Joubert[3]). (b) The British Drug Houses Ltd.

m.p. 217–218°), and N-methylbenzoylacetanilide yielded 1-methyl-4-phenyl-2-quinolone (VIII, R = C_6H_5; R_1 = CH_3; R_2 = H; 0.72 g.; colorless needles from dilute ethanol, m.p. 143–144°, lit.[4] m.p. 141–142°; no coloration with alcoholic ferric chloride; NH stretching absent, amide–CO stretching at 6.05 μ).

Action on Benzoylacet-*o*-toluidide of Concentrated Sulfuric Acid–Glacial Acetic Acid.—A solution of the anilide (II, R_2 = 2-CH_3; 1 g.) in glacial acetic acid (10 ml.) was warmed at about 90° for 1 hr.; treatment with water precipitated unchanged anilide (0.90 g.) and negligible Knorr product. Use of a mixture of glacial acetic acid (7 ml.) and concentrated sulfuric acid (3 ml.) as solvent in the reaction led to a trace of 4-phenyl-8-methyl-2-hydroxyquinoline (IX, R_2 = 8-CH_3; 0.02 g.; colorless crystals from dilute ethanol, m.p. and m.m.p. 220–221° with authentic specimen[13]) and unchanged anilide (0.86 g.).

Action on Benzoylacetanilide (III) of *o*-Phosphoric Acid Alone, and in the Presence of Phosphorus Pentoxide. A.—The anilide (1 g.) and sirupy H_3PO_4 (0.75 g., *d* 1.75, 88–93%) were reacted at 140–150° for 15 min.; the mixture was then made alkaline and extracted with ether; acidification of the aqueous layer with glacial acetic acid deposited unchanged III (0.12 g.), while the ethereal layer was found to contain aniline and acetophenone. On addition of ethyl benzoylacetate (0.5 g.) and P_2O_5 (0.8 g.) to the reaction mixture prior to the treatment with alkali and continuation of the heating at 140–150° for a further 25 min., there resulted 0.24 g. of crude (m.p. 220–230°) 2-phenyl-4-hydroxyquinoline (XIII, colorless needles from ethanol, m.p. and m.m.p. 254–255°).

B.—A mixture of acid (0.7 g.) and P_2O_5 (1.2 g.) was warmed at 140° for 10 min. and III (1.5 g.) then was added. Further heating at 140° for 20 min. produced 0.42 g. of crude XIII. In the absence of the pentoxide, warming of the acid (0.7 g.) and III (1.5 g.) at 140° for 30 min. led to hydrolysis to aniline and acetophenone, 0.3 g. anilide being recovered.

Relatively small amounts of H_3PO_4 at 140° similarly hydrolyzed benzoylacet-*p*-toluidide (II, R_2 = 4-CH_3) to *p*-toluidine and acetophenone. Use of 4 g. of acid with 0.4 g. of anilide at 140° for 20 min. furnished 4-phenyl-6-methyl-2-hydroxyquinoline (0.15 g., crude m.p. 240–243°) as well as *p*-toluidine and acetophenone.

Action of PPA on Benzoylacetanilide (III).—A mixture of the anilide (5 g.) and PPA (5 g., B.D.H.[21b] "tetraphosphoric acid," approx. 80% P_2O_5) was heated with manual stirring at 140–150° for 30 min.; the yellow viscous mass frothed considerably during the course of the reaction and the odor of acetophenone was detected. The orange product was warmed with 2 *N* sodium hydroxide and some brown, gummy alkali-insoluble material (A) was removed. Acidification of the alkaline filtrate (treated with charcoal) with glacial acetic acid deposited the crude 2-phenyl-4-hydroxyquinoline (XIII, 1.13 g.; 24%; m.p. 205–245°; negligible purple color with alcoholic $FeCl_3$; colorless woolly needles from dilute ethanol, m.p. and m.m.p. 254–255°; with authentic sample[13,22] infrared spectrum identical with that of 2-phenyl-4-hydroxyquinoline[13,22]).

The alkali-insoluble A was warmed with 95% ethanol and the sparingly-soluble product B (0.4–0.5 g.) was removed. The ethanolic filtrate on treatment with water deposited material from which was isolated a small amount (*ca.* 0.05 g.) of alkali-insoluble 4-phenyl-2-hydroxyquinoline (X). Substance B was recrystallized from glacial acetic acid containing traces of water and was obtained as colorless, tiny crystals, m.p. 200–201°, insoluble in dilute acid and alkali and in ether, sparingly soluble in hot 95% ethanol, soluble in hot methanol and in glacial acetic acid. The methanolic solution gave no coloration with $FeCl_3$. On heating with soda-lime, B furnished acetophenone. Hydrolysis with *ca.* 70% sulfuric acid yielded acetophenone and a nitrogen-free substance, m.p. 139–140°. The infrared spectrum of B differed from that of 4-phenyl-2-hydroxyquinoline and showed a NH stretching band at 3.2 and strong CO absorption at 6.0 μ. The possibility of B being a *3*-O-substituted cinnamanilide derivative is being considered.

The XIII obtained from equal weights of PPA and III was contaminated with negligible unchanged anilide (as indicated by the melting point range of the crude product and by the relative absence of a purple coloration with alcoholic ferric chloride). However, on employment of a smaller proportion of reagent (Table I), a mixture of quinoline and anilide resulted. The amount of the former component was determined by refluxing the weighed, crude, alkali-soluble product with dilute (1:1) sulfuric acid (which hydrolyzed III), and subsequently precipitating the unaffected XIII with ammonium hydroxide.

Reaction in the Presence of Ethyl Benzoylacetate (or Aniline).—The anilide (II), ester (or aniline), and PPA after warming (Table I) was treated with dilute sodium hydroxide, and the alkaline mixture either was extracted with ether (to remove acetophenone, etc.) or filtered. Acidification of the alkaline aqueous layer or filtrate deposited the 4-hydroxyquinoline (XII) contaminated with negligible anilide. During the course of the reaction, the ethyl benzoylacetate appeared to hydrolyze to acetophenone.

2-Phenyl-4-hydroxyquinoline from N-Ethylbenzoylacetanilide (IV, R_1 = C_2H_5), Aniline, and PPA.—After warming of the anilide (1.5 g.), aniline (0.5 g.), and PPA (1.5 g.) at 145–150° for 40 min., the mixture was made alkaline and was extracted with ether; the aqueous layer (charcoal) on acidification with glacial acetic acid precipitated the crude quinoline (XIII, 0.4 g.). Recrystallization from dilute ethanol yielded colorless needles, m.p. and m.m.p. (with 2-phenyl-4-hydroxyquinoline[13]) 254–255°. In the absence of aniline, the anilide underwent hydrolysis to N-ethylaniline and little if any 1-ethyl-2-phenyl-4-quinolone (XI, R = C_6H_5; R_1 = C_2H_5; R_2 = H) was formed.

***β*-Phenylamino-*β*-phenylacrylanilide (XVI).**—Benzoylacetanilide (2 g.), aniline (0.9 g.), and PPA (1 g.) were stirred together at 140–150° for 15 min.; the yellow, viscous, semisolid mass was warmed (*ca.* 50°) with 2 *N* sodium hydroxide, and the alkali-insoluble material was removed (the filtrate on acidification with glacial acetic acid deposited some unchanged III) and triturated with cold 2 *N* hydrochloric acid (to remove aniline). the acid-insoluble residue was dissolved in warm, slightly alkaline 95% ethanol, and the filtered solution was treated with water and chilled when 0.7–0.8 g. of crude product separated; pale yellow needles from dilute ethanol had m.p. 117–118°, lit.[10] m.p. 133°.

Anal. Calcd. for $C_{21}H_{18}N_2O$: N, 8.92. Found: N, 9.07.

The substance was insoluble in dilute acid and alkali and gave no immediate coloration with alcoholic $FeCl_3$; a purple color developed gradually as hydrolysis to III occurred. The infrared spectrum showed NH stretching at 3.15 and amide–CO stretching at 6.2 μ.

Hydrolysis to Benzoylacetanilide.—The acrylanilide (XVI, 0.2 g.) was dissolved in dilute ethanol containing a few drops of concentrated hydrochloric acid and the solution was warmed (*ca.* 50°) for 10 min. Water was added and precipitated crude III, m.p. 105–108°; when recrystallized from dilute ethanol it had m.p. and m.m.p. 107–108° and gave an immediate purple coloration with $FeCl_3$.

Conversion to 2-Phenyl-4-hydroxyquinoline. A.—The acrylanilide (XVI, 0.15 g.) in *ca.* 6 ml. of medicinal liquid paraffin was heated at 240–250° for 15 min. Ether was added to the cooled viscous mass, and the crude quinoline (m.p. 245–255°) was removed. This was dissolved in 2 *N* sodium hydroxide, the solution was treated with charcoal, and the practically pure substance (m.p. and m.m.p. 254–255° with authentic sample[13]) precipitated with glacial acetic acid.

B.—PPA (0.4 g.) and acrylanilide (0.4 g.) were warmed together at 140–145° for 20 min. during which period only slight effervescence occurred (*cf.* with the anilides II which froth considerably). The mixture was treated with 2 *N* sodium hydroxide, negligible alkali-insoluble impurity was removed, the filtrate was treated with charcoal, and XIII (0.22 g., m.p. 240–255°) precipitated with glacial acetic acid. Recrystallization from dilute ethanol furnished colorless woolly needles, m.p. and m.m.p. 254–255°.

Conversion to 4-Phenyl-2-hydroxyquinoline.—XVI (0.2 g.) was warmed with *ca.* 3 ml. of 74% sulfuric acid (2 ml. of concentrated acid + 1 ml. of water) on the water bath (about 90°) for 80 min. Water was added and the precipitate was removed, washed, and dried. The product, which melted over a range and gave a purple coloration with $FeCl_3$, was separated into benzoylacetanilide (III) and alkali-insoluble X (m.p. 253–257°) by means of 2 *N* sodium hydroxide; colorless crystals formed from dilute ethanol with m.p. and m.m.p. (with authentic sample[13]) 256–257°. Benzoylacetanilide (0.2 g.) when similarly treated led also to a mixture of unchanged III and X.

Action on Benzoylacetanilides of Aluminum Chloride to Form (A) 4-Hydroxyquinolines.—The procedure is illustrated using benzoylacet-*o*-toluidide (II, R_2 = 4-CH_3). The anilide (2 g.,

(22) B. Staskun, *J. S. African Chem. Inst.*, **9**, 89 (1956).

TABLE II

ACTION OF ANHYDROUS ALUMINUM CHLORIDE ON BENZOYLACETANILIDES AT 200° FOR 1 HR.

Anilide[a] (2 g.)	Aluminum chloride, g.	Mole reagent per mole anilide	% yield[b] 2-Hydroxyquinoline	% yield[b] 4-Hydroxyquinoline	Recovered anilide,[b] g.
III	1.1	1.0	Negligible	35[c]	Negligible
	2.4	2.2	30[d]	Negligible	0.3
	2.6	2.4	35	Negligible	0.15
II, R_2 = 2-CH_3	1.1	1.0	Negligible	25[e]	Negligible
	3.0	3.0	90[f]	Negligible	
II, R_2 = 4-CH_3	1.1	1.0	Negligible	46[g]	Negligible
	2.2	2.1	40[h]	Negligible	0.4
	3.3	3.2	91	Negligible	
II, R_2 = 2,4-diCH_3	1.0	1.0	Negligible	20[i]	Negligible
	3.1	3.0	90[j]	Negligible	
II, R_2 = 4-NO_2	1.0	1.1	Decomposition products		0.15
	3.0	3.2			
IV, R_1 = CH_3[k]	1.1	1.0	Negligible	Negligible	0.33
	3.4	3.3	67[l]	Negligible	

[a] Ref. 13. [b] See footnote *b* in Table I. [c] XIII, m.p. 254–255°. [d] X, m.p. 256–257°. [e] XII, R_2 = 8-CH_3, m.p. 226–227°. [f] IX R_2 = 8-CH_3, m.p. 220–221°. [g] XII, R_2 = 6-CH_3, m.p. 296–297°. [h] IX, R_2 = 6-CH_3, m.p. 243–244°. [i] XII, R_2 = 6,8-diCH_3, m.p. 228–229°. [j] IX, R_2 = 6,8-diCH_3, m.p. 250–251°. [k] M.p. 97–98°, lit.[4] m.p. 97–98°. [l] M.p. 143–144°, lit.[4] m.p. 141–142°.

0.008 mole) and powdered anhydrous aluminum chloride (1.1 g., 0.008 mole), after intimate mixing in a mortar (undue exposure to the atmosphere being avoided), was transferred to a 50-ml. round-bottomed flask fitted with an air condenser carrying a cotton-wool plug and then warmed at 160–180° for several minutes when preliminary fuming occurred. The mixture was then kept at about 200° for 1 hr. during which period hydrogen chloride was evolved and a small amount (0.05–0.1 g.) of *p*-toluidine hydrochloride (m.p. 230–238°) sublimed onto the walls of the flask. The dark red viscous product was dissolved in the minimum volume of hot 95% ethanol, the solution was treated with 2 *N* hydrochloric acid, the mixture was chilled, and the sparingly soluble quinoline hydrochloride was removed. (The yellow acid filtrate, when made alkaline, furnished a little *p*-toluidine.) The crude hydrochloride was warmed with 2 *N* sodium hydroxide, negligible alkali-insoluble material was removed, and the warm filtrate (charcoal) containing the somewhat sparingly soluble sodium salt of the 4-hydroxyquinoline was acidified with glacial acetic acid when the crude 2-phenyl-6-methyl-4-hydroxyquinoline (XII, R_2 = 6-CH_3) was deposited (0.87 g., 46%, m.p. 275–285°). Recrystallization from 50% acetic acid furnished colorless crystals, m.p. and m.m.p. (with authentic specimen[13,22]) 296–297°. The results using other anilides are collected in Table II.

(B) 2-Hydroxyquinolines.—The procedure using benzoylacet-*p*-toluidide is typical. The anilide (2 g., 0.008 mole) and aluminum chloride (3.3 g., 0.025 mole) reacted at 200° for 1 hr. as above; hydrogen chloride was evolved readily, but little if any *p*-toluidine hydrochloride sublimated. The crude sparingly soluble quinoline hydrochloride was isolated as before and warmed with 2 *N* sodium hydroxide, and the insoluble 4-phenyl-6-methyl-2-hydroxyquinoline (IX, R_2 = 6-CH_3) was washed (with dilute acetic acid) and dried (1.6 g., m.p. 225–235°). The alkaline filtrate on acidification with glacial acetic acid deposited a small amount of crude carbostyril (IX, R_2 = 6-CH_3, 0.1 g., m.p. 175–210°); 2-phenyl-6-methyl-4-hydroxyquinoline was absent. The combined product (1.7 g., 91%), when recrystallized from dilute ethanol, gave colorless woolly needles, m.p. and m.m.p. (with authentic specimen[13]) 243–244°. Table II lists the details and results using other anilides.

Action of Hydrogen Chloride on Benzoylacet-*p*-toluidide (II, R_2 = 4-CH_3).—Dry hydrogen chloride was passed over 2 g. of recrystallized and dried anilide (contained in a 50-ml. round-bottomed flask and protected from atmospheric moisture) at 200° for 1 hr. A reaction occurred and a pale yellow oil and *p*-toluidine hydrochloride collected slowly on the upper portion of the flask during the passage of the gas. The dark red viscous residue was extracted with 2 *N* sodium hydroxide, and the alkali-insoluble material (0.5 g.; m.p. 170–190°; needles from dilute acetic acid, m.p. 230–235°; mixture melting point with IX, R_2 = 6-CH_3, was depressed; infrared spectra were dissimilar) was removed. The alkaline filtrate (charcoal) on acidification with glacial acetic acid deposited XII (R_2 = 6-CH_3, 0.06 g., m.p. 280–290°). Recrystallization from dilute ethanol gave colorless crystals, m.p. and m.m.p. 296–297° with authentic sample.[22] Benzoylacetanilide (III) and benzoylacet-*o*-toluidide (II, R_2 = 2-CH_3) likewise furnished traces (about 3%) of the respective 4-hydroxyquinolines and little if any of the 2-hydroxyquinolines.

A Synthesis of 1,3,4,5-Tetrahydropyrrolo[4,3,2-*de*]quinoline

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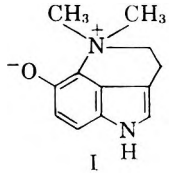
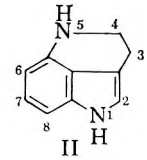
1,3,4,5-Tetrahydropyrrolo[4,3,2-*de*]quinoline (II) has been prepared by catalytic reduction of 4-nitroindol-3-ylacetonitrile. Methods for selectively alkylating both nitrogens of II have been developed.

The recent revision of the dehydrobufotenin[1,2] structure (I) prompted us to prepare II, the simplest member of the 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline ring system for biological evaluation.

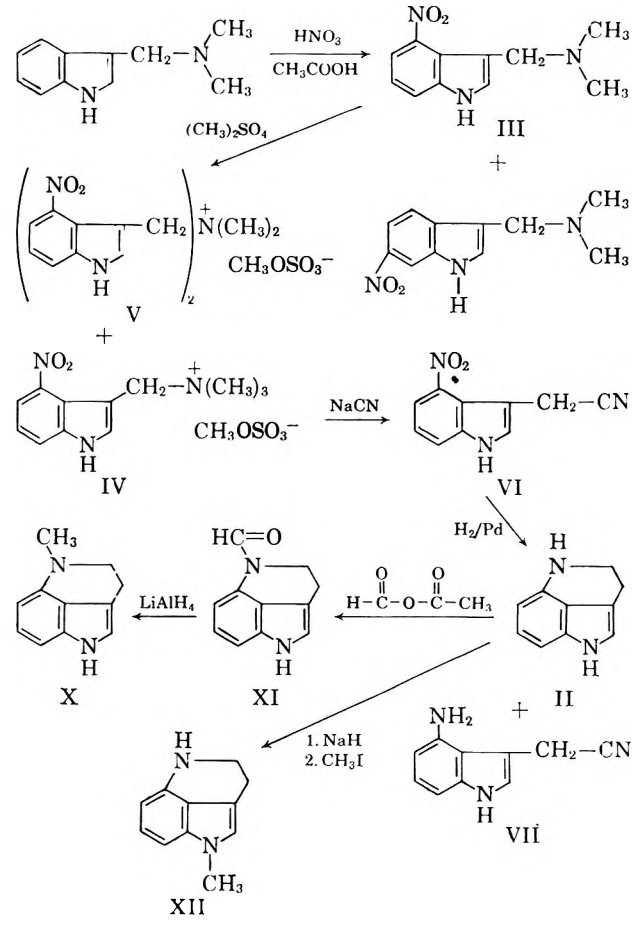


I

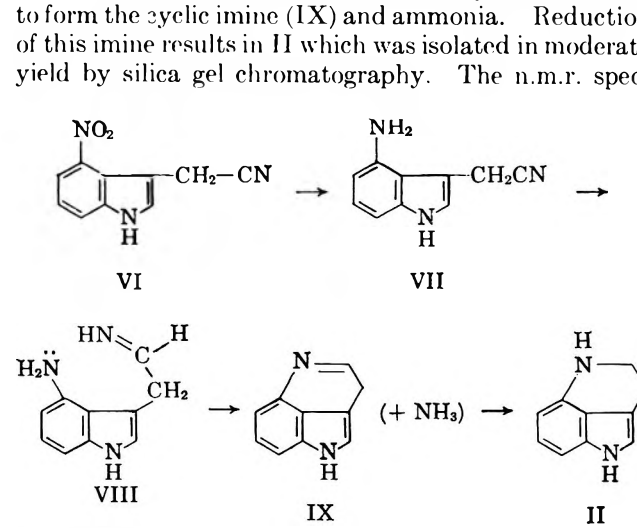


II

4-Nitrogramine (III), the starting material for this synthesis, was obtained by direct nitration of gramine.[3] The mixture of nitrogramines thus obtained was separated by fractional precipitation. 6-Nitrogramine, the major product, is a weaker base than the 4-nitro isomer and was precipitated selectively from an aqueous solution of the acetic acid or nitrate salts with ammonium hydroxide. When the filtrate from this precipitation was made strongly alkaline with sodium hydroxide, practically pure 4-nitrogramine was obtained. To facilitate nitrile formation, 4-nitrogramine was converted to a mixture of crystalline methosulfates (IV, V). Although no experimental conditions could be found that would preclude V, its formation was minimized by the dropwise addition of a tetrahydrofuran solution of the gramine to a large excess of dimethyl sulfate in ice-cold tetrahydrofuran.[4] (The reaction of gramine with methyl iodide to form a bis adduct, analogous to V, and trimethylamine has been discussed by Geissman and Armen.[5]) Fractional crystallization of the methosulfate mixture from methanol afforded a separation of the slightly soluble bis adduct (V) from IV. Displacement of trimethylamine from IV to yield the nitrile (VI) was best effected in a pH 4.7 acetate buffer with sodium cyanide by a modified procedure of Brown and Garrison.[6] Under these conditions, the bis adduct V reacted with sodium cyanide to yield the nitrile (VI) and 4-nitrogramine which could be recovered. For this reason it was unnecessary to fractionate the crude methosulfate mixture before carrying out the nitrile displacement. Catalytic hydrogenation of 4-nitroindol-3-ylacetonitrile (VI) with a palladium catalyst at about 70° yielded the expected product, 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline (II), a cyclization reminiscent of two published approaches to indoles.[7-9] This reaction probably proceeds in four steps. Initial,



facile reduction of the nitro group yields an aminonitrile (VII) which has been isolated as a by-product from the reaction mixture. As is characteristic of nitriles under these conditions,[10] reduction of VII yields an imine (VIII) which condenses with the primary amine at C-4, to form the cyclic imine (IX) and ammonia. Reduction of this imine results in II which was isolated in moderate yield by silica gel chromatography. The n.m.r. spec-



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(2) B. Robinson, *et al.*, *Proc. Chem. Soc.*, 310 (1961).
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(4) A. Allais and J. Meier, U. S. Patent 3,042,685 (July 3, 1962).
(5) T. A. Geissman and A. Armen, *J. Am. Chem. Soc.*, **74**, 3916 (1952).
(6) R. K. Brown and R. A. Garrison, *ibid.*, **77**, 3839 (1955).
(7) G. N. Walker, *ibid.*, **77**, 3844 (1955).
(8) H. Plieninger and I. Nogradi, *Chem. Ber.*, **88**, 1961 (1955).
(9) H. R. Snyder, E. P. Merica, C. G. Force, and E. G. White, *J. Am. Chem. Soc.*, **80**, 4622 (1958).
(10) C. F. Wirans and H. Adkins, *ibid.*, **54**, 306 (1932).

trum of II shows two well-defined triplets centered at 177.0 and 203.5 c.p.s. (apparent J = 5.5 c.p.s.), downfield from tetramethylsilane, which have been assigned to the methylene protons on C-3 and C-4, respectively.[1,2] A singlet at 231 c.p.s. was assigned to the proton at N-5. When this nitrogen was methylated, the 231-c.p.s. peak was replaced by a strong singlet at 175 c.p.s. which was assigned to the N-methyl protons of X (*vide infra*). Structure II was supported also by its ultraviolet spectrum which was similar to that reported for 4-amino-2,3-dimethylindole.[11]

When II was allowed to react with formic acetic anhydride,[12] the expected N-formyl derivative (XI) was obtained. Reduction of XI with lithium aluminum hydride resulted in the N-methyl derivative (X). Methylation of the indole nitrogen to yield XII was accomplished by treatment of a dimethylformamide solution of the sodium salt of II (prepared *in situ* with sodium hydride) with methyl iodide.

Experimental[13]

4-Nitrogramine and 6-Nitrogramine.—A stirred mixture of 207.4 g. (1.19 moles) of gramine and 1040 ml. of acetic acid was cooled to 10° and treated dropwise with a solution of 178.5 ml. of nitric acid (*d* 1.37) in 415 ml. of acetic acid during 40 min. The mixture was allowed to warm to 20° and stand for 8.5 hr. The nitrate salt which had crystallized from the mixture was collected by filtration, washed with absolute ethanol, and dried at 40° *in vacuo* (yield 185.6 g.). The filtrate was concentrated to a small volume, diluted with ethanol, and allowed to crystallize. The combined product was dissolved in warm water and decolorized with activated carbon; the resulting solution was made strongly ammoniacal. The precipitate, a mixture of 4-nitrogramine and 6-nitrogramine, was washed with water and dissolved in dilute acetic acid.

This stirred solution was treated dropwise with dilute ammonium hydroxide until the mixture was strongly ammoniacal (pH 8). The precipitate was collected by filtration, washed with water, and redissolved in dilute acetic acid. Reprecipitation of 6-nitrogramine with ammonium hydroxide yielded a further separation of the two isomers; an additional quantity of the 4-nitrogramine remained in solution. The precipitate was collected by filtration, washed with water, and dried *in vacuo* at 40° to yield 131.9 g. (50.5%) of 6-nitrogramine, m.p. 172–175°. Final purification was effected by recrystallizing this material from methanol, m.p. 176–179° (lit.[3] m.p. 176–178°). The ultraviolet spectrum (ethanol) had end absorption and λ_{max} 251, 325, and 366 mμ (ε 10,500, 8410, and 7300, respectively) with an inflection at 262 mμ (ε 9750). The infrared spectrum (Nujol) showed NO_2, 1515 and 1330 cm.$^{-1}$.

Each of the filtrates from the three ammonium hydroxide precipitations was made strongly basic with concentrated sodium hydroxide. The resulting crystalline precipitate was collected by filtration, washed with water, and dried *in vacuo* at 40° to yield 41.15 g. (18.8%) of 4-nitrogramine, m.p. 120–123°. Purification of this material was effected by methanol–water crystallization, m.p. 126–128.5° (lit.[3] m.p. 120–122°). The infrared spectrum (Nujol) showed NO_2, 1510 and 1320 cm.$^{-1}$. The ultraviolet spectrum (ethanol) had end absorption and λ_{max} 350 and 379 mμ (ε 4020 and 4190, respectively) with an inflection at 234 mμ (ε 9180).

Reaction of 4-Nitrogramine with Dimethyl Sulfate.—A solution of 500 mg. (2.28 mmoles) of 4-nitrogramine and 0.03 ml. of acetic acid in 10 ml. of dry tetrahydrofuran was added slowly, at room temperature under nitrogen, to a stirred solution of 1.07 ml. of dimethyl sulfate and 0.03 ml. of acetic acid in 5 ml. of dry tetrahydrofuran. After 3 hr., the product had separated from the reaction mixture as a gummy precipitate. The solvent was removed by decantation, and the product was washed with ether and treated with methanol. Crystallization of the methanol-soluble material from methanol–ether yielded 264 mg., m.p. 160° dec., of 4-nitrogramine methosulfate (IV). An analytical sample, m.p. 157–159°, was prepared by recrystallizing this material from methanol–ether. The ultraviolet spectrum (ethanol) had λ_{max} 223 and 368 mμ (ε 8600 and 4880, respectively) with an inflection at 328 mμ (ε 3880). The infrared spectrum (Nujol) showed NH, 5290 cm.$^{-1}$; and NO_2, 1525 and 1325 cm.$^{-1}$.

Anal. Calcd. for $C_{13}H_{19}N_3O_6S$: C, 45.21; H, 5.55; N, 12.16; S, 9.29. Found: C, 45.66; H, 5.49; N, 12.05; S, 9.24.

The methanol-insoluble product (V) from this reaction, which was collected by filtration and washed with methanol, amounted to 251 mg., m.p. 182° dec. It was recrystallized from hot methanol for analysis, m.p. 182–183°. The infrared spectrum (Nujol) showed NH, 3200 cm.$^{-1}$; and NO_2, 1515 and 1315 cm.$^{-1}$. The ultraviolet spectrum (ethanol) had end absorption and λ_{max} 234 and 370 mμ (ε 17,630 and 9250, respectively) with an inflection at 328 mμ (ε 7170).

Anal. Calcd. for $C_{21}H_{23}N_5O_6S$: C, 49.89; H, 4.59; N, 13.86; S, 6.34. Found: C, 50.13; H, 4.45; N, 13.48; S, 6.03.

4-Nitroindol-3-ylacetonitrile (VI). A.—A mixture of 4.58 g. (13.3 mmoles) of methosulfate (IV), 140 ml. of a sodium acetate–acetic acid buffer (3.0 g. of acetic acid + 4.1 g. of sodium acetate dissolved in 500 ml. of water), and 300 ml. of ether, contained in a 500-ml. hydrogenation bottle, was treated with 4.58 g. of sodium cyanide. The bottle was sealed and allowed to shake at room temperature for 11.25 hr. The reaction mixture was extracted with a mixture of ethyl acetate and ether; the extracts were washed with saturated sodium chloride, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. Crystallization of the residue from ethyl acetate yielded 1.73 g. (64.7%) of 4-nitroindol-3-ylacetonitrile, m.p. 196–199°. The analytical sample, m.p. 199–200°, was prepared by recrystallizing this material from ethyl acetate. The ultraviolet spectrum (ethanol) had λ_{max} 234 and 374 mμ (ε 9600 and 4800) with an inflection at 332 mμ (ε 3700). The infrared spectrum (Nujol) showed NH, 3400 cm.$^{-1}$; C≡N, 2160 cm.$^{-1}$; and NO_2, 1520 and 1320 cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_7N_3O_2$: C, 59.70; H, 3.51; N, 20.89. Found: C, 59.48; H, 3.42; N, 20.84.

B.—A solution of 20.0 g. (91.3 mmoles) of 4-nitrogramine and 1.2 ml. of acetic acid in 500 ml. of dry tetrahydrofuran was added, under nitrogen, dropwise to an ice-cold, stirred solution of 60 ml. of dimethyl sulfate and 1.2 ml. of acetic acid in 300 ml. of dry tetrahydrofuran during 1.5 hr. The resulting mixture was allowed to warm slowly to room temperature and stand for 5.33 hr. The product then was collected by filtration, washed with anhydrous ether, and dried *in vacuo* over potassium hydroxide to yield 31.3 g. of the methosulfate, m.p. 141–155°. This material was divided into four equal parts. Each part (7.83 g.) was mixed with 240 ml. of the sodium acetate buffer (3.0 g. of acetic acid + 4.1 g. of sodium acetate dissolved in 500 ml. of water), a small amount of ether, and 7.83 g. of sodium cyanide in a 500-ml. hydrogenation bottle. The bottle was sealed and allowed to shake at room temperature for 12.5 hr. It was then allowed to stand without shaking for an additional 11 hr. The combined reaction mixtures were extracted with a mixture of ethyl acetate and ether. The extract was washed successively with water, dilute acetic acid, saturated sodium chloride solution, dilute ammonium hydroxide, and saturated sodium chloride solution; dried over anhydrous sodium sulfate; and concentrated at room temperature to yield 9.03 g. of the crystalline nitrile, m.p. 196–199°. Concentration of the mother liquors yielded an additional 2.83 g. of the product, m.p. 190–196°.

The acetic acid extracts were filtered and made alkaline with sodium hydroxide. 4-Nitrogramine recovered in this manner was recrystallized from methanol–water to yield 3.67 g., m.p. 126–128°. The total yield of 4-nitroindol-3-ylacetonitrile based on the recovered starting material was 79%.

1,3,4,5-Tetrahydropyrrolo[4,3,2-*de*]quinoline (II) and 4-Aminoindol-3-ylacetonitrile (VII).—A mixture of 4.0 g. (19.9 mmoles) of the nitrile (VI), 2.0 g. of 10% palladium on carbon, and 300 ml. of pure ethyl acetate was hydrogenated for 2.6 hr. in a Parr shaker at an initial pressure of 45 p.s.i. The temperature was

(11) E. Shaw and D. W. Woolley, *J. Am. Chem. Soc.*, **75**, 1877 (1953).

(12) E. Shaw, *ibid.*, **76**, 1384 (1954).

(13) Melting points were taken in a capillary tube and are corrected. Ultraviolet spectra were determined in 95% ethanol with a Cary spectrophotometer, Model 14. Infrared spectra were determined in Nujol with a Perkin-Elmer recording infrared spectrophotometer, Model 421. N.m.r. spectra were determined in deuteriochloroform with a 60-Mc. instrument. Skellysolve B is a commercial hexane, b.p. 60–70°, made by Skelly Oil Co., Kansas City, Mo.

raised by external heating from 25° at the start of the reaction to about 70° at the end. Filtration of the mixture through Celite yielded a colorless filtrate which was concentrated *in vacuo*, under nitrogen to yield a colorless gum. A benzene solution of this material was adsorbed on 100 g. of silica gel in a chromatographic column. Elution of the column with a 10% solution of ether in benzene yielded 1.31 g. (41.4%), m.p. 131–134°, of 1,3,-4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline. The analytical sample, m.p. 132.5–133.5°, was prepared by recrystallizing some of this material from methanol–water. This material could also be crystallized from ether, ether–Skellysolve B, and benzene–Skellysolve B. The white, crystalline compound turned dark when exposed to air and light for several days. The ultraviolet spectrum (ethanol) had λ_{max} 227, 277, 290, and 299 mμ (ε 33,650, 6600, 5950, and 6050, respectively).

Anal. Calcd. for $C_{10}H_{10}N_2$: C, 75.92; H, 6.37; N, 17.71. Found: C, 76.11; H, 6.18; N, 17.32.

Further elution of the silica gel column with ether yielded 0.386 g. (11.3%), m.p. 134–136°, of 4-aminoindol-3-ylacetonitrile. The analytical sample, m.p. 135–136°, was prepared by recrystallizing a portion of this material from ethyl acetate–Skellysolve B. The ultraviolet spectrum (ethanol) had λ_{max} 225, 273, and 295 mμ (ε 45,300, 7100, and 5000, respectively) with an inflection at 288 mμ (ε 5300). The infrared spectrum (Nujol) showed NH, 3400, 3350, 3330, and 3240 cm.$^{-1}$; and –C≡N, 2250 cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_9N_3$: C, 70.15; H, 5.30; N, 24.55. Found: C, 70.39; H, 5.45; N, 24.24.

5-Formyl-1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline (XI).—Formic acetic anhydride was prepared by mixing 9.45 ml. of acetic anhydride with 3.98 ml. of 98% formic acid. To 3 ml. (21.4 mmoles) of this solution, cooled in an ice bath, was added slowly 1.54 g. (9.73 mmoles) of the amine (II). The resulting solution was allowed to stand at room temperature for 5 hr. Ether was added and the solution was allowed to stand for 18 hr. It then was washed successively with water, dilute ammonium hydroxide, and brine. The resulting ether solution was dried over anhydrous sodium sulfate and concentrated *in vacuo* under nitrogen. Crystallization of the residue from ethyl acetate–Skellysolve B yielded 1.55 g., m.p. 138–139°, and 0.173 g., m.p. 128–132° (95.1%), of the N-formyl derivative. The analytical sample, m.p. 131–134°, was prepared by recrystallizing this material from ethyl acetate–Skellysolve B. The ultraviolet spectrum (ethanol) had λ_{max} 225 and 294 mμ (ε 31,750 and 9300, respectively) with an inflection at 288 mμ (ε 9500). The infrared spectrum (Nujol) showed NH, 3250 cm.$^{-1}$; and C=O, 1663 cm.$^{-1}$.

Anal. Calcd. for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41. Found: C, 70.83; H, 5.04.

5-Methyl-1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline (X).—To an ice-cold mixture of 1.5 g. of powdered lithium aluminum hydride in 200 ml. of dry tetrahydrofuran was added 1.69 g. (9.08 mmoles) of the amide (XI). The resulting mixture was allowed to stir at room temperature under nitrogen for 20 hr. After the mixture had been allowed to reflux for 1 hr., it was cooled in an ice bath and treated successively with 1.5 ml. of water, 1.5 ml. of 15% sodium hydroxide, and 4.5 ml. of water. The inorganic salts were collected by vacuum filtration through Celite and washed with ether. Concentration of the combined filtrates under nitrogen and reduced pressure yielded an oil which was dissolved in benzene and chromatographed on silica gel with 2% ether–benzene to yield 1.39 g. (89.3%) of 5-methyl-1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline, m.p. 119–121°. The analytical sample, m.p. 121–123°, was prepared by recrystallizing this material from benzene–Skellysolve B. The ultraviolet spectrum (ethanol) had λ_{max} 227, 282, and 299 mμ (ε 33,850, 7250, and 7900, respectively). The infrared and n.m.r. spectra supported the proposed structure.

Anal. Calcd. for $C_{11}H_{12}N_2$: C, 76.71; H, 7.02; N, 16.27. Found: C, 76.74; H, 7.39; N, 15.96.

1-Methyl-1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline Hydrochloride (XII).—To a stirred solution of 2.00 g. (12.7 mmoles) of the amine (II) in 150 ml. of dry dimethylformamide was added, under nitrogen, 600 mg. (13.3 mmoles) of a 53.2% mineral oil suspension of sodium hydride. After 1.5 hr., methyl iodide (0.828 ml., 13.3 mmoles) was added to the mixture; the resulting solution was allowed to stand at room temperature for 2 hr. It then was poured into about 1 l. of water, and the resulting mixture was saturated with sodium chloride and extracted with ether. The ether extract was washed with brine, dried over anhydrous potassium carbonate, and concentrated to yield, after preliminary silica gel chromatography, 2.06 g. of a mixture of product and starting material. Careful chromatography of this material on silica gel with 0.5% ether–benzene resulted in a pure product which was converted to the hydrochloride and crystallized from methanol–ethyl acetate to yield 1.05 g. (39.7%), m.p. >200° dec., of 1-methyl-1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]-quinoline hydrochloride. A sample of this material was recrystallized three times from methanol–ethyl acetate for analysis and had m.p. 220–235° (sublimation and decomposition in a sealed capillary). The ultraviolet spectrum (ethanol) had λ_{max} 228, 284, and 310 mμ (ε 32,900, 5700, and 7050, respectively) with an inflection at 303 mμ (ε 6500). The infrared spectrum supported the proposed structure.

Anal. Calcd. for $C_{11}H_{13}ClN_2$: C, 63.31; H, 6.28; Cl, 16.99; N, 13.43. Found: C, 63.46; H, 6.39; Cl, 17.08; N, 13.42.

Acknowledgment.—The author is indebted to Dr. R. W. Rinehart and his associates for microanalyses, to Mrs. B. F. Zimmer and Miss L. M. Pschigoda for ultraviolet and infrared spectra, and to Dr. G. Slomp and Mr. F. A. MacKellar for n.m.r. spectra.

A Search for the Sulfonium Radical Intermediate

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The existence of a sulfonium and sulfonium-type radical intermediate in some free-radical reactions of phenyl sulfide has been studied. It has been found that the *t*-butoxy radical with phenyl sulfide gives phenyl sulfoxide and the *t*-butyl radical; these could form *via* a sulfonium-type radical intermediate. The cumyloxy radical and benzophenone triplet were apparently not reactive enough to give the intermediate, and alkyl radicals gave indefinite products.

Recent work by Walling and Rabinowitz[2] has offered substantial evidence that the phosphorus atom undergoes an expansion of its valence shell to accommodate nine electrons under certain free-radical reaction conditions. This state was described as an intermediate consisting of four groups bonded to and a free electron associated with the central phosphorus atom.

Research both by Price and Zomlefer[3] on free-radical additions to vinyl sulfides and Martin and Bentrude[4] on the rates of decomposition of *o*-methylthiophenyl peresters indicates that a d-orbital of a sulfur atom might also be capable of accepting an unpaired electron, thus elevating its octet to a nonet. The resulting transient intermediate, with three alkyl or aryl groups and an un-

(1) (a) IBM Research Laboratory, San Jose 14, Calif.; to whom inquiries should be sent; (b) from the M.S. thesis of D. J. C., June, 1963.

(2) C. Walling and R. Rabinowitz, *J. Am. Chem. Soc.*, **81**, 1243 (1959).

(3) C. C. Price and J. Zomlefer, *ibid.*, **72**, 14 (1950).

(4) W. G. Bentrude and J. C. Martin, *ibid.*, **84**, 1561 (1962).

TABLE I

Reactants	Conditions	Products
Ph_2S and $(CH_3)_3CBr$	Ultraviolet	Polyisobutylene and a solid, m.p. 182–185°, which contained no S or Br
	Heat, 60°	N.r.[b]
Ph_2S and CH_3I	Ultraviolet	Solids, m.p. 150–153° and 143–147°, neither containing S or I
Ph_2S + $Ph_2C{=}O$	Ultraviolet	N.r.
	Heat, 170°	N.r.
Ph_2S + $(CH_3)_3COOC(CH_3)_3$	Heat, 150°	Phenyl sulfoxide (1%), phenyl tolyl sulfide,[a] acetone (0.75%)
Ph_2S	Heat, 150°	N.r.
Ph_2S + $(CH_3)_3COCl$	Spontaneous	Phenyl sulfoxide (28%), *t*-butyl chloride, and acetone
	Ultraviolet	Phenyl sulfoxide (46%)
	Dark	Phenyl sulfoxide after a 4-min. induction period
Ph_2S + $PhC(CH_3)_2OOC(CH_3)_2Ph$	Heat, 135°	Acetophenone, phenyl tolyl sulfide,[a] and no phenyl sulfoxide
Ph_2S + $Ph(CH_3)_2COCl$	Ultraviolet	Acetophenone, no sulfoxide

[a] Tentative identification. [b] N.r. = no reaction.

paired electron about the sulfur atom, would be the sulfonium radical.

This study was conducted in an effort to investigate and substantiate the existence of the postulated sulfonium and sulfonium-type radical intermediates. Proof for such intermediates could assist in explaining other free-radical reactions with organic sulfur compounds, *i.e.*, the breakdown of sulfur containing amino acids,[5] disulfides,[6] thiosulfones,[7] and arylsulfenyl chlorides.[8] In contrast, Pryor[9] has indicated that radicals may cleave disulfides at the S–S bond by a reaction that could be a direct displacement.

The free-radical forming reagents used were selected on the basis of the reaction conditions which would be necessary to obtain homolytic bond scission of the reagent, and on the feasibility of obtaining and investigating the products from the decomposition of the proposed sulfonium radical intermediate.

Results and Discussion

Phenyl sulfide was selected as the sulfur compound for this investigation for two reasons. First, the homolysis of the phenyl–sulfur bond in the postulated sulfonium radical, as described in eq. 1, would not be expected to

$$Ph_2\dot{S}\text{–}R \longrightarrow PhS\text{–}R + Ph\cdot \qquad (1)$$

occur, because the phenyl radical is too unstable. Second, it has been found that phenyl sulfide does not undergo autoxidation with molecular oxygen, even when the oxidation is catalyzed by peroxides.[10] This absence of the autoxidation of phenyl sulfide was confirmed.

Evidence for a sulfonium-type radical intermediate is available from the studies done with peroxide. The following sequence summarizes a possible mechanism for phenyl sulfide–*t*-butyl peroxide reactions (Table I).

$$((CH_3)_3CO)_2 \longrightarrow 2(CH_3)_3CO\cdot \qquad (2)$$

$$(CH_3)_3CO\cdot + Ph_2S \longrightarrow Ph_2\text{–}\dot{S}\text{–}O\text{–}C(CH_3)_3 \qquad (3)$$

$$Ph_2\dot{S}\text{–}O\text{–}C(CH_3)_3 \longrightarrow Ph_2SO + (CH_3)_3C\cdot \qquad (4)$$

$$(CH_3)_3C\cdot \longrightarrow \text{dimer, isobutylene, and other hydrocarbon products} \qquad (5)$$

Phenyl sulfoxide and acetone were the compounds identified from a number of products formed in the thermally initiated reaction. The other products (minor amounts) were probably formed by the abstraction, disproportionation, and addition reactions of the alkoxy and alkyl radicals. Gas chromatography gave evidence for the formation of phenyl tolyl sulfide, undoubtedly from the attack of the methyl radical on the sulfide.

The formation of acetone indicates that the *t*-butyl peroxide was reacting by a free-radical mechanism. It would be difficult to explain the formation of acetone by an ionic mechanism proceeding through either the alkoxonium cation, RO^+, or the alkoxide anion, RO^-, since the formation of the latter two species usually requires extensive solvation and the presence of a strong Lewis base or Lewis acid, respectively. Thus, the identified products and the conditions employed strongly support the existence of a sulfonium-type radical intermediate in this reaction.

t-Butyl hypochlorite and phenyl sulfide (Table I) reacted exothermically at a rapid rate to produce a number of products: phenyl sulfoxide, *t*-butyl chloride, and acetone, but no phenyl sulfone. A proposed radical mechanism to explain these results is as described above, plus the following reaction.

$$(CH_3)_3C\cdot + (CH_3)_3COCl \longrightarrow (CH_3)_3CCl + (CH_3)_3CO\cdot \qquad (6)$$

Support for a radical mechanism may be derived from the work of Walling and Thaler,[11] and Greene and coworkers,[12] from the large increase in the rate of reaction in the presence of light, and from the formation of both *t*-butyl chloride and acetone.

Cumyl peroxide–phenyl sulfide and the cumyl hypochlorite–phenyl sulfide reactions (Table I) were carried out under the same conditions in order to obtain additional information concerning the sulfonium-type radical, and to compare the reactions of the electrophilic cumyloxy radical with those of the electrophilic *t*-butoxy radical. The proposed mechanism for the cumyl peroxide–phenyl sulfide reactions involves a sequence like that above. Acetophenone from the decomposition of the cumyl radical was identified as a reaction product in both the cumyl peroxide and cumyl hypochlorite reactions with phenyl sulfide. However, phenyl sulfoxide was *not* identified as a reaction product in either case.

The absence of phenyl sulfoxide suggests that the sulfonium-type radical intermediate, $Ph(CH_3)_2C\dot{O}S$-

(5) P. Markakis and A. L. Toppel, *J. Am. Chem. Soc.*, **82**, 1613 (1960).
(6) W. Groebel, *Chem. Ber.*, **93**, 284 (1960).
(7) J. Degani, S. Ghersetti, and A. Tundo, *Ann. chim.* (Rome), **51**, 461 (1961).
(8) D. Spinelli and A. Salvemini, *ibid.*, **51**, 389 (1961).
(9) W. A. Pryor and T. L. Pickering, *J. Am. Chem. Soc.*, **84**, 2705 (1962); See also **85**, 1496 (1963).
(10) L. Bateman and J. I. Cunneen, *J. Chem. Soc.*, 1596 (1955).
(11) C. Walling and W. Thaler, *J. Am. Chem. Soc.*, **83**, 3877 (1961).
(12) F. D. Greene, *et al.*, *J. Org. Chem.*, **28**, 55 (1963).

Ph_2, was not formed under the reaction conditions. A possible explanation for the failure of the electrophilic cumyloxy radical and phenyl sulfide to react and form the intermediate lies in the stability of the cumyloxy radical. The *t*-butoxy radical, which apparently forms a sulfonium-type radical intermediate, has a reactivity comparable to that of a chlorine atom,[13,14] while the cumyloxy radical, which does not give the intermediate, is the only alkoxy radical which is known to dimerize.[15] Thus, from a comparison of the two oxy radicals, the cumyloxy radical appears to be stable in this type of reaction in relation to the very reactive *t*-butoxy radical.

The studies with alkyl halides and benzophenone (Table I) did not afford evidence for the intermediate. Neither *t*-butyl bromide nor methyl iodide gave sulfonium halide, which would have to form by subsequent electron transfer from the intermediate to the halogen atom as depicted in reaction 7. The polyisobutylene isolated came from isobutylene, undoubtedly formed

$$Ph_2\dot{S}\text{–}R + X\cdot \longrightarrow Ph_2S\text{–}R + X^- \qquad (7)$$

by the photolytic dehydrohalogenation of the halide. Benzophenone when photolytically activated to its triplet state[16] did not give rise to the expected phenyl sulfoxide and the diphenylmethyl diradical (eq. 8).

$$Ph_2\dot{C}\text{–}O\text{–}\dot{S}Ph_2 \longrightarrow Ph_2\dot{C}\cdot + Ph_2SO \qquad (8)$$

The latter also did not form in a thermal reaction similar to one by Poshkus and Herweh[17] with phenylphosphine.

The results of this investigation suggest that the formation of the sulfonium radical with phenyl sulfide requires a reactive, electrophilic radical. This might be explained by stating that the *t*-butoxy radical, in comparison to the cumyloxy radical and benzophenone triplet, is the only free radical of the three which has the necessary reactivity to supply the energy required to reach a transition state with phenyl sulfide. This transition state would be expected to be closer to the products than to the reactants. The absence of reaction with the alkyl radical is probably due to the polar effect.[13] The polar effect would also readily explain why no sulfone was formed, even in the reactions in which large amounts of sulfoxide was produced.

Experimental

Reagents.—These two were used without purification: benzophenone (Paragon Testing Laboratories, m.p. 48–49°) and dicumyl peroxide (Hercules Powder Co., m.p. 38°). The following were distilled through an 18-in. column equipped with glass helices: *t*-butyl bromide (Eastman Kodak Co., White Label, b.p. 42°, $n^{21}D$ 1.5291), and all the solvents that were used for column and thin layer chromatography. Phenyl sulfide (Eastman Kodak Co., White Label, b.p. 76–77° at 0.08 mm.) was distilled through a 6-in. column equipped with a tantalum-wire spiral. Purity of the phenyl sulfide was checked by gas chromatography before use. *t*-Butyl peroxide (Lucidol Corp., $n^{20}D$ 1.3889) was distilled through a 14-in. column equipped with a tantalum-wire spiral.

Ultraviolet-Initiated Reaction of Phenyl Sulfide and *t*-Butyl Bromide.—A solution of *t*-butyl bromide (0.54 mole, 73.6 g.) and phenyl sulfide (0.54 mole, 100.0 g.) was placed in a Kharasch-Friedlander type of ultraviolet irradiation vessel and illuminated for 24 hr. at 40–60°. Distillation gave about 5 g. of residue. Chromatography gave a number of oils and tars, but no solid product.

Heat-Initiated Reaction of Phenyl Sulfide and *t*-Butyl Bromide.—A control reaction of *t*-butyl bromide (0.054 mole, 7.36 g.) and phenyl sulfide (0.054 mole, 10.0 g.) was conducted at 60° with stirring for 24 hr. The temperature was maintained with a Thermocap relay. Distillation of the reaction mixture yielded only the starting components.

Ultraviolet-Initiated Reaction in Benzene Solvent.—When the reaction above was run in benzene, distillation gave a sublimate, m.p. 73.5°. The residue was chromatographed to give a solid B, m.p. 182–185°. Compounds A and B both gave negative tests for ionic halogen and sulfur. Compound A was shown to be polyisobutylene by its infrared spectrum.

Ultraviolet-Initiated Reaction of Phenyl Sulfide and Iodomethane.—Phenyl sulfide (0.54 mole, 100.0 g.), iodomethane (0.54 mole 76.29 g.), and benzene (350 ml.) were placed in an ultraviolet chamber and irradiated for a 24-hr. period. Work-up by chromatography gave two compounds, A and B. Compound A, m.p. 150–153°, was recrystallized from petroleum ether (b.p. 60–80°), and compound B, m.p. 143–147°, from ethanol. A silver nitrate test for halogen and a sodium fusion analysis for sulfur and halogen were negative for both compounds.

Phenyl Sulfide and Benzophenone.—Phenyl sulfide and benzophenone in various solvents and with cyclohexene both present and absent were heated at 170° for 72 hr. or irradiated at room temperature with different ultraviolet sources for varying lengths of time. Analysis of the mixtures by thin layer and gas chromatography (5-ft. 5% Carbowax column, 215°, 20 lb. He) indicated the presence of starting compounds plus a small amount of unknown materials.

Phenyl Sulfide and *t*-Butyl Peroxide (A).—A mixture of phenyl sulfide (0.054 mole, 10.0 g.) and *t*-butyl peroxide (0.009 mole, 1.31 g.) was placed in a steel bomb fitted with a Pyrex liner and heated for 2 hr. at 150°. The resultant mixture was analyzed by gas chromatography (10-ft. silicone column, 235°, 16 lb. He), to yield peaks corresponding to phenyl sulfide at 4.8 min. and phenyl sulfoxide at 10.2 min. The phenyl sulfoxide peak was sharp and uniform and remained so even when phenyl sulfoxide was added and the height of the phenyl sulfoxide peak of the reaction mixture changed correspondingly with each addition. A peak immediately following the phenyl sulfide peak (5.0 min.) was tentatively identified as phenyl tolyl sulfide. Acetone was also identified as a reaction product by gas chromatography (10-ft. Ucon Polar column, 106°, 4 lb. He at 4.4 min.). Acetone to sulfoxide molar ratio was 0.74:1 and sulfide to sulfoxide molar ratio was 800:1.

Phenyl Sulfide without Peroxide.—A reaction of phenyl sulfide (0.054 mole, 10.0 g.) was carried out under the same conditions as stated above except no peroxide was present. The resultant liquid was analyzed under exactly the same conditions as previously stated, but no phenyl sulfoxide was observed.

Phenyl Sulfide and *t*-Butyl Peroxide (B).—Phenyl sulfide (0.027 mole, 5.0 g.), *t*-butyl peroxide (0.0135 mole, 1.98 g.), and benzene (10 ml.) were placed in a glass ampoule which was cooled to −80°, flushed with nitrogen, sealed, and heated at 160° for 4 hr. Thin layer analysis using a solution of 3% glacial acetic acid, 20% benzene, and ligroin as solvent showed the presence of phenyl sulfoxide (blue color when sprayed with sulfuric acid followed by heating). The mixture was analyzed by gas chromatography (5-ft. 5% Carbowax column, 210°, 10 lb. He), and the peaks at 5.4 min. and 18.2 min. corresponded to a prepared mixture of the phenyl sulfide and phenyl sulfoxide, respectively. The apparent phenyl tolyl sulfide peak was also present. Acetone was also identified as a reaction product by gas chromatography (10-ft. Ucon Polar column, 106°, and 4 lb. He at 4.4 min.).

Phenyl Sulfide and *t*-Butyl Hypochlorite (A).—A mixture of phenyl sulfide (0.054 mole, 10.0 g.) and benzene (150 ml.) was placed in a flask fitted with a condenser, dropping funnel, magnetic stirrer, and gas inlet and outlet tubes. The system was flushed with nitrogen for several minutes. *t*-Butyl hypochlorite (0.054 mole, 5.9 g.), prepared by the method of Teeter and Bell,[18] was added slowly through the dropping funnel. Approximately 1 min. after the addition of the *t*-butyl hypochlorite an exothermic reaction took place. After approximately 5 min.

(13) G. A. Russell, *J. Org. Chem.*, **24**, 300 (1959).
(14) K. B. Wiberg and L. H. Slaugh, *J. Am. Chem. Soc.*, **80**, 3033 (1958).
(15) P. Gray and A. Williams, *Chem. Rev.*, **59**, 239 (1959).
(16) G. S. Hammond and W. M. Moore, *J. Am. Chem. Soc.*, **81**, 6334 (1959).
(17) A. C. Poshkus and J. E. Herweh, Abstracts of Paper, 141st National Meeting of the American Chemical Society, Washington, D. C., March, 1962, p. 17O.
(18) H. M. Teeter and E. W. Bell, *Org. Syn.*, **32**, 20 (1952).

the reaction subsided and the system had reached room temperature. The reaction mixture was worked up by distillation and trituration with ligroin to give a crystalline solid. The recrystallized product, m.p. 69°, 3.1 g., was obtained in 28% yield. The infrared spectrum of the solid coincided with that of the prepared phenyl sulfoxide. Mixture melting technique gave no depression.

Analysis of the reaction mixture, prior to distillation, by gas chromatography (10-ft. silicone column, 125°, 4 lb. He) showed the presence of *t*-butyl chloride at 3.4 min. and a trace amount of acetone at 3 min. Each of the peaks were raised by successive additions of pure samples. Gas and thin layer chromatography also verified the presence of phenyl sulfide and possibly phenyl tolyl sulfide, but no phenyl sulfone.

Phenyl Sulfide and *t*-Butyl Hypochlorite (B).—A solution of phenyl sulfide (0.054 mole, 10.0 g.) and benzene (150 ml.) was treated exactly the same as in A. The *t*-butyl hypochlorite was added slowly, and the reaction was allowed to proceed for a period of 24 hr. with an ultraviolet light source placed outside of the reaction vessel. The yield of phenyl sulfoxide was 5.15 g., 46%.

Phenyl Sulfide and *t*-Butyl Hypochlorite (C).—The reaction of phenyl sulfide and *t*-butyl hypochlorite was carried out in the dark under a nitrogen atmosphere. The reactants, in the same molar ratio as above but on smaller scale, were placed in a dark room for a period of 30 min. before the addition of the *t*-butyl hypochlorite to the solution of phenyl sulfide in benzene. The *t*-butyl hypochlorite was added and a 4-min. induction period was recorded before the exothermic reaction took place. Thin layer analysis showed the presence of phenyl sulfoxide and phenyl sulfide.

Phenyl Sulfide and Cumyl Peroxide (A).—Phenyl sulfide (0.027 mole, 5.0 g.), cumyl peroxide (0.0135 mole, 3.64 g.), and dry benzene (10 ml.) were placed in a glass ampoule which cooled to −80°, flushed with nitrogen, sealed, and heated at 135° for 8 hr. Thin layer chromatography using a 3% glacial acetic acid, 20% benzene, and ligroin solvent mixture showed the presence of phenyl sulfide and a tar which diffused over the plate. Gas chromatography (5-ft. 5% Carbowax column, 210°, 10 lb. He) indicated the presence of various products, *i.e.* phenyl tolyl sulfide, but the presence of the phenyl sulfoxide or phenyl sulfone was not detected.

Phenyl Sulfide and Cumyl Peroxide (B and C).—The reactants were as stated above in A with a change in reaction conditions. An ultraviolet light source was placed 1 in. from the flask, and the reaction was allowed to proceed for a period of 24 hr. under a nitrogen atmosphere. The analysis of the reaction mixture was carried out as stated above, but neither phenyl sulfoxide nor phenyl sulfone was detected. In reaction C, acetophenone was definitely shown to be present by gas chromatography.

Phenyl Sulfide and Cumyl Hypochlorite.—Phenyl sulfide (0.054 mole, 10.0 g.) was dissolved in benzene (150 ml.) and placed in a flask equipped with a magnetic stirrer and a condenser. The system was flushed with nitrogen. Cumyl hypochlorite (0.054 mole, 9.2 g.) prepared in a manner similar to the *t*-butyl hypochlorite, b.p. 20° (1 mm.), 90% yield, was added and the mixture was irradiated externally. Samples of the reaction mixture were removed after 14 and 24 hr. Gas chromatography (5-ft. 5% Carbowax column, 180–210°, 4–20 lb. He; 10-ft. silicone column, 214–240°, 4–20 lb. He) on two columns showed the presence of a number of products, but the phenyl sulfoxide and phenyl sulfone were not detected. Gas chromatography (10-ft. silicone column, 125°, 10 lb. He) showed the presence of acetophenone at 10.6 min. The size of the acetophenone peak, in comparison with the other products, indicated that it was one of the major products of the reaction. The peak was identified by additions of pure sample as described in previous portions of the experimental section.

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Free-Radical Reactions of Pyrroles

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The free radical resulting from hydrogen atom abstraction from the methyl group of N-methylpyrrole has been shown to dimerize, forming 1,1′-ethylenedipyrrole, and to attack the diene system of N-methylpyrrole, giving 1-methyl-3-(1-pyrrolylmethyl)pyrrole after radical chain transfer. Pyrrole under similar conditions gave 2,2′-(1′-pyrrolinyl)pyrrole. The structure of the latter product indicates that hydrogen atom abstraction occurs at the 2-position of pyrrole and that the pyrrole ring acts as an effective free-radical trap. In addition, the reactivities toward free-radical attack of a number of related compounds have been established and shown to lie in the order N-methylpyrrole > toluene > 4-picoline > benzene for the compounds examined.

Much research has been done to determine the position of attack of a free radical on organic molecules; these studies have included both addition and abstraction reactions.[2] For example, the benzene aromatics have been studied extensively in terms of addition reactions and to a limited degree in terms of abstraction reactions. In comparison, the free-radical chemistry of heterocyclic aromatics had been investigated only sparsely, with most of this work being done on pyridine. The radical addition and abstraction reactions of pyrrole have been studied to a lesser extent and, therefore, offer a fertile field for investigation.

Most of the free-radical research which has been published on pyrrole has dealt with the reactions of the pyrrole ring under thermal cleavage conditions. In 1958, Jacobsen, Heady, and Dinneen[3] studied the kinetics of the decomposition of N-methylpyrrole to a variety of products in the temperature range 477–745°. These workers suggested no mechanism for the pyrolysis reactions. Subsequent work by Patterson, Brasch, and Drenchko,[4] who repeated the experiments and extended them, implied that the pyrolyses were radical in nature. The latter workers used cycloalkyl pyrroles as illustrated, where n = 3, 4, and 5. The cycloalkyl pyrroles were assumed to undergo homolytic thermal cleavage of a carbon to nitrogen bond; resulting radicals were thought to follow these reaction paths (p. 1164). The same type of cleavage occurs with N-butylpyrrole as shown by Jacobsen and Jensen.[5]

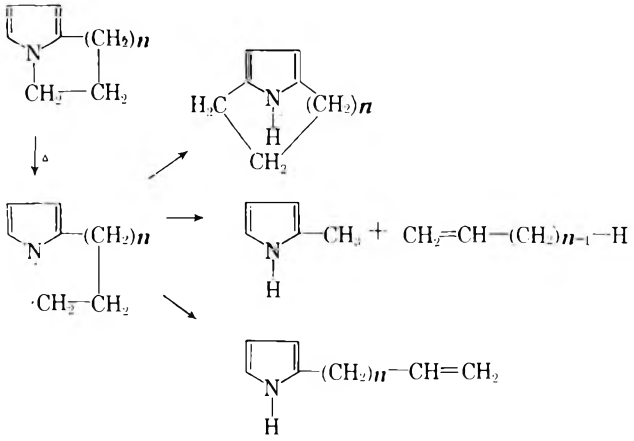
(1) (a) IBM Research Laboratory, San Jose 14, Calif.; (b) from the M.S. thesis of R. J. C., June 1963.

(2) C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957.

(3) I. A. Jacobsen, Jr., H. H. Heady, and G. U. Dinneen, *J. Phys. Chem.*, **62**, 1563 (1958).

(4) J. M. Patterson and P. Drenchko, *J. Org. Chem.*, **27**, 1650 (1962); J. M. Patterson, J. Brasch, and P. Drenchko, *ibid.*, **27**, 1652 (1962).

(5) I. A. Jacobsen, Jr. and H. B. Jensen, *J. Phys. Chem.*, **66**, 1245 (1962).



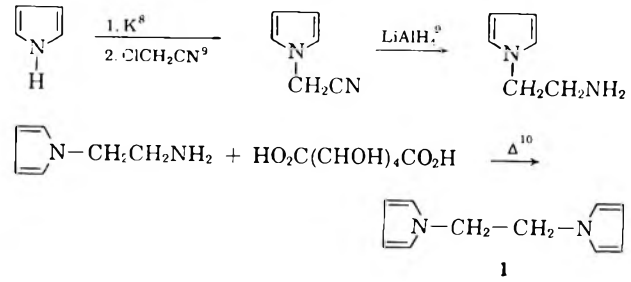
No work dealing with the positions of hydrogen atom abstraction from pyrroles has appeared in the literature, and only one discrete addition reaction has been reported. In 1933, Conant and Chow[6] reported on the reaction of the triphenylmethyl radical with various dienes. Pyrrole was chosen as one of the representative compounds because of its butadiene system. When brought into reaction with the triphenylmethyl radical, an adduct was isolated in 60% yield and by a series of degradative reactions was shown to be 2,5-bis(triphenylmethyl)-3-pyrroline. From the 1,4-addition product isolated, these authors concluded that the reaction was a more sensitive test for the diene character of pyrrole than the familiar Diels–Alder reaction with maleic anhydride, which does not give a normal adduct with pyrrole.

Comparisons are quite valuable in the study of particular areas of chemistry and especially in free-radical chemistry. Thus, N-methylpyrrole was one of the compounds chosen for study because of its similarity to toluene. *t*-Butyl peroxide was chosen as the radical source because it would produce the *t*-butoxy radical which should abstract a hydrogen atom from N-methylpyrrole and afford an intermediate free radical similar to the benzyl radical. Pyrrole itself was then considered. The absence of substituent alkyl groups would cause hydrogen atom abstraction to take place from the aromatic ring. The chemistry of the resulting pyrrolyl radical should be influenced by the presence of the nitrogen, and this effect should be evident when the reactions of the pyrrolyl radical are compared to those of the phenyl radical.

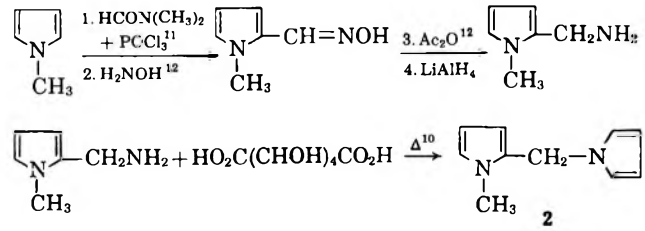
The best way of comparing the reactivities of aromatic ring hydrogen atoms with alkyl hydrogen atoms would be by an exact measurement of the rate of free-radical formation by appropriate compounds. To make this comparison, compounds were considered in pairs as follows: benzene and toluene, pyridine and 4-picoline, and pyrrole and N-methylpyrrole. Work was then directed toward obtaining a quantitative measurement of the ease of formation of intermediate free radicals from the above compounds.

Results

The thermal decomposition of *t*-butyl peroxide in the presence of N-methylpyrrole gave two isomeric products, m.p. 60–61° and 108°. The products were isolated in 0.42% and 0.28% yield, respectively, from the polymeric materials produced in the reaction. The compound having a melting point of 108° was shown to be 1,1′-ethylenedipyrrole (**1**) by comparison with the unequivocally synthesized compound. This compound had been previously prepared by McKeever and coworkers[7] by a multistep synthesis. This started with the reaction of acetylene, cuprous chloride, formaldehyde, and bis(dimethylamino)methane to give an intermediate which, after isomerization with sodium, could be brought into reaction with ethylenediamine to give a compound which upon heating gave the pyrrole. Because of the difficulties involved in using acetylene in the above reaction, a different sequence was employed as described below.



The structure of the compound melting at 60–61° was deduced to be 1-methyl-3-(1-pyrrolylmethyl)pyrrole. This compound could not be directly synthesized. Its structure was shown by a comparison of the ultraviolet and infrared spectra of the product in question with those of other pyrroles and the isomeric compound 1-methyl-2-(1-pyrrolylmethyl)pyrrole (**2**). The latter compound was synthesized by the following series of reactions.



Several olefin addition reactions were attempted with *t*-butyl peroxide and N-methylpyrrole. In the reaction with 1-octene, no adduct could be found. The reaction was also carried out repeatedly in the presence of 1,3-butadiene with the result that only a polymeric product was found.

t-Butyl peroxide was also thermally decomposed in pyrrole. A free-radical reaction product, m.p. 162.5–163°, was isolated and shown to be 2,2′-(1′-pyrrolinyl)-pyrrole by a comparison with the same compound synthesized in an unequivocal manner. The latter synthesis involved the following steps.

(6) J. B. Conant and B. F. Chow, *J. Am. Chem. Soc.*, **55**, 3475 (1933).

(7) M. F. Fegley, N. M. Bortnick, and C. H. McKeever, *ibid.*, **79**, 4145 (1957).

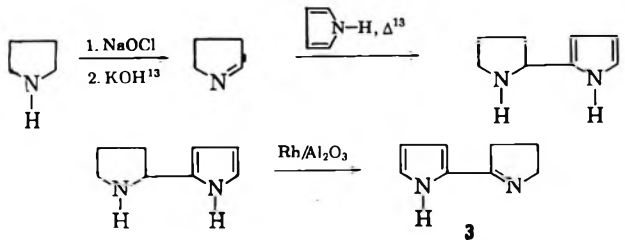
(8) G. R. Clemo and G. R. Ramage, *J. Chem. Soc.*, 49 (1931).

(9) W. Herz, D. S. Raden, and D. R. K. Murty, *J. Org. Chem.*, **21**, 896 (1956).

(10) A. I. Vogel, "Practical Organic Chemistry," Longmans, Green and Co., Inc., New York, N. Y., 1956, p. 838.

(11) R. M. Silverstein, E. E. Ryskiewicz, C. Willard, and R. C. Koehler, *J. Org. Chem.*, **20**, 668 (1955).

(12) H. J. Anderson, *Can. J. Chem.*, **37**, 2056 (1959).



Relative reactivities toward the *t*-butoxy radical were determined for benzene, 4-picoline, toluene, and N-methylpyrrole. These were measured indirectly from the relative quantities of *t*-butyl alcohol and acetone produced in each case, as previously outlined by others.[14,15] The reactivities of the compounds examined were found to be as given in Table I.

TABLE I

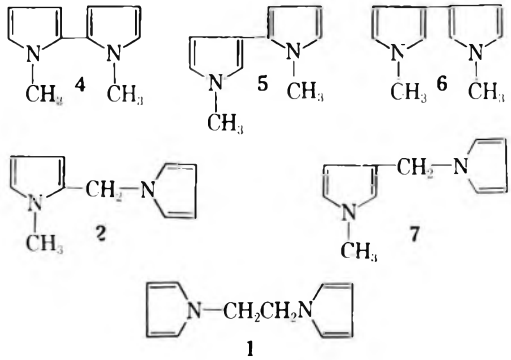
REACTIVITY OF COMPOUNDS TOWARD FREE-RADICAL ATTACKS

Compound	Obsd. *t*-butyl alcohol–acetone	Cor. *t*-butyl alcohol–acetone	Reactivity[a]	Relative reactivity
Toluene	0.743	0.658	0.162	1.00
N-Methylpyrrole	1.69	1.52	0.312	1.93
4-Picoline	0.585	0.473	0.106	0.65
Benzene	0.260	0.206	0.0227	0.14

[a] Corrected for the effect of the chromatography column.

Discussion

The lower melting product of the free-radical reaction of N-methylpyrrole and *t*-butyl peroxide was thought to be 1-methyl-2-(1-pyrrolylmethyl)pyrrole. This compound was synthesized by the series of reactions outlined above. Surprisingly, infrared spectra, thin layer chromatography, and X-ray diffraction patterns showed that the compounds in question were not identical. The infrared spectra showed, however, that the compounds were quite similar in structure. The possible nonbasic free-radical products with formula $C_{10}H_{12}N_2$ containing two pyrrole rings per molecule are as follows.

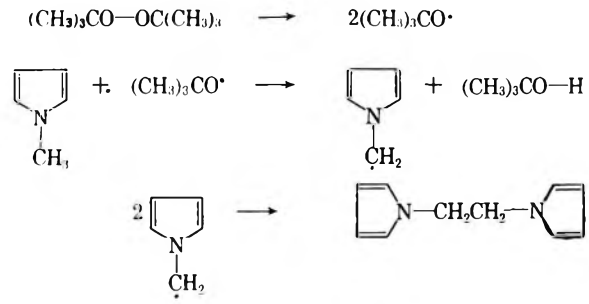


The compound shown by structure **1** was available, and readily discounted by a comparison of the infrared spectra. Structures **4**–**6** contained pyrrole rings which are conjugated with each other. The ultraviolet spectrum of 2,2′-bipyrrole was available and should have resembled the spectra of **4**–**6** because these structures all contained conjugated pyrrole rings.[16] The additional methyl groups in these structures would be expected to have little or no influence on the spectra of these compounds when compared to the nonmethylated compounds. Ultraviolet spectra were taken of the authentic 1-methyl-2-(1-pyrrolylmethyl)pyrrole (**2**) and of the low melting compound from the radical reaction of N-methylpyrrole. The spectra were virtually identical but not the same, and indicated the presence of two nonconjugated pyrrole rings in each molecule. These structural requirements eliminated structures **4**–**6**, leaving structure **7** as the only remaining possibility. Thus the identity of the low melting product was deduced to be that represented by structure **7**. The difficulties which would be encountered in the direct synthesis of 1-methyl-2-(1-pyrrolylmethyl)pyrrole (**7**) precluded a more positive means of identification.

Synthesis of the product from the pyrrole–*t*-butyl peroxide reaction was quite straightforward and was described above. It was thought that the dehydrogenation of 2,2′-pyrrolidinylpyrrole would give 2,2′-bipyrrole. If this had occurred, the free-radical product would have to be dehydrogenated to the same product to show that the compounds in question contained the same carbon skeleton. When 2,2′-pyrrolidinylpyrrole was dehydrogenated, it was found that the resulting product was identical with that which formed in the free-radical reaction. It was also shown by Rapoport[17] that the major product of the dehydrogenation of 2,2′-pyrrolidinylpyrrole was 2,2′-(1′-pyrrolinyl)pyrrole (**3**).

Discussion of Free-Radical Products

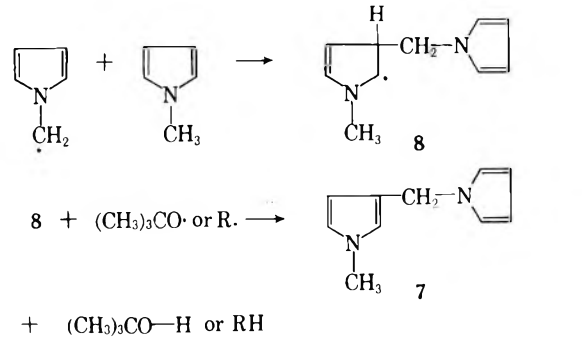
From a consideration of the two dimeric products formed, 1,1′-ethylenedipyrrole (**1**) and 1-methyl-3-(1-pyrrolylmethyl)pyrrole (**7**), it has been adequately demonstrated that the *t*-butoxy radical abstracts a hydrogen atom from the methyl group of N-methylpyrrole. This radical may then dimerize to give 1,1′-ethylenedipyrrole, a reaction similar to that which occurs when a hydrogen atom is abstracted from the alkyl group of toluene giving dibenzyl as a product. It can be inferred



that the benzyl radical and the pyrrolylmethyl radical are stabilized in like manner by resonance forms involving their respective aromatic nuclei. In addition, they should both be nucleophilic in nature.[18]

The unexpected product of the *t*-butyl peroxide and N-methylpyrrole reaction, *i.e.*, 1-methyl-3-(1-pyrrolylmethyl)pyrrole (**7**), was quite interesting in view of the fact that N-methylpyrrole was alkylated in the 3-position. This is probable mechanism for its formation.

(13) D. W. Fuhlhage and C. A. VanderWerf, *J. Am. Chem. Soc.*, **80**, 6249 (1958).
(14) K. M. Johnston and G. H. Williams, *J. Chem. Soc.*, 1446 (1960).
(15) E. L. Patmore and R. J. Gritter, *J. Org. Chem.*, **27**, 4196 (1962).
(16) H. Rapoport and K. Holden, *J. Am. Chem. Soc.*, **84**, 635 (1962).
(17) H. Rapoport and N. Castagnoli, *ibid.*, **84**, 2178 (1962).
(18) G. H. Williams, "Homolytic Aromatic Substitution," Pergamon Press, Inc., New York, N. Y., 1960, p. 66.



Roberts[19] has performed LCAO-MO calculations on pyrrole and has arrived at the following charge distributions: position 1 = +0.32, position 2 = −0.10, and position 3 = −0.06. From these values it is readily apparent that C-2 is much preferred as the position of attack by an electrophilic radical. Attack on the 3-position, as shown by the product, indicated that the pyrrolylmethyl radical was nucleophilic in nature, as would be predicted.

Another interesting observation can be made concerning the reactivity of the butadiene system of pyrrole toward free-radical attack. The lack of reaction of 1-octene with *t*-butyl peroxide and N-methylpyrrole showed that the pyrrolylmethyl radical did not have sufficient reactivity to add to simple olefins typified by 1-octene. The 3-alkylated product which was isolated indicated that the pyrrole molecule was a more reactive species toward free-radical attack than an ordinary olefin.[6]

The product of the reaction of pyrrole with *t*-butyl peroxide further substantiated the proposition that the pyrrole ring is a reactive diene when in the presence of free radicals. The 2,2′-(1′-pyrrolinyl)pyrrole isolated established the fact that the *t*-butoxy radical abstracted a hydrogen atom from the 2-position of pyrrole. The resulting radical then attacked the diene system of pyrrole and gave an intermediate radical which probably chain terminated as above.

The outstanding feature of this reaction was the position of attack by the pyrrolyl radical. Attack by this radical on the pyrrole ring occurred at the 2-position and suggested an electrophilic type of radical as opposed to the nucleophilic radical implied by the 3-attack of the pyrrolylmethyl radical in the previously described reaction. This similarity to the electrophilic phenyl radical[18] adequately demonstrates that the pyrrolyl radical is electrophilic in nature.

The order found in the relative reactivities of N-methylpyrrole, toluene, 4-picoline, and benzene is in agreement with that predicted, if one considers that the electron availability from the aromatic ring will determine the stability of the resulting radical in the transition state. N-Methylpyrrole is considered to be "superaromatic" and as such would form a very stable radical.[20] Toluene behaves as a moderately reactive aromatic compound and would, therefore, be expected to give a moderately stable radical. 4-Picoline, next in order, resembles an alkylated nitrobenzene in its reactions. This compound is relatively deficient in electron availability and would be expected to give a relatively unstable radical. This, indeed, was found to be the case. The phenyl radical resulting from the hydrogen atom abstraction on benzene is one of the most unstable radicals known and would be expected to fall last in the above order.[2]

(19) J. D. Roberts, "Notes on Molecular Orbital Calculations," W. A. Benjamin, Inc., New York, N. Y., 1961, p. 80.

(20) H. Gilman and E. B. Towne, *Rec. trav. chim.*, **51**, 1054 (1932).

Experimental

Reagents.—The following reagents were used without further purification: acetic anhydride (Baker and Adamson reagent grade), alumina (Woelm), lithium aluminum hydride (Metal Hydrides, Inc.), mucic acid (Matheson Coleman and Bell), 1,3-butadiene (The Matheson Co.), and chloroacetonitrile (Eastman Kodak Co., White Label).

The following reagents were distilled before use through a 14-in. column equipped with a tantalum-wire spiral: *t*-butyl peroxide (Lucidol Corp., b.p. 45° at 68 mm., $n^{20}D$ 1.3892), pyrrolidine (Matheson Coleman and Bell, b.p. 88°), 4-picoline (Reilly Tar and Chemical Co., b.p. 143°, $n^{20}D$ 1.5062), xylene (Fisher Scientific Co., b.p. 140–142°), 1-octene (Matheson Coleman and Bell, b.p. 120°, $n^{20}D$ 1.4140), and toluene (Matheson Coleman and Bell, b.p. 110°, $n^{20}D$ 1.4970).

N-Methylpyrrole (Ansul Chemical Co.) and pyrrole (Ansul Chemical Co.) were dried for 4 hr. over potassium hydroxide and were distilled through a Podbielniak concentric tube column (Model No. 2208). Immediately before use, the N-methylpyrrole (b.p. 113.5–114°, $n^{20}D$ 1.4885) and pyrrole (b.p. 130°, $n^{20}D$ 1.5091) were redistilled through an 18-in. column fitted with a tantalum-wire spiral.

Free-Radical Reactions. N-Methylpyrrole and *t*-Butyl Peroxide Reactions.—N-Methylpyrrole (1.9 moles, 157.3 g.) and *t*-butyl peroxide (0.13 mole, 19.04 g.) were treated in a glass-lined stainless steel bomb for 8 hr. at 150° in a nitrogen atmosphere. The reaction mixture was distilled through a 14-in. column equipped with a tantalum-wire spiral to give a residue (13.9 g.). One-gram portions of the residue were chromatographed on 30-g. portions of basic alumina (activity grade I). Elution with benzene–pentane solvent mixtures gave two white crystalline products, m.p. 60–61° (shown to be 1,1′-ethylenepyrrole) and 108° (deduced to be 1-methyl-3-(1-pyrrolylmethyl)pyrrole), the lower melting compound being eluted first.

Anal. Calcd. for $C_{10}H_{12}N_2$: C, 74.97; H, 7.54; N, 17.49. Found (m.p. 60–61°): C, 74.80; H, 7.44; N, 17.56. Found (m.p. 108°): C, 75.11; H, 7.56; N, 17.47.

Because of the extremely small yields (0.7% based on conversion), the reaction was repeated using (a) N-methylpyrrole (1.9 moles, 148.1 g.) and *t*-butyl peroxide (0.19 mole, 27.70 g.), (b) N-methylpyrrole (1.7 moles) and peroxide (0.17 mole), and (c) N-methylpyrrole (1.1 moles) and peroxide (0.12 mole). The isolation of the products from the other three reactions was accomplished in the same manner. The yields were virtually the same in all cases, 0.42% and 0.28%, respectively.

N-Methylpyrrole, *t*-Butyl Peroxide and 1-Octene Reaction.—N-Methylpyrrole (1.9 moles, 149.3 g.), 1-octene (0.13 mole, 14.26 g.), and 5 ml. (0.03 mole) of *t*-butyl peroxide were treated as above to give a 7.0 g. residue. No product could be separated by chromatography which corresponded to the expected product.

N-Methylpyrrole, *t*-Butyl Peroxide, and 1,3-Butadiene Reactions.—The three reactants were treated in the same ratio and way as above. A residue (12.42 g.) was formed which was hydrogenated and chromatographed, but no product could be separated. When repeated with twice the amount of butadiene, polymeric material resulted.

Pyrrole and *t*-Butyl Peroxide Reactions.—Pyrrole (2.3 moles, 152.3 g.) and 5 ml. (0.03 mole) of *t*-butyl peroxide were treated in a glass liner in a stainless steel container for 8 hr. at 150° in a nitrogen atmosphere. Vacuum distillation of the reaction mixture left a residue (2.5 g.). The residue was chromatographed on basic alumina (activity grade I) using a number of solvent systems. No separation could be effected although the product became somewhat less viscous. Steam distillation gave a white crystalline compound (2.0 g., 80% yield based on the 2.5 g. of product, m.p. 162°). The product, subsequently shown to be 2,2′-(1′-pyrrolinyl)pyrrole, was sublimed at 110° at atmospheric pressure after which the melting point was raised to 163.5–164°.

Anal. Calcd. for $C_8H_{10}N_2$: C, 71.60; H, 7.51; N, 20.87. Found: C, 71.71; H, 7.54; N, 20.78.

The reaction was rerun under the same conditions using pyrrole (4.3 moles, 291.0 g.) and 25 ml. (0.15 mole) of *t*-butyl peroxide. Vacuum distillation left a crude residue (4.2 g.). The crude product was purified by steam distillation followed by double sublimation to give the same product. Minimum yield based on the per cent conversion to products (4.2 g.) was 75%.

Synthesis of 1,1′-Ethylenedipyrrole

Potassium pyrrole was prepared in quantitative yield[8] and treated with chloroacetonitrile in xylene to give the nitrile.[9] Reduction with lithium aluminum hydride[9] and isolation by the method of Amundsen and Nelson[21] gave the corresponding amine.

Preparation of 1,1′-Ethylenedipyrrole.[10]—Mucic acid (0.0055 mole, 1.2 g.) was neutralized with 1-(2-aminoethyl)pyrrole (0.0055 mole, 0.60 g.) dissolved in distilled water (3 ml.). The resulting solution was evaporated to dryness over a steam bath and allowed to stand for 24 hr. The salt was powdered and subjected to red heat until no more distillate was obtained. The remains were broken up and boiled in benzene (50 ml.). The benzene solution was washed several times with dilute sulfuric acid (6 *M*) and evaporated to dryness leaving a residue (0.5 g.). The residue was chromatographed using the procedure previously described for the isolation of the higher melting (m.p. 108°) product of the N-methylpyrrole and *t*-butyl peroxide reaction. Approximately 10 mg. (1.27%) of 1,1′-ethylenedipyrrole was isolated, m.p. 107.5–108°, lit.[7] m.p. 107.5–108°. The crystal structure appeared to be in the shape of a parallelogram. The infrared spectrum matched perfectly with that of the compound (m.p. 108°) isolated from the free-radical reaction.

Synthesis of 1-Methyl-2-(1-pyrrolylmethyl)pyrrole

1-Methyl-2-pyrrolecarboxaldehyde was prepared as reported[11] and its oxime immediately was prepared by the method of Anderson.[12] Hydride reduction and isolation as above[21] or reduction with sodium in ethanol (40% yield)[22] gave 1-methyl-2-(ammomethyl)pyrrole. The highly unstable amine was treated with phenyl thioisocyanate to give a thiourea, m.p. 143–144°, which was recrystallized from absolute ethanol.

Anal. Calcd. for $C_{13}H_{15}N_3S$: S, 13.07. Found: S, 12.90.

Preparation of 1-Methyl-2-(1-pyrrolylmethyl)pyrrole.—Preparation and isolation was accomplished by the sequence used for 1,1′-ethylenedipyrrole.[10] Mucic acid (0.0107 mole, 2.25 g.) was neutralized with 1-methyl-2-(aminomethyl)pyrrole (0.0213 mole, 2.35 g.) dissolved in distilled water (5 ml.). Pyrolysis of the salt gave 0.160 g. (9%) of the desired compound (m.p. 71–72°). The infrared spectrum differed from that of the compound melting at 60–61° which was isolated from the free-radical reaction of N-methylpyrrole. An X-ray diffraction pattern confirmed the nonidentity of the two compounds. The ultraviolet spectra were virtually identical and indicated that both compounds possessed the same type of conjugation. Ultraviolet absorption in 95% ethanol showed 1-methyl-2-(1-pyrrolylmethyl)pyrrole, λ_{max} 218 mμ (ε 13,000); product of free-radical reaction (m.p. 60–61°), λ 217 mμ (ε 13,600); and 2,2′-bipyrrole, λ 282 mμ (ε 16,700) and 277 (17,300). No elemental analysis could be obtained for the compound because of its extremely short shelf life, although thin layer chromatography indicated that the product was pure.

Synthesis of 2,2′-(1′-Pyrrolinyl)pyrrole

Preparation of 2,2′-Pyrrolidinylpyrrole.—This compound was prepared by the method of Fuhlhage and VanderWerf[13] with the modification that the sodium hypochlorite used was prepared by the reaction of sodium carbonate on 70% calcium hypochlorite (Pittchlor). This sequence gave 7.0 g. of 2,2′-pyrrolidinylpyrrole, m.p. 85°, lit.[13] m.p. 84–86°, in 20% yield.

Preparation of 2,2′-(1′-Pyrrolinyl)pyrrole.—A mixture of 2,2′-pyrrolidinylpyrrole (0.0585 mole, 0.796 g.), 5% rhodium on alumina (0.786 g.), and cumene (20 ml.) were placed in a flask with a reflux condenser and magnetic stirrer. The mixture was heated under reflux with vigorous stirring under a stream of nitrogen for 12 hr. The resulting mixture was poured into a chromatography column containing 30 g. of neutral alumina (activity grade III). Elution with benzene–chloroform (3:1) gave 0.64 g. (82%) of the desired compound melting at 163–164° after sublimation (110°). The reported[17] m.p. is 162–163°. The infrared showed strong C=N bands at 1630 cm.$^{-1}$. The ultraviolet spectrum (95% ethanol) of the prepared compound gave λ 279 mμ (ε 16,500).

Determination of the Relative Reactivities

Each of the compounds used in this determination was distilled through a 14-in. column fitted with a tantalum-wire spiral immediately before use. Purity was established by gas chromatographic analysis.

The following procedure was used for each compound studied. A standard solution of *t*-butyl peroxide in benzene was prepared (7.64% *t*-butyl peroxide by weight). A standard amount (5 ml.) of this solution and the individual compound was pipeted into a Pyrex ampoule. The sample was cooled in a chloroform–carbon tetrachloride–Dry Ice-cooling bath, flushed with nitrogen, and sealed. The sample was placed in an oil bath at 150 ± 0.2° for approximately 12 hr., which corresponds to at least 99% decomposition of the peroxide. At the end of this time the sample was removed, allowed to cool, and placed in the Dry Ice mixture. After solidification was complete, the sample was removed, its seal was broken, and its warmed contents were analyzed by gas chromatography. The ratio of *t*-butyl alcohol to acetone was obtained by determining the ratio of counts of the alcohol and acetone peaks from the chromatogram obtained using a recorder equipped with a Disc-Integrator. The concentration of the compound was calculated from the known weights and from the density at 150°.

It was observed that experimentally determined values for alcohol to acetone ratios resulting from an analysis of known ratios did not correspond exactly to the calculated values. The magnitude of the variation depended upon the nature of the chromatography column and upon the nature of the mixture in which the alcohol and acetone were found. The following procedure was used for each compound studied, to determine the effect of the compound and column on the ratios determined above. From the molar ratio of alcohol to acetone observed, the gram ratio was calculated. A known ratio was prepared corresponding exactly to the observed ratio. A portion of this prepared ratio was added to benzene such that the alcohol–acetone portion of the mixture comprised approximately 7% of the total solution by weight. To the solution of benzene, alcohol, and acetone was added an equal volume of the appropriate compound. A sample of the final solution was transferred to a Pyrex ampoule and the ampoule was cooled, sealed, heated, and analyzed in exactly the same manner as previously described. The results of the ratio determinations are summarized in Table I.

Gas Chromatography Conditions.—The gas chromatographic unit (Aerograph Master A-100, Wilkens Instrument and Research, Inc., Walnut Creek, Calif.) was equipped with a Leeds and Northrup recorder (S-60,000) with a Disc-Integrator (Model K-3, Disc Instrument Co.). The gas chromatographic unit was operated under the following conditions: Ucon polyethyleneglycol column, 1-mv. recorder range, 7.5-lb./in.^{2} helium pressure, 200-ma. filament current, and 103–105° temperature oven.

Determination of Volume Change of Samples with Temperature.—The volume expansions with temperature (20–150°) of the compounds used in this study were determined by an extrapolation of the results of the work of Patmore and Gritter[15] whose values were determined in the range 25 to 135°. Patmore[15] found 12% average expansion; extrapolation gave 14%.

Acknowledgment.—The authors wish to thank the Ansul Chemical Company for a gift of N-methylpyrrole, Dr. James M. Bobbitt of this department for his advice and help, and the Quartermaster Corps, U. S. Army, for financial assistance through Contracts No. DA-19-129-QM-1051 and 1708.

(21) L. H. Amundsen and L. S. Nelson, *J. Am. Chem. Soc.*, **73**, 242 (1951).

(22) N. I. Putochin, *Ber.*, **59**, 1996 (1926).

The Synthesis and Thermal Decomposition of *p*-Nitrobenzoic *t*-Butylcarbonic Anhydride[1]

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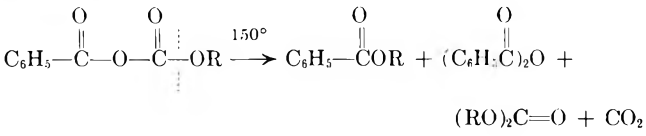
Received November 27, 1963

The crystalline *p*-nitrobenzoic *t*-butylcarbonic anhydride has been made by two methods: the action of *t*-butyl chlorocarbonate on *p*-nitrobenzoic acid (27% yield) and the action of *p*-nitrobenzoyl chloride on potassium *t*-butyl carbonate (64% yield). Decomposition of *p*-nitrobenzoic *t*-butylcarbonic anhydride at 100° yielded carbon dioxide (90%), isobutene (61%), *p*-nitrobenzoic anhydride (52–84%), *p*-nitrobenzoic acid (7–34%), *t*-butyl *p*-nitrobenzoate (*ca.* 5%), *t*-butyl alcohol (*ca.* 25%), and *t*-butyl carbonate (*ca.* 10%). The reaction thus proceeds mainly by alkyl–oxygen cleavage, and possible mechanisms are discussed.

Previous work has made it probable that the decomposition of benzoic alkylcarbonic anhydrides, derived from primary and secondary alcohols, is an ionic chain reaction proceeding by acyl–oxygen cleavage. This



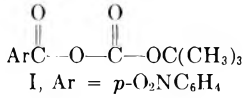
$$C_6H_5{-}\overset{O}{\overset{\|}{C}}{-}O{-}\overset{O}{\overset{\|}{C}}{-}OR \xrightarrow{150^\circ} C_6H_5{-}\overset{O}{\overset{\|}{C}}OR + (C_6H_5\overset{O}{\overset{\|}{C}})_2O +$$

$$(RO)_2C{=}O + CO_2$$

conclusion was based on the kinetic characteristics of the reaction,[3] the retention of configuration during the reaction when R was an optically active *s*-octyl group,[4] and the result of an oxygen-18 labeling study which showed that the alkyl–oxygen bond was left intact during the decomposition.[5]

It is well-known that both the base- and the acid-catalyzed hydrolysis of carboxylic acid esters, derived from primary and secondary alcohols, usually proceeds by acyl–oxygen cleavage.[6] The acid-catalyzed hydrolysis of esters derived from tertiary alcohols, however, involves the cleavage of the alkyl–oxygen bond.[7] The present work was undertaken to prepare a mixed carboxylic–carbonic anhydride with a *t*-alkyl group, and to determine the mode of its thermal decomposition; it has been found that alkyl–oxygen cleavage is predominant over acyl–oxygen cleavage.

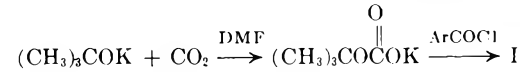
Treatment of the rather unstable *t*-butyl chlorocarbonate[8] with benzoic acid and triethylamine in the usual way[9] yielded an oil which had the two expected anhydride bands in the carbonyl region,[9] but it did not give a satisfactory elementary analysis and could not be purified. The use of *p*-nitrobenzoic acid in this procedure yielded the crystalline *p*-nitrobenzoic *t*-butylcarbonic anhydride (I), m.p. 92–93°



$$ArC{-}O{-}\overset{O}{\overset{\|}{C}}{-}OC(CH_3)_3$$

I, Ar = p-$O_2NC_6H_4$

The mixed anhydride I was prepared more readily and in better yield by another method, using potassium *t*-butyl carbonate.[10] Potassium *t*-butyl carbonate in dimethylformamide (DMF) was treated dropwise with a solution of *p*-nitrobenzoyl chloride in DMF. The carbonate salt was made by passing carbon dioxide through a solution of potassium *t*-butoxide in DMF. The yield of the mixed anhydride I was 64%. After one recrystallization from chloroform and petroleum ether, the product had m.p. 92–93°, undepressed by mixture with the product prepared by the chlorocarbonate method. The infrared spectra of the samples of the anhydride prepared by both methods were identical, exhibiting the characteristic anhydride doublet at 1803 and 1743 cm.$^{-1}$ (carbon tetrachloride solution).[9]



$$(CH_3)_3COK + CO_2 \xrightarrow{DMF} (CH_3)_3COCOK \xrightarrow{ArCOCl} I$$

The decomposition of the mixed anhydride was carried out on neat samples at 100°. The products and their yields are listed in Table I.

TABLE I

PRODUCTS OF DECOMPOSITION OF Ar COCOOC$(CH_3)_3$ AT 100° (Ar = p-$O_2NC_6H_4$)

Product	Yield, %	Number of runs
CO_2	90 ± 5	12
$CH_2{=}C(CH_3)_2$	61 ± 4	7
$(ArCO)_2O$	52–84	4
ArCOOH	7–34	4
$AcCOOC(CH_3)_3$	2–9	4
$(CH_3)_3COH$	23–28	2
$[(CH_3)_3CO]_2CO$	6–12	2

The large variation in yield of *p*-nitrobenzoic anhydride and of the corresponding acid is probably due to the fact that these products are the result of several competing reactions: the decompositions were carried out without solvent, and minor variations in conditions or the amount of catalytic impurities[3] could affect markedly the relative rates of competing reactions.

The most interesting product from the standpoint of the original purpose of this work was isobutene. The possibility that this compound arose from the decomposition of *t*-butyl *p*-nitrobenzoate was eliminated by the demonstration that the ester was completely stable under the reaction conditions, both in the presence and absence of *p*-nitrobenzoic acid. The value obtained for isobutene (Table I) in seven runs suggests that the compound arose from a unimolecular process

(1) (a) A preliminary account appeared in *Chem. Ind.* (London), 369 (1964); (b) aided by Grant G-11240 from the National Science Foundation.

(2) Esso Education Foundation Fellow, 1961–1962.

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(6) M. Polanyi and A. L. Szabo, *Trans. Faraday Soc.*, **30**, 508 (1934); S. C. Datta, J. N. E. Day, and C. K. Ingold, *J. Chem. Soc.*, 838 (1939); I. Roberts and H. C. Urey, *J. Am. Chem. Soc.*, **60**, 2391 (1938).

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(8) A. R. Choppin and J. W. Rogers, *J. Am. Chem. Soc.*, **70**, 2967 (1948).

(9) D. S. Tarbell and N. A. Leister, *J. Org. Chem.*, **23**, 1149 (1958).

(10) L. A. Carpino, *J. Am. Chem. Soc.*, **82**, 2725 (1960).

which was largely independent of the medium. An attractive mechanism for the formation of isobutene is a concerted cleavage of the mixed anhydride I to yield the *p*-nitrobenzoate ion, carbon dioxide, and the *t*-butyl carbonium ion. The carbonium ion would be expected to lose a proton rapidly to form isobutene.

$$\text{I} \longrightarrow \text{ArCOO}^- + \text{CO}_2 + (\text{CH}_3)_3\text{C}^+$$

The *p*-nitrobenzoate ion could then react with the unchanged mixed anhydride, leading to the other products as shown below.

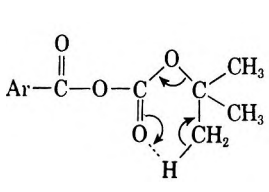
$$\text{Ar—COO—COOC(CH}_3)_3 + \text{Ar—COO}^- \longrightarrow \underset{\text{I}}{} \quad (\text{Ar CO})_2\text{O} + \bar{\text{O}}\text{COOC(CH}_3)_3$$

$$\bar{\text{O}}\text{COOC(CH}_3)_3 \longrightarrow \bar{\text{O}}\text{C(CH}_3)_3 + \text{CO}_2 \xrightarrow{\text{H}^+} \text{HOC(CH}_3)_3$$

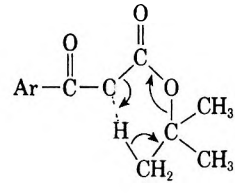
$$\bar{\text{O}}\text{C(CH}_3)_3 + \text{I} \begin{cases} \longrightarrow \text{Ar COOC(CH}_3)_3 + \bar{\text{O}}\text{COOC(CH}_3)_3 \\ \longrightarrow \text{Ar COO}^- + [(\text{CH}_3)_3\text{CO}]_2\text{CO} \end{cases}$$

$$\text{Ar COO}^- + \text{H}^+ \longrightarrow \text{Ar COOH}$$

The yield of isobutene indicates that the decomposition of the mixed anhydride I thus proceeds mainly by alkyl–oxygen cleavage. This mode of decomposition is probably the direct result of the stability of the *t*-butyl carbonium ion. The possibility that the alkyl–oxygen cleavage involves transition states such as II or III cannot be excluded on the present evidence.



II



III

Experimental[11]

Preparation of *p*-Nitrobenzoic *t*-Butylcarbonic Anhydride. A. Chlorocarbonate Method.—*t*-Butyl chlorocarbonate was prepared many times essentially by the method of Choppin and Rogers.[8] Phosgene (50 g., large excess) was condensed in a flask which was equipped with a stirrer and a Dry Ice condenser and was chilled by a Dry Ice–acetone bath. Dry ether (200 ml.) was added, followed by 33.6 g. (0.3 mole) of potassium *t*-butoxide,[12] which was added to the rapidly stirred reaction in portions, over a period of 1 hr. The reaction was allowed to stir for an additional 5 hr.; at the end of that time, it was filtered rapidly by suction. The excess phosgene and the ether were removed *in vacuo*, without allowing the solution to warm above 0°. The residue then was distilled, bulb to bulb, at 0.1 mm., to give 13.4 g. (33%) of *t*-butyl chlorocarbonate. The carbamate derivative had the m.p. 107–108°; the reported value[8] is 108–108.5°.

In a flask, equipped with a stirrer and an addition funnel, was placed 300 ml. of dry ether. The ether was chilled to −15° by an ice–salt bath; then 10.8 g. (0.065 mole) of *p*-nitrobenzoic acid and 8.8 g. (0.065 mole) of *t*-butyl chlorocarbonate were added in one portion. The solution was stirred, and 6.5 g. (0.065 mole) of triethylamine in 10 ml. of ether was added dropwise over a period of 1 hr. Stirring was continued for an additional hour and the mixture was allowed to come to room temperature. The amine hydrochloride was filtered off, and the filtrate was washed thoroughly with dilute hydrochloric acid, dilute sodium bicarbonate, and water, and dried over magnesium sulfate. The ether was evaporated at reduced pressure to yield 7.2 g. (27%) of pale yellow crystals which had a melting point of 92–93°. Recrystallization from chloroform and petroleum ether failed to change the melting point.

Anal. Calcd. for $C_{12}H_{13}NO_6$: C, 53.93; H, 4.90. Found: C, 54.19; H, 4.86.

B. Potassium *t*-Butyl Carbonate Method.—In a flask equipped with a stirrer, an addition funnel, and a gas dispersion tube was placed a solution of 13 g. (slightly more than 0.1 mole) of potassium *t*-butoxide in 100 ml. of carefully purified[13] DMF. Dry carbon dioxide was passed into the reaction flask for 0.5 hr. The mixture required cooling because the reaction was exothermic. At the end of the addition of carbon dioxide, the reaction mixture was a thick gel. A solution of 18.5 g. (0.1 mole) of *p*-nitrobenzoyl chloride in 50 ml. of DMF was added dropwise to the mixture over a period of 45 min. Stirring was continued for an additional 2 hr. The mixture then was diluted with 100 ml. of ether and filtered to yield a clear filtrate and a water soluble, nearly neutral residue. The filtrate was extracted very thoroughly with water and dried over magnesium sulfate and potassium carbonate. Removal of the solvent yielded 17.2 g. (64%) of crude product, which on one recrystallization from chloroform and petroleum ether had m.p. 92–93°. The infrared spectrum of this product was identical with that of the product prepared by the chlorocarbonate procedure. The mixture melting point was not depressed.

Decomposition of *p*-Nitrobenzoic *t*-Butylcarbonic Anhydride.—The mixed anhydride was decomposed without solvent at 100°. The decomposition apparatus consisted of a 5-ml. flask equipped with a side arm for the admission of prepurified nitrogen and a short (10-cm.) condenser. The top of the condenser was connected to a U-trap cooled to −42° (chlorobenzene slurry). The U-trap in turn was connected to an Ascarite-filled gas absorption tower. The Ascarite tower was attached to a spiral trap cooled to −196° (liquid nitrogen). This trap vented into the atmosphere through a mercury bubbler.

In a typical run, the apparatus was cleaned and flushed thoroughly with prepurified nitrogen. A sample of *p*-nitrobenzoic *t*-butylcarbonic anhydride was weighed (0.1–0.2 g.) into the decomposition vessel, the Ascarite tower was weighed, and the system again was flushed with nitrogen. The decomposition vessel then was heated with an oil bath maintained at 100–110°. The anhydride first melted and then bubbled vigorously. After *ca.* 15 min. of heating, the material in the vessel solidified; heating was continued for an additional 15–30 min. During the decomposition a slow stream of prepurified nitrogen was passed through the system. At the end of the decomposition, the Ascarite tower was disconnected for immediate weighing. The increase in weight corresponded to the amount of carbon dioxide evolved during the reaction. The contents of the spiral trap were shown to be almost pure isobutene by comparison of its mass spectrum with that of a known sample. The amount of isobutene was determined manometrically.

The solid residue from the decomposition was analyzed by the method of Lukoshevich.[14] One portion of the residue was dissolved in dry methanol and pyridine (2:1) and another portion was dissolved in water and pyridine (1:1). The two solutions were titrated with 0.1 *N* sodium hydroxide to the phenolphthalein end point. The first portion yielded the acidity due to the free acid and one equivalent of acid per mole of anhydride. The second portion yielded the acidity due to the free acid plus two equivalents of acid per mole of anhydride. From the two titers the per cent of the anhydride and the acid in the residue could be calculated readily. The ester was obtained by difference.

The amounts of *t*-butyl alcohol and *t*-butyl carbonate were estimated by vapor phase chromatography.

Stability of *t*-Butyl *p*-Nitrobenzoate.—An authentic sample of the ester was subjected to the mixed anhydride decomposition conditions, both in the presence and absence of *p*-nitrobenzoic acid. Heating of the acid and the ester overnight at 100 ± 10° produced no decrease in the weight of the mixture. The infrared spectra of the mixture before and after heating were identical. No isobutylene was detected in any of these experiments.

(11) We are indebted to J. Souto, Joanne Woroscz, and Robert Labarge for preliminary work on this problem.

(12) The commercial material, obtained from the MSA Corp., was used.

(13) DMF was purified by heating under reflux overnight with barium oxide and then distilling from that reagent at atmospheric pressure. The distillate then was redistilled from phosphorus pentoxide at reduced pressure.

(14) C. W. Hammond, "Organic Analysis," Vol. III, Interscience Publishers Inc., New York, N. Y., 1956, p. 106.

The Effect of Methoxyl Groups on Carbonyl Infrared Absorption and on Optical Rotatory Dispersion. 2-Methoxy-3-keto- and 3-Methoxy-2-ketocholestanes[1]

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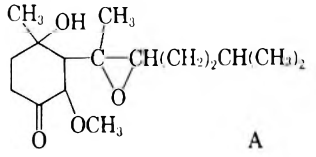
2α- and 2β-methoxy-3-ketocholestanes and 3α- and 3β-methoxy-2-ketocholestanes have been prepared from the corresponding alcohols. The alcohols were prepared by acid-catalyzed methanolysis from 2α,3α-epoxycholestane and 2β,3β-epoxycholestane, which were obtained by known routes. The equatorial methoxyl group in the ketones shifts the carbonyl absorption to higher frequency, but the axial methoxyl group causes no appreciable shift. The optical rotatory dispersion curves of these ketones show shifts similar to those observed with the corresponding acetoxy ketones.

Structural elucidation of the antibiotic fumagillin[2] involved, as one key degradation product, a methoxy ketone which was assigned structure A, with the methoxyl group adjacent to the carbonyl group.[2] The carbonyl absorption of A was at a higher frequency

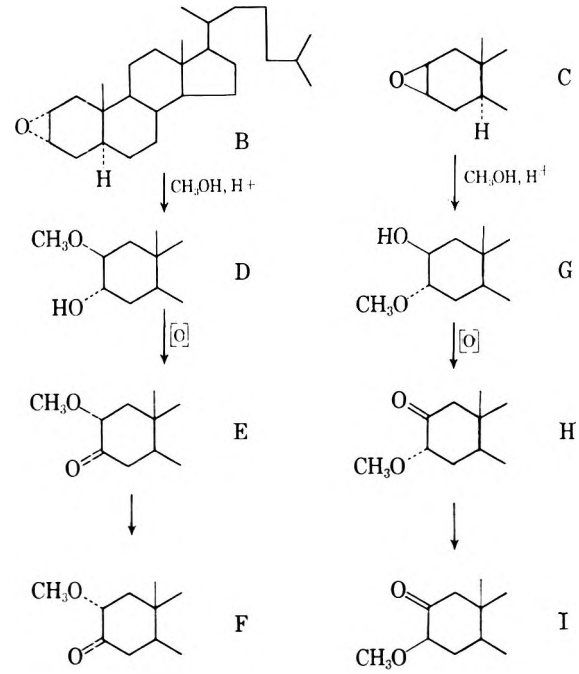


A

(1724 cm.$^{-1}$) than is normal for cyclohexanones, and it was suggested that the methoxyl group was equatorial and that it, like an equatorial bromine atom, raised the carbonyl frequency. Since that time, the stereochemistry of the fumagillin series has been established by X-ray crystallography[3] and by chemical methods,[4] and it has been found that the methoxyl group is in fact equatorial.

The effect of equatorial halogen in raising the frequency of carbonyl absorption in the infrared is well-documented,[5] but at the time the present work was undertaken, there did not appear to be any data available about the effect of an equatorial or axial methoxyl group on the absorption of an adjacent carbonyl group. We have, therefore, prepared the axial and equatorial 2-methoxy-3-ketocholestanes, and the corresponding pair of 3-methoxy-2-ketocholestanes. It appears that, analogous to the bromo ketones, the equatorial methoxyl raises the carbonyl frequency, while the axial methoxyl group does not affect it appreciably. The optical rotatory dispersion (O.R.D.) curves for the four ketones have also been obtained.[6]

The methoxy ketones in the present work were prepared from 2α,3α-epoxycholestane (B), and from the corresponding 2β,3β-epoxy compound[7] C, by treatment with methanolic sulfuric acid, followed by oxidation.



The α-epoxide[8] B was obtained by peracid oxidation of Δ^2-cholestene. The latter was prepared by two methods: the dehydrohalogenation of 3β-chlorocholestane,[8,9] and the reduction of the 2α-bromo-3-hydroxycholestanes with zinc and acetic acid.[10] Treatment of the α-epoxide with methanol containing a trace of sulfuric acid or of *p*-toluenesulfonic acid gave 2-β methoxy-3α-hydroxycholestane (D), m.p. 159–160°, whose structure was assigned on the basis of the known[7,11] diaxial mode of ring opening of steroid epoxides. The structure D was also supported by the C–OH stretching frequency of 1012 cm.$^{-1}$, which is close to that found (996–1002 cm.$^{-1}$) for the axial hydroxyl in comparable compounds, as contrasted to that for equatorial hydroxyls (1037–1040 cm.$^{-1}$).[12]

In several runs, a compound (m.p. 149–150°), isomeric with D, was also obtained in the ring opening; the two products were separated by chromatography, but, in spite of some study, it was not possible to establish the structure of the second product. It

(1) Supported in part by grant E-1138 of the U. S. Public Health Service.

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(4) J. R. Turner and D. S. Tarbell, *Proc. Natl. Acad. Sci. U. S.*, **48**, 733 (1962).

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(6) We are indebted to Professor Carl Djerassi of Stanford for the O.R.D. measurements.

(7) *Cf.* K. L. Williamson and W. S. Johnson, *J. Org. Chem.*, **26**, 4563 (1961).

(8) A. Furst and P. A. Plattner, *Helv. Chim. Acta*, **32**, 275 (1949).

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TABLE I

CHARACTERISTIC INFRARED ABSORPTION OF CHOLESTANONES[a, b]

Ketones	Configuration[c] of $-OCH_3$	ν, cm.$^{-1}$ C=O	Δ C=O	C–OCH_3	Others
3-Ketocholestane		1718			
2β-Methoxy-3-ketocholestane (E)	ax	1719–1720 (s)	−1–+2	1082–1085 (s)	
2α-Methoxy-3-ketocholestane (F)	eq	1728–1729 (s)	+10–+11	1128	
3-Ketocholestane		1712			
3α-Methoxy-2-ketocholestane (H)	ax	1710–1717 (s)	−2–+5	1077 (s), 1084–1085 (sh), 1103–1101 (s)	1185 (w), 1198 (w), 1283 (w)
3β-Methoxy-2-ketocholestane (I)	eq	1720–1721 (s)	+8–+9	1120 (s), 1140 (s), 1150 (sh), 1137 (sh)	1193 (w), 1270–1278 (w, b)
2α-Bromo-3-ketocholestane	eq	1734–1735			

[a] The spectra were taken on 3–6 mg. of compound in 0.2–0.3 ml. of carbon tetrachloride; the values are given in cm.$^{-1}$. [b] b = broad, s = strong; w = weak; sh = shoulder. [c] ax = axial, eq = equatorial. [d] Taken in carbon disulfide [E. G. Cummins and J. E. Page, *J. Chem. Soc.*, 3847 (1957)].

could not be obtained in later runs, even after considerable variations in the conditions of ring opening. The oxidation of D to E and F was carried out using the chromic oxide–pyridine complex[13] or the chromic oxide–acetone–sulfuric acid reagent.[14] The axial methoxy ketone E was rapidly epimerized to F, and E was difficult to obtain analytically pure; in some runs, no attempt was made to isolate pure E, and the reaction mixture was epimerized directly to F by treatment with methanolic potash at room temperature. The stable equatorial methoxy ketone F was readily obtained pure, m.p. 127–128°.

2β,3β-Epoxycholestane (C), obtained by the action of base on 2α-bromo-3β-hydroxycholestane,[15] was converted to the 2-keto-3-methoxy compounds (H and I) by analogous procedures. Compound G showed a double m.p. 135–139° and 150–153°, which was not affected by chromatography or crystallization. Its precursors and the equatorial methoxy ketone I were obtained pure.

Infrared Absorption.—Table I shows that the equatorial methoxyl group does raise the carbonyl absorption frequency, but that the axial methoxyl group does not have a significant effect; there is thus a parallelism between the effect of the bromine[4] and the methoxyl, although the bromine has a larger effect.

The C–OCH_3 infrared frequency is also increased in the equatorial methoxy ketone, compared to the axial epimer. Thus, 2β-methoxy-3-ketocholestane (axial methoxyl) has the C–OCH_3 peaks in the 1085 cm.$^{-1}$ region, whereas in the 2α-methoxy-3-ketocholestane (equatorial methoxyl) the band is at 1128 cm.$^{-1}$, a shift of +43 cm.$^{-1}$. Similarly, 3α-methoxy-2-ketocholestane (axial) shows a doublet at 1079 and 1100 cm.$^{-1}$, which is shifted to 1120 and 1140 cm.$^{-1}$ in the equatorial compound. Page[16] reports a shift of +14 cm.$^{-1}$ in going from the axial to the equatorial isomer in 3α- and 3β-methoxycholestanes.

The results tabulated for the methoxy ketones E, F, H, and I are in agreement with several observations that have appeared while this work was in progress, showing that equatorial methoxyl groups increase the carbonyl frequency. Oxodihydroundulatine[17] shows carbonyl absorption at 1724 cm.$^{-1}$; epimerization, which presumably converts the axial methoxyl to the equatorial position, shifts the carbonyl band to 1730 cm.$^{-1}$. 2-Methoxy-*trans*-1-decalone (axial methoxyl) absorbs at 1715 cm.$^{-1}$, and the equatorial compound, obtained by epimerization, absorbs[18] at 1724 cm.$^{-1}$.

2α-Methoxy-3-keto-4,4-dimethylcholestane and the epimeric 2β-methoxy compound[19] were prepared by a displacement reaction of sodium methoxide on 2α-bromo-3-keto-4,4-dimethylcholestane; the 2β-methoxy compound absorbs at 1721 cm.$^{-1}$, and the 2α-methoxy compound at 1712 cm.$^{-1}$. The parent ketone, 4,4-dimethyl-3-ketocholestane, absorbs at 1692 cm.$^{-1}$. The increase in the carbonyl frequency of the 2β-methoxy compound, in which the methoxyl group should be axial, is attributed to the fact that this compound exists with ring A in the boat form, which puts the methoxyl group equatorial.[19] Similar relationships have been shown earlier for the 2α- and 2β-bromo-8-lanosten-3-ones.[20a]

It is possible, from the preceding observations, that the configurations assigned to the epimeric 16-methoxy-3β-hydroxy-17a,17a-dimethyl-D-homoandrostan-17-ones[20b] should be reversed. The observed carbonyl frequencies[20b] indicate this; the configurations were assigned on the assumption that an α-bromo ketone will be displaced by methoxide by a mechanism involving inversion, and this is an uncertain assumption at best. Both the carbonyl frequencies and C–OCH_3 stretching frequencies would fit better with reversed configurations at C-16 for the methoxyl groups.

Optical Rotatory Dispersion Values.—The observed values[6] for E, F, H, and I are given in Table II, along with the reported values for 2- and 3-ketocholestanes[21] and the values for the acetoxy analogs of E, F, H, and I.[22]

From Table II, it can be seen that an axial methoxyl group shifts the first extremun (peak) to longer wave

(13) G. I. Poos, G. B. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 422 (1953).

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(21) (a) C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p. 42; (b) C. Djerassi, W. Closson, and A. E. Lippman, *J. Am. Chem. Soc.*, **78**, 3163 (1956).

(22) K. L. Williamson and W. S. Johnson, *ibid.*, **83**, 4623 (1961).

TABLE II

OPTICAL ROTATORY DISPERSION VALUES OF STEROIDAL METHOXY KETONES AND RELATED COMPOUNDS

Compound	Peak, mμ	$\Delta\lambda_{ax}$[a]	$\Delta\lambda_{eq}$[a]	a × 10^{-2}[b]
2-Ketocholestane	310			
3α-Methoxy-2-ketocholestane (H)	327	+17		+18.8
3β-Methoxy-2-ketocholestane (I)	314		+4	+23.8
3-Ketocholestane	307			
2β-Methoxy-3-ketocholestane (E)	310	+3		+5.09
2α-Methoxy-3-ketocholestane (F)	304		−3	+12.8
3α-Acetoxy-2-ketocholestane[c]	317	+7		+11.7
3β-Acetoxy-2-ketocholestane[c]	305		−5	+27.2
2β-Acetoxy-3-ketocholestane[c]	290	−17		+2.7
2α-Acetoxy-3-ketocholestane[c]	305		−2	+14.1

[a] $\Delta\lambda_{ax}$ and $\Delta\lambda_{eq}$ are the shifts from the parent ketone of the axial and equatorial methoxy ketones. [b] a = amplitude; this is the amplitude when $[\alpha] \times 10^{-2}$ is plotted against λ; the values for the acetoxy ketones and the unsubstituted ketocholestanes were taken from the published[21,22] curves. [c] These values were taken from ref. 22.

lengths, whereas an equatorial group has a smaller effect, shifting the wave length slightly higher in one case and slightly lower in the other case. This is similar to the 12-acetoxy-11-keto steroids[23] where the axial acetoxy group shifts the wave length +15 mμ, while the equatorial substituent shifts the wave length −7 and −2.5 mμ. The shift in the 3α- and 3β-methoxy ketones is also similar to the corresponding 3α- and 3β-acetoxy ketones in Table II.

There is, however, a considerable difference in the shift associated with the 2β-methoxy-3-ketocholestane and that associated with the 2β-acetoxy-3-ketocholestane. Williamson and Johnson[22] consider the unusual effect of the 2β-acetoxy group as evidence for a distortion of ring A from the normal chair form to a twist conformation. Their n.m.r. data also indicate this distortion.

It is interesting to note that the amplitudes of the dispersion curves of the equatorial methoxy ketones are higher than those of the axial compounds. This is in direct contrast to 12-acetoxy-11-keto steroids, which show an increase in amplitude for the axial substituent compared with its equatorial epimer.[24]

Experimental[25]

Δ²-Cholestene, prepared from 3β-chlorocholestane and quinoline,[8,9] was purified in two ways: by chromatography on alumina or by conversion to the dibromide, followed by debromation. The material from the dibromide melted at 73–74°; the chromatographic purification gave material of m.p. 71°, $[\alpha]^{27}D$ +70.1°; lit.[10,25] m.p. 74–75°, $[\alpha]D$ +66°.

Δ²-Cholestene from the zinc–acetic acid reduction of the 3α-bromo-3-hydroxycholestanes[10] melted at 75°, after chromatography and crystallization from ether–methanol.

2α,3α-Epoxycholestane (B) was prepared from Δ²-cholestene and standardized monoperthalic acid[27] in 72% yield, after recrystallization from ether–methanol; it showed m.p. 103–105°, $[\alpha]^{28}D$ +35.1°. Furst and Plattner[5] reported the properties as m.p. 105–106°, $[\alpha]D$ +36.0°.

2β-Methoxy-3α-hydroxycholestane (D). A.—To a stirred solution of 2α,3α-epoxycholestane (B, 4.61 g.) dissolved in anhydrous methanol (750 ml.) was added one drop of concentrated sulfuric acid. After 15 hr. of continuous stirring, barium carbonate was added, and the mixture was filtered. Evaporation to near dryness produced a white crystalline compound. Recrystallization from ether–methanol gave 4.39 g. (88%) of an alcohol mixture, m.p. range 130–150°. The infrared spectrum of this mixture showed characteristic peaks at 1012 (C–OH), 1031 (C–OH), and 1089 cm.$^{-1}$ (broad, C–OCH_3).

Anal. Calcd. for $C_{28}H_{50}O_2$: C, 80.32; H, 12.04. Found: C, 80.31; H, 11.76.

Two alcohols could be separated from this mixture by repeated chromatography (both eluted with 19:1 benzene–ethyl acetate). The lower melting unknown compound X (m.p. 149–150°) was eluted first, and showed characteristic infrared peaks at 1031 (C–OH) and 1089 cm.$^{-1}$ (broad, –OCH_3); $[\alpha]^{26}D$ +35.1 ± 7° (*c* 1.270).

Anal. Calcd. for $C_{28}H_{50}O_2$: C, 80.32; H, 12.04. Found: C, 80.58; H, 11.81.

The second compound, **2β-methoxy-3α-hydroxycholestane (D)**, m.p. 159–160°, showed characteristic infrared peaks at 1031 (shoulder), 1012 (C–OH), and 1089 cm.$^{-1}$ (broad, C–OCH_3); $[\alpha]D$ +28.6 ± 3.2 (*c* 2.155), +22.6 ± 5.2° (c 1.520).

Anal. Calcd. for $C_{28}H_{50}O_2$: C, 80.32; H, 12.04. Found: C, 80.17; H, 12.11.

B.—2α,3α-Epoxycholestane (0.111 g.) was dissolved in anhydrous methanol (100 ml.), and to this solution were added a few crystals of *p*-toluenesulfonic acid. The resulting solution was stirred for 3.5 hr. in a dry nitrogen atmosphere. The catalyst was neutralized with sodium carbonate, and the crude product was obtained as in procedure A in almost quantitative yield. The infrared spectrum of the crude material showed C–OH absorption mostly at 1012 cm.$^{-1}$ and the presence of unchanged epoxide. A single chromatography gave the pure alcohol D, m.p. 158–160°.

In a dry nitrogen atmosphere, catalysis with a trace of concentrated sulfuric acid gave results analogous to those with *p*-toluenesulfonic acid as catalyst.

The two alcohols gave a markedly depressed mixture melting point. Attempts to prepare quantities of unknown X by procedure A were unsuccessful, for the reaction proved to be inconsistent. In later runs, no X was observed, and, as in procedure B, one chromatography gave D, m.p. 159–160°, exclusively.

2β-Methoxy-3-ketocholestane (E). A.—Chromic acid–pyridine complex[12] (0.25 g. in 1 ml.) was added to 2β-methoxy-3α-hydroxycholestane (D), 0.208 g.) dissolved in pyridine (3 ml.). This mixture was left at room temperature for 27 hr., after which time it was poured into water (80 ml.). The aqueous solution was extracted four times with ether (50-ml. portions) and the ether layer was then washed three times with water (50-ml. portions) and once with a very dilute solution of hydrochloric acid. The ether solution was dried, filtered, and concentrated. Dilution with methanol gave a 50% yield of a solid which, when recrystallized from ether–methanol, had m.p. 77–80°. The infrared spectrum of this compound showed characteristic peaks at 1082–1085 (C–OCH_3) and at 1719–1720 cm.$^{-1}$ (C=O).[28] In other runs, the sharp carbonyl absorption of the 2β-methoxycholestan-3-one ranged from a low of 1716 cm.$^{-1}$ to a high of 1721 cm.$^{-1}$.

(23) Ref. 21a, p. 114.

(24) W. Klyne, "Advances in Organic Chemistry," Vol. 1, R. A. Raphael, Ed., Interscience Publishers, Inc., New York, N. Y., 1960, p. 292. We are indebted to Professor Klyne for informing us of this reference.

(25) All melting points are uncorrected. Microanalyses are by Mr. V. Landeryou and Mr. A. Revilla in this laboratory, and by Micro-Tech Laboratories, Skokie, Ill. Infrared spectra obtained on Perkin-Elmer Models 21 and 421 spectrophotometers. All infrared spectra were taken in carbon tetrachloride unless otherwise indicated. All optical rotations are at room temperature in chloroform. Chromatography was carried out on neutral activity grade I Woelm alumina unless otherwise indicated. The O.R.D. curves for the four methoxy ketones described in this paper are given in the Ph.D. thesis of S. S. Stradling, University of Rochester, 1963.

(26) D. H. R. Barton and W. J. Rosenfelder, *J. Chem. Soc.*, 2459 (1949); 1048 (1951).

(27) E. E. Royals and L. L. Harrell, Jr., *J. Am. Chem. Soc.*, **77**, 3405 (1955).

(28) The λ_{max} values listed for this and subsequent ketones were taken directly from the machine at very slow scanning times; for the other spectra, the values were taken from the paper.

B.—To a stirred solution of 2β-methoxy-3α-hydroxycholestane (0.027 g.) in acetone (3 ml.) at room temperature was added one drop of 8 *N* chromic acid–sulfuric acid solution.[14] This solution was stirred for 2 min. and was quenched with 2 ml. of 10% aqueous sodium bicarbonate. It was poured into a 3:1 water–ether mixture and, after shaking, the ether was poured through anhydrous sodium sulfate. Crystallization from ether–methanol yielded 2β-methoxy-3-ketocholestane. Recrystallization from this solvent mixture gave a 40% yield of a compound melting 75–76.5°. Further recrystallization raised the melting point to 77.5–79°. The infrared spectrum showed absorption at 1080–1083 (C–OCH_3) and 1716 cm.$^{-1}$ (C=O).

The 2β-methoxyl group appears to be very labile[7] and, consequently, contact with acidic or basic substances causes some epimerization. Attempts to separate pure 2β-methoxy-3-ketocholestane by column chromatography on neutral alumina (either activity grade I or III) or on silica gel caused partial epimerization, and though the ketones could be separated from unchanged alcohol and other oxidation products, they could not be separated from each other.

The infrared spectrum of the ketone obtained by either procedure A or procedure B indicates nearly absolute configurational purity of the methoxyl group and very little, if any, unchanged alcohol.

The rotatory dispersion curve in methanol (*c* 0.052) shows $[\alpha]_{600}$ +96, $[\alpha]_{589}$ +106, $[\alpha]_{310}$ +576, $[\alpha]_{265}$ +67.2, and $[\alpha]_{250}$ +163°.

2α-Methoxy-3-ketocholestane (F).—To a stirred solution of 2β-methoxy-3α-hydroxycholestane (D, 0.240 g.) in acetone (35 ml.) at 5° was added dropwise an 8 *N* solution of chromic acid–sulfuric acid[14] until a permanent orange-brown color was imparted to the solution. After 10 min., the solution was poured into water and the water solution was extracted with ether (60 ml.). The ether layer was washed with water and dried with anhydrous magnesium sulfate. The drying agent was filtered, and the solvent was evaporated under reduced pressure to give an oil. This oil was crystallized from an ether–methanol mixture, to yield 0.166 g. of a mixture of the two epimeric ketones (2β-methoxy- and 2α-methoxy-3-ketocholestane) along with other products.

The product mixture was dissolved in 25 ml. of a 4% solution of potassium hydroxide in methanol, was stirred for 3 hr. in a nitrogen atmosphere, and was neutralized with dilute aqueous hydrochloric acid. The resulting solution was extracted twice with ether (40-ml. portions), and the ether solution was dried. Concentration of the ether solution with subsequent dilution with methanol gave 0.142 g. of product mixture. The crude ketonic product was chromatographed on 4.2 g. of neutral alumina and 40 mg. of the pure product was eluted with 49:1 benzene–ethyl acetate. Recrystallization from ether–methanol gave 2α-methoxy-3-ketocholestane (F), m.p. 127–128°. The ketone showed infrared absorption at 1728–1729 (C=O) and 1128 cm.$^{-1}$ (C–OCH_3). In some other samples, the carbonyl peak was observed as low as 1726 cm.$^{-1}$.

Anal. Calcd. for $C_{28}H_{48}O_2$: C, 80.71; H, 11.61. Found: C, 80.89; H, 11.51.

The rotatory dispersion curve in methanol (*c* 0.108) shows $[\alpha]_{596}$ +18.5, $[\alpha]_{589}$ −18.5, $[\alpha]_{304}$ +850, $[\alpha]_{264-260}$ −426, and $[\alpha]_{240}$ −222°.

2β,3β-Epoxycholestane (C) was prepared in 80% yield by Corey's procedure,[15] and had the properties, m.p. 89–90°, $[\alpha]_D$ +50.1°. Furst and Plattner[8] report for this compound m.p. 87.5–88.5°, $[\alpha]_D$ +50.5° (*c* 1.492), while Corey[15] reports m.p. 89–90°, $[\alpha]^{25}D$ +57.4 ± 1.0° (*c* 1.53). The infrared spectrum of this compound shows characteristic absorption at 1255, 1080–1085, and 1005–1020 cm.$^{-1}$.

3α-Methoxy-2β-hydroxycholestane (G).—The same procedures were used for the preparation of G that were employed for the preparation of 2β-methoxy-3-ketocholestane (E).

Recrystallization of the crude material from ether–methanol gave a compound which exhibited a double melting point, m.p. 135–139° and m.p. 150–153°. Chromatography on neutral alumina and recrystallization from acetone gave unchanged material. The infrared spectrum showed characteristic peaks at 3623 (C–OH), 1087 (C–OCH_3), and 1016 cm.$^{-1}$ (broad, C–OH); $[\alpha]^{27}D$ +41.1 ± 5.6°.

Anal. Calcd. for $C_{28}H_{50}O_2$: C, 80.32; H, 12.04. Found: C, 80.22; H, 11.75.

3α-Methoxy-2-ketocholestane (H). A.—3α-Methoxy-2β-hydroxycholestane was oxidized with chromic acid–pyridine complex as described previously for the preparation of the isomeric ketone E. Recrystallization of the material obtained by this procedure from either ether–methanol or ether–ethanol gave silky needles in 51% yield, m.p. 125–127°.

B.—3α-Methoxy-2β-hydroxycholestane was also oxidized with chromic acid–sulfuric acid as described previously for the preparation of E. Recrystallization of the ketone obtained from ether–methanol gave silky needles in 76% yield, m.p. 125–127°.

The infrared spectra of the ketones obtained by these two procedures were identical and showed characteristic absorption at 1713–1710 (C=O), 1100, and 1079 cm.$^{-1}$.

Anal. Calcd. for $C_{28}H_{48}O_2$: C, 80.71; H, 11.61. Found: C, 80.00; H, 11.55; residue, 1.02.

The analysis, as indicated, showed that this material was slightly impure and contained a noncombustible residue. This residue may be due to some type of chromium compound from the oxidation which is not removed by recrystallization. No chromatographic separation was attempted for fear that some epimerization of the methoxyl group might occur.

The rotatory dispersion curve in methanol (*c* 3.84 mg./2 ml.) shows $[\alpha]_{589}$ +60, $[\alpha]_{327}$ +1100, and $[\alpha]_{285}$ −780°.

3β-Methoxy-2-ketocholestane (I).—The epimerization of the 3α-methoxy ketone H to the 3β-methoxy ketone I was carred out with potassium methoxide as described previously for the conversion of E to F. The compound obtained was recrystallized from ether–methanol to give pure material, m.p. 106.5–108°. The infrared absorption was at 1720–1721 (C=O), 1140, and 1120 cm.$^{-1}$ (C–OCH_3).

Anal. Calcd. for $C_{28}H_{48}O_2$: C, 80.71; H, 11.61. Found: C, 81.00; H, 11.62.

The rotatory dispersion curve in methanol (*c* 3.64 mg./2 ml.) shows $[\alpha]_{589}$ +90, $[\alpha]_{414}$ +1400, and $[\alpha]_{276}$ −980°.

"*p*-Urazine" and "Dithio-*p*-urazine"[1]

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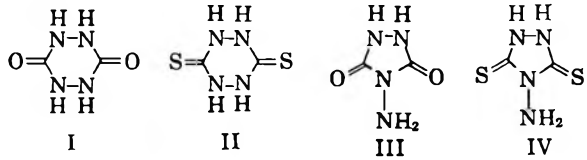
Received January 28, 1963

Two literature references purported to give *p*-urazine were re-examined and the product in each case shown to be biurea. A literature preparation claimed to be dithio-*p*-urazine was shown to be instead an isomer, N-aminodithiourazole. Certain other reaction discrepancies are also discussed.

The literature[2] records many times the synthesis of compounds presumed to have the structures of *p*-urazine (I)[3] and dithio-*p*-urazine (II). For example, Guha and De[4] have reported that the fusion of urea



I II III IV

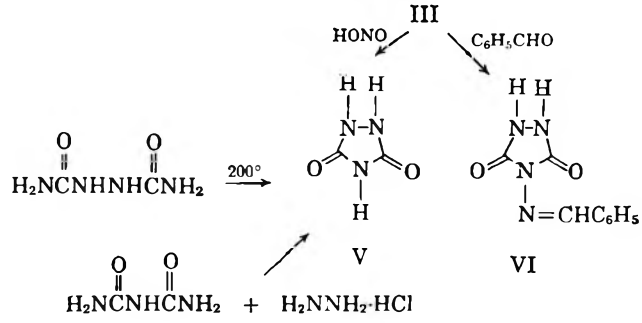
with carbohydrazide yields I. Re-examination of the product of this reaction by us has clearly established it to be not I nor its isomer III, but biurea.[5]

Chattaway[6] has reported the synthesis of I from the action of ammonium hydroxide on chlorinated urea, but the product appears to be biurea again.[7] Consequently, the *p*-urazine reported by Datta and Gupta,[8] who varied the reaction of Chattaway only by using either allylamine or benzylamine instead of ammonium hydroxide, probably also is biurea.

Elemental analysis of the purified "*p*-urazine" obtained from the Guha and De preparation showed it to possess two additional hydrogen atoms and hence suggested it was biurea. This was established by comparison of its infrared spectra with an authentic sample of biurea as well as its conversion to urazole[9] (V) (Chart A). The latter compound, for comparison, was also prepared by heating biuret and hydrazine hydrochloride together.[10]

Confirmation of the structure assigned III (synthesized by two different routes[11]) was obtained *via* demonstration of the presence of a free primary amine group by preparing the known benzylidene derivative (VI), and deamination of III to give V. The infrared spectra of urazole (V) prepared by the three different routes shown in Chart A were identical with each other.

CHART A



A brief discussion of the infrared spectrum of III is pertinent. A double band between 1600 and 1650 cm.$^{-1}$ resembles that present in the spectrum of succinimide and is assigned to carbonyl absorption. A 1620-cm.$^{-1}$ band is due to NH deformation, while the broad absorption from 2700 to 3500 cm.$^{-1}$ is similar to absorption found in dimeric lactams.

It has been found that the $Na_3[Fe(CN)_5NH_3]$ reagent[12] is of diagnostic value for certain types of compounds discussed in this paper. An intense blue color is obtained with triazoles embodying either a –NHNH– or a =NNH– group within the ring.

Turning to the structure of dithio-*p*-urazine (II) it now has been also ascertained that the reaction of 3-thiocarbohydrazide with potassium ethyl xanthate in a sealed tube[4] does not give II,[13,14] but its isomer IV. Guha and De[4] were not able to obtain a benzylidene derivative of their "dithio-*p*-urazine," but we have found that *via* the ammonium salt of these authors' compound a readily recrystallizable benzylidene derivative (VII Chart B) with m.p. 175–177° can be prepared. The benzylidene derivative reported by Arndt and Bielich[15] had low m.p. 136°. When Guha and De's compound was treated with nitrous acid, an intractable yellow powder was obtained, reacting sluggishly with NaN_3/I_2 reagent (test for thiol group) and having m.p. 105° (indefinite). Although attempts

(1) Presented before the Division of Organic Chemistry at the 139th National Meeting of the American Chemical Society, St. Louis, Mo., March, 1961.

(2) P. F. Wiley, "The 1,2,4,5-Tetrazines" in "The Chemistry of Heterocyclic Compounds," Interscience Publishers, Inc., New York, N. Y., 1956, pp. 191–196.

(3) Confusion on this topic has been compounded by the use of "*p*-urazine" to mean both I and III (*e.g.*, ref. 11b and those references included therein). While neither "urazine" nor "urazole" are systematic names, the "ine" and "ole" endings imply six-membered and five-membered rings, respectively, and are so used in this paper.

(4) P. C. Guha and S. C. De, *J. Chem. Soc.*, **125**, 1215 (1924).

(5) After this work was completed, F. Eloy and C. Moussebois, *Bull. soc. chim. Belges*, **68**, 432 (1959), published a similar observation. These authors also have confirmed that the product of five previously reported reactions is III. *Chemical Abstracts* [**54**, 7625*h* (1960)] is misleading in that the abstract implies that the sole product of *all* reactions previously claimed to give I or III gave III, rather than just *some* reactions. We thank a referee for calling this to our attention.

(6) F. D. Chattaway, *J. Chem. Soc.*, **95**, 235 (1909).

(7) Since the completion of this work, C. S. Grove, G. F. Grillot, and R. C. Chang, *J. Org. Chem.*, **26**, 1131 (1961), have obtained from Chattaway's preparation a substance which appeared to them to be biurea. These authors also claim the preparation of authentic *p*-urazine (I) after the method of T. Curtius and K. Heidenreich, *Ber.*, **27**, 2684 (1894); *J. prakt. Chem.* [2]**52**, 454 (1895). However, since Curtius and Heidenreich reported their compound gave a benzylidene derivative which melted at 253°, the compound most certainly must be III and not I.

(8) R. L. Datta and S. D. Gupta, *J. Am. Chem. Soc.*, **35**, 1183 (1913).

(9) J. Thiele and O. Stange, *Ann.*, **283**, 1 (1894).

(10) G. Pellizzari and G. Cuneo, *Gazz. chim. ital.*, **24**, I, 499 (1894).

(11) (a) A. Purgotti, *ibid.*, **27**, II, 60 (1897); (b) L. F. Audrieth and E. B. Mohr, *Inorg. Syn.*, **4**, 29 (1953).

(12) F. Feigl, "Spot Tests. II. Organic Applications," Elsevier Publishing Co., New York, N. Y., 1954, pp. 212–213.

(13) J. Sandström, *Acta Chem. Scand.*, **15**, 1295 (1961), has shown that heating 3-thiocarbohydrazide and carbon disulfide in a sealed tube [P. G. Guha and S. C. De, *J. Indian Chem. Soc.*, **1**, 141 (1925)] does not give II either.

(14) J. Sandström, *Acta Chem. Scand.*, **15**, 1575 (1961), herein reports the first authentic preparation of dithio-*p*-urazine (II).

(15) F. Arndt and F. Bielich, *Ber.*, **56**, 809 (1923).

CHART B

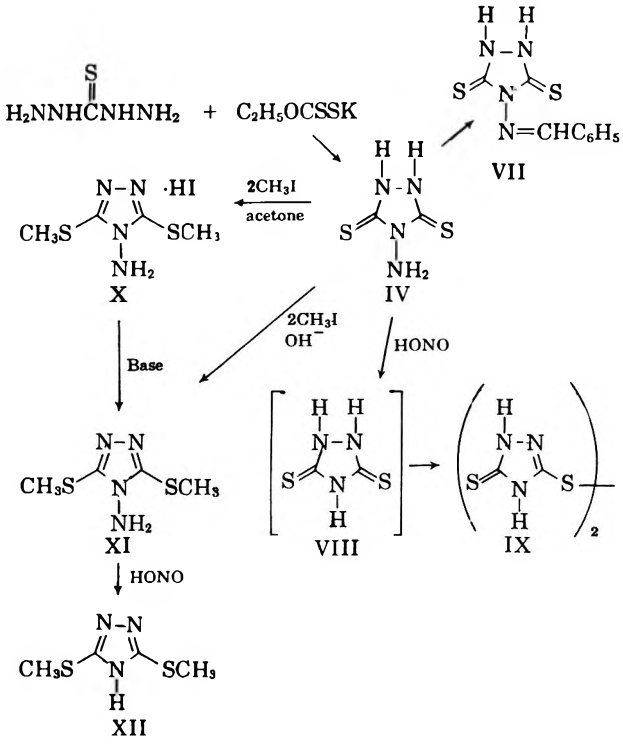


CHART C

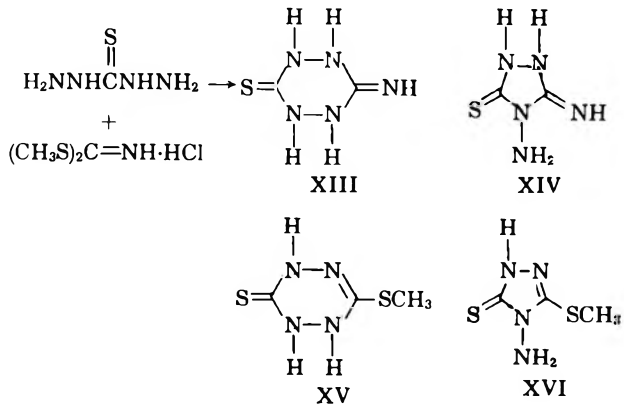
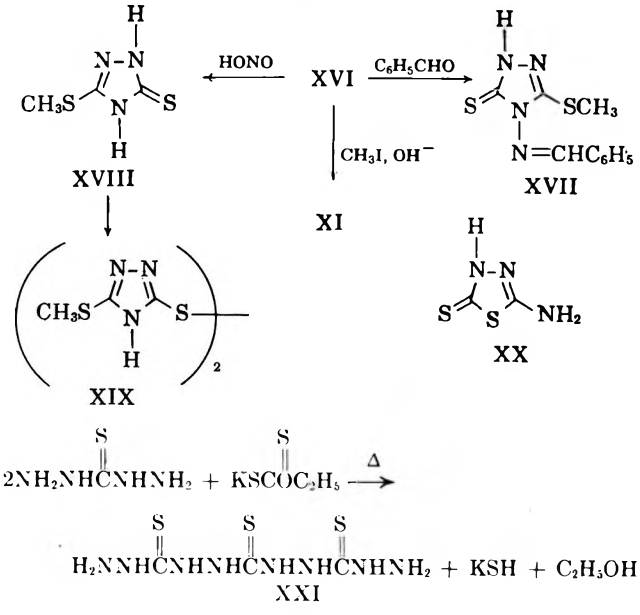


CHART D



to purify this product for proper characterization were fruitless, it is assumed that this substance is the disulfide IX resulting from oxidation of the deamination product, dithiourazole (VIII). That this is a reasonable assumption is shown by a similar transformation of XVI to XIX. Arndt and Milde[16] and Fromm[17] both reported difficulties working with compound IX.

Evidence for a free amino group was obtained by converting IV to 4-amino-3,5-bis(methylthio)-4H-1,2,4-triazole (XI), which subsequently smoothly deaminated to the known 3,5-bis(methylthio)-4H-1,2,4-triazole (XII).[16,18] Finally, the Guha and De compound proved to be identical by melting point and infrared spectrum with a sample of IV prepared by the method of Hoggarth.[19]

In the course of this work a novel synthesis of an aminodithiourazole was discovered. When equimolar quantities of 3-thiocarbohydrazide and dimethyl dithioimidocarbonate hydrochloride reacted in water, a homogeneous white solid precipitated. It gave a positive test with NaN_3/I_2 reagent, dissolved in dilute sodium hydroxide, and was precipitated upon acidification. Four products are possible depending upon the cyclization route taken (Chart C). Elemental analysis excluded XIII and XIV, while XV was eliminated by the ready formation of a benzylidene derivative XVII (Chart D). Deamination of the reaction product afforded two known compounds, 3-methylthio-Δ^2-1,2,4-triazoline-5-thione (XVIII) and its oxidation product, the disulfide (XIX). These compounds agree in melting point with those prepared by Arndt and Milde[16] in different fashion. Therefore, the correct configuration of this previously unknown compound must be XVI.

An attempt was made to prepare "monothio-p-urazine,"[4] but biurea was the product obtained.[20] Numerous efforts were made to repeat the preparation of IV by the acid cyclization of 1-thiocarbamylthiocarbohydrazide[21] using a sample of the latter compound synthesized after the method of Scott and Audrieth,[22] but the product proved to be 2-amino-Δ^2-1,3,4-thiadiazoline-5-thione (XX).[23]

During one of the preparations of the Guha and De "dithio-p-urazine," a shorter heating period was employed leading to the formation of a compound having the empirical formula, $C_3H_{10}N_8S_2$. Although no proof of structure is presented, 1,1′-(thiocarbonyl)bis(3-thiocarbohydrazide) (XXI) is offered as a possible structure. This compound has not been reported in the literature. It was thought that XXI might be an intermediate in the preparation of IV, particularly since it melts, resolidifies, and remelts at 203–205° dec. However, an attempt to effect this conversion on a 1-g. scale gave no IV.

Compounds IV, VIII, IX, XVI, XVIII, and XX showed medium to strong absorption in the infrared

(16) F. Arndt and E. Milde, *Ber.*, **54B**, 2089 (1921).
(17) E. Fromm, *Ann.*, **426**, 313 (1922).
(18) L. Loewe and M. Türgen, *Rev. faculte sci. univ. Istanbul*, **14A**, 227 (1949).
(19) E. Hoggarth, *J. Chem. Soc.*, 4817 (1952).
(20) We thank Mr. D. W. Long of this laboratory for this experiment.
(21) See Guha and De reference in ref. 13.
(22) E. S. Scott and L. F. Audrieth, *J. Org. Chem.*, **19**, 742 (1954).
(23) H. Beyer and C. F. Kröger, *Ann.*, **637**, 126 (1960), have independently obtained similar results.

between 1500–1550 cm.$^{-1}$ attributed to the C(=S)—NH vibration.[24] There was also medium to strong absorption between 1190–1330 and 940–1060 cm.$^{-1}$ associated with the —CNH(=S) symmetric and asymmetric stretching vibrations.

Experimental

Melting points were determined in a Thomas–Hoover capillary melting point apparatus or on a Fisher-Johns block and are uncorrected. Microanalyses were performed by the microanalytical laboratory of the American Cyanamid Co. or by Galbraith Laboratories, Inc.

"*p*-Urazine." After Guha and De's Procedure.—This compound was purchased from the Aldrich Chemical Co. which had prepared it after the method of Guha and De.[4] Recrystallization from hot 0.1 *M* HCl and then water gave m.p. 250–252° dec. (block). It had an infrared spectrum identical with an authentic sample of biurea.

Anal. Calcd. for $C_2H_4N_4O_2$: C, 20.69; H, 3.47; N, 48.27. Found: C, 20.33; H, 5.03; N, 48.01. Biurea $C_2H_6N_4O_2$ required C, 20.34; H, 5.12; N, 47.43.

Guha and De's "*p*-urazine" has a solubility of 1 g./*ca.* 75 ml. hot 0.1 *M* HCl and is insoluble in DMF. Compound III has a solubility of 1 g./*ca.* 22 ml. hot 0.1 *M* HCl and is soluble in DMF; it could be quantitatively titrated in a 3:7 DMF–pyridine mixture with 0.1 *N* tetrabutylammonium hydroxide to give a value of 99.7% purity. The solution turned green at the end point suggestive of a polyphenol. Lack of solubility prevented titration of "*p*-urazine."

N-Aminourazole (III). (a).—The procedure used was that of Audrieth and Mohr[11b] with the one modification of reducing the reaction time from 4 to 2.5 hr. Heating of carbohydrazide (30.2 g.) in hydrochloric acid gave 6.34 g. of product after one recrystallization, with m.p. 269–274° dec. (capillary tube), 272–275° dec. (block) (lit. m.p. 275° dec.).

Anal. Calcd. for $C_2H_4N_4O_2$: C, 20.69; H, 3.47; N, 48.27. Found: C, 21.05; H, 3.50; N, 48.10.

(b).—The method followed was that of Purgotti.[11a] The reaction of biurea (23.5 g.) with hydrazine sulfate (26.0 g.) gave as a first crop of crude product 6.40 g., m.p. 254–258° dec. (capillary tube), and a second crop, 0.50 g., m.p. 241–245° dec. (lit. m.p. 266–267°).

The benzylidene derivative (VI) was prepared in hot 80% ethanol and recrystallized from 95% ethanol to give needles, m.p. 258–259° (lit.[11b] m.p. 253°). Guha and De's "*p*-urazine," when treated under similar conditions, failed to react.

Anal. Calcd. for $C_9H_7N_4O_2$: C, 53.20; H, 3.47; N, 27.57. Found: C, 53.21; H, 3.56; N, 27.53.

Urazole (V) from N-Aminourazole.—N-Aminourazole (1.2 g., 0.01 mole) was dissolved in 1 *N* HCl (20 ml.) and this solution diluted with water (50 ml.). The solution was rapidly cooled with stirring and to the fine suspension which resulted was added dropwise a solution of sodium nitrite (0.69 g. in 20 ml. water) at a temperature of 10–15°. The solid dissolved and the solution took on a faint yellow color. After evaporation to dryness the solid residue was recrystallized from water to give 0.38 g. of product, m.p. 229–238° dec. (capillary tube) (lit.[9,10] m.p. 244°). The infrared spectrum of this preparation and the spectra of the samples prepared according to these references were superimposable on each other.

N-Aminodithiourazole (IV). (a).—The procedure followed was that of Guha and De[4]; crude yield was 49.6%. Recrystallization from water gave a lemon-colored solid, m.p. 202–204°. The product, when dissolved in ammonium carbonate solution, treated with decolorizing charcoal, boiled until no ammonia evolution occurred, cooled, and then acidified, gave a white powder, m.p. 205–207° dec. (capillary tube).

Anal. Calcd. for $C_2H_4N_4S_2$: C, 16.21; H, 2.72; N, 37.80; S, 43.26. Found: C, 16.38; H, 2.96; N, 37.92; S, 43.18.

(24) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, p. 350, assigns the 1470–1500-cm.$^{-1}$ region to this grouping.

The benzylidene derivative (VII) was prepared by dissolving IV (0.74 g., 5 mmoles) in 10 ml. of ammonium hydroxide and boiling to discharge excess ammonia. A solution of benzaldehyde (1.06 g., 10 mmoles) in ethanol (5 ml.) was added and the mixture refluxed for 2 hr., whereupon the yellow solution was poured into water. The unchanged aldehyde was removed by ether extraction and the aqueous phase acidified to give a white gum. The gum was taken up in ether, water washed, and dried; ether was removed. The resulting gum (404 mg., 33.9%) hardened upon standing, and, after two recrystallizations from benzene followed by sublimation at 110° (0.3 mm.), gave an off-white solid, m.p. 175–177°.

Anal. Calcd. for $C_9H_8N_4S_2$: C, 45.74; H, 3.41; N, 23.71; S, 27.13. Found: C, 45.84; H, 3.38; N, 23.63; S, 26.97.

(b).—Hoggarth's procedure[19] was adhered to as closely as possible using the same scale preparation. After the first acidification stage, 9.95 g. (m.p. 209–214° dec.) of a side product, 3,4-diamino-Δ^2-1,2,4-triazoline-5-thione, precipitated, and by allowing the filtrate to stand overnight at room temperature an additional 4.50 g. (m.p. 205–209° dec.) were obtained. Hoggarth obtained a total of 6.6 g. of the diaminotriazolinethione at this point. The filtrate from the above compound after further acidification gave IV (5.0 g., m.p. 197–200° dec.), contaminated with a trace of the diaminotriazolinethione as determined by its infrared spectrum. Purification gave a white solid (3.75 g.) with m.p. 199–205° dec. (block), 204–206° dec. (capillary). The infrared spectrum was identical in all respects with that of the sample prepared in part a.

Disulfide of Dithiourazole (IX).—IV (741 mg., 5.0 mmoles) was stirred into 12 ml. of 1 *N* HCl diluted with 50 ml. water at 75°. The suspension was rapidly cooled to 5° with stirring and a solution of sodium nitrite (355 mg., 5.0 mmoles in 20 ml. of water) added in small portions. The resulting solid was taken up in 95% ethanol and allowed to separate slowly at room temperature. A yellow powder was deposited, m.p. 105° (indefinite). The infrared spectrum was different from that of an authentic sample of dithiourazole (m.p. 219–220°).

4-Amino-3,5-bis(methylthio)-4H-1,2,4-triazole Hydriodide (X).—To a solution of IV (1.48 g., 0.01 mole) in 25 ml. of refluxing anhydrous acetone was added all at once excess methyl iodide (5.68 g., 0.04 mole). Warming was continued for 15 min., the solvent stripped, and the dark residue triturated with anhydrous ether to give a yellow solid, 1.25 g. (41.0%).

Two recrystallizations from absolute ethanol containing enough water to effect solution (addition of ether to the cooled solution aided crystallization) gave the analytical sample as white needles, m.p. 175–176.5°. The product darkened upon short standing (no infrared spectral changes), but the coloration was readily removed by an ether wash.

Anal. Calcd. for $C_4H_9IN_4S_2$: C, 15.79; H, 2.98; I, 41.72; N, 18.42; S, 21.08. Found: C, 16.16; H, 2.81; I, 41.50; N, 18.60; S, 20.69.

4-Amino-3,5-bis(methylthio)-4H-1,2,4-triazole (XI).—To a filtered solution of IV (10.0 g., 68 mmoles) in 136 ml. of 2 *N* sodium hydroxide (0.27 mole) was added 125 ml. of 95% ethanol, followed by methyl iodide (38.6 g., 0.27 mole). The mixture was permitted to stand at room temperature for several hours and evaporated to dryness. The residue was not very soluble in ether or in hot benzene, but could be dissolved in chloroform. After concentration of the chloroform extracts, filtration of the sodium iodide, and ice cooling, tan needles separated which partially turned purple upon air exposure. One recrystallization from ethyl acetate gave a yellow solid which again partially turned purple. Sublimation at 90° (0.5 mm.) removed the color bodies as volatiles leaving the unsublimed material as white needles, 8.46 g. (71.2%), m.p. 146–148°, identical by melting point and infrared spectrum with the free base prepared from the hydriodide (X).

Anal. Calcd. for $C_4H_8N_4S_2$: C, 27.26; H, 4.58; N, 31.79; S, 36.38. Found: C, 27.28; H, 4.98; N, 31.62; S, 36.12.

3,5-Bis(methylthio)-4H-1,2,4-triazole (XII).—To a filtered solution of XI (4.41 g., 0.25 mmole) in 100 ml. of 0.5 *N* hydrochloric acid was added with stirring at 0–5° a solution of sodium nitrite (1.73 g., 0.25 mmole) in 10 ml. of water. The first few drops turned the colorless solution orange-brown, then, as the addition proceeded, gray, and finally blue. After the addition was completed (30 min.), the mixture was allowed to warm to room temperature (1 hr.), and a light blue solid (1.34 g., m.p. 90–91° dec., turned white upon standing) filtered off. The filtrate

upon evaporation left mostly as a residue the triazole hydrochloride, m.p. 148° (acetone). The hydrochloride salt was converted to the triazole by solution in a minimum amount of water and treatment with 6 *N* sodium hydroxide to give product with m.p. 93–94° (lit.[16,18] m.p. 91°, 93–94°). Total yield of product was 2.75 g. (68.3%). An analytical sample prepared by slow evaporation of an aqueous solution has m.p. 92.5–93°.

Anal. Calcd. for $C_4H_7N_3S_2$: C, 29.80; H, 4.38; N, 26.07; S, 39.77. Found: C, 29.97; H, 4.58; N, 26.22; S, 39.57.

Dimethyl Dithioimidocarbonate Hydrochloride.[25]—Addition of hydrogen chloride to about equal amounts of methyl mercaptan and methyl isothiocyanate in chloroform at 0° afforded the crystalline product (87%), m.p. 158–159° dec.

4-Amino-3-(methylthio)-Δ^2-1,2,4-triazoline-5-thione (XVI).—To a solution of 3-thiocarbohydrazide (5.31 g., 0.05 mole) in 75 ml. of water was added in small portions, over a 10-min. period, dimethyl dithioimidocarbonate hydrochloride with stirring. This reagent slowly dissolved with a steady evolution of methyl mercaptan. After 25 min., a solid began to precipitate. The thick paste which was present after 2 hr. was filtered to give 4.31 g., m.p. 174–208° (capillary). The filtrate was evaporated to dryness; the residue and product combined and recrystallized from a minimum amount of water to give 4.91 g., m.p. 186–190° (60.5%). Recrystallization again from water gave white fluffy needles, m.p. 197–197.5°.

Anal. Calcd. for $C_3H_6N_4S_2$: C, 22.21; H, 3.73; N, 34.54; S, 39.53. Found: C, 22.20; H, 4.34; N, 34.33; S, 39.43.

The benzylidene derivative (XVII) prepared at room temperature in ethanol containing a trace amount of hydrochloric acid had m.p. 205–207°.

Anal. Calcd. for $C_{10}H_{10}N_4S_2$: C, 47.99; H, 4.03; N, 22.39; S, 25.62. Found: C, 48.35; H, 4.23; N, 22.27; S, 25.58.

3-Methylthio-Δ^2-1,2,4-triazoline-5-thione (XVIII) and 3,3′-Dithiobis[5-(methylthio)-4H-1,2,4-triazole] (XIX).—XVI (4.05 g., 0.25 mmole) was dissolved in 250 ml. of water containing 60 ml. of 1 *N* hydrochloric acid and warmed to 75° to effect solution. To the solution, which was cooled rapidly to 5–10° with stirring (slush formed), a solution of sodium nitrite (1.72 g., 0.25 mmole) in 50 ml. of water was added dropwise with stirring. After the addition was complete, the reaction mixture was stirred at 5–10° for 15 min. and then allowed to warm to room temperature. A solid was removed and the filtrate was evaporated to dryness. The residual solid was extracted with boiling 95% ethanol several times to obtain additional product. The original precipitate was then dissolved in these combined extracts, the solution filtered, and three crops of crystals collected. Fractional crystallization of these crops from absolute ethanol and then acetone permitted the separation of three compounds. These were the triazolinethione, 0.85 g. (23.2%, least soluble absolute ethanol and acetone), the disulfide, 1.13 g. (30.9%), and unchanged starting material (most soluble). A final recrystallization of the triazolinethione from water gave white plates, m.p. 248–250° (lit.[16] m.p. 254°).

Anal. Calcd. for $C_3H_5N_3S_2$: C, 24.48; H, 3.42; N, 28.55; S, 43.56. Found: C, 24.47; H, 3.23; N, 28.45; S, 43.45.

A final recrystallization of the disulfide from absolute ethanol gave white prisms, m.p. 210–211° (lit.[16] m.p. 203°).

Anal. Calcd. for $C_6H_8N_6S_2$: C, 24.64; H, 2.76; N, 28.74; S, 43.85. Found: C, 24.88; H, 3.09; N, 28.75; S, 43.98.

Attempted Preparation of IV from 1-Thiocarbamylthiocarbohydrazide.—The hydrazide[22] (11.3 g.) in 50 ml. of concentrated hydrochloric acid was heated for 40 min. at 90°. This solution after evaporation to dryness left a solid residue which was recrystallized twice from water to give tan needles, 1.1 g., m.p. 228–231° dec. Sublimation gave raised m.p. 230–232° dec., no melting point depression upon admixture with authentic 2-amino-Δ^2-1,3,4-thiadiazoline-5-thione.[26] The infrared spectra of the two samples were identical.

Anal. Calcd. for $C_2H_3N_3S_2$: C, 18.04; H, 2.27; N, 31.56; S, 48.16. Found: C, 18.39; H, 2.24; N, 30.92; S, 48.38.

1,1′-(Thiocarbonyl)bis(3-thiocarbohydrazide) (XXI).—3-Thiocarbohydrazide (50.0 g., 0.47 mole) and potassium ethyl xanthate (75.5 g., 0.47 mole) were heated in 500 ml. of 95% ethanol in a rocking autoclave at 100° for 2 hr. (instead of 5 hr.). The contents were washed out of the autoclave with water (300–500 ml.) and filtered from some gray solid. The latter was extracted with boiling water, and the extracts were combined with the original solution. The yellow solid (22.4 g.) which separated upon acidification of the reaction mixture was recrystallized from 500 ml. of hot water to give 18.0 g. (31.4%) of tan needles, m.p. 163–166°, with resolidification and remelting at 202–204° dec. Recrystallization from water three times gave a pure sample, m.p. 170–172° (203–205°).

Anal. Calcd. for $C_3H_{10}N_8S_4$: C, 14.17; H, 3.96; N, 44.07; S, 37.82. Found: C, 14.29; H, 4.18; N, 43.95; S, 37.77.

Acknowledgment.—The author is grateful to the following for their contributions: N. B. Colthup for interpreting the infrared spectra, Dr. C. A. Streuli for the nonaqueous titration data, and Dr. R. J. Magee, Dr. G. Berkelhammer, and Dr. R. W. Addor for helpful discussions.

(25) We thank Dr. R. W. Addor of this laboratory for this preparation.

(26) L. L. Bambas, "Five-Membered Heterocyclic Compounds with Nitrogen and Sulfur or Nitrogen, Sulfur, and Oxygen," Interscience Publishers, Inc., New York, N. Y., 1952, pp. 149–153.

Reaction of Eugenol with Synthesis Gas. Synthesis of 5,6,7,8-Tetrahydro-3-methoxy-2-naphthol

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The reaction of eugenol with synthesis gas, in the presence of dicobalt octacarbonyl, leads to a ring closure with the formation of 5,6,7,8-tetrahydro-3-methoxy-2-naphthol. The isolation of 5,6-dihydro-3-methoxy-2-naphthol in short time experiments suggests a mechanism of ring closure with the latter as precursor. For testing purpose, 4-(3-methoxy-4-hydroxyphenyl)-1-butanol and 1(2H)-3,4-dihydro-6-methoxy-7-hydroxynaphthalenone were synthesized and treated under the same conditions.

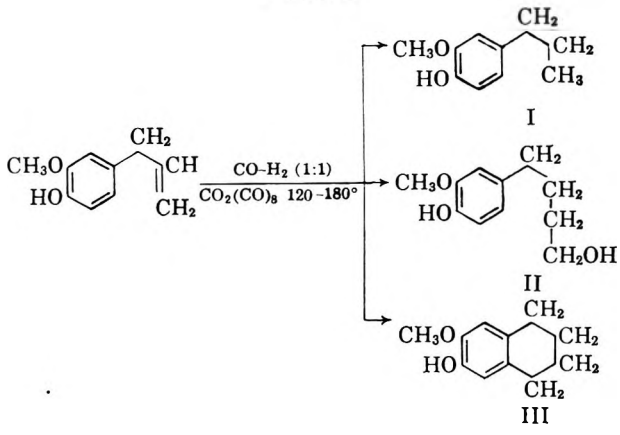
In previous work from this laboratory,[1] it was shown that the reaction of wood or lignin with pressurized synthesis gas, in the presence of dicobalt octacarbonyl, provides good yields of phenols through an homogeneous phase catalyzed hydrogenation and/or hydroformylation of these materials.

In order to acquire some insight in the reaction occurring with wood, we have now treated eugenol and isoeugenol, as lignin model compounds, under "hydroformylation conditions."[2] Experiments with eugenol were carried out at 120–180° under a pressure of

(1) F. Gaslini (to Vita Mayer and Co.), U. S. Patent 2,947,739 (Aug. 2, 1960).

(2) The term "hydroformylation conditions" has the same meaning as in I. Wender, H. W. Sternberg, and M. Orchin, *J. Am. Chem. Soc.*, **75**, 3041 (1953).

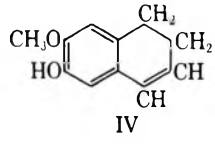
CHART A



200–400 atm. of 1:1 CO–H_2. When the reaction reached the point where gas consumption ceased (2.6–2.8 moles of gas/mole of eugenol), the products isolated were those shown in Chart A.

The yields were about 40% for 3-methoxy-4-hydroxy-1-*n*-propylbenzene (I), 30–40% for 5,6,7,8-tetrahydro-3-methoxy-2-naphthol (III), and 5% for 4-(3-methoxy-4-hydroxyphenyl)-1-butanol (II).

When the reaction was interrupted in its early stages (1.3–1.7 moles of gas/mole of eugenol), we obtained, in addition to the above-mentioned compounds, the hitherto unknown dihydronaphthol, IV, and a compound (V) which on the basis of its molecular weight and analysis could be formulated as $C_{20}H_{16}(OCH_3)_2(OH)_2$, a dimer of IV. The structure of V was not investigated further. In addition to the elemental and functional groups analysis, the identity of IV was established as follows: hydrogenation in alkaline solution with Raney alloy gave a compound melting at



81–81.5°, the infrared spectrum of which was identical with the spectrum of III. The infrared spectrum of IV reasonably indicated the existence of a double bond conjugated with the aromatic ring. In fact, we noted two bands at 3040 and 3004; a weak band at 1625 associated with a medium strong at 1585, indicating conjugation of the aromatic ring; reversed ratio of intensity between the bands at 1464 and 1445, the latter (cyclic CH_2 deformation) being stronger in III and the former in IV; and finally a medium intensity band at 750 cm.$^{-1}$, lacking in III, indicating *cis* CH=CH structure.

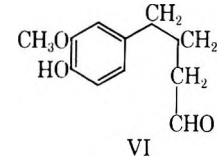
With isoeugenol, the reaction principally was straightforward hydrogenation; after 1 hr. at 140°, more than 80% of I was obtained; the remaining high boiling materials contained both phenolic and hydroxyl groups.

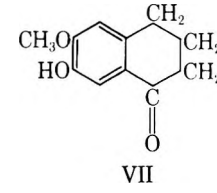
Discussion

The high yields of I obtained from isoeugenol are in agreement with the well-known tendency of conjugated double bonds to undergo hydrogenation rather than hydroformylation.[3] In this connection we observed that 60% of eugenol was converted into isoeugenol when treated with dicobalt octacarbonyl and 150 atm. of pure CO at 180° for 1 hr.

The most interesting results seem to be the absence of carbonyl compounds before decobalting, the interrupted, low temperature experiments with eugenol, and the formation in high yields of compounds III and IV. The kind of ring closure leading to III and IV is rather unusual in the field of cobalt carbonyl-catalyzed reactions, since all previously reported examples involve the presence of an N or O hetero atom at the insertion point of the C unit.[4]

Since experiments with the butanol II and the dimer V, under the same conditions, gave no III or IV, the former compounds may be excluded as their precursors. Among other possible precursors, the aldehyde VI and the naphthalenone VII require consideration. Unfortunately, our attempts to prepare VI failed. VII





was prepared through an eight-step synthesis and was treated under the same conditions as eugenol. A 50% yield of III was obtained, the remaining ketone being recovered unchanged. Thus it appears doubtful that VII could be an actual precursor, since carbonyl compounds were never found in the reaction products of our experiments. Incidentally, this criterion could perhaps hold also for the aldehyde VI, the complete disappearance of which would seem highly improbable in short time, low temperature reactions.[5]

On the other hand, the presence of the unsaturated compound IV in the early stage of the reaction strongly suggests that this ring closure occurs with the direct formation of IV, which actually gave III when hydrogenated either in "hydroformylation conditions" or in alkaline solution with Raney alloy. Following the up-to-date interpretation of the hydroformylation and related reactions,[4] we may think that cyclization occurs through some intermediates (Chart B).

Experimental

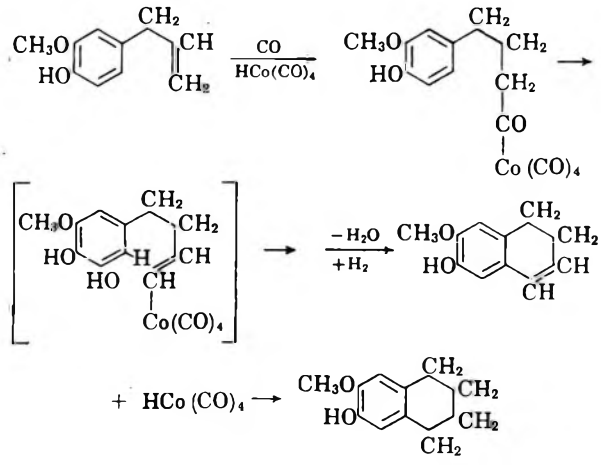
Reaction of Eugenol with Synthesis Gas. A. To Complete Absorption of Gas.—A 150-g. sample of freshly distilled eugenol, 50 ml. of benzene, and 3 g. of dicobalt octacarbonyl were charged to a stainless steel oscillating autoclave of 500-ml. capacity in which synthesis gas (1:1) then was compressed to 300 atm. The autoclave was heated at 180° and maintained at this temperature until gas absorption was complete (1 hr.). The reaction product was discharged and decobalted by heating for 2 hr. on a steam bath, followed by extraction with diluted hydrochloric acid.

(3) I. Wender, H. W. Sternberg, and M. Orchin, "Catalysis," P. H. Emmett, Ed., Vol. V, Reinhold Publishing Corp., New York, N. Y., 1957, p. 86.

(4) H. W. Sternberg, R. Markby, and I. Wender, *Chim. Ind.* (Milan), **42**, 41 (1960).

(5) A referee asked us what is presumed to be the precursor of the butanol II. We do not at all exclude that aldehyde VI may be transitionally formed and hydrogenated in the high temperature experiments, giving butanol II. Aldehyde VI, in this enolic form, may be a possible intermediate for the ring closure to give IV; but, as carbonyl compounds are absent even before the decobalting experiments at low temperature, the point as to whether the aldehyde is formed, subsequently enolized, and finally cyclized becomes more formal than substantial.

CHART B



After evaporation of the solvent, 153 g. of a viscous oil was obtained, which was fractionated by distillation.

The first fraction (61.6 g.) boiled at 125–126° (13 mm.). Its benzoate had a melting point of 72.6–73° and did not depress the melting point of the benzoyl derivative of an authentic sample of 3-methoxy-4-hydroxy-1-propylbenzene, obtained by catalytic hydrogenation of eugenol.[6]

Anal. Calcd. for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.55; H, 7.03.

The second fraction distilled at 158–160° (13 mm.) giving 60 g. of a white crystalline compound which, after crystallization from *n*-heptane, was identified as 5,6,7,8-tetrahydro-3-methoxy-2-naphthol (III), m.p. 81.5–82°, lit.[7] m.p. 81–82°.

Anal. Calcd. for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92; OCH_3, 17.39. Found: C, 74.12; H, 7.92; OCH_3, 17.47.

III, methylated with dimethyl sulfate, yielded 5,6,7,8-tetrahydro-3,4-dimethoxynaphthalene, m.p. 56.4–56.8°. It did not depress the melting point of an authentic sample prepared by Clemmensen reduction of 1(2H)-3,4-dihydro-6,7-dimethoxynaphthalenone.[8]

New derivatives of III are the benzoate, m.p. 109.5–110.3° (from ethanol), and 1-naphthylurethane, m.p. 145–145.5° (from ligroin).

Anal. Calcd. for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43; OCH_3, 10.98. Found: C, 75.97; H, 6.41; OCH_3, 11.03.

Anal. Calcd. for $C_{22}H_{21}O_3N$: C, 76.06; H, 6.09; N, 4.03. Found: C, 76.15; H, 6.30; N, 4.10.

The third fraction, distilling at 150–160° (2.5 mm.), yielded 18 g. of a viscous liquid containing about 50% of 4-(3-methoxy-4-hydroxyphenyl)-1-butanol, which was identified through its bis-*p*-nitrobenzoate, melting at 124–126°; the melting point was not depressed on admixture with a sample obtained by synthesis.

B. **Low Temperature, Controlled Absorption of Gas.**—An 80-g. sample of eugenol, 100 ml. of benzene, 1.5 g. of dicobalt octacarbonyl, and 200 atm. of synthesis gas were charged in the autoclave and heated at 120°. When 1.7 moles of gas/mole of eugenol was absorbed, the reaction was stopped by cooling the autoclave. The reaction product was decobalted as previously described and distilled under a pressure of 2.5 mm., giving 22 g. of a fraction boiling at 145–150°, solid at room temperature. After repeated crystallizations from aqueous ethanol, colorless plates were obtained melting at 108–109°, which were identified as 5,6-dihydro-3-methoxy-2-naphthol (IV).

Anal. Calcd. for $C_{11}H_{12}O_2$: C, 74.97; H, 6.86; OCH_3, 17.58; OH, 9.65. Found: C, 75.04; H, 6.92; OCH_3, 17.55; OH, 9.63.

The hydroxyl group was determined by acetylation with acetic anhydride.

When the same reaction was allowed to proceed until gas absorption was 1.3 moles/mole of eugenol, a nondistillable brownish residue was obtained which was suspended in diethyl ether and filtered. A white compound (V), slightly soluble in ether, insoluble in *n*-heptane, was isolated which, after crystallization from benzene, melted at 197–198°. The yield was 10–15% of the reaction product.

Anal. Calcd. for $C_{20}H_{16}(OCH_3)_2(OH)_2$: C, 74.97; H, 6.86; O, 18.16; OCH_3, 17.67; OH, 9.64. Found: C, 74.87; H, 6.92; O, 18.16; OCH_3, 17.44; OH, 9.72.

The hydroxyl group was determined by acetylation with acetic anhydride. The molecular weight, determined by cryoscopy in benzene, was 300 (calcd. for $C_{22}H_{24}O_4$: 352.4).

Derivatives of V were benzoate, m.p. 223–224° (from ethanol); methyl ether, m.p. 131.5–132° (from aqueous ethanol); and acetate, m.p. 159.5–160° (from aqueous ethanol).

Hydrogenation of IV with Raney Alloy.—A 1-g. sample of Raney alloy was added in small portions to 0.65 g. of IV, dissolved in 40 ml. of 5% aqueous sodium hydroxide. The reaction product was filtered, and the filtrate was poured into dilute hydrochloric acid. The precipitate was filtered and crystallized from aqueous ethanol to give 0.51 g. of pure product, melting at 81–82°. It did not depress the melting point of a sample of III.

Hydrogenation of IV with Synthesis Gas.—A 5.75-g. sample of IV in 50 ml. of benzene was treated with synthesis gas at 180° under the same conditions as in A. After decobalting and evaporation of the solvent, a residue was obtained which was crystallized from aqueous ethanol, after boiling with charcoal, giving 1.51 g. melting at 82–83°. After recrystallization from *n*-heptane, it had m.p. 81–81.7° and did not depress the melting point of III.

3-(3-Methoxy-4-hydroxyphenyl)propanoic Acid (VIII).—A solution of 41 g. of ferulic acid in 1600 ml. of 8% sodium hydroxide was treated with stirring with 40 g. of Raney alloy in 1-g. amounts over 30 min. After stirring an additional 30 min., the mixture was filtered and the filtrate was poured with stirring into a mixture of ice and excess hydrochloric acid. The solution was extracted with ether and the ether was dried and distilled, giving 40 g. of a residue which, after crystallization from water, gave pure VIII, melting at 91–91.5°, lit.[9] m.p. 90–91°.

4-(3-Methoxy-4-hydroxyphenyl)butanoic Acid (X).—A 20-g. sample of VIII was dissolved in sodium hydroxide and acetylated with acetic anhydride. The product was crystallized from water giving 17.5 g. of crystals, melting at 97.5–98.5°, lit. m.p.[9] 93–94°.

Anal. Calcd. for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92; acid equiv. wt., 238.2. Found: C, 60.60; H, 5.82; acid equiv. wt., 238.2.

A 40-g. sample of the acetate was refluxed with 240 ml. of redistilled thionyl chloride during 30 min. The excess thionyl chloride was distilled then at the water pump at room temperature. To the residue, 50 ml. of dry benzene was added and then evaporated *in vacuo*, and this procedure was repeated. The crystalline residue (41 g.) was dissolved in 50 ml. of absolute ether and added dropwise to a stirred solution of diazomethane at 0–5°, prepared from 110 g. of nitrosomethylurea in 1200 ml. of ether. After one night at room temperature, the solution was filtered and the ether was removed under reduced pressure, giving 46 g. of crude diazo ketone. The crystalline diazo ketone was dissolved in 650 ml. of anhydrous ethanol and, to the stirred solution, at 70°, a slurry of 3 g. of silver oxide in 50 ml. of ethanol was added in small amounts over 3 hr. The mixture was refluxed several hours; when no more unchanged diazo ketone could be detected, the mixture was filtered and evaporated. Distillation yielded 26 g. of ethyl 4-(3-methoxy-4-acetoxyphenyl) butanoate (IX), boiling at 168–170° (2 mm.). By saponification with 10% aqueous potassium hydroxide, followed by crystallization from water, 20 g. of pure X was obtained, melting at 120.5–121.5°, lit.[10] m.p. 114–116°.

Anal. Calcd. for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71. Found: C, 63.04; H, 6.67.

4-(3-Methoxy-4-hydroxyphenyl)-1-butanol (II).—A solution of 22 g. of IX was added dropwise, over a period of 3 hr. to a suspension of 10 g. of lithium aluminum hydride in 1200 ml. of anhydrous ether. Upon completion of the addition, the mixture was stirred an additional hour, treated with 300 ml. of water, and acidified with 2 *N* sulfuric acid. The ether layer was removed and the aqueous layer was extracted with ether. The combined ether solutions were dried and evaporated. The residue was distilled. A crystalline fraction (15 g.), boiling at 163–170° (2 mm.), was obtained. After crystallization from carbon tetrachloride, pure II was obtained, melting at 58–58.7°.

Anal. Calcd. for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22; OH, 17.33. Found: C, 67.36; H, 8.10; OH, 17.25.

(6) D. E. Levin and A. Lovy, *J. Am. Chem. Soc.*, **55**, 1955 (1933).

(7) T. Momose and S. Goya, *Chem. Pharm. Bull.* (Tokyo), **7**, 849 (1959).

(8) T. Momose, H. Hoya, Y. Ohkura, and M. Iwasaki, *ibid.*, **2**, 119 (1954).

(9) I. A. Pearl, *J. Org. Chem.*, **24**, 736 (1959).

(10) H. L. Holmes and L. W. Trevoy, *Can. J. Research*, **22B**, 109 (1944).

1(2H)-3,4-Dihydro-6-methoxy-7-hydroxynaphthalenone (VII).—A 20-g. sample of X dissolved in aqueous alkali was acetylated with acetic anhydride, giving 19 g. of the acetyl derivative (XI) which, after crystallization from water, melted at 65.5–66.5°.

Anal. Calcd. for $C_{13}H_{16}O_5$: C, 61.89; H, 6.39. Found: C, 61.72; H, 6.30.

To a cooled stirred solution of 20 g. of XI in 130 ml. of dry benzene at 0°, was added 20 g. of phosphorus pentachloride in portions. The mixture was warmed to room temperature to complete the reaction and then cooled until benzene began to solidify. At this point, a solution of 20 g. of anhydrous stannic chloride in 20 ml. of dry benzene was added with stirring. After standing for 3 hr. at 0°, the mixture was hydrolyzed by the addition of ice followed by 60 ml. of concentrated hydrochloric acid. A 120-ml. portion of ether was added and the mixture was shaken until complete solution occurred. The organic layer was then washed with 5% hydrochloric acid, 5% sodium hydroxide, and water. After evaporation of the ether, 11 g. of residue, melting at 118–120°, was obtained. This residue was saponified with 10% potassium hydroxide, whereupon 8 g. of VII, melting at 150.2–150.9° after crystallization from water, was obtained.

Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29; OCH_3, 16.14. Found: C, 68.46; H, 6.16; OCH_3, 16.0.

By methylation with dimethyl sulfate, 1(2H)-3,4-dihydro-6,7-dimethoxynaphthalenone was obtained, m.p. 98–98.5° (from *n*-heptane), lit.[11] m.p. 99°.

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84; OCH_3, 30.06. Found: C, 69.61; H, 6.54; OCH_3, 30.01.

The semicarbazone had m.p. 226.5–227° (from ethanol).

Anal. Calcd. for $C_{13}H_{17}N_3O_3$: N, 15.96. Found: N, 15.81.

(11) K. N. Campbell, A. Scharge, and B. K. Campbell, *J. Org. Chem.*, **15**, 1135 (1950).

The Synthesis of 7-Alkylamino-1-naphthols

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1,7-Dihydroxynaphthalene, when heated with aqueous solutions of methylamine, ethylamine, isopropylamine, and dimethylamine, gave good yields of the corresponding 7-alkylamino-1-naphthols uncontaminated with the other position isomer. The selectivity of the reaction is explained in terms of steric effects.

In the course of searching for new couplers for the preparation of azo dyes, it became desirable to develop a synthesis of 7-alkylamino-1-naphthols. The method described for the primary amine, alkali fusion of 7-aminonaphthalene-1-sulfonic acid,[1a,b] was not suitable for the substituted derivatives. Although the precursors, the 7-alkylaminonaphthalene-1-sulfonic acids, were easily prepared by the Bucherer reaction with 2-naphthol-8-sulfonic acid, alkali fusion of the N-methyl compound was accompanied by at least 50% demethylation and gave a mixture of 7-methylamino-1-naphthol (**8a**) and 7-amino-1-naphthol, while fusion of the N-isopropyl compound resulted in extensive degradation of the molecule. The Bucherer reaction using various primary aliphatic amines with 1,7-dihydroxynaphthalene, under a wide variety of conditions, gave only mixtures of both possible monosubstitution products, 1,7-diamine, and recovered starting material.

An early report[2] that 1,7-dihydroxy-2-naphthoic acid gave 7-amino-1-naphthol when heated at 180° with concentrated ammonia solution led us to investigate the reaction of aliphatic amines with 1,7-dihydroxynaphthalene in the absence of the bisulfite usually used in the Bucherer reaction.

Uncatalyzed reactions of amines with naphthols have been previously reported.[3] For example, N-methyl-β-naphthylamine was obtained in 80% yield on heating β-naphthol with aqueous methylamine at 200–220° for 7 hr.[4] Depending on the reaction temperature, either 3-amino-2-naphthol or 2,3-naphthalenediamine could be obtained from 2,3-dihydroxynaphthalene,[5] while the corresponding diamines were formed when 1,5-,[6] 1,8-,[6] and 2,7-dihydroxynaphthalenes[7] were heated to 250–300° with aqueous ammonia. Similar conditions were used to prepare α- and β-naphthylamine from the corresponding naphthols.[8] However, there is but a single example reported in which a simple dihydroxynaphthalene, containing both an α- and a β-hydroxy group, has been treated under these conditions. When 1,3-dihydroxynaphthalene was heated with ammonia at 130–140°, 3-amino-1-naphthol (preferential replacement of the β-hydroxy group) and some diamine were obtained.[9] Treatment with aniline gave 3-anilino-1-naphthol.

In the present work, when aqueous methylamine was heated with 1,7-dihydroxynaphthalene, a single aminonaphthol was produced. Reasonable yields of 7-methylamino-1-napthol (**8a**) were obtained over a considerable range of temperature (130–180°) and molar ratios of amine to dihydroxynaphthalene. In addition, it was only when forcing conditions were used (180°, four equivalents of methylamine) that any significant amount of 1,7-diamine was formed. There was no detectable amount of the other isomer, 8-methylamino-2-naphthol, present. Ethylamine, isopropylamine, and dimethylamine also reacted, at increasingly higher temperatures, to give the corresponding 7-amino-1-naphthols uncontaminated by the other possible position isomers and with no significant formation of diamines. In a single experiment, using aqueous ammonia at 130°, only starting material was recovered. Similarly, none of the desired product was obtained when *t*-butylamine was used.

(1) (a) A. C. Mueller and C. S. Hamilton, *J. Am. Chem. Soc.*, **66**, 860 (1944); (b) V. V. Perekalin and N. M. Slabachevskaya, *J. Gen. Chem. USSR*, **21**, 985 (1951).

(2) P. Friedländer and S. Zinberg, *Ber.*, **29**, 37 (1896).

(3) For a comprehensive discussion of the preparation of amines by substitution of the hydroxy group, see H. Glaser, "Methoden der Organischen Chemie," Vol. XI/1, E. Muller, Ed., Georg Thieme Verlag, Stuttgart, 1957, p. 160.

(4) G. T. Morgan and F. P. Evans, *J. Chem. Soc.*, 1140 (1919).

(5) P. Friedlander and S. Zakrzewski, *Ber.*, **27**, 761 (1894).

(6) H. Erdmann, *Ann.*, **247**, 306 (1888).

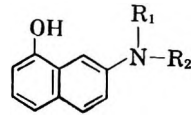
(7) F. Kaufler and V. Karrer, *Ber.*, **40**, 3262 (1907).

(8) V. V. Kozlov and I. K. Veselovskaya, *Zh. Obshch. Khim.*, **31**, 2662 (1961); *Chem. Abstr.*, **56**, 11508 (1962).

(9) P. Friedlander and H. Rudt, *Ber.*, **29**, 1609 (1896).

TABLE I

PROPERTIES OF AMINONAPHTHOLS



8

Compound	R_1	R_2	M.p., °C., dec.	λ_{max}, mμ (EtOH)	$\epsilon_{max} \times 10^{-3}$	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
8a	H	CH_3	132–133[a]	250, 291, 301, 350	37.0, 9.0, 8.0, 2.04	76.27	6.40	8.09	76.37	6.30	7.79
8b	H	CH_2CH_3	89–90[b]	251, 292, 303, 347	33.2, 7.8, 6.9, 1.8	76.97	7.00	7.48	77.06	7.14	7.72
8c	H	$CH(CH_3)_2$	88–89[b]	253, 293, 304, 349	46.0, 11.6, 10.6, 2.68	77.58	7.51	6.96	77.61	7.48	7.22
8d	CH_3	CH_3	106.5–108.0[c]	256, 296, 306, 350	32.4, 9.4, 8.6, 1.92	76.97	7.00	7.48	76.89	6.86	7.39

Recrystallization solvents: [a] Carbon tetrachloride. [b] Hexane. [c] Cyclohexane.

TABLE II

DERIVATIVES OF N-SUBSTITUTED 7-AMINO-1-NAPHTHOLS

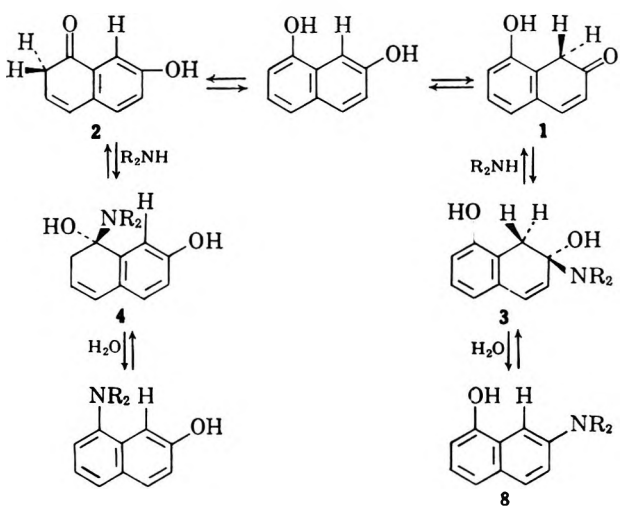
	Derivative	M.p., °C.	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
8a	O,N-Bis(3,5-dinitrobenzoyl)	214–215[a]	53.48	2.69	12.48	53.52	2.91	12.69
8b	Picrate	170–171 dec.[b]	51.92	3.87	13.46	52.39	4.12	13.21
8c	Picrate	147–148 dec.[c]	53.02	4.22	13.02	53.36	4.26	12.91
8d	Picrate	178.5–179.5 dec.[d]	51.92	3.87	13.46	51.87	3.96	13.16

Recrystallization solvents: [a] Acetonitrile. [b] Toluene. [c] Chloroform. [d] Ethanol.

To confirm the structures assigned to these products, an authentic sample of 7-ethylamino-1-naphthol (**8b**) was prepared by the lithium aluminum hydride reduction of 7-acetamido-1-naphthol[1a] and proved to be identical with the product of the reaction of ethylamine with 1,7-dihydroxynaphthalene. The properties of the aminonaphthols and their derivatives are listed in Tables I and II.

It seems reasonable to assume that this reaction proceeds by addition of the amine to the carbonyl group of the keto form of the naphthol[3,10] as shown in Scheme I. What appears remarkable about the present reaction is the high degree of preference for replacement of the β-hydroxy group. The differences in reactivities of α- and β-naphthol would be expected to be small. Wheland[11] calculated that there is no difference in ΔE (−10 kcal. per mole) between α- and β-naphthol upon conversion to their keto forms.

SCHEME I



(10) A. Rieche and H. Seeboth, *Ann.*, **638**, 43, 52, 66, 78 (1960).

(11) G. W. Wheland, "Resonance in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1955, p. 405.

Quantitative kinetic and thermodynamic data which permit direct comparison between α- and β-naphthol are largely lacking in the literature. A few scattered observations have been reported, however. The heat of formation[12] of β-naphthol (34.2 kcal./mole) exceeds that of α-naphthol (31.3 kcal./mole) by 2.9 kcal./mole, while the difference for the corresponding acetates is 3.5 kcal./mole. The rate of esterification with acetic anhydride in acetic acid is slower for α-naphthol.[13] When α- and β-naphthol were treated with aqueous ammonia[8] for 3 hr. at 250°, β-naphthylamine was obtained in 58% yield, while the α isomer gave only 23.2%. In the Bucherer reaction, β-naphthols react more readily than α-naphthols with arylamines,[14] even if, as in 1,6-dihydroxynaphthalene-4-sulfonic acid where both α- and β-positions are available, the α-position is activated by a 4-sulfo group, a situation which normally leads to preferential replacement by ammonia of the activated group.

Although the above information is hardly adequate enough to allow any definitive conclusions to be drawn, we believe that the selectivity of the reaction reported here can be best interpreted in terms of the effects that steric interactions with the *peri*-position of the naphthalene ring have on three aspects of the proposed reaction sequence: namely, the positions of the keto–enol equilibria of the α- and β-hydroxyl groups; the ease of addition of amine to the two ketonic forms, **1** and **2** (or the relative positions in the equilibria between **1** and **3** *vs.* **2** and **4**); and the relative ease of the loss of water from intermediates **3** and **4**. Such effects would be expected to be small but significant, especially when bulkier groups are involved. In general, a reaction leading to an increase in spatial requirements at an α-position should be less favorable energetically than the same reaction at a β-position. Similarly, a reaction which re-

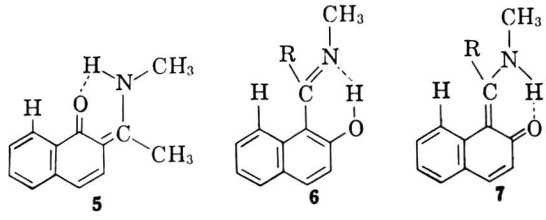
(12) A. Leman and G. Lepoutre, *Compt. rend.*, **226**, 1978 (1948).

(13) A. Leman, *Ann. chim.*, **9**, 357 (1938).

(14) N. L. Drake, "Organic Reactions," Vol. 1, R. Adams, Ed., John Wiley and Sons, Inc., New York, N. Y., 1942, p. 105; see also ref. 3, p. 148.

sults in a decrease in *peri*-interactions should be correspondingly more favorable. Thus, a greater relief of *peri*-interactions should result on going from the dihydroxynaphthalene (OH· · · ·H interaction) to the β-keto form (**1**, Scheme I, no interaction) than on going to the α-form, **2** (=O· · · ·H interaction), and, consequently, at equilibrium, there should be a higher concentration of **1** than **2**. Addition of a primary or secondary amine might be expected to proceed more readily with the β-keto form than the α-form, because in the latter there is the possibility of steric repulsion by interaction of the incoming (solvated) amine with the *peri*-hydrogen atom. Finally, rearomatization of the addition products **3** and **4** should be less favorable for **4**, in that a bulky amino group would be brought into a position coplanar with the *peri*-hydrogen atom.

Recent work by Dudek[15] has shown that *peri*-effects can influence the direction and ease of the ketonization of substituted α- and β-naphthols. Thus, N-methyl-1-hydroxy-2-acetonaphthoneimine exists in the ketoamine form **5**, while N-methyl-2-hydroxy-1-acetonaphthoneimine (**6**, R = CH_3) is more stable in the hydroxyimine form because interactions between the C-methyl group and the *peri*-hydrogen atom can be relieved by rotation about the single bond to the α-substituent, a condition not possible in the ketoamine form (**7**, R = CH_3). In N-methyl-2-hydroxy-1-naphthaldehydeimine (**6**, R = H), where the methyl group has been replaced by a less bulky hydrogen atom, the ketoamine form is again more stable (**7**, R = H).



5 **6** **7**

With a large excess of ammonia at 250°, 1,7-dihydroxynaphthalene was reported to give 79.5% of "aminonaphthol" and 21.5% of diamine.[16] Addition of 1 equiv. of sodium hydroxide increased the yield of "aminonaphthol" to 90%. Although the authors describe their product as 7-amino-1-naphthol, the combination of the more vigorous conditions and the smaller size of the amine has resulted in the loss of selectivity, for the melting point given (130°) is considerably less than that reported for this compound (156–158°,[1a] 155–156°[1b]), and suggests that the product was a mixture of both isomers.

Experimental[17]

1,7-Dihydroxynaphthalene.—The melting point of a commercial grade, from Aldrich Chemical Co., Inc., was raised from 175–176° to 179–181° (lit.[18] m.p. 181°) by recrystallization from 1% aqueous hydrochloric acid containing a trace of stannous chloride.

7-Methylamino-1-naphthol (8a).—In a 250-ml. steel bomb were placed 40 g. (0.25 mole) of 1,7-dihydroxynaphthalene, 43.5 ml. (0.5 mole) of 40% aqueous methylamine, and 55 ml. of water. The bomb was sealed and heated while rocking at 140° for 8 hr. After cooling and opening the bomb, the contents were dissolved in 100 ml. of 50% sodium hydroxide solution and 300 ml. of water. The solution was filtered from a little crude 1,7-di(methylamino)naphthalene (4.21 g., m.p. 74–75°). The filtrate was acidified with 300 ml. of concentrated hydrochloric acid and chilled in an ice bath. The precipitated solid was collected by suction filtration and dissolved in 300 ml. of water. In other preparations (using different ratios of reactants and temperatures) from which 1,7-dihydroxynaphthalene was recovered, it was separated from the product at this point by filtration. The acidic solution of the product was neutralized with aqueous ammonium carbonate (prepared by saturating concentrated ammonium hydroxide solution with carbon dioxide), and the precipitated product was collected, washed with a little cold water, and dried to give 27.7 g. of crude product, m.p. 124–127° dec. Neutralization of the strongly acidic filtrate from above gave an additional 3.1 g. of product, total yield 71%. An analytical sample was prepared by crystallization to constant melting point from carbon tetrachloride. The properties of the aminonaphthols are reported in Table I.

7-Ethylamino-1-naphthol (8b). A.—In a 250-ml. steel bomb were placed 40 g. (0.25 mole) of 1,7-dihydroxynaphthalene, 41.2 ml. (0.5 mole) of 70% aqueous ethylamine, and 60 ml. of water. The bomb was sealed and heated while rocking at 155° for 8 hr. The contents of the bomb were dissolved in 100 ml. of 50% aqueous sodium hydroxide solution and 300 ml. of water and were filtered from a trace of solid. The filtrate was acidified with 300 ml. of concentrated hydrochloric acid and chilled in an ice bath. The aqueous phase was decanted from the heavy oil which separated, the oil was mixed with 300 ml. of water, and the mixture was filtered from 8.6 g. of recovered starting material. The filtrate was neutralized with ammonium carbonate solution and the precipitated product was collected, washed with water, and dried to give 22.4 g. of crude product, m.p. 68–70° dec. An additional 2.1 g. of product was obtained by neutralization of the above decanted hydrochloric acid solution to give a total yield of 52% (66% corrected for recovered starting material). An analytical sample was prepared by crystallization to constant melting point from hexane.

B.—By Lithium Aluminum Hydride Reduction.—To a suspension of 2 g. of lithium aluminum hydride in 50 ml. of dry tetrahydrofuran was added, over 20 min., a solution of 5.03 g. (0.025 mole) of 7-acetamido-1-naphthol[1a] in 75 ml. of tetrahydrofuran. The mixture was stirred under reflux for 15 hr. A solution of 2 ml. of water in 20 ml. of tetrahydrofuran was then added slowly to the mixture with cooling, and the entire reaction mixture was evaporated to dryness under reduced pressure. The residue was heated with two 100-ml. portions of acetic acid and filtered. The combined acetic acid extracts were evaporated to dryness, and the residue was stirred with 200 ml. of 6 *N* hydrochloric acid. The solution was filtered through a pad of Celite and neutralized with ammonium carbonate solution to give, after washing with water and drying, 3.04 g. (65%) of 7-ethylamino-1-naphthol which, after recrystallization from hexane, proved to be identical in all respects (melting point, mixture melting point, infrared and ultraviolet spectra) with the product obtained from 1,7-dihydroxynaphthalene and ethylamine.

Hydrochloride of 7-Isopropylamino-1-naphthol (8c).—In a 250-ml. steel bomb were placed 40 g. (0.25 mole) of 1,7-dihydroxynaphthalene, 42.5 ml. (29.5 g., 0.5 mole) of isopropylamine, and 55 ml. of water. The bomb was sealed and heated while rocking at 170° for 16 hr. The contents of the bomb were dissolved in 100 ml. of 50% sodium hydroxide solution and 300 ml. of water, the solution was filtered through a Celite pad, and the filtrate was acidified with 300 ml. of concentrated hydrochloric acid. The resulting heavy oil was separated by decanting the aqueous layer and mixed with 200 ml. of ethyl acetate. The solid which separated was collected, washed with a second 200-ml. portion of ethyl acetate, and dried to give 33.0 g. (56%) of the hydrochloride, m.p. 198–202° dec.

An analytical sample of the hydrochloride, obtained by two recrystallizations from 5% hydrochloric acid, melts at 117–118°, resolidifies, and decomposes at 222–224°. This compound was hygroscopic.

(15) G. O. Dudek, *J. Am. Chem. Soc.*, **85**, 694 (1963); *Spectrochim. Acta*, **19**, 691 (1963).

(16) V. V. Kozlov and I. K. Veselovskaya, *Zh. Obshch. Khim.*, **31**, 3030 (1961); *Chem. Abstr.*, **57**, 739 (1962).

(17) Melting points are uncorrected and were obtained on a Mel-Temp capillary melting point apparatus. Elemental analyses were by Dr. S. M. Nagy of the Microchemical Laboratory, Massachusetts Institute of Technology, and by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Ultraviolet spectra were determined on a Cary Model 11 spectrophotometer.

(18) N. Donaldson, "The Chemistry and Technology of Naphthalene Compounds," Edward Arnold Ltd., London, 1958, p. 286.

Anal. Calcd. for $C_{13}H_{16}ClNO$: C, 65.68; H, 6.78; Cl, 14.91; N, 5.89. Found: C, 65.35; H, 7.05; Cl, 14.60; N, 5.97.

Evaporation of the ethyl acetate extracts gave 16 g. of recovered starting material. The yield of hydrochloride, corrected for recovered starting material, is 92%.

7-Isopropylamino-1-naphthol (8c).—The free amine was obtained by neutralization of an aqueous solution of its hydrochloride with sodium acetate. An analytical sample was obtained by two recrystallizations from hexane.

7-Dimethylamino-1-naphthol (8d).—In a 250-ml. steel bomb were placed 40 g. (0.25 mole) of 1,7-dihydroxynaphthalene and 96 ml. (90 g., 0.5 mole) of 25% aqueous dimethylamine. The bomb was sealed and heated while rocking at 180° for 8 hr. The reaction mixture was worked up as described for **8b**. No starting material was recovered, and there was obtained 27 g. of crude product (m.p. 101–104° dec.) from the oily precipitated hydrochloride and 4 g. of additional product by neutralization of the hydrochloric acid solution; the yield was 66%. An analytical sample was obtained by crystallization from cyclohexane.

Derivatives.—The derivatives were prepared by conventional means[19] and crystallized to constant melting point. Their properties are reported in Table II.

(19) 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.

The Acid-Catalyzed Decomposition of N,N′-Diaryl-1,3-diaminopropanes

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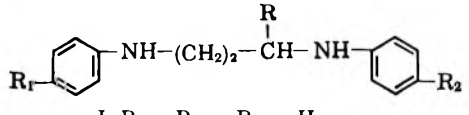
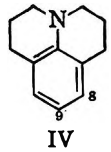
The scope of the previously reported acid-catalyzed thermal decomposition of N,N′-diaryl-1,3-diaminopropanes to give arylamines, tetrahydroquinolines, and julolidines has now been investigated. The aryl groups that can be employed are probably limited to alkyl-, aryl-, alkoxy-, and halophenyl. Further, decomposition of *ortho*- and *para*-substituted diarylдiamines gives considerable quantities of N-alkylanilines, making purification of the tetrahydroquinolines difficult. Nevertheless, the method offers useful syntheses for 5- and 7-substituted tetrahydroquinolines and for alkyl- and halojulolidines. The results presented support the previously suggested mechanism. The investigation has been extended to the breakdown of the trimethylenediamines formed from indoline, tetrahydroquinoline, and carbazole. The first two diamines gave indoline and lilolidine, and tetrahydroquinoline and julolidine, respectively; the third is remarkably stable and a reason is suggested for this. The breakdown of N′-benzyl-N′-phenyl-1,2-diaminoethane gives toluene, aniline, benzylamine, and N-phenyl-1,2-diaminoethane, but tetrahydroisoquinoline was not detected.

We have recently reported[1,2] that N,N′-diphenyl-1,3-diaminopropane (I) decomposes smoothly at about 230° in the presence of hydrogen bromide to give aniline, tetrahydroquinoline (XI), and julolidine[3] (IV). It was also shown that the corresponding tolyl- and naphthyldiamines decomposed in a similar manner, although no julolidines were obtained from N,N′-*o*-tolyl-1,3-diaminopropane or from the two naphthyldiamines.



I, R = R_1 = R_2 = H
II, R = CH_3, R_1 = R_2 = H
III, R = H, R_1 = CH_3, R_2 = Cl



IV

This reaction offered the possibility of synthesizing both tetrahydroquinolines and julolidines in a simple manner from the corresponding arylamines, the diaryldiamines being readily prepared by heating the arylamines with 1,3-dibromopropane. Substituted tetrahydroquinolines are usually prepared by the reduction of the respective quinolines, but this does not always lead to readily purified products and may also remove halogen atoms.[4] Thus, only one of the four possible chlorotetrahydroquinolines substituted in the aromatic ring has been reported. Julolidines are less well-known. Heating the respective tetrahydroquinolines with 1,3-chlorobromopropane or 1,3-dibromopropane yields julolidine (IV),[5–7] 8-methyl-,[8] 9-methyl-,[6] or 9-methoxyjulolidine.[6] This method is probably of limited further application,[9] and the tetrahydroquinoline must first be obtained. A number of 9-substituted julolidines have also been prepared[9] by electrophilic substitution in the parent compound, but oxidizing conditions must be avoided.

Results and Discussion

Decompositions were carried out in a simple Claisen apparatus under a pressure suitably reduced to ensure that any products significantly more volatile than the diamine would be distilled. Decompositions in sealed tubes were found to give much larger quantities of inseparable residues.

The effect of various amounts of hydrogen bromide on the decomposition of N,N′-diphenyl-1,3-diaminopropane was studied. The relative amounts of the volatile products were little affected, but, while the rate of decomposition increased with larger amounts of the acid, so also did the amount of intractable residue; 0.1 mole of acid was judged to be the best compromise, giving about 90% of the diamine as volatile material in a reasonable time. Other catalysts such as sulfuric acid

(1) A. Fischer, R. D. Topsom, and J. Vaughan, *J. Org. Chem.*, **25**, 463 (1960).

(2) G. B. Russell, G. J. Sutherland, R. D. Topsom, and J. Vaughan, *ibid.*, **27**, 4375 (1962).

(3) 2,3,6,7-Tetrahydro-1H,5H-benzo[*ij*]quinolizine.

(4) "Heterocyclic Compounds," Vol. 4, R. C. Elderfield, Ed., John Wiley and Son, Inc., New York, N. Y., 1952, p. 286.

(5) Z. J. Vejdelek, B. Kakac, and M. Protiva, *Chem. Listy*, **47**, 1676 (1953); *Chem. Abstr.*, **49**, 1046 (1955).

(6) G. Pinkus, *Ber.*, **25**, 2798 (1892).

(7) D. Glass and A. Weissberger, *Org. Syn.*, **26**, 40 (1946).

(8) M. S. Raasch, U. S. Patent 2,707,681 (May 3, 1955); *Chem. Abstr.*, **50**, 717 (1956).

(9) P. A. S. Smith and T. Y. Yu, *J. Org. Chem.*, **17**, 1281 (1952).

TABLE I

DECOMPOSITIONS OF N,N'-DIARYL-1,3-DIAMINOPROPANES[a]

Compound	Phenyl- (230)	*o*-Tolyl- (235)	*m*-Tolyl- (200)	*p*-Tolyl- (240)	*o*-Methoxyphenyl- (270)	*m*-Methoxyphenyl- (200)	*p*-Methoxyphenyl- (250)	*o*-Chlorophenyl- (300)	*m*-Chlorophenyl- (235)	*p*-Chlorophenyl- (280)
Arylamine	1.09	0.76	1.00	1.04	0.36	0.84	0.70	0.81	1.08	0.35
N-Methylarylamine		0.09		0.08	0.29	0.14	0.20[b]			0.10
N-Ethylarylamine		0.11		0.11	0.13[b]		0.37[b]			0.19
N,N-Dimethylarylamine							0.19[b]			
N-Allylarylamine								0.37		
Aminophenol					0.20	0.03				
Tetrahydroquinoline	0.33	0.82	0.59[c]	0.26	0.15	0.53[c]	0.06	0.35	0.56[c]	0.19
Alkyl tetrahydroquinoline				0.06[b]			0.05	0.08[b]		0.05[b]
Quinoline				0.04[b]			0.05			0.05
Julolidine	0.22		0.19	0.23		0.03[d]	0.05[e]		0.23	0.20

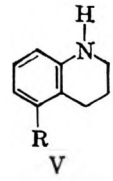
[a] The amount of each component, determined by gas chromatography, is expressed in moles per mole of diamine decomposed. The temperature (°C.) at which decomposition first occurs is shown in parentheses below each diamine. [b] Not isolated; identified by comparison of gas chromatograph retention times, on two columns, with authentic samples. [c] Mixture of 5- and 7-substituted tetrahydroquinolines. [d] Quantity isolated. [e] Provisional identification.

and cobaltous chloride also caused decomposition, but only the aniline could be isolated in significant yield.

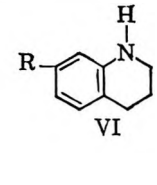
It was found that the ease of reaction depended quite markedly on both the nature and the position of an introduced substituent. Thus Table I shows that for *meta*-substituted diaryldiamines, the ease of breakdown is MeO ~ Me > H ~ Cl, while for *ortho* and *para* substituents it is Me ~ H > MeO > Cl. Each of the chosen substituents allowed the most ready decomposition when in the *meta* position. It has previously been suggested[2] that the reaction involves ring closure synchronous with the splitting off of the arylamine molecule. The above results are consistent with this. It was also found that with *ortho*- and *para*-substituted diaryldiamines, significant cleavage of the trimethylene chain occurred, leading to N-alkylarylamines and similar products. Gas chromatograms showed that such products were not present as impurities in the original diamines. Such cleavage represents reduction, and the corresponding oxidation appears to be the conversion of tetrahydroquinolines into quinolines, some of which were isolated from the reaction products. These additional products made separation and purification of the tetrahydroquinolines difficult. With the *meta* compounds, such fission appears to be absent[10]; the tetrahydroquinolines were formed in satisfactory yield and were easily isolated.

With the chloro-substituted diamines, higher temperatures were required for decomposition and an increased number of products was formed. These features, together with the greater difficulty experienced in isolating products of low volatility indicated that breakdown of diaryldiamines containing more deactivating substituents, such as nitro and carboxyl groups, would be unprofitable. However, N,N'-bis(*o*-biphenylyl)-1,3-diaminopropane decomposed to give the expected *o*-aminobiphenyl and 8-phenyltetrahydroquinoline. It is thus likely that the useful decompositions of simple N,N'-diaryldiamines are limited to alkoxy, alkyl, aryl, and halo substituents.

No julolidine can be formed from *ortho*-substituted diaryldiamines, but these did not in general give increased amounts of the tetrahydroquinolines. In fact, the best yield of tetrahydroquinoline usually resulted from the *meta* isomers. These gave mixtures of the 5- (V) and 7-substituted (VI) tetrahydroquinolines.



V



VI

The separation of these tetrahydroquinolines required a preparative gas chromatograph, but the derived 8-substituted julolidine was readily isolated in each case. The relative amounts of the two isomers obtained with each substituent are shown in Table II, together with the proportions of 5- and 7-substituted quinoline reported[11] for the Skraup reaction with *m*-arylamines. There is a striking similarity between the product ratios obtained in the two reactions, and this may be linked with closely similar cyclizing entities (see ref. 11).

TABLE II

RELATIVE AMOUNTS OF TETRAHYDROQUINOLINES PRODUCED FROM BIS(*m*-SUBSTITUTED PHENYL)-1,3-DIAMINOPROPANES[a]

m-Substituent	Diamine decomposition, % tetrahydroquinoline		Skraup reaction, % quinoline	
	5-	7-	5-	7-
Methyl-	40	60	41	59
Methoxy-	22	78	21	79
Chloro-	47	53	49	51

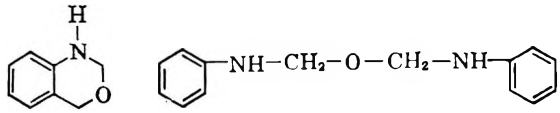
[a] The relative amounts of the corresponding quinolines produced in the Skraup reaction are also given.

Three other related diaryldiamines were also decomposed. N,N'-Diphenyl-1,3-diaminobutane (II) decomposed to give aniline and both the 2- and 4-methyltetrahydroquinolines as expected. Chain cleavage, particularly to give N-ethylaniline, was extensive and 2-methylquinoline was produced. No julolidines were isolated. The decomposition of N-*p*-chlorophenyl N'-*p*-tolyl-1,3-diaminopropane (III) gave both *p*-chloroaniline and *p*-toluidine. That the former was in considerable excess is consistent with the suggested mechanism. An attempt also was made to obtain

(10) The N-methyl-*m*-anisidine formed probably results from the methylation of initially formed *m*-anisidine. Thus, no N-ethyl-*m*-anisidine was detected.

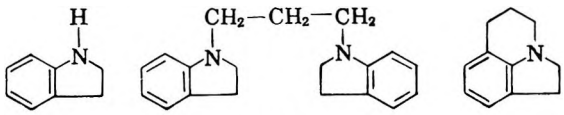
(11) M. H. Palmer, *J. Chem. Soc.*, 3645 (1962).

1,2-dihydro-4H-3,1-benzoxazine (VII) by the decomposition of N,N′-diphenylbis(aminomethyl) ether (VIII), but the only volatile product obtained was aniline.



VII VIII

Decomposition of Some Related Diamines.—The diamines discussed above contain only secondary amine groups. Some tertiary diamines were also examined. 1,3-Bis(N-indolinyl)propane (IX) gave, on decomposition, a mixture of indoline (X) and lilolidine[12] (XI).



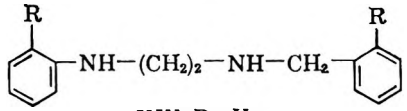
X IX XI

Similarly, 1,3-bis(N-tetrahydroquinolinyl)propane gave tetrahydroquinoline and julolidine. By analogy, the trimethylenediamines derived from carbazole and acridan should yield the previously unreported trimethylenecarbazole[13] (XII) and trimethyleneacridan[14] (XIII).

XII XIII

Attempts to prepare the bis(acridanyl)propane were unsuccessful and, while the corresponding carbazolyl compound could be made, it proved to be remarkably stable, being recovered unchanged after heating for several hours at 300–350° in the presence of hydrogen bromide. This stability is explicable in terms of a rate-determining cyclization since the 1-position in carbazole is known[15] to be very much less nucleophilic than the corresponding *ortho* carbon of an alkylaniline.[16] This factor probably accounts also for the failure of an attempt to prepare the trimethylenecarbazole by refluxing carbazole with 1,3-bromochloropropane.[17]

N-Benzyl-N′-phenyl-1,2-diaminoethane (XIV) and N-*o*-xylyl-N′-*o*-tolyl-1,2-diaminoethane (XV) were decomposed also. No evidence could be found for the presence of tetrahydroisoquinolines in the reaction products. The compounds detected were the respective aromatic hydrocarbons, benzene and toluene, the arylamines and benzylamines, and the N-aryl-1,2-diaminoethanes.



XIV, R = H
XV, R = CH_3

Experimental

Melting and boiling points are uncorrected. Analyses were by the Microanalytical Laboratory of the University of Otago. The analytical gas chromatograph used was fitted with an integrating amplifier. The column used for analyses was packed with 10% w./w. Apiezon L on Celite 545; the column temperature was 150–200°. The instrument was calibrated for linearity of response and for response to different components. The samples used for these purposes were generally those isolated from the decomposition mixtures, and only with the chloro substituent was the uncorrected peak area estimation significantly in error. A Beckman Megachrom preparative gas chromatograph was used to separate components of similar boiling points. The columns were packed with 35% w./w. Apiezon J on C22 firebrick and were used at a temperature of 180°. Infrared spectra were determined on a Perkin-Elmer Model 221 spectrograph using sodium chloride optics. All starting materials were redistilled or recrystallized before being used.

N,N′-Diaryl-1,3-Diaminopropanes.—N,N′-Diphenyl- and the three N,N′-ditolyl-1,3-diaminopropanes were prepared as already reported.[1,2] The following diamines were similarly obtained, in the yields given, by the interaction at elevated temperatures of 1,3-dibromopropane with a 10 *M* amount of the corresponding arylamine:[18] N,N′-bis(*o*-methoxyphenyl)-1,3-diaminopropane[19] [72%, b.p. 230–240° (1 mm.). *Anal.* Calcd. for $C_{17}H_{22}N_2O_2$: C, 71.32; H, 7.69; N, 9.78. Found: C 71.00; H, 7.81; N, 9.37.], N,N′-bis(*m*-methoxyphenyl)-1,3-diaminopropane [72%, b.p. 220–230° (1 mm.), $n^{20}D$ 1.6415. *Anal.* Calcd. for $C_{17}H_{22}N_2O_2$: C, 71.32; H, 7.69; N, 9.78. Found: C, 71.40; H, 7.42; N, 9.21.], N,N′-bis(*p*-methoxyphenyl)-1,3-diaminopropane [44%, m.p. 99°, lit.[19] m.p. 96.5°. *Anal.* Calcd. for $C_{17}H_{22}N_2O_2$: C, 71.32; H, 7.69; N, 9.78. Found: C, 71.00; H, 8.00; N, 9.52. Dihydrochloride, m.p. 208–209°.], N,N′-bis(*o*-chlorophenyl)-1,3-diaminopropane [86%, b.p. 220–225° (1 mm.), m.p. 77–78°. *Anal.* Calcd. for $C_{15}H_{16}Cl_2N_2$: C, 61.10; H, 5.43; N, 9.49. Found: C, 60.98; H, 5.64; N, 9.47.], N,N′-bis(*m*-chlorophenyl)-1,3-diaminopropane [60%, b.p. 260–270° (1 mm.), $n^{20}D$ 1.6415. *Anal.* Calcd. for $C_{15}H_{16}Cl_2N_2$: C, 61.10; H, 5.43; N, 9.49. Found: C, 60.91; H, 5.55; N, 9.28.], N,N′-bis(*p*-chlorophenyl)-1,3-diaminopropane [58%, b.p. 280–290° (1 mm.), m.p. 77°, lit.[20] m.p. 75°. *Anal.* Calcd. for $C_{15}H_{16}Cl_2N_2$: C, 61.10; H, 5.43; N, 9.49. Found: C, 61.21; H, 5.67; N, 9.80.], and N,N′-bis-(*o*-biphenyl)-1,3-diaminopropane [53%, b.p. 273–274° (0.5 mm.), m.p. 77°. *Anal.* Calcd. for $C_{27}H_{26}N_2$: C, 85.70; H, 6.89; N, 7.40. Found: C, 85.89; H, 7.01; N, 7.14. Dihydrochloride, m.p. 172° (from ethanol).].

Prepared in an analogous manner were N,N′-diphenyl-1,3-diaminobutane [89%, b.p. 210–200° (1 mm.), $n^{20}D$ 1.6060. *Anal.* Calcd. for $C_{16}H_{19}N_2$: C, 80.00; H, 8.33; N, 11.67. Found: C, 80.28; H, 8.61; N, 11.62.], and N,N′-diphenylbis-(aminomethyl) ether [36%, b.p. 214–220° (1 mm.), $n^{20}D$ 1.6399. *Anal.* Calcd. for $C_{14}H_{16}N_2O$: C, 73.68; H, 7.02; N, 12.28. Found: C, 73.53; H, 7.63; N, 12.08.].

N-*p*-chlorophenyl-N′-*p*-tolyl-1,3-diaminopropane.—N-(3-Bromopropyl)*p*-toluidine hydrobromide (18 g., m.p. 152–153°, lit.[21] m.p. 151°) was neutralized with 10% sodium hydroxide solution and the free base was extracted with ether. The ether solution was dried over magnesium sulfate and was then added dropwise, over 1.5 hr., to 100 g. of stirred, molten *p*-chloroaniline on a water bath. The ether was distilled as the addition proceeded. The mixture was heated for an additional hour; it then was neutralized and the bases were extracted with ether. The extract was washed with water and dried over magnesium sulfate. Distillation gave 15 g. (91%) of the required compound, b.p. 245–250° (1 mm.).

Anal. Calcd. for $C_{16}H_{19}ClN_2$: C, 69.95; H, 6.92; N, 10.20. Found: C, 70.37; H, 7.23; N, 10.06.

(12) 1,2,5,6-Tetrahydro-4H-pyrrolo[3,2,1-*ij*]quinoline.
(13) 2,3-Dihydro-1H-pyrido[3,2,1-*jk*]carbazole.
(14) 2,3-Dihydro-1H,7H-pyrido[3,2,1-*de*]acridine.
(15) M. J. S. Dewar and D. S. Urch, *J. Chem. Soc.*, 3079 (1958).
(16) P. B. D. De la Mare and J. H. Ridd, "Aromatic Substitution, Nitration and Halogenation," Butterworth and Co., Ltd., London, 1959, p. 139.
(17) T. Y. Yu, *Dissertation Abstr.*, **12**, 254 (1952).
(18) The reactions are exothermic and with *p*-anisidine it is necessary to add the dibromopropane dropwise with stirring.
(19) R. Daniels and B. D. Martin, *J. Org. Chem.*, **27**, 178 (1962).
(20) W. L. C. Veer, *Rec. trav. chim.*, **57**, 589 (1938).
(21) L. W. Deady, G. J. Leary, R. D. Topsom, and J. Vaughan, *J. Org. Chem.*, **28**, 511 (1963).

1,3-Bis(N-indolinyl)propane was available as a by-product of an attempt to prepare lilolidine by refluxing indoline with 1,3-dibromopropane.[22] It had b.p. 220–223° (0.5 mm.).

Anal. Calcd. for $C_{19}H_{22}N_2$: C, 81.98; H, 7.98; N, 10.05. Found: C, 82.34; H, 8.20; N, 9.40.

1,3-Bis(N-tetrahydroquinolinyl)propane was prepared by heating 93 g. of tetrahydroquinoline with 31 g. of 1,3-dibromopropane at 55° for 2.5 hr. The deep red reaction mixture was dissolved by shaking with a mixture of dichloromethane and aqueous sodium hydroxide. The organic layer was washed with aqueous sodium hydroxide and with water and was dried over magnesium sulfate. After evaporation of the solvent, distillation under reduced pressure gave 62 g. of tetrahydroquinoline, 9.0 g. of julolidine, and 9.0 g. of the required diamine.[23] The diamine had b.p. 208–212° (0.5 mm.) and gave a dipicrate, m.p. 162° (from benzene).

Anal. Calcd. for $C_{33}H_{32}N_8O_{14}$: C, 51.83; H, 4.19. Found: C, 51.75; H, 4.30.

1,3-Bis(N-carbazolyl)propane.[24]—Carbazole (16.7 g., 0.1 mole) was fused for 45 min. at 260° with 6 g. (0.107 mole) of potassium hydroxide. The material obtained was pulverized and refluxed for 15 min. in 100 ml. of sodium-dried toluene.

The potassium salt was filtered from the hot toluene and cooled in a vacuum desiccator. The salt (17.6 g., 0.086 mole) was refluxed for 5 hr. with 8.75 g. (0.043 mole) of 1,3-dibromopropane in 50 ml. of sodium-dried toluene. The solvent was removed by steam distillation, and the residue was heated under reduced pressure to sublime carbazole (3 g.). The residue was recrystallized twice from toluene to give 8.7 g. (54%) of the required compound, m.p. 183°.

Anal. Calcd. for $C_{30}H_{24}N_2$: C, 86.58; H, 5.93; N, 7.48. Found: C, 86.45; H, 6.07; N, 7.14.

The picrate had m.p. 152° from benzene.

Attempted Preparation of 1,3-Bis(N-acridanyl)propane.—Refluxing acridan with dibromopropane gave only acridine and an intractible black tar. A preparation analogous to that used to make the carbazole analog could not be attempted because sodio or potassio derivatives of acridan could not be formed under mild conditions with sodium, potassium, or sodium hydride; more stringent conditions gave acridine.[25] Acridanylmagnesium iodide[26] was prepared and refluxed with dibromopropane but only acridan and a black tar were formed.

N-Benzyl-N′-phenyl-1,2-diaminoethane.[27]—N-(2-Bromoethyl)-aniline hydrobromide[28] (74 g., m.p. 138°) was neutralized with 10% sodium hydroxide solution and extracted with 600 ml. of ether. The extract was washed with water and dried over potassium carbonate. Benzylamine (100 g.) was added, and the ether was distilled. The mixture was refluxed for 5 hr. and then shaken with 200 ml. of 10% sodium hydroxide solution and 1 l. of ether. The organic layer was washed with water and dried over potassium carbonate. Distillation gave 42 g. (66.5%) of the product, b.p. 220–223° (20 mm.). The dipicrate had m.p. 161°, lit.[27] m.p. 158–160°.

Anal. Calcd. for $C_{27}H_{24}N_8O_{14}$: C, 47.38; H, 3.51; N, 16.37. Found: C, 47.35; H, 3.72; N, 16.57.

N-*o*-Xylyl-N′-*o*-tolyl-1,2-diaminoethane (36.6 g., 37%) was prepared[29] from 125 g. of *o*-xylamine hydrochloride[30] and 117 g. of N-(2-bromoethyl)-*o*-toluidine hydrobromide[31,32] in a manner similar to the previous preparation. It had b.p. 206–213° (0.5 mm.) and gave a picrate, m.p. 177°.

Anal. Calcd. for $C_{23}H_{25}N_5O_7$: C, 57.14; H, 5.18; N, 14.49. Found: C, 57.18; H, 5.50; N, 14.29.

Breakdown of N,N′-Diaryl-1,3-Diaminopropanes.—Decomposition of the diamines was carried out in a Claisen distillation apparatus at temperatures from 200–300° as necessary and under reduced pressures (20 mm. unless otherwise stated). The catalyst was added as 48% hydrobromic acid. Decomposition always commenced quite suddenly as the temperature was raised, and the temperature at which this first occurred was reproducible to within 5°. Heating was continued until little further material distilled.

The distillate (86–94%, except for the methoxyphenyldiamines where it was 79–86%) was, in general, first analyzed on the gas chromatograph and then separated into components which, after identification, could be used to assign and calibrate the peaks in the original chromatogram. Compounds present in small amounts (<5%) could not always be separated from the decomposition mixture and the corresponding peaks were identified by retention time comparisons, on two columns,[33] with synthetic samples prepared for this purpose by literature methods. Semiquantitative chemical separations, made for the distillates obtained from the breakdown of the diphenyl- and ditolyldiamines,[12] confirmed the v.p.c. analyses.

The separation of pure compounds from the decomposition mixtures obtained from *ortho*- and *para*-substituted diamines was more difficult than with the *meta* isomers. It was usual first to fractionate the distillate. When the v.p.c. indicated the presence of more than one component in a fraction, the compounds were isolated either with the preparative gas chromatograph or by chemical means (particularly by fractional recrystallization of picrates), by the Hickinbottom method[34,35] of separating primary amines, and by the Hinsberg method. The latter process, involving treatment of mixtures with benzenesulfonyl chloride, allowed easy recovery of the unaffected julolidines.

The small amounts of tarry residues obtained were, in general, too complex to allow further separation. Significant quantities of the aminophenols were, however, isolated by alkali extraction of the corresponding decomposition residues from the methoxyphenyldiamines.

Compounds isolated were fully characterized by a combination of physical measurements, infrared spectra, preparation of derivatives, and elemental analysis. In cases of ambiguity, authentic samples were synthesized for comparison. Tetrahydroquinolines were also dehydrogenated to the corresponding quinolines by heating with sulfur.

Previously unreported tetrahydroquinolines and julolidines isolated from diamine decompositions are listed below. Infrared spectra, where not specifically mentioned, confirmed the structure.

5-Chlorotetrahydroquinoline, a pale green oil, $n^{20}D$ 1.6137, was obtained *via* the preparative gas chromatograph from the fraction, b.p. 110–120° (1 mm.), resulting from the breakdown of N,N′-bis(*m*-chlorophenyl)-1,3-diaminopropane. The infrared

(22) Following the method described by J. von Braun [*Ber.*, **51**, 1215 (1918)], except that 1,3-dibromopropane was substituted for 1,3-chlorobromopropane.

(23) The amount of tetrahydroquinoline recovered is greater than the excess originally added and this, with the corresponding presence of julolidine, indicates that some breakdown of the diamine has occurred under the reaction conditions. Indeed, it is hard to purify as distillation leads to some concurrent decomposition.

(24) Refluxing carbazole with dibromopropane for several days gives only a low yield of the diamine, and the product is hard to purify.

(25) Although it has been claimed (A. Albert in "Heterocyclic Compounds," Vol. 4, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1952, p. 537) that acridan forms a sodio derivative with sodium, we could find no reference to this in the literature. It was also stated that acridans substituted on the nitrogen atom may be obtained by reacting N-sodioacridan with an alkyl iodide, but the reference quoted describes only the reaction with the sodio derivative of 5,5-dimethylacridan which is stabilized as it cannot form an acridine.

(26) V. V. Chelintzev and B. V. Tronov, *J. Russ. Phys. Chem. Soc.*, **46**, 1886 (1914); *Chem. Abstr.*, **9**, 2072 (1915).

(27) Only literature references [P. Karrer and C. Gränacher, *Helv. Chim. Acta*, **7**, 763 (1924) and C. Gränacher, V. Schilling, and E. Schlatter, *ibid.*, **8**, 873 (1925)] describe its preparation by a three-stage process from hippuric acid.

(28) W. M. Pearlman, *J. Am. Chem. Soc.*, **70**, 871 (1948).

(29) Preparation by R. G. Mathews of this department.

(30) Prepared in 71% yield from *o*-xylyl bromide *via* the hexamine complex following the procedure described for similar conversions by J. Graymore [*J. Chem. Soc.*, 1116 (1947)].

(31) Prepared by the action of PBr_3, followed by HBr, on N-(3-hydroxypropyl)-*o*-toluidine. This was found preferable to the method described in ref. 32 which, in our hands, led to incomplete reaction.

(32) H. W. Heine, B. L. Kapur, J. L. Bove, R. W. Griener, K. H. Klinger, and C. Mitch, *J. Am. Chem. Soc.*, **76**, 2503 (1954).

(33) The two columns were the Apiezon L on Celite 545 column and one consisting of polyethyleneglycol 4000 also on Celite 545.

(34) W. J. Hickinbottom, *J. Chem. Soc.*, 992 (1930).

(35) The method involves the precipitation of the zinc chloride complexes of any primary amine present by treating a mixture with concentrated zinc chloride solution. The complexes, of form $[ArNH_2]_2 \cdot ZnCl_2$, are then washed with water, dried, and weighed. In a previous publication (ref. 2), we suggested that this method of separation was far less satisfactory than the Hinsberg method. We have since found that the difficulty arises from the partial hydrolysis of the arylamine complex on washing with water. Thus, it is preferable to wash the complexes free of other amines with concentrated zinc chloride and with ether and then to deliberately hydrolyze them; the liberated primary amine can be isolated and weighed.

spectrum (pure liquid) showed a medium peak at 14.20 μ and a strong peak at 13.10 μ corresponding to the out-of-plane vibrations of three adjacent aromatic C–H bonds.[36]

Anal. Calcd. for $C_9H_{10}ClN$: C, 64.48; H, 5.97; N, 8.36. Found: C, 64.53; H, 6.21; N, 8.00.

The hydrochloride had m.p. 120–122°.

7-Chlorotetrahydroquinoline was a white solid, m.p. 63–63.5° after recrystallization from petroleum ether (b.p. 30–40°). It was obtained as the 5-chloro isomer above. The infrared spectrum (melt) showed a strong peak at 12.80 μ (2 adjacent aromatic C–H bonds) and a medium peak at 11.95 μ (isolated aromatic C–H bond).[36]

Anal. Calcd. for $C_9H_{10}ClN$: C, 64.48; H, 5.97; N, 8.36. Found: C, 64.31; H, 6.13; N, 8.51.

The hydrochloride had m.p. 206–208°.

8-Chlorotetrahydroquinoline, a light green oil, was obtained by recrystallization of the picrates from the fraction, b.p. 95–110° (1 mm.), obtained in the decomposition of N,N'-bis(*o*-chlorophenyl)-1,3-diaminopropane.

Anal. Calcd. for $C_9H_{10}ClN$: C, 64.48; H, 5.97; N, 8.36. Found: C, 64.71; H, 5.82; N, 8.01.

It gave a benzoyl derivative, m.p. 134°, and a picrate, m.p. 130–131°.

Anal. Calcd. for $C_{15}H_{13}ClN_4O_7$: C, 45.54; H, 3.28; N, 14.14. Found: C, 45.58; H, 3.40; N, 14.07.

It gave 8-chloroquinoline on dehydrogenation (standard procedure using sulfur), b.p. 110° (1 mm.), methiodide m.p. 165° (lit.[37] m.p. 165°).

8-Chlorojulolidine, an oil, was readily obtained as the fraction, b.p. 135–140° (1 mm.), from the decomposition of the N,N'-bis(*m*-chlorophenyl)-1,3-diaminopropane.

Anal. Calcd. for $C_{12}H_{14}ClN$: C, 69.39; H, 6.75; N, 6.75. Found: C, 69.39; H, 6.77; N, 7.12.

It gave a hydrochloride, m.p. 162–163° after recrystallization from ethanol–ether, and a picrate, m.p. 161–162° after recrystallization from ethanol.

Anal. Calcd. for $C_{18}H_{17}ClN_4O_7$: N, 12.83. Found: N, 12.75.

9-Chlorojulolidine was a white solid, m.p. 46° after recrystallization from petroleum ether (b.p. 40–50°). It was easily obtained as the nonvolatile (steam) component of the fraction left after removal of the primary amine from the breakdown of N,N'-bis(*p*-chlorophenyl)-1,3-diaminopropane.

Anal. Calcd. for $C_{12}H_{14}ClN$: C, 69.39; H, 6.75; N, 6.75. Found: C, 69.49; H, 7.01; N, 6.42.

It gave a hydrochloride, m.p. 240–241°, and a picrate, m.p. 152–153°.

Anal. Calcd. for $C_{18}H_{17}ClN_4O_7$: N, 12.83. Found: 12.43.

8-Methoxyjulolidine, an oil, was easily isolated as the fraction, b.p. 140–160° (3 mm.), from the breakdown of the *m*-anisyldiamine after washing with alkali.

Anal. Calcd. for $C_{13}H_{17}NO$: C, 52.78; H, 4.63; N, 12.96. Found: C, 52.50; H, 4.91; N, 12.96.

It gave a picrate, m.p. 147–148° after recrystallization from ethanol.

Anal. Calcd. for $C_{16}H_{16}N_4O_8$: N, 6.90. Found: N, 6.73.

N-Allyl-*o*-chloroaniline, a previously unreported oil, was obtained after fractional recrystallization and decomposition of the picrates from the fraction, b.p. 80–90° (1 mm.), arising from the decomposition of the di-*o*-chlorophenyldiamine.

Anal. Calcd. for $C_9H_{10}ClN$: C, 64.48; H, 5.97; N, 8.36. Found: C, 64.03; H, 5.96; N, 7.82.

It gave a picrate, m.p. 167–168°.

Anal. Calcd. for $C_{13}H_{13}ClN_4O_7$: N, 14.12. Found: N, 14.07.

Breakdown of N,N'-Bis(*o*-biphenyl)-1,3-diaminopropane (32.5 g.) at 245–255° (45 mm.) gave 29.9 g. of distillate. From this was obtained 14.7 g. of *o*-aminobiphenyl and 9.8 g. of 8-phenyltetrahydroquinoline, b.p. 186–202° (15 mm.). The latter gave a picrate, m.p. 160°.[38]

Anal. Calcd. for $C_{21}H_{18}N_4O_7$: C, 57.51; H, 4.11; N, 12.78. Found: C, 57.70; H, 4.41; N, 12.36.

Breakdown of N,N'-diphenylbis(aminomethyl) ether (26.7 g.) at 260–270° gave 9.0 g. of aniline and 16.5 g. of an intractible residue.

Breakdown of N,N'-diphenyl-1,3-diaminobutane (19 g.) at 250–260° gave 16.5 g. of distillate. Gas chromatography showed that the distillate consisted essentially of six components: aniline, 4.8 g.; N-methylaniline, 0.4 g.; N-ethylaniline, 3.7 g.; 2-methylquinoline, 1.3 g.; 2-methyltetrahydroquinoline, 1.9 g.; and 4-methyltetrahydroquinoline, 2.9 g. The aniline was isolated *via* its zinc chloride complex, and the other three major components were obtained using the preparative gas chromatograph.

Breakdown of N-*p*-chlorophenyl-N'-*p*-tolyl-1,3-diaminopropane (9.8 g.) at 260–270° gave 8.8 g. of distillate. The twelve major components in the distillate were identified (retention times on two columns) and estimated by v.p.c. as *p*-chloroaniline, 3 g.; *p*-toluidine, 1.9 g.; N-methyl-*p*-toluidine, 0.1 g.; N-ethyl-*p*-toluidine, 0.4 g.; N-methyl-*p*-chloroaniline, 0.3 g.; N-ethyl-*p*-chloroaniline, 0.3 g.; 6-methylquinoline, 0.1 g.; 6-methyltetrahydroquinoline, 0.65 g.; N-ethyl-6-methyltetrahydroquinoline, 0.3 g.; 6-chlorotetrahydroquinoline, 0.3 g.; 9-methyljulolidine, 1.0 g.; and 9-chlorojulolidine, 0.3 g.

Breakdown of 1,3-bis(N-indolinyl)propane at 270° (45 mm.) gave a distillate consisting almost entirely of indoline and lilolidine (b.p. 150–160° at 20 mm.) in the molar ratio 1:0.7. Lilolidine gave a picrate, m.p. 170° (lit.[39] m.p. 170°).

Anal. Calcd. for $C_{17}H_{16}N_4O_7$: C, 52.59; H, 4.15; N, 14.43. Found: C, 52.65; H, 4.32; N, 14.39.

Breakdown of 1,3-bis(tetrahydroquinolinyl)propane (7.6 g.) at 205° gave a distillate (6.8 g.) which was shown by v.p.c. to consist only of tetrahydroquinoline and julolidine (molar ratio 1:0.82).

Breakdown of N-benzyl-N'-phenyl-1,2-diaminopropane (107 g.) at 255–260° (70 mm.) gave 78.6 g. of distillate and 35.3 g. of an intractible residue. The distillate was shown by fractionation, v.p.c., and infrared spectra to contain 6% toluene, 38% aniline, 8% benzylamine, 21% N-phenyl-1,2-diaminoethane (b.p. 115–116° at 0.5 mm., dibenzoyl derivative m.p. 149°, lit.[40] m.p. 150°, unchanged by addition of an authentic sample[41] of m.p. 150°), and 10% of unchanged diamine.

Breakdown of N-*o*-xylyl-N'-*o*-tolyl-1,2-diaminoethane gave the methyl analogs of the compounds above. The N-*o*-tolyl-1,2-diaminoethane, b.p. 155–160° (18 mm.), gave a picrate, m.p. 148–149° (lit.[42] m.p. 148°), and a bisphenylisothiocyanate derivative, m.p. 128°, unchanged when mixed with an authentic sample.

Acknowledgment.—The authors are indebted to the New Zealand Universities Research Committee for financial assistance.

(36) The spectral identification of the two isomers was confirmed by the similarity of the spectra of 5-chloro- and 8-chlorotetrahydroquinolines and of 6-chloro- and 7-chlorotetrahydroquinolines in the 11–15-μ region.

(37) A. Claus and M. Scholler, *J. prakt. Chem.*, [2]**48**, 140 (1893).

(38) M. Arramoff and Y. Sprinzak [*J. Org. Chem.*, **22**, 571 (1957)] prepared 8-phenyltetrahydroquinoline, b.p. 160° (3 mm.), and list a picrate, m.p. 164–166°, of the unusual formula $2C_{15}H_{13}N \cdot 3C_6H_3N_3O_7$.

(39) G. Barger and E. Dyer, *J. Am. Chem. Soc.*, **60**, 2414 (1938).

(40) S. C. Dickermann and A. J. Besozzi, *J. Org. Chem.*, **19**, 1855 (1954).

(41) C. Benko and M. Tisle, *Croat. Chem. Acta*, **30**, 243 (1958); *Chem. Abstr.*, **54**, 2221 (1960).

(42) H. E. Newman, *Ber.*, **24**, 2191 (1891).

The Thermal and the Photolytic Decomposition of 1-Phenyldiazoethane

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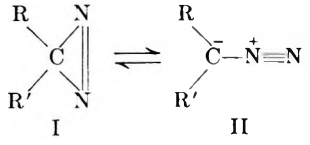
Received October 2, 1963

The thermal and the photolytic decomposition of 1-phenyldiazoethane is described and the mechanisms which may explain the formation of the observed products are discussed.

Our interest in cyclic azo compounds coupled with the fact that diazirines (I) and diazoalkanes (II) are valence tautomers[1] led us to investigate the chemistry of these compounds. Recently Schmitz and Ohme[2] reported that phenylmethyldiazirine (III) thermally decomposed to give styrene. This is to be contrasted with the behavior of 1-phenyldiazoethane (IV) which gave acetophenone azine as the sole product of decomposition. No styrene could be detected.[3]



I II

The purpose of this work was to investigate the causes of these unusual findings and to elucidate the mechanisms involved.

Results

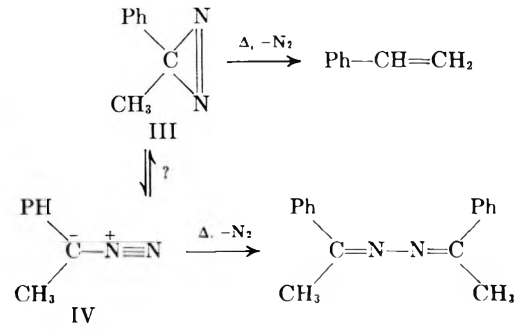
The thermal decomposition of 1-phenyldiazoethane was carried out by dropping a hexane solution of the diazoalkane into boiling benzene and by refluxing the red solution until complete decomposition had occurred. The decomposition product consisted essentially of acetophenone azine. Trace amounts of acetophenone and of benzoic acid were detected. Careful examination of the residue from the separation of the azine failed to reveal the presence of any styrene. Similarly, no trace of 2,3-diphenylbutane could be detected.

However, when a hexane solution of 1-phenyldiazoethane was photolyzed at 0–5° by a Hanovia high pressure mercury immersion lamp, three hydrocarbons were isolated by the careful work-up of the residue from the separation of acetophenone azine, the main product of the decomposition (95%). Two of these were characterized as styrene and *trans*-α,α'-dimethylstilbene. The third hydrocarbon was tentatively identified as 1,2-diphenyl-1-methylcyclopropane. Again, no 2,3-diphenylbutane could be detected on careful examination of the residue.

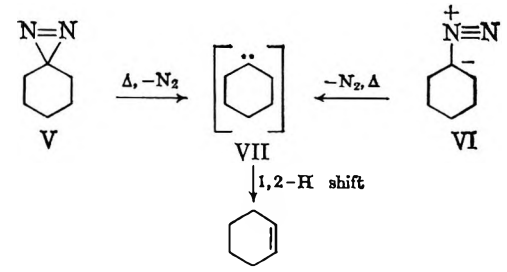
We could not duplicate the synthesis of phenylmethyldiazirine (III) as reported by Schmitz and Ohme.[2] A product having the physical properties of the diazirine (III) was obtained in very small yield. This colorless liquid (A) slowly took on a reddish coloration (B) upon standing in the presence of light. The infrared spectrum of the reddish material (B) had a strong absorption at 2042 cm.$^{-1}$ (C—N=N), while the colorless liquid (A) was devoid of any peaks in this region.[4]

Discussion

The thermal decomposition of phenylmethyldiazirine (III) to give styrene compared with that of 1-phenyldiazoethane (IV) which gave acetophenone azine is to be contrasted with the results of the thermal decomposition of pentamethylenediazirine (V) and of diazocyclohexane (VI); cyclohexene was isolated in 97% yield from V[2] and 100% yield from VI.[5] Similarly, purely aliphatic diazoalkanes generally give good yields of hydrocarbons. The introduction of a phenyl group evidently had a significant effect on the course of the decomposition, since no hydrocarbon could be isolated from the thermal decomposition of 1-phenyldiazoethane. Presumably, the decomposition of V and VI must have had a common intermediate, the singlet state carbene (VII) which underwent a 1,2-hydrogen shift to give cyclohexene. The formation of a divalent carbon (phenylmethylcarbene) is not essential in the generation of acetophenone azine from 1-phenyldiazoethane. In fact, it is probably not at all involved since no product resulting from hydrogen abstraction (from solvent) by the triplet state species was detected. The formation of acetophenone azine can be viewed as resulting *via* the dimerization of the diazoalkane.[6]



III IV



V VII VI

(1) C. G. Overberger and J.-P. Anselme, *Tetrahedron Letters*, 1405 (1963). We suggest that the term *electroisomers* is more appropriate for the special cases involving dipolar species.

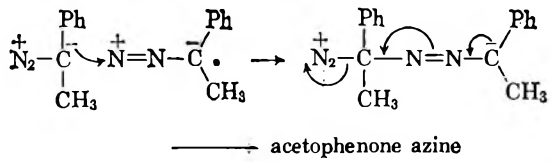
(2) E. Schmitz and R. Ohme, *Ber.*, **94**, 2166 (1961).

(3) H. Staudinger and A. Gaule, *ibid.*, **49**, 1887 (1916).

(4) See ref. 1 for a discussion of this phenomenon.

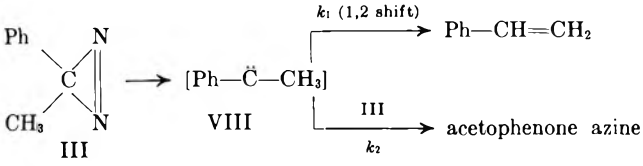
(5) L. Friedman and H. Schechter, *J. Am. Chem. Soc.*, **83**, 3159 (1963).

(6) P. Yates, D. G. Farnum, and D. H. Wiley, *Tetrahedron*, **18**, 881 (1962).

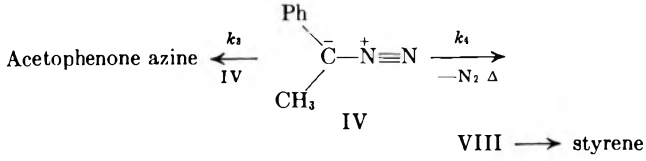


acetophenone azine

On the other hand, the formation of styrene from the thermal decomposition of phenylmethyldiazirine (III) must have involved the intermediacy of the corresponding carbene (VIII, singlet state). Schmitz[7] has noted the unusual inertness of diazirines (I) and it is reasonable to assume that a 1,2-hydrogen shift of the intermediate carbene would be favored over its reaction with unchanged diazirine ($k_1 >>> k_2$).

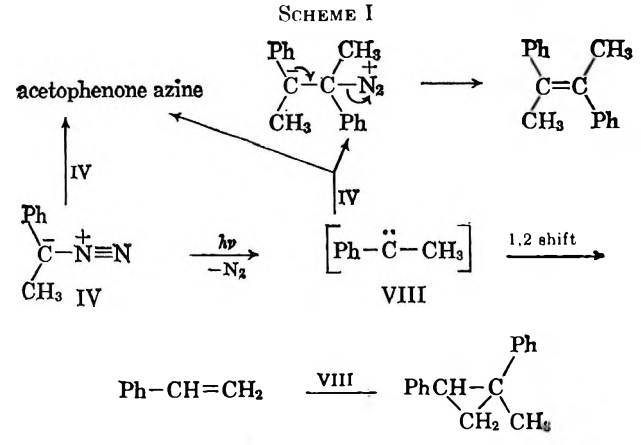


In the thermal decomposition of IV, the competition between the dimerization of the diazoalkane to acetophenone azine and the loss of nitrogen to give phenylmethylcarbene (VIII) seems to be the important factor. The overwhelming preference of the former (dimerization) may explain the sole formation of acetophenone azine ($k_3 >>> k_4$). The absence of any 2,3-diphenylbutane is, therefore, not surprising, since apparently VIII was not formed during thermal decomposition.



The formation of styrene during the photolysis of 1-phenyldiazoethane was significant, since, in this case, phenylmethylcarbene (singlet) must have been involved. Whether or not prior tautomerization to the diazirine (IV → III → VIII) took place cannot be ascertained from the present data. The large amount of acetophenone azine isolated mitigated against the possibility that styrene arose *via* the photolytic decomposition of the azine.[8] Furthermore, it has been shown that fairly high temperatures were required to convert azines to the corresponding olefins.[9] The absence of 2,3-diphenylbutane indicated that the triplet state carbene did not exist during the photolysis. The dimerization of 1-phenyldiazoethane (*vide supra*) probably contributed a very large extent to the formation of the azine. The various paths leading to the observed products are depicted in Scheme I.

SCHEME I



From the data presented, it can be concluded that the thermal decomposition of 1-phenyldiazoethane proceeded without the intermediacy of a divalent carbon; acetophenone azine arose solely *via* dimerization of the diazoalkane. The participation of a divalent carbon in the singlet state must have been involved in order to explain the formation of styrene during the photolytic decomposition of 1-phenyldiazoethane. No triplet state apparently was formed.

Experimental[10]

N-Benzylacetophenone Imine.—The general procedure used by Overberger, Marullo, and Hiskey[11] for the preparation of N-methylbenzylidene α-methylbenzylamine was followed. A mixture of 173.1 g. (1.44 moles) of acetophenone, 154.5 g. (1.44 moles) of benzylamine, 400 ml. of benzene, and 0.1 g. of *p*-toluenesulfonic acid was refluxed with stirring in a 2-l. flask equipped with a condenser and a Dean–Stark trap. After the theoretical amount of water had collected, the resulting yellow solution was cooled to 0° and washed with dilute solution of sodium bicarbonate and water until neutral. The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed *in vacuo*. The residual viscous yellow oil then was distilled. After a forerun consisting mainly of acetophenone and benzylamine, 148 g. (49%) of a pale yellow liquid was collected at 125–126° (0.4 mm.). Upon standing overnight in the refrigerator, the product crystallized completely. Recrystallization from methanol–water (4:1) gave the pure product, m.p. 43–44°, lit.[12] m.p. 43.5–44.5°, prepared by condensation without removal of water and without solvent.

Attempted Synthesis of Phenylmethyl-1-diazacyclopropene[2] (Phenylmethyldiazirine).—To a mixture of 150 ml. of liquid ammonia and 240 ml. of methanol at −60° was added 83.9 g. (0.40 mole) of N-benzylacetophenone imine in 200 ml. of methanol. The mixture was stirred for 3 hr. and the temperature was allowed to rise to −30°. Then 54 g. (0.40 mole) of 85% hydroxylamine-O-sulfonic acid in 350 ml. of methanol, cooled to −10°, was added rapidly and the reaction mixture was stirred for 3 hr. at −30°. After that time, the cooling bath was removed and the reaction mixture was allowed to stand overnight. The residual oil obtained after filtration of the salts and removal of the solvents was dissolved in 1500 ml. of ether and dried over anhydrous sodium sulfate. Then excess powdered Dry Ice was added and the carbonate salt of benzylamine was collected. The solvent was evaporated *in vacuo* and, upon cooling, 1.5 g. of acetophenone azine, m.p. 120–121°, precipitated. Distillation of the oily filtrate through a 6-in. Vigreux column gave the separation shown in Table I.

TABLE I

Fraction (g.)	Temp., °C.	Pressure, mm.	Remarks
I (∼1)	35–45	1.0	Reddish pink liquid which deposited some white crystals
II (∼4)	45–86	0.9	Slight pinkish color
III (∼0.3)	87–88	0.8	Slight amber color, crystallized in freezer, m.p. 39–40° (hydrazine)
IV (∼5)	90–94	0.7	Colorless, crystallized upon standing, m.p. 57–59° (acetophenone oxime)

(7) E. Schmitz, *Sitzber. Deut. Akad. Wiss. Berlin Kl. Chem. Geol. Biol.*, **6**, 23 (1962).

(8) C. H. Wang, *Proc. Chem. Soc.*, 309 (1961).

(9) H. E. Zimmerman and S. Somasekhara, *J. Am. Chem. Soc.*, **82**, 5865 (1960); C. G. Overberger and P. Chien, *ibid.*, **82**, 5874 (1960).

(10) All melting and boiling points are uncorrected.

(11) C. G. Overberger, N. P. Marullo, and R. O. Hiskey, *J. Am. Chem. Soc.*, **83**, 1374 (1961).

(12) G. Reddelien, *Ber.*, **53**, 338 (1920).

Fraction II was redistilled and gave a colorless liquid, b.p. 53–55° (3.7 mm.), main fraction. Upon standing in the light for 2 days, this colorless oil took on a pinkish tinge which deepened to a pinkish red. The infrared spectrum of the colorless oil was free of any absorption between 2600 and 2000 cm.$^{-1}$ while the reddish material had a strong band at 2042 cm.$^{-1}$; 1-phenyldiazoethane absorbs strongly at 2040 cm.$^{-1}$.

Thermal Decomposition of 1-Phenyldiazoethane.—To 75 ml. of refluxing benzene was added 100 ml. of a hexane solution of 1-phenyldiazoethane [prepared from 30 g. (0.22 mole) of acetophenone hydrazone and 60 g. (0.30 mole) of mercuric oxide[3]]. After 12 hr., the nitrogen evolution had stopped and the color of the solution had changed from deep red to yellow, indicating that complete decomposition had occurred. The yellow solution was dried over anhydrous sodium sulfate and the solvent was evaporated *in vacuo;* acetophenone azine, m.p. 119–120°, m.m.p. 119–121°, was collected with the aid of small portions of hexane. More azine was obtained from the successive filtrates until almost no color remained in the filtrate. Evaporation of the last filtrate gave trace amounts of acetophenone (identified by comparison of its infrared spectrum with that of an authentic sample) and benzoic acid; mixture melting point with a commercial sample was 120–122°.

Photolysis of 1-Phenyldiazoethane.—A solution of 1-phenyldiazoethane prepared from 47.4 g. (0.35 mole) of acetophenone hydrazone and 112 g. (0.52 mole) of mercuric oxide[3] in 330 ml. of hexane was photolyzed at 0–5° by means of a Hanovia high pressure mercury immersion lamp (200 watts). The progress of the reaction was followed by the evolution of nitrogen and the disappearance of the red color. When the red color had changed completely to canary yellow, the irradiation was stopped and the precipitated azine was collected. Further concentration of the resulting filtrates gave more acetophenone azine, m.p. 120–121°. A total of about 17 g. of azine was collected. The yellowish residue was taken up in 100 ml. of hexane and passed through a column of alumina; elution with hexane and benzene gave, after the removal of the solvents *in vacuo*, an almost colorless oil (~5 ml.). Distillation of this oil *in vacuo* gave a colorless liquid (~1.5 ml.), b.p. 80–81° (0.1 mm.). This clear oily liquid on standing crystallized almost completely as tiny needles, m.p. 105–106°. The n.m.r. of this solid in carbon tetrachloride solution had two sharp singlets at τ 2.71 (aromatic protons) and 8.03 (methyl protons). The spectrum was consistent with that expected for *trans*-α,α'-dimethylstilbene, m.p. 106–107°. The colorless filtrate was too small to be characterized conclusively. Its infrared spectrum had strong absorptions at 3058 and 1027 cm.$^{-1}$ (cyclopropane) and was almost identical with that of the product prepared by the addition of phenyldiazomethane to α-methylstyrene, followed by thermal decomposition of the intermediate 1-pyrazoline; the expected 1,2-diphenyl-1-methylcyclopropane was obtained as a colorless oil, b.p. 113–114° at 1 mm., but was contaminated by some olefin and the isomeric cyclopropane (*dl-cis* and *-trans* are possible here). From the Dry Ice trap used during the distillation was obtained a colorless liquid having a strong odor of styrene, positively identified by its infrared, ultraviolet, and n.m.r. spectra. Bromination of this liquid gave styrene dibromide, m.p. 74–75°. The residue from the distillation was examined and only small amounts of acetophenone azine and polymeric material were present. No 2,3-diphenylbutane could be detected.

Acknowledgment.—We gratefully wish to acknowledge the support of this work by the National Science Foundation, Grant No. NSF G-17448 and the technical assistance of Mr. Ned Weinshenker.

Derivatives of Sulfenic Acids. XLIV. The Kinetics of the Reaction of 2,4-Dinitrobenzenesulfenyl Chloride with Phenylacetylene and 3-Hexyne[1]

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Received December 5, 1963

The rates of additions of 2,4-dinitrobenzenesulfenyl chloride (I) to phenylacetylene and 3-hexyne, in dry acetic acid at 45° and 55°, follow second-order kinetics, $-d(ArSCl)/dt = k[ArSCl][RC{\equiv}CR']$. Addition of I to phenylacetylene is about 1/100th as fast as to styrene, while the addition to 3-hexyne is about 1/10th as fast as to cyclohexene. The addition of I to diphenylacetylene is also slower than are those of I to the stilbenes. Values for the activation energies and entropies of activation for the reactions of I with the acetylenes are given and compared with recorded values of these parameters for olefin additions. The rates of reactions of I with alkynes and alkenes are compared with available comparable data for bromine additions, and the need for further study of selected examples is noted. The structure of the adduct of I to phenylacetylene was shown to be $C_6H_5C(Cl){=}CH(SAr)$, where Ar = 2,4-dinitrophenyl, with a *trans* disposition of ArS and Cl groups assumed.

Earlier studies from this laboratory concerned additions of 2,4-dinitrobenzenesulfenyl chloride (I) to styrene,[2] *p*-substituted styrenes,[2a] and certain related compounds, including some symmetrical alkynes.[3-5] Studies of the reactions of I with cyclohexene were described by Hogg and Kharasch,[6] with *cis*- and *trans*-2-butene by Kharasch and Havlik,[7,8] with the *cis*- and *trans*-stilbenes by Slobodkin and Kharasch,[9] and with olefin oxides by Peters and Kharasch.[10] Related reactions with several olefins[11,12] and some bicyclic olefins[11-13] have also been examined.

For several additions of I to olefins, the kinetics of the reactions were investigated and the mechanism of addition to the carbon–carbon double bond was discussed.[2,6,9] Interest in the corresponding additions to the carbon–carbon triple bond prompted the present study. Phenylacetylene was selected because kinetic data are available for quantitative comparison with styrene, the corresponding olefin. Reaction rates for the addition of I to 3-hexyne were also determined, although quantitative data for the reaction with the corresponding olefin, 3-hexene, are not available.

(1) This study was supported by grants from the National Science Foundation and the Office of Army Research (Durham).

(2) (a) W. L. Orr and N. Kharasch, *J. Am. Chem. Soc.*, **75**, 6030 (1953); (b) **78**, 1201 (1956).

(3) N. Kharasch and S. J. Assony, *ibid.*, **75**, 1081 (1953).

(4) N. Kharasch and S. J. Assony, *ibid.*, **77**, 3390 (1955).

(5) S. J. Assony and N. Kharasch, *Chem. Ind.* (London), 1388 (1954).

(6) D. R. Hogg and N. Kharasch, *J. Am. Chem. Soc.*, **78**, 2728 (1956); *cf.* D. S. Campbell and D. R. Hogg, *J. Chem. Soc.* (submitted).

(7) N. Kharasch and A. J. Havlik, *J. Am. Chem. Soc.*, **75**, 3734 (1953).

(8) A. J. Havlik and N. Kharasch, *ibid.*, **78**, 1207 (1956).

(9) N. R. Slobodkin and N. Kharasch, *ibid.*, **82**, 5837 (1960).

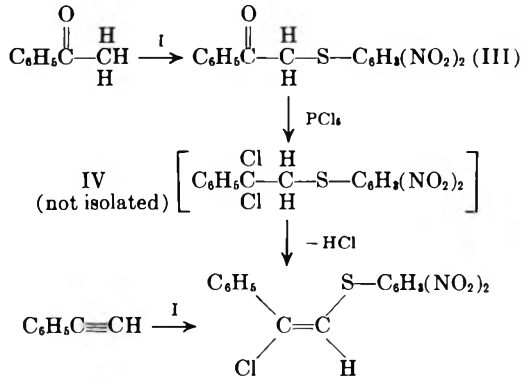
(10) D. Peters and N. Kharasch, *J. Org. Chem.*, **21**, 590 (1956).

(11) N. Kharasch and C. M. Buess, *J. Am. Chem. Soc.*, **71**, 2724 (1949).

(12) E. W. Melmberg and F. G. H. Lee, paper presented before the Organic Division, at the 127th National Meeting of the American Chemical Society, Minneapolis, Minn., April, 1955.

(13) H. Kwart and R. K. Miller, *J. Am. Chem. Soc.*, **78**, 5682 (1956).

The reaction of I with phenylacetylene in acetic acid led to a high yield of 1:1 adduct which was shown to be 2-chloro-2-phenylethenyl 2′,4′-dinitrophenyl sulfide (II), $C_6H_5(Cl)C{=}C(H){-}S{-}C_6H_3(NO_2)_2$. The question as to whether the chlorine and ArS moieties are *cis* or *trans* in II has not been fully resolved. However, in view of the *trans* additions of I to olefins and the ionic nature of the reactions, the *trans* configuration is suggested. The basis for assigning the attachment of chlorine in II was the reaction of III with phosphorus pentachloride, which gave II as the major product.[14]



The product of the reaction of I with 3-hexyne has been reported previously as 4-chloro-3-(2′,4′-dinitrophenylthio)-3-hexene, isolated in 93% yield.[3] This adduct is also tentatively assumed to have the *trans* configuration for the ArS and Cl groups.

Kinetic Data.—The rates of addition of I to phenylacetylene and 3-hexyne were determined in dry acetic acid solution. The reactions were followed by measuring the rates of disappearance of the sulfenyl chloride (I) by the methods previously described.[1,15]

The reaction with phenylacetylene was inconveniently slow at 35 and 45°, but satisfactory rate measurements were obtained at the latter temperature and at 55°. The reaction with 3-hexyne was considerably faster and the rates were measured conveniently at 35 and 45°. Data for typical rate runs are given in Tables I and II and are shown in Fig. 1 and 2, plotted as second-order reactions—first order in each reactant. Concentrations were varied in the different rate runs and, although only a limited number of runs were made, there was no indication of deviations from simple second-order kinetics. The calculated second-order rate constants for the reactions of I with the acetylenes are therefore directly comparable to the second-order rate constants previously reported for the reactions of I with olefins.

TABLE I

REACTION OF 2,4-DINITROBENZENESULFENYL CHLORIDE WITH PHENYLACETYLENE IN ACETIC ACID AT 55.00 ± 0.02°

Time, sec.	Concn. of ArSCl, moles/l. $(b - x)$	Concn. of acetylene, moles/l. $(a - x)$	$\log \frac{b(a-x)}{a(b-x)}$	k, (moles/l.)$^{-1}$ sec.$^{-1}$ × 10^3
0	0.03985	0.20000		
6,900	0.03522	0.19537	0.04346	9.06
11,100	0.32151	0.19266	0.07217	9.35
15,000	0.03070	0.19085	0.09295	8.91
17,160	0.02980	0.18995	0.10381	8.70
21,000	0.02739	0.18754	0.13490	9.24
25,200	0.02619	0.18634	0.15157	8.65

Mean k = 8.98

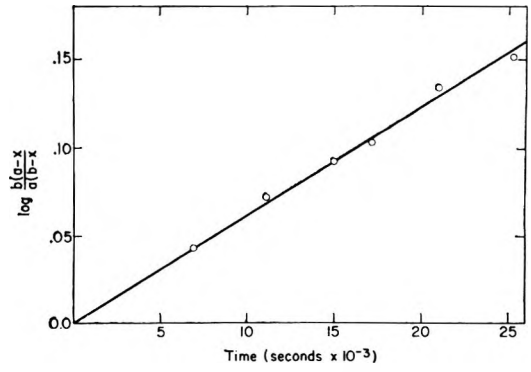


Fig. 1.—Second-order plot for the reaction of phenylacetylene with 2,4-dinitrobenzenesulfenyl chloride at 55 ± 0.02°.

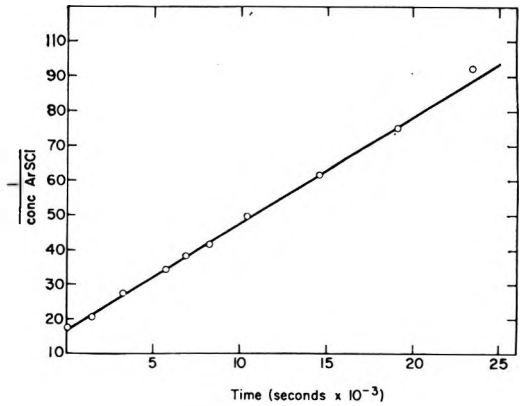


Fig. 2.—Second-order plot for the reaction of 3-hexyne with 2,4-dinitrobenzenesulfenyl chloride at 45 ± 0.02°.

TABLE II

REACTION OF 2,4-DINITROBENZENESULFENYL CHLORIDE WITH 3-HEXYNE IN ACETIC ACID AT 45.00 ± 0.02°

Time, sec.	Concn. of ArSCl,[a] moles/l. $(a - x)$	$1/(a - x)$	k, (moles/l.)$^{-1}$ sec.$^{-1}$ × 10^3
0	0.05690	17.57	
1,440	0.04876	20.51	(2.04)[b]
3,240	0.03642	27.46	3.05
5,700	0.02920	34.25	2.93
6,900	0.02619	38.19	2.99
8,280	0.02408	41.53	2.89
10,380	0.02017	49.59	3.08
14,700	0.01625	61.52	2.97
19,080	0.01330	75.17	3.02
23,400	0.01080	92.29	(3.19)[b]

Mean k = 2.99

[a] Both reactants were at equal initial concentrations. [b] Values in parentheses were neglected in calculating the mean value of k.

The rate constants for the reactions of I with phenylacetylene and 3-hexyne are summarized in Table III, together with the derived values for the energy and entropy of activation.

Besides the reactions already mentioned, the rate of reaction of I with diphenylacetylene was explored in a single experiment. In acetic acid at 45°, the reaction was found to be extremely slow and the reaction was followed to only 10% completion. The rate appears

(14) A small amount of an isomer of II, presumably the *cis* isomer, was also isolated from the reaction of III with phosphorus pentachloride (see Experimental).

(15) N. Kharasch and M. M. Wald, *Anal. Chem.*, **27**, 996 (1955).

TABLE III

RATE CONSTANTS AND ARRHENIUS PARAMETERS FOR THE REACTION OF 2,4-DINITROBENZENESULFENYL CHLORIDE WITH ACETYLENES IN ACETIC ACID

Acetylene	Temp., °C.	k, (moles/l.)$^{-1}$ sec.$^{-1}$	E_a, kcal./mole[a]	log A	ΔS^*, cal./deg.[b]
Phenylacetylene	45.00 ± 0.02	2.55×10^{-5}			
		2.79×10^{-5}			
		Av. (2.67×10^{-5})			
	55.00 ± 0.02	8.98×10^{-5}			
		8.25×10^{-5}			
		Av. (8.61×10^{-5})	24.3 ± 1.3	12.12	−3.3 ± 4.1
3-Hexyne	35.00 ± 0.02	1.27×10^{-3}			
		1.32×10^{-3}			
		Av. (1.29×10^{-3})			
	45.00 ± 0.02	2.89×10^{-3}			
		2.99×10^{-3}			
		Av. (2.94×10^{-3})	16.1 ± 0.7	8.52	−19.7 ± 2.2

[a] Calculated from the Arrhenius equation in the form $k = Ae^{-E_a/RT}$. [b] Calculated from the value of A by the equation $A = (kT/h)e^{\Delta S^*/R}$.

to be about one-half that of phenylacetylene under comparable conditions. The estimated rate constant was 1.6×10^{-5} (moles/l.)$^{-1} \times$ sec.$^{-1}$, at 45°.

Experimental

Materials and Methods.—Dry acetic acid and 2,4-dinitrobenzenesulfenyl chloride (I) were prepared by techniques previously reported.[1] Phenylacetylene (Eastman Organic Chemicals) was redistilled, 47–48° at 24 mm., using a few drops of octylic alcohol to prevent foaming. The 3-hexyne (Farchan Research Laboratories) was redistilled at atmospheric pressure. The center cut, distilling at 80–80.5°, was used. Diphenylacetylene was prepared in pure form by the method in "Organic Syntheses."[16]

Rate runs were made by essentially the same procedures and techniques as used by Orr and Kharasch.[1,2] Stock solutions of sulfenyl chloride and unsaturated compounds were prepared by dissolving weighed amounts of freshly purified materials in the desired volume of dry acetic acid at the temperature of each run. The second-order rate constants were calculated in the usual manner, as described previously.[1,2]

Adduct of I and Phenylacetylene. 2-Chloro-2-phenylvinyl-2′,4′-dinitrophenyl Sulfide (II).—To 1.0 g. (0.0042 mole) of 2,4-dinitrobenzenesulfenyl chloride in 20 ml. of acetic acid, 1.6 g. (0.0156 mole) of phenylacetylene was added. The reaction mixture was allowed to stand for 2 days at room temperature (28°) until the iodine–starch test was negative. The mixture was then poured into 100 g. of ice–water. The yellow oil which first separated solidified while being washed with water to remove acetic acid. The crude dry product (1.13 g., 79% yield, m.p. 119–124°) was recrystallized from 95% ethanol, yielding a yellow solid, m.p. 124–130°. Further purification was achieved by chromatography on a 20-cm. column of alumina using Skellysolve A–benzene mixture, 1:1 by volume, for development and elution. The residue from the eluent was recrystallized from 95% ethanol yielding yellow needles, m.p. 138.7–141°. Further recrystallizations gave a constant melting point of 139–141°.

Anal. Calcd. for $C_{14}H_9ClN_2O_4S$: C, 49.94; H, 2.69; Cl, 10.54; N, 8.3; S, 9.5. Found: C, 50.27; H, 2.77; Cl, 10.79.

A similar experiment carried out at 80° was complete in 3 hr. and gave a 91% yield of crude product.

2,4-Dinitrophenyl Phenacyl Sulfide (III).—Ten grams of I was dissolved in 130 ml. of glacial acetic acid and an excess of acetophenone (10 g.) was added. The mixture was heated at 82–85° until the iodine–starch test for the sulfenyl chloride was negative (5 hr.). The major portion of the product precipitated upon cooling and was removed by filtration. A small additional amount was precipitated by dilution of the filtrate with water. The total yield of crude product was 10 g., 75% yield. Recrystallization from acetic acid gave 9 g. of product, m.p. 170–170.5°, lit.[17] m.p. 168°

(16) L. I. Smith and M. M. Falkof, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 350; *cf. Org. Syn.*, **34**, 42 (1954).

(17) N. Kharasch, H. L. Wehrmeister, and H. Tigerman, *J. Am. Chem. Soc.*, **69**, 1612 (1947).

Reaction of 2,4-Dinitrophenyl Phenacyl Sulfide with Phosphorus Pentachloride.—Phosphorus pentachloride, 4.0 g. (0.02 mole), was dissolved in 25 ml. of carbon tetrachloride by heating in a 100-ml. three-necked flask equipped with a thermometer, condenser, and mechanical stirrer. A solution of 3.0 g. (0.0094 mole) of 2,4-dinitrophenyl phenacyl sulfide in 20 ml. of ethylene chloride was added, and the mixture refluxed for 24 hr. The solution was transferred to a separatory funnel, washed twice with water, and dried over anhydrous sodium sulfate; the solvent was removed by aspiration. The yellow residue (2.78 g., m.p. 129–144°) was dissolved in Skellysolve A–benzene (1:1 by volume) and chromatographed through a 20-cm. alumina column. The yellow material was eluted with the same solvent mixture. The residue from the eluent, upon recrystallization from methyl alcohol, deposited a mixture of both yellow plates and needles. The plates and needles were separated mechanically, with the aid of a microscope. Melting points for the needles and plates, respectively, were 122–130° and 157–158°. A second chromatographic separation of this mixture on a 45-cm. column and using a 3:1 mixture of Skellysolve A–benzene for elution resolved the mixture into two bands, a pale yellow band, followed by a deep yellow band. The material from the pale yellow band was recrystallized from 95% ethanol to obtain light yellow needles with a constant melting point of 141.5–142°. Chlorine analysis, melting point, and the infrared spectrum established that this product was identical with the adduct II obtained from the reaction of 2,4-dinitrobenzenesulfenyl chloride with phenylacetylene.

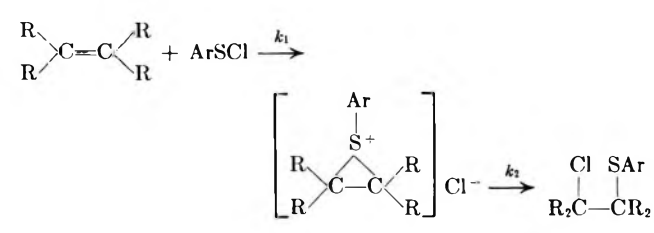
Anal. Calcd. for $C_{14}H_9ClN_2O_4S$: Cl, 10.54. Found: Cl, 11.07.

The product from the deep yellow band reached a constant melting point of 154.5–156° after several recrystallizations from ethanol. Chlorine analysis and the infrared spectrum suggest that this product is an isomer of II, presumably the *cis* isomer.

Anal. Calcd. for $C_{14}H_9ClN_2O_4S$: Cl, 10.54. Found: Cl, 10.47.

Discussion

There is now considerable evidence which indicates that addition of 2,4-dinitrobenzenesulfenyl chloride to olefins in acetic acid solution proceeds by a polar mechanism, represented as a two-step process in which the electrophilic attack on the double bond is believed to be the rate-determining step.[1,2]



The direction of addition to unsymmetrical olefins, the demonstration of stereospecific addition, and the effect of substituents on the reaction velocities are consistent with this mechanism, which is entirely analogous to the generally accepted mechanism for bromine addition to olefins in polar solvents.[18]

While the reactions at ethylenic and acetylenic bonds are formally analogous, it has long been suggested that the unsaturation electrons of acetylenes are more tightly held then are those of corresponding alkenes.[19]

Hence the rates of electrophilic attack by ArSCl, or Br_2, may be expected to be slower than similar reactions with olefins. While it is somewhat surprising that this phenomenon has not been more fully studied, both the present results for the additions of I to acetylenes and the earlier data of Robertson, *et al.*,[20] for rates of bromine addition, in acetic acid, confirm the lower reaction rates for the alkynes.

Rate data for the reaction of I with a number of olefins are collected in Table IV for reference. Comparison of the present results for the addition of I to acetylenes (Table III) with those for the appropriate olefins shows significantly lower reaction velocities for the acetylenes. Thus, the rate ratio for styrene–phenylacetylene is about 106. Using the approximate value for the reaction of diphenylacetylene, the rate ratio for the pair, *trans*-stilbene–diphenylacetylene, is about 7. Robertson's data[20] for bromine addition in acetic acid at 25° show the same trends, but with considerably greater differences in reactivity between the ethylenes and acetylenes. For examples, the rate ratios for the pairs styrene–phenylacetylene and stilbene–diphenylacetylene were reported as about 3000 and 250, respectively, in this reaction.

TABLE IV

SUMMARY OF KINETIC PARAMETERS FOR THE REACTIONS OF 2,4-DINITROBENZENESULFENYL CHLORIDE WITH OLEFINS IN ACETIC ACID AT 45°

Olefin	k, (moles/l.)$^{-1}$ sec.$^{-1}$ × 10^3	E_a, kcal./mole	log A	S^*, cal./mole	Ref.
Cyclohexene	27.6	11.1	6.06	−32.7	6
p-Methylstyrene	9.43[a]	12.0	6.20	−32.2	2
Styrene	2.90	12.9	6.34	−31.6	2
Stilbene (*cis*)	0.109[b]	13.8	5.52	−33.4	9
p-Chlorostyrene	0.093	15.9	7.91	−24.4	2
p-Nitrostyrene	0.0693	16.9	7.46	−26.5	2

[a] This is the experimental value for a single determination at 44.9°; the value of k calculated from E_a and log A is 9.1. [b] All rate constants in ref. 9 have been found to be high by a factor of ten. The values tabulated here have been corrected for this error, which was kindly pointed out to us by Dr. D. R. Hogg of the University of Aberdeen, Scotland. It should also be noted that the plot of log k *vs.* $1/T$ for the *trans*-stilbene reaction in ref. 9 showed a slight curvature. A subsequent determination of the rate at 35° by Hogg indicated that the curvature is real and sufficient to preclude the calculation of an activation energy for the reaction. The reported activation energy for the *trans*-stilbene reaction should thus be questioned. Further work to check these points is in progress.

The intrinsic mechanism of the addition of bromine, or of other electrophilic reagents, to acetylenes has not been established although much speculation exists on the subject. Robertson, *et al.*,[20] believed that the addition of bromine proceeds similarly to the addition to alkenes, *viz*, initiation by electrophilic attack, but he also stated that some acetylenic compounds may add bromine by a nucleophilic mechanism.[20,21] Bohlmann,[22] in discussing various reactions of acetylenes, favored an ionic mechanism for bromine addition to acetylenes in acetic acid, but suggested that the reaction was initiated by a nucleophilic attack of the bromine.

Sinn[23] reported the effect of *p*-nitro substituents in stilbenes and diphenylacetylenes (tolanes) on the rates of bromine addition. Whereas the reaction with stilbene was much faster than with *p,p'*-dinitrostilbene, as expected for an electrophilic attack by bromine, the reaction with *p,p'*-dinitrotolane was slightly *faster* than with tolane. The latter result was difficult to reconcile with an electrophilic attack, and Sinn, therefore, proposed a homolytic mechanism for the reaction with acetylenes. It is evident that further studies are required to clarify the mechanism, or mechanisms, of additions of bromine to acetylenes.

The direction of addition of I to phenylacetylene, as shown by the established structure of II, can be rationalized on the basis of an electrophilic attack on the acetylenic bond similar to the postulated mechanism for the reaction with ethylenes. The higher activation energies and less negative entropies of activation for the acetylene reactions, compared to the olefin reactions, are also in the direction consistent with the postulation of similar ionic addition mechanisms. Nevertheless, it is clear that further studies are desirable also in the case of sulfenyl halide additions to alkynes.

Acknowledgment.—We are deeply indebted to the National Science Foundation and to the Army Research Office (Durham) for support of this work, and to Dr. Wilson L. Orr for his assistance in verification of calculations and for helpful discussions.

(18) P. B. D. de la Mare, *Quart. Rev.* (London), **3**, 126 (1949).

(19) A. D. Welch, *Ann. Rept. Progr. Chem.* (Chem. Soc. London), **44**, 35 (1947); *Quart. Rev.* (London), **2**, 78 (1948).

(20) P. W. Robertson, W. E. Dasent, R. M. Milburn, and W. H. Oliver, *J. Chem. Soc.*, 1628 (1950).

(21) R. Daniels and L. Bauer, *J. Chem. Educ.*, **35**, 444 (1958).

(22) F. Bohlmann, *Angew. Chem.*, **69**, 82 (1957).

(23) H. Sinn, *ibid.*, **69**, 754 (1957).

The Addition of Trifluoromethanesulfenyl Chloride to Tetracyanoethylene[1]

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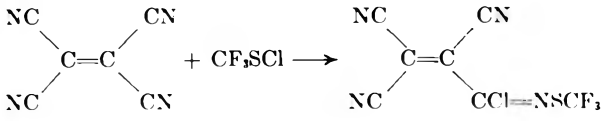
Trifluoromethanesulfenyl chloride adds to a nitrile of tetracyanoethylene in a chloride ion-catalyzed reaction to give 2-chloro-1-trifluoromethylthio-3,4,4-tricyano-1-aza-1,3-butadiene (1). Compound 1 is a weak π-acid as is shown by the formation of charge transfer complexes with aromatic hydrocarbons. Dienes add rapidly to 1 to give the expected substituted cyclohexenes. Electron-deficient olefins react rapidly at the carbon–nitrogen double bond of 1 to give substituted azetidines.

A large number of addition reactions of tetracyanoethylene (TCNE) have been reported.[1-3] The overwhelming majority of these reactions are nucleophilic additions to the carbon–carbon double bond[1-3] or cycloadditions to the carbon–carbon double bond.[1,4,5] Additions to a nitrile of TCNE have been few but are found with ethyl diazoacetate[6] and benzonitrile oxide.[7] This paper reports the addition of trifluoromethanesulfenyl chloride to TCNE to give 2-chloro-1-trifluoromethylthio-3,4,4-tricyano-1-aza-1,3-butadiene (1) and describes the unusual behavior of 1 in cycloaddition reactions.



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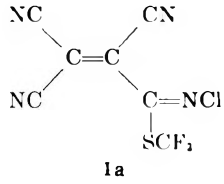
Formation of 1.—A 1:1 adduct of TCNE and trifluoromethanesulfenyl chloride is formed in about 50% yield when an equimolar mixture of the reactants is held for thirty hours in acetonitrile at room temperature. Since the adduct, recrystallized from hexane,[8] is yellow [λ_{max} 335 mμ (ϵ 8700)], addition to the carbon–carbon double bond is excluded. The infrared spectrum of the adduct showed absorption due to conjugated nitrile (4.48 μ), tricyanovinyl double bond (6.35 μ), carbon–nitrogen double bond (6.55 μ), and carbon–fluorine (8 μ). The spectral evidence is in agreement with structure 1 or its isomer 1a. Evidence

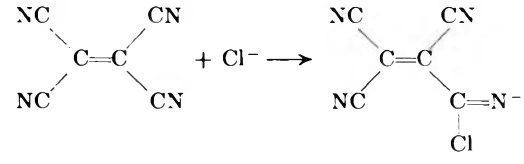


1a

in support of 1 is given below in the reactions of azetidines obtained from cycloaddition reactions of 1 where the $NSCF_3$ group is converted to NH.

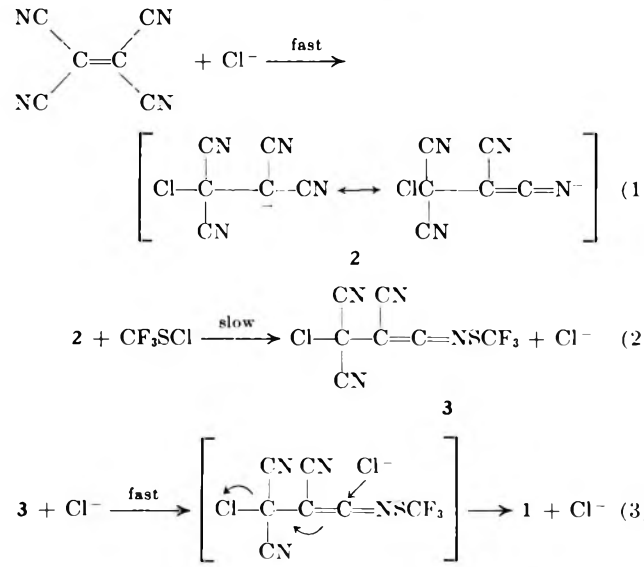
Pure TCNE and trifluoromethanesulfenyl chloride react very slowly in methylene chloride at room temperature. A 77% yield of 1 is obtained after five days, however, if anhydrous tetraethylammonium chloride is added to the system. TCNE is recovered in 90% yield after five days, if the salt is not present. Chloride ion catalysis has been observed previously in the chlorination of tricyanoethylene[9] and TCNE.[10] In these cases, chlorination occurs in acetonitrile solution without added chloride ion, but chloride ion is readily produced from reaction of chlorine with solvent.

It seems unlikely that chloride ion adds directly to a nitrile carbon of TCNE. The resultant anion would



not be expected to have any resonance stabilization. Moreover, under conditions similar to the addition to TCNE we have been unable to detect addition of trifluoromethanesulfenyl chloride to other negatively substituted nitriles, such as cyanogen chloride, trifluoroacetonitrile, tricyanovinylbenzene, and 1.

The following reaction sequence is suggested as a preferable alternative to direct attack on the nitrile.



(1)

2

(2)

3

(3)

Step 1 is known to occur rapidly in the chlorination of TCNE. Step 2 has ample precedent in the addition of alcohol and amines to cyanoform ion to form 1,1-dicyanoethylene derivatives, probably by way of keten-

(1) W. J. Middleton, R. E. Heckert, E. L. Little, and C. G. Krespan, *J. Am. Chem. Soc.*, **80**, 2783 (1958).

(2) W. J. Middleton and V. A. Engelhardt, *ibid.*, **80**, 2788 (1958).

(3) B. C. McKusick, R. E. Heckert, T. L. Cairns, D. D. Coffman, and H. F. Mower, *ibid.*, **80**, 2806 (1958).

(4) J. K. Williams, *ibid.*, **81**, 4013 (1959).

(5) J. K. Williams, D. W. Wiley, and B. C. McKusick, *ibid.*, **84**, 2210 (1962).

(6) R. M. Scribner, G. N. Sausen, and W. W. Prichard, *J. Org. Chem.*, **25**, 1440 (1960).

(7) Unpublished work of Dr. C. L. Dickinson and Dr. C. D. Weis.

(8) The trifluoromethylthio substituent has a tremendous solubilizing effect on polycyano compounds.

(9) C. L. Dickinson, D. W. Wiley, and B. C. McKusick, *J. Am. Chem. Soc.*, **82**, 6132 (1960).

(10) Unpublished work of Dr. C. L. Dickinson of this laboratory.

imines.[11,12] Step 3 looks eminently feasible thermodynamically, for a cumulative double bond system is being isomerized to a highly conjugated system.

Since we have been unable to obtain any spectral evidence for **3**, we must conclude that step 3 occurs much more rapidly than does 2 or that the entire reaction scheme is untenable. The former explanation is preferred.

Chemical Reactivity of 1.—Compound **1** gives many of the reactions expected of a negatively substituted unsaturated system. Polarographic reduction of **1** in acetonitrile solution occurs at +0.1 v. *vs.* s.c.e. as compared with the reduction of TCNE at +0.15 v. under these conditions. The reduction of **1**, however, is irreversible and appears to involve more than one electron.

Weak π-complexes are formed with **1** and aromatic hydrocarbons. Wave lengths of maximum absorption, extinction coefficients, and association constants for some of these complexes are given in Table I. The

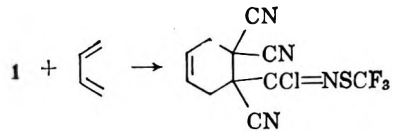
TABLE I

π-COMPLEXES BETWEEN 1 AND AROMATIC HYDROCARBONS IN METHYLENE CHLORIDE AT 25°

Base	λ_{max}, mμ	ϵ	K
p-Xylene	460	2600	4
Durene	500	2600	15
Hexamethylbenzene	537	5000	33
Pyrene	470, 670	1600, 1750	11, 12

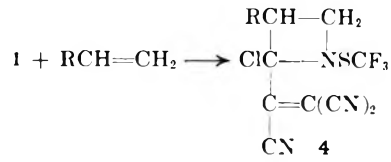
association constants for complex formation were calculated by the method of Keefer and Andrews.[13] Although **1** is reduced polarographically almost as readily as is TCNE, the association constants of **1** with aromatic hydrocarbons are much smaller than those of TCNE.[14] Interaction of **1** with benzene and toluene was too weak to measure spectroscopically.

As a dienophile, **1** is nearly as reactive as is TCNE. Aliphatic dienes, such as butadiene and 2,3-dimethylbutadiene, react exothermically with ethereal solutions of **1** at room temperature. With anthracene, a π-complex is obtained at room temperature which is converted to the adduct by warming to 60°. These addi-



tions occur across the tricyanovinyl double bond of **1** as is evidenced by the infrared spectra of the adducts. The spectra show the absorptions of nonconjugated nitrile, carbon–nitrogen double bond (6.15 to 6.2 μ), and nonconjugated carbon–carbon double bond (in the adducts from butadiene and 2,3-dimethylbutadiene).

While TCNE reacts with electron-rich olefins to give tetracyanocyclobutanes, **1** reacts with vinyl ethers and styrenes at the carbon–nitrogen double bond to give substituted azetidines **4**. These reactions occur even more rapidly than do the reactions of TCNE with the



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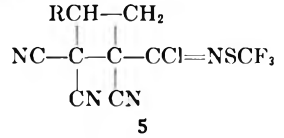
corresponding olefin. The reactions are usually exothermic upon mixing ethereal solutions of the reactants at room temperature. A list of the azetidines of structure **4** which have been prepared is given in Table II.

The structural assignments of the adducts **4** are based primarily on spectral evidence. The presence of a tricyanovinyl group is clearly indicated by infrared absorptions near 4.5 (conjugated nitrile) and 6.3 μ (tricyanovinyl double bond), and ultraviolet absorption at 260 to 268 mμ with molar extinction coefficient around 16,000. The isomeric cyclobutane structures **5** are clearly excluded. Structures **6** are discarded in favor of **4** on the basis of the ultraviolet absorption spectrum of the adduct of **1** with *p*-methoxystyrene (**4**,



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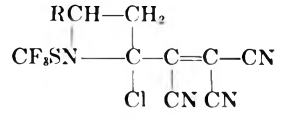

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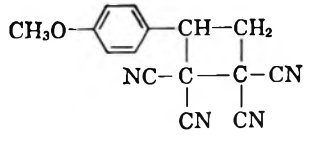
R = *p*-methoxyphenyl). The absorptions of the tricyanovinyl group [λ_{max} 268 mμ (ϵ 18,300)] and the *p*-methoxyphenyl group [λ_{max} 230 mμ (ϵ 15,000)] are more intense than would be expected for the isolated chromophores. The extinction coefficient of the tricyanovinyl group is typically ~16,000 for the azetidines **4**, and compound **7** has λ_{max} 238 μ (ϵ 13,000).[5] The most reasonable explanation for the increased in-



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tensity of absorption is spatial proximity of the two groups. Thus, not only is **4** the preferred structure, but when R = *p*-methoxyphenyl, it is probably *cis* to the tricyanovinyl group.

The n.m.r. spectra of the azetidines **4** are in good agreement with the proposed structures. The ring hydrogens give an ABX pattern common to all the azetidines. Thus, **4** with R = CH_3O has a proton spectrum with the methoxy hydrogens at τ 6.50, the methine hydrogen as four peaks centered at τ 4.80, and the methylene hydrogens as a weak, strong, strong, weak pattern with each split into doublets and centered at τ 7.25.

The rate of formation of tetracyanocyclobutanes, such as **7**, from TCNE and an electron-rich olefin is markedly dependent upon solvent polarity.[5] The rates of adduct formation are larger in solvents of high dielectric constant. The rates of formation of the azetidines **4** are likewise markedly solvent dependent, although not to the extent of the TCNE reactions. When cycloadditions of **1** and vinyl ethers were run in polar solvents such as acetonitrile, the course of addition was not changed. There was still no addition to the tricyanovinyl double bond. The rate dependence on solvent suggests that there is appreciable charge

(11) A. Hantzsch and G. Oswald, *Ber.*, **32**, 641 (1899).

(12) S. Trofimenko, E. L. Little, Jr., and H. F. Mower, *J. Org. Chem.*, **27**, 433 (1962).

(13) R. M. Keefer and L. J. Andrews, *J. Am. Chem. Soc.*, **72**, 4677 (1950); L. J. Andrews and R. M. Keefer, *ibid.*, **73**, 462 (1951).

(14) R. E. Merrifield and W. D. Phillips, *ibid.*, **80**, 2778 (1958).

TABLE II

2-CHLORO-2-TRICYANOVINYL-1-TRIFLUOROMETHYLTHIOAZETIDINES

R	Empirical formula[a]	M.p., °C.	Recrystallization solvent	Yield, %	Carbon, %		Hydrogen, %		Nitrogen, %		Fluorine, %		Chlorine, %	
					Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
CH_3CH_2O	$C_{11}H_5ON_4F_3ClS$	112–112.4	Heptane	76	39.2	38.9	2.40	2.45	16.6	16.2	16.9	17.0	10.6	11.0
$CH_3CH_2CH_2CH_2O$	$C_{13}H_{11}ON_4F_3ClS$	106–106.6	Hexane	89	42.8	42.9	3.31	3.46	15.4	15.5	. .	. .	. .	. .
CH_3O	$C_{10}H_6ON_4F_3ClS$	139–140	Hexane–benzene	82	37.2	37.1	1.87	2.29	17.4	17.2	. .	. .	11.0	11.2
$CH_3{-}CHO$	$C_{11}H_6ON_4F_3ClS$	132.8–134	Hexane–benzene	74	39.5	39.9	1.81	2.11	16.7	16.7	. .	. .	10.6	10.5
C_6H_5	$C_{15}H_8ON_4F_3ClS$	115–117	Hexane	91	48.8	48.4	2.20	2.19	15.2	15.5	. .	. .	. .	. .
$CH_3O{-}C_6H_4$	$C_{16}H_{10}ON_4F_3ClS$	132.8–133.6	Hexane–benzene	87	48.2	48.1	2.54	2.65	14.0	13.7	14.3	14.3	8.89	8.90

[a] These compounds may merit consideration as unknowns in organic qualitative elemental analysis.

separation in the transition state. On this basis the transition state leading to **4** appears much more reasonable than one leading to the isomeric **6**. Thus, **8** allows a greater delocalization of charge than does **9**. The

8

9

transition state **8** leading to **4** has a charge distribution of the azomethine double bond which is opposite that of simpler azomethines in their cycloaddition reactions with ketenes.[15] The reversal in polarity is a consequence of the ability of the adjacent tricyanovinyl group to stabilize a negative charge.

The addition of styrene to **1** is a reversible reaction. When the resultant azetidine is dissolved in benzene, the red color of the π-complex of **1** and styrene develops. This indicates the ease of dissociation of the azetidine into its components. The reversal of the cycloaddition reaction gives additional support to the thesis that there is considerable charge separation in the transition states of these cycloadditions. There is no reason to expect homolytic fission of the carbon–carbon bond in question in **8**. Starting materials were recovered from the attempted addition of **1** to 2,3-dimethyl-2-butene.

The reaction of **1** with N-vinylpyrrolidone gave a compound without a trifluoromethylthio group. Spectral evidence similar to that cited above showed the presence of the tricyanovinyl group. In addition, N–H absorption was apparent in the infrared spectrum. The product has been assigned structure **10**. Conver-

10

sion of the trifluoromethylthioazetidines **4** to the azetidines **10** has been found to be a general reaction conveniently effected by nucleophilic reagents, such as alcohols or pyridine. The properties of the azetidines **10** are given in Table III.

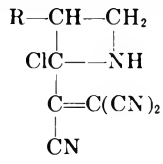
Although the conversion of **4** → **10** generally required heating **4** with an alcohol for several hours, the reaction is not a thermal fission of the nitrogen–sulfur bond. The azetidines **4** may be quantitatively recovered from solutions in refluxing dimethoxyethane after several days. The reaction probably proceeds by way of nucleophilic attack on sulfur. No attempt was made to isolate the thiaperoxides which are presumed to have been formed.

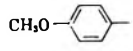
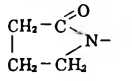
The azetidine **10** with R = *p*-methoxyphenyl also shows the increased intensities of the *p*-methoxyphenyl [λ_{max} 230 mμ (ϵ 15,500)] and the tricyanovinyl [λ_{max} 269 mμ (ϵ 19,400)] absorptions, indicating an adjacent *cis* relationship of the two groups.

(15) H. Staudinger, *Ber.*, **40**, 1145 (1907); *Ann.*, **356**, 93 (1907).

TABLE III

2-CHLORO-2-TRICYANOVINYLAZETIDINES



R	Empirical formula	M.p., °C.	Recrystallization solvent	Yield, %	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found
	$C_{15}H_{11}N_4OCl$	262–263.5	Ethylene chloride	73	60.3	60.3	3.71	3.99	18.7	18.4	11.9	12.1
CH_3O-	$C_9H_7N_4OCl$	166–167.4	Methanol	64	48.6	48.8	3.17	3.27	25.2	25.3	15.9	15.9
CH_3CH_2O-	$C_{10}H_9N_4OCl$	154–155.5	Ethylene chloride	60	50.8	51.4	3.83	3.97	23.7	24.0	15.0	14.9
	$C_{12}H_{10}N_5OCl$	222–223	[a]	70	52.3	52.3	3.66	3.52	25.4	25.8	12.9	12.8

[a] Recrystallization was not effected. Purification was by rinsing with dimethoxyethane.

The conversion of **4** → **10** provides the evidence mentioned previously for the selection of structure **1** rather than **1a** for the adduct of TCNE and trifluoromethanesulfenyl chloride.

Experimental[16]

2-Chloro-1-trifluoromethylthio-3,4,4-tricyano-1-aza-1,3-butadiene (I).—A slurry of 64 g. of TCNE, 75 g. of trifluoromethanesulfenyl chloride, and about 2 g. of tetraethylammonium chloride in 500 ml. of methylene chloride was stirred under nitrogen at room temperature for 5 days. The mixture was then filtered and the filtrate was evaporated to dryness. The residue was crystallized from hexane to give **1** as yellow plates, m.p. 86–87°, 103 g. (77%).

Anal. Calcd. for $C_7ClF_3N_4S$: C, 31.8; Cl, 13.4; F, 21.5; N, 21.2; S, 12.1. Found: C, 32.5; Cl, 13.5; F, 21.2; N, 21.1; S, 12.0.

The infrared spectrum of **1** showed the absorption of conjugated nitrile at 4.48 μ, conjugated carbon–carbon and carbon–nitrogen double bonds at 6.35 and 6.55 μ, and carbon–fluorine at 8 μ. The ultraviolet spectrum of **1** in acetonitrile showed absorption at 355 mμ (ϵ 8700), 258 (7430), and 223 (7400).

1 with Trifluoromethanesulfenyl Chloride.—Compound **1** was recovered in 90% yield after standing for 1 day with excess trifluoromethanesulfenyl chloride in acetonitrile solution at room temperature.

1 with 2,3-Dimethylbutadiene. 1,1,2-Tricyano-2-[chloro(trifluoromethylthioimino)methyl]-4,5-dimethyl-4-cyclohexene.—A solution of 1.0 g. of the diene in 5 ml. of ether was added to a solution of 2.66 g. of **1** in 30 ml. of ether. The temperature rose to 30°. After stirring overnight, the solvent evaporated, and the residue was crystallized from hexane–benzene (1:3) to give 2.51 g. (73%) of adduct, m.p. 110–115°. Another recrystallization gave pure adduct, m.p. 115–116°.

Anal. Calcd. for $C_{13}H_{10}ClF_3N_4S$: C, 45.0; H, 2.92; Cl, 10.2; F, 16.4; N, 16.2; S, 9.25. Found: C, 45.4; H, 3.36; Cl, 10.7; F, 16.4; N, 16.0; S, 8.85.

The infrared spectrum is consistent with the Diels–Alder adduct structure. There is weak absorption at 4.46 μ attributable to the nonconjugated nitrile, at 6.10 and 6.15 μ for the carbon–carbon and carbon–nitrogen double bonds, and strong absorption at 8 to 9 μ of the carbon–fluorine.

1 with Butadiene.—A mixture of 13.5 g. of **1**, 4 g. of butadiene, and 100 ml. of ether was stirred at room temperature for 2 hr. The ether was evaporated, and pentane (50 ml.) was added. The adduct crystallized and was filtered to give 10.7 g. (66%) of crude product, m.p. ~90°. Recrystallization from dibutyl ether raised the melting point to 104–104.6°.

Anal. Calcd. for $C_{11}H_6ClF_3N_4S$: C, 41.5; H, 1.90; Cl, 11.1; N, 17.6; S, 10.1. Found: C, 41.7; H, 2.19; Cl, 11.3; N, 17.7; S, 9.95.

The infrared spectrum of the adduct was very similar to that of the adduct with 2,3-dimethylbutadiene.

1 with Anthracene.—A solution of 2.70 g. of **1**, 1.8 g. of anthracene, and 50 ml. of benzene was heated at 60° for 18 hr. The green color of the π-complex which had formed on mixing the reactants disappeared. The mixture was cooled in ice, filtered, and the white solid was rinsed with ether to give 1.16 g. of crude adduct, m.p. 111–117°. A second crop of 2.0 g. was obtained from the filtrate. Attempts to recrystallize or sublime the crude adduct were unsuccessful. Purification was achieved by rinsing the adduct with ether. The purified adduct melted at 143–147°.

Anal. Calcd. for $C_{21}H_{10}ClF_3N_4S$: C, 57.0; H, 2.28; N, 12.7. Found: C, 57.0; H, 2.17; N, 12.8.

The infrared spectrum of the adduct exhibited absorptions of carbon–carbon and carbon–nitrogen double bonds at 6.1 and 6.2 μ, carbon–fluoride at 8 to 9 μ, and very weak nitrile absorption at 4.5 μ. The infrared spectrum was completely consistent with the assigned structure.

1 with Vinyl Ethers and Styrenes.—The products which have been obtained are given in Table II. The general procedure is illustrated by the reaction of **1** with styrene.

A solution of 2.70 g. of **1**, 2.10 g. of styrene, and 25 ml. of ether was stirred at room temperature. The red color of the π-complex between **1** and styrene formed upon mixing. The mixture was warmed overnight at 40°. The mixture was cooled, and the solvent was removed under nitrogen. Addition of 20 ml. of pentane caused the residue to crystallize. Filtration gave a light tan solid (3.56 g.); crystallization from hexane gave the azetidine, m.p. 115–117°, 3.35 g. (91%).

The infrared spectrum of the adduct showed the intense tricyanovinyl absorption at 6.34 μ and conjugated nitrile absorption at 4.5 μ. The spectrum was completely consistent with the azetidine structure. The ultraviolet spectrum of the adduct in acetonitrile solution showed the presence of the tricyanovinyl group, λ_{max} 268 mμ (ϵ 16,400). When the adduct is dissolved in benzene solution, the red color of the π-complex of **I** and styrene develops.

2-Chloro-2-tricyanovinylazetidines.—These products are given in Table III. The general procedure is illustrated with the preparation of 2-chloro-3-methoxy-2-tricyanovinylazetidine. A solution of 16.2 g. of 2-chloro-3-methoxy-2-tricyanovinyl-1-trifluoromethylthioazetidine and 4.6 g. of ethanol in 50 ml. of glyme was heated at reflux for 2 days. The solvent was evaporated. The residue was triturated with ether and filtered to give 8.3 g. of azetidine, m.p. 159–161°. Recrystallization from methanol gave the pure product (7.09 g., 64%), m.p. 166–167.4°.

The ultraviolet spectrum of the product in acetonitrile solution shows the tricyanovinyl absorption at 261 mμ (ϵ 16,100). The infrared spectrum shows the absorptions of NH at 3.04 μ, conjugated nitrile at 4.53 μ, tricyanovinyl double bond at 6.27 μ, and carbon–oxygen single bond at 9 μ.

1 with N-Vinylpyrrolidone.—A slurry of 10.8 g. (0.04 mole) of **1** in 50 ml. of ether was stirred at room temperature while N-vinylpyrrolidone (4.5 g.) was added dropwise. The temperature rose to reflux. A reddish solution formed, and a tan solid was deposited. The mixture was cooled to room temperature and filtered to give 6.72 g. of crude adduct, m.p. 220–225°.

(16) Melting points are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Model 21, ultraviolet and visible spectra on a Cary Model 14, and n.m.r. spectra on a Varian A60 spectrometer.

Recrystallization of the adduct was not successful. Purification was achieved by rinsing the adduct with glyme. This gave material of m.p. 222–223° dec.

Anal. Calcd. for $C_{12}H_{10}ClN_5O$: C, 52.3; H, 3.66; Cl, 12.9; N, 25.4. Found: C, 52.3; H, 3.52; Cl, 12.8; N, 25.8.

The infrared spectrum of the azetidine confirms the fact that the CF_3S group has been removed during the reaction. There was absorption of the conjugated nitrile and the tricyanovinyl double bond as in the other azetidines. CF and SCF_3 absorptions were absent. Additional absorption due to NH and C=O was apparent. The ultraviolet absorption of the adduct in acetonitrile solution showed the presence of the tricyanovinyl group, λ_{max} 265 mμ (ε 15,300).

Acknowledgment.—The author is greatly indebted to Dr. H. E. Simmons for advice and suggestions.

Free-Radical Additions Involving Fluorine Compounds. VII.[1] The Addition of Perhaloalkanes to Vinyl Ethyl Ether and Vinyl 2,2,2-Trifluoroethyl Ether

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The addition of perhaloalkanes to some vinyl and allyl ethers were carried out satisfactorily in the presence of ultraviolet irradiation. Adducts obtained from vinyl trifluoroethyl ether showed a marked increase in thermal and hydrolytic stabilities over the vinyl ethyl ether adducts. The products, α-bromo ethers, were converted into a variety of fluorine-containing compounds.

As part of a program designed to prepare new fluorine-containing monomers, the synthesis of some unsaturated fluoro ethers has been investigated. Earlier work[1] had shown that free-radical addition of perhaloalkanes such as bromotrichloromethane, dibromodifluoromethane, and 1,2-dibromo-2-chloro-1,1,2-trifluoroethane to allyl ethers could be accomplished easily to give adducts capable of transformation to both olefinic and dienic ethers. Consequently, this reaction was extended to include addition of CCl_3Br, CF_2Br_2, and $CF_2BrCFClBr$ to some vinyl ethers. Vinyl ethyl ether and vinyl 2,2,2-trifluoroethyl ether were chosen because of their availability and also in order to compare the effect of the β-fluorine atoms on the properties of the adducts.

A number of investigators have shown the high reactivity of vinyl ethers in free-radical additions. Glickman[3] added carbon tetrachloride, carbon tetrabromide, and dibromodichloromethane to a number of vinyl ethers using peroxides or ultraviolet irradiation to give high yields of 1-halo-3-trihalopropyl ethers. Similar additions have been reported by Levas[4] and Shostakovskii.[5]

Initial attempts to carry out radical additions to vinyl ethyl ether in an autoclave using benzoyl peroxide initiator at 75° resulted, in every case, in decomposition of product as evidenced by heavy fuming and formation of black, spongy polymer. This thermal instability, characteristic of most α-haloalkyl ethers,[6] necessitated the adoption of a procedure in which materials could react at temperatures lower than the decomposition temperature of the products. Such a method was found in the use of ultraviolet irradiation as a free-radical initiator. An additional advantage of this procedure is the absence of contaminants resulting from the decomposition of the peroxide. It was subsequently found that ultraviolet-catalyzed additions to allyl ethers could be carried out in conversions comparable to those from peroxide-catalyzed reactions.[1]

The following free-radical addition reactions were carried out using ultraviolet initiation.

$$CCl_3Br + CH_2{=}CHOC_2H_5 \longrightarrow \underset{\text{I}}{CCl_3CH_2CHBrOC_2H_5} \quad (1)$$

$$CF_2Br_2 + CH_2{=}CHOC_2H_5 \longrightarrow \underset{\text{II}}{CF_2BrCH_2CHBrOC_2H_5} \quad (2)$$

$$CF_2BrCFClBr + CH_2{=}CHOC_2H_5 \longrightarrow \underset{\text{III}}{CF_2BrCFClCH_2CHBrOC_2H_5} \quad (3)$$

$$CCl_3Br + CH_2{=}CHOCH_2CF_3 \longrightarrow \underset{\text{IV}}{CCl_3CH_2CHBrOCH_2CF_3} \quad (4)$$

$$CF_2Br_2 + CH_2{=}CHOCH_2CF_3 \longrightarrow \underset{\text{V}}{CF_2BrCH_2CHBrOCH_2CF_3} \quad (5)$$

$$CF_2BrCFClBr + CH_2{=}CHOCH_2CF_3 \longrightarrow \underset{\text{VI}}{CF_2BrCFClCH_2CHBrOCH_2CF_3} \quad (6)$$

Adducts from vinyl ethyl ether (I, II, III) fumed heavily on exposure to moist air and decomposed rapidly with evolution of hydrogen halide between 70–85° during distillation. Consequently, only II could be satisfactorily fractionated owing to its lower boiling point, although apparent boiling points for the CCl_3Br and $CF_2BrCFClBr$ adducts (I, III) are reported (see Table I for properties of the compounds prepared). These adducts, although not isolated could be treated to give stable derivatives which will be described later. Satisfactory analysis of the α-bromoalkyl ethyl ethers was not accomplished owing to their rapid decomposition. Compounds I, II, and III were also found to be extremely reactive hydrolytically. Upon basic hydrolysis, I was found to give appreciable quantities of a highly lachrymatory material identified as dichloroacrolein, $CCl_2{=}CHCHO$. Hydrolysis of the CF_2Br_2 and $CF_2BrCFClBr$ adducts (II and III) resulted in vigorous reactions leading to the formation of extremely lachrymatory compounds which were not

(1) Preceding paper in this series: P. Tarrant and E. C. Stump, Jr., *J. Org. Chem.*, **26**, 4646 (1961).

(2) To whom requests for reprints should be sent at Peninsular Chem-Research, Inc., P. O. Box 14318, Gainesville, Fla.

(3) S. A. Glickman, U. S. Patent 2,560,219 (1951).

(4) M. Levas, *Ann. chim.* (Paris), **7**, 697 (1952); *Chem. Abstr.*, **48**, 1243d (1954).

(5) M. F. Shostakovskii, A. V. Bogdanova, M. M. Zverov, and G. I. Plotnikova, *Izv. Akad. Nauk SSSR Otd. Khim. Nauk*, 1236 (1956); *Chem. Abstr.*, **51**, 5730e (1957).

(6) L. Summers, *Chem. Rev.*, **55**, 337 (1955).

TABLE I

PROPERTIES OF ETHERS AND ACETALS PREPARED

No.	Structure	% conversion	B.p., °C.	Pressure, mm.	$n^{25}D$	d^{25}
I	$CCl_3CH_2CHBrOC_2H_5$		51	0.7	1.4835	1.395
II	$CF_2BrCH_2CHBrOC_2H_5$	83	53.5	5	1.4490	1.734
III	$CF_2BrCFClCH_2CHBrOC_2H_5$		71	1	*a*	*a*
IV	$CCl_3CH_2CHBrOCH_2CF_3$	91	45	0.4	1.4488	1.739
V	$CF_2BrCH_2CHBrOCH_2CF_3$	72	29	1.5	1.4052	1.901
VI	$CF_2BrCFClCH_2CHBrOCH_2CF_3$	72	55	0.5	1.4188	1.935
VII	$CCl_3CH_2CH_2OC_2H_5$	40[b]	67	7.5	1.4615	1.305
VIII	$CF_2BrCH_2CH_2OC_2H_5$	21[b]	36	20	1.4026	1.410
IX	$CF_2BrCFClCH_2CH_2OC_2H_5$	33[b]	42	3	1.4185	1.526
X	$CCl_3CH_2CH_2OCH_2CF_3$	21[c]	54	6	1.4119	1.460
XI	$CF_2BrCH_2CH_2OCH_2CF_3$	24[c]	56	40	1.3604	1.613
XII	$CF_2BrCFClCH_2CH_2OCH_2CF_3$	21[c]	43	2.5	1.3840	1.705
XIII	$CF_2{=}CHCH_2OC_2H_5$	36	67	760	1.3548	1.007
XIV	$CF_2{=}CFCH_2CH_2OC_2H_5$	35	96	760	1.3555	1.069
XV	$CF_2{=}CHCH_2OCH_2CF_3$	45	81	760	1.3207	1.299
XVI	$CF_2{=}CFCH_2CH_2OCH_2CF_3$	42	103	760	1.3302	1.307
XVII	$CF_2BrCH_2CH(OC_2H_5)_2$	75	64	14	1.4057	1.325
XVIII	$CF_2BrCFClCH_2CH(OC_2H_5)_2$	38	52	0.5	1.4190	1.440
XIX	$CF_2BrCH_2CH(OCH_2CF_3)_2$	21	78	20	1.3512	1.670
XX	$CF_2BrCFClCH_2CH(OCH_2CF_3)_2$	67	50	0.5	1.3745	1.754
XXI	$CF_2BrCH_2CH(CH_3)OC_2H_5$	19[b]	55	41	1.4020	1.335
XXII	$CF_2{=}CHCH(CH_3)OC_2H_5$	45	76	760	1.3588	0.969
XXIII	$(CH_3)_2C(OCH_2CF_3)_2$	10	120–126	760	1.3270	1.261

[a] Pure sample not isolated. [b] Based on vinyl ethyl ether. [c] Based on vinyl 2,2,2-trifluoroethyl ether.

TABLE II

ANALYSES OF COMPOUNDS PREPARED

	MRD		% C		% H		% halogen		Mol. wt.[a]	
No.	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
I		*b*							270.4	
II	42.46	43.61[b]	21.30	23.26	2.86	3.52	56.70[c]	54.95	281.9	
III		*b*							348.6	
IV	49.30	50.02	18.50	18.58	1.56	1.63	81.09[c]	81.80	324.4	
V	42.46	43.10	17.87	17.87	1.50	1.77	47.58[c]	47.25	335.9	
VI	51.95	52.41	17.90	18.06	1.25	1.55			402.6	
VII	41.53	40.50	31.34	31.54	4.74	4.88	55.54[d]	55.45	191.5	
VIII	34.71	35.10	29.58	29.64	4.47	4.58	39.46[c]	39.60	203.0	205
IX	44.18	44.48	26.74	26.77	3.37	3.43	134.7[e]	133.0	269.5	
X	41.53	42.10	24.47	24.52	2.46	2.45	43.33[d]	43.33	245.5	
XI	34.71	35.20	23.36	23.50	2.35	2.45	31.09[c]	30.83	257.0	250
XII	44.18	44.51	22.28	22.41	1.87	1.98	161.8[e]	163.5	323.5	
XIII	26.47	26.56	49.18	49.18	6.63	6.58			122.1	130
XIV	31.08	31.41	46.77	46.51	5.89	5.99			154.1	154
XV	26.47	27.05	34.10	34.25	2.86	3.14			176.1	175
XVI	31.08	32.50	34.58	34.63	2.73	2.91			208.1	208
XVII	45.58	45.13	33.99	37.30	5.30	5.64	32.34[c]	30.57	247.1	
XVIII	55.06	54.95	30.63	31.01	4.18	4.43			313.6	
XIX	45.58	46.08	23.68	23.81	1.97	2.25			355.1	
XX	55.06	54.92	22.80	23.06	1.67	1.88			421.5	
XXI	39.32	39.50	33.20	33.48	5.11	5.27	36.82[c]	37.15	217.1	
XXII	31.08	30.97	52.93	52.93	7.40	7.53			136.2	
XXIII	37.81	38.50	35.01	35.21	4.20	4.36			240.2	

[a] By freezing point depression in benzene. [b] Sample decomposes. [c] % bromine. [d] % chlorine. [e] Silver equivalent.

identified, partially owing to their tendency to polymerize to viscous liquids. Similar results were observed by Durrell[7] in handling the adducts of CF_2Br_2 and $CF_2BrCFClBr$ and vinyl acetate.

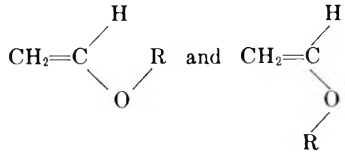
Adducts obtained from the addition of perhaloalkanes to vinyl 2,2,2-trifluoroethyl ether (IV, V, VI) exhibited a marked increase in thermal and hydrolytic stabilities over those of the vinyl ethyl ether adducts. They showed little tendency to hydrolyze in moist air, could be stored several months without decomposition, and gave good analytical results (see Table II for analyses of compounds prepared). The thermal stability of these compounds was so greatly enhanced that a 62-g. sample of V was recovered unchanged after passing through a hot tube at 220°.

The reactivity of the bromine atom in alkyl α-bromoalkyl ethers may be attributed to the possibility of resonance involving an oxonium form. Physical evidence supporting this has been presented by Brey and

$$RCH(\ddot{Br})-\ddot{O}-R' \longleftrightarrow RCH=\overset{+}{\ddot{O}}-R'$$

(7) W. Durrell, WADC Technical Report 58-589 (May, 1959); W. Durrell, A. M. Lovelace, and R. L. Adamczak, *J. Org. Chem.*, **25**, 1662 (1960).

Tarrant[8] who noted a doublet in the infrared spectra of vinyl alkyl ethers arising from the existence of rotational isomers. To explain the presence of rotational isomers, Batuev[9] postulated a resonance structure for vinyl ethers, $\bar{C}H_2$–CH=$\overset{+}{O}$–R, for which rotation of the alkyl group about the carbon–oxygen bond would be hindered; this resulted in these following isomers.



However, when R′ is a CF_3CH_2– group, the negative (electron-withdrawing) inductive effect of the three fluorine atoms is evidently strong enough to inhibit drastically the ability of the oxygen atom to denote its unshared electrons in the formation of the oxonium structure. Brey and Tarrant found only a single carbon–carbon double bond stretching region in vinyl α,α-difluoro ethers. This result was attributed to the strong inductive effect of the α-fluorine atoms which prevented resonance of the oxygen electrons with the double bond. However, the inductive effect of fluorine in the β-position, insulated from the oxygen atom by a methylene group, is not sufficient to overcome the resonance completely, as evidenced by the appearance of doublet in the carbon–carbon double bond stretching region in the spectra of all vinyl β-fluoro ethers examined.

The comparative unreactivity of the α-bromoalkyl 2,2,2-trifluoroethyl ethers reported here is unusual in that this effect is transmitted through the methylene group. Thus, this appears to be a case in which the resonance interactions are not inhibited enough to change the physical (*i.e.*, infrared absorption) properties but are inhibited sufficiently to cause a marked change in chemical reactivity.

In contrast to the additions of perhaloalkanes to allyl ethers, it was found that additions to vinyl ethers resulted in high conversions (72–91%) to the 1:1 adducts. Moreover, very little telomerization occurred, evidenced by the very small amount of high boiling material remaining after distillation of the reaction products, even though smaller ratios of perhaloalkane to ether were used.

Attempts to dehydrobrominate the α-bromo compounds (I–VI) to give α,β-unsaturated ethers using pyridine or aqueous base were not successful. Reaction of II with pyridine resulted only in the formation of higher boiling material. Reactions with aqueous base resulted in rupture of the carbon–oxygen bond, as previously mentioned, apparently to give an unsaturated aldehyde. Attempts to prepare an acetate (to be followed by pyrolysis to the α,β-unsaturated ether) from II by reaction with sodium acetate were also unsuccessful, resulting in decomposition involving the elimination of hydrogen fluoride.

A suitable method for converting the α-bromo ethers to unsaturated fluoro ethers was found in the reduction of the α-bromo atom with lithium aluminum hydride

$$CF_2BrCH_2CHBrOR \xrightarrow{LiAlH_4} CF_2BrCH_2CH_2OR \quad (7)$$
VIII and XI

$$CF_2BrCFClCH_2CHBrOR \xrightarrow{LiAlH_4} CF_2BrCFClCH_2CH_2OR \quad (8)$$
IX and XII
(where R = C_2H_5 and CH_2CF_3)

(eq. 7 and 8), followed by dehydrohalogenation or dehalogenation of the products.

Although the reduction of I resulted in the formation of several impurities as determined by gas chromatography, the desired $CCl_3CH_2CH_2OC_2H_5$ was shown to be a product of the reaction by its conversion to $C_2H_5O_2CCH_2CH_2OC_2H_5$ with ethanolic potassium hydroxide.

The unsaturated fluoro ether derivatives were prepared as shown in eq. 9 and 10. Characteristic in-

$$CF_2BrCH_2CH_2OR \xrightarrow[\text{mineral oil}]{KOH} CF_2{=}CHCH_2OR \quad (9)$$
XIII and XV

$$CF_2BrCFClCH_2CH_2OR \xrightarrow[\text{alcohol}]{\text{zinc}} CF_2{=}CFCH_2CH_2OR \quad (10)$$
XIV and XVI
(where R = C_2H_5 and CH_2CF_3)

frared carbon–carbon double bond stretching absorption peaks were observed in the 5.72–5.73-μ region for the compounds (XIII, XV, XXII) containing the CF_2=CH– group and in the 5.53–5.54-μ region for compounds (XIV, XVI) containing the CF_2=CF– group.

The α-bromo ethers were also found to react with alcohols to give acetals as illustrated in eq. 11 and 12. Preparation of the mixed acetals was not attempted.

$$CF_2BrCH_2CHBrOC_2H_5 + C_2H_5OH \longrightarrow CF_2BrCH_2CH(OC_2H_5)_2 + HBr \quad (11)$$
XVII

$$CF_2BrCH_2CHBrOCH_2CF_3 + CF_3CH_2OH \longrightarrow CF_2BrCH_2CH(OCH_2CF_3)_2 + HBr \quad (12)$$
XIX

An attempt to pyrolyze XVII to $CF_2BrCH{=}CHOC_2H_5$ by passing it over anhydrous monosodium phosphate[10] at 300° gave only unchanged starting material. Attempts to obtain the unsaturated ether by passage of XVII through a glass-packed hot tube at 400° were also unsuccessful.

The relative unreactivity of the α-bromoalkyl 2,2,2-trifluoroethyl ethers was again demonstrated in the reaction of methylmagnesium bromide with II and V. The ethyl ether (II) reacted vigorously to give the methyl-substituted compound (XXI) as shown in eq. 13 but the 2,2,2-trifluoroethyl ether (V) did not react

$$CF_2BrCH_2CHBrOC_2H_5 + CH_3MgBr \longrightarrow CF_2BrCH_2CH(CH_3)OC_2H_5 + MgBr_2 \quad (13)$$
XXI

under the same conditions to give the desired methyl-substituted ether.

Finally, in attempting the synthesis of 1-methylvinyl 2,2,2-trifluoroethyl ether by the base-catalyzed reaction of trifluoroethanol with methylacetylene, the new acetal $(CH_3)_2C(OCH_2CF_3)_2$ (XXIII) was obtained in low yield. This product could be accounted for by

(8) M. L. Brey and P. Tarrant, *J. Am. Chem. Soc.*, **79**, 6533 (1957).

(9) M. I. Batuev, E. N. Prilezhaeva, and M. F. Shostakovskii, *Bull. acad. ci. URSS Classe sci. chim.*, 123 (1947); *Chem. Abstr.*, **42**, 4463i (1948).

(10) I. N. Nazorov, S. M. Makin, B. K. Kruptsov, and V. A. Miranov, *J. Gen. Chem. USSR* (Eng. Transl.), **29**, 116 (1959).

the reaction of the desired methylvinyl ether with trifluoroethanol as shown in eq. 14.

$$CH_2{=}C(CH_3)OCH_2CF_3 + CF_3CH_2OH \xrightarrow{KOH} (CH_3)_2C(OCH_2CF_3) \quad (14)$$
XXIII

Experimental[11,12]

Materials.—Vinyl ethyl ether was obtained from Union Carbide Chemicals Co., bromotrichloromethane from Dow Chemical Co., dibromodifluoromethane from E. I. du Pont de Nemours and Co., 1,2-dibromo-2-chloro-1,1,2-trifluoroethane from Peninsular ChemResearch, Inc., and trifluoroethanol from Pennsalt Chemicals Corp. A typical preparation of vinyl 2,2,2-trifluoroethyl ether is described elsewhere in this section.

Description of Apparatus.—A Pyrex tube fitted with a Vycor 7910 immersion well[13] was used to carry out the addition reactions. The volume of the outer Pyrex tube with immersion well in place was 750 ml. A vent at the top of the outer tube allowed for pressure changes. The Vycor immersion well with standard taper 60/50 joint was double walled, with inlet and outlet tube to provide for air or water cooling. A type 60B A-36 quartz mercury arc lamp[13] with 2.9-in. arc length was suspended in the immersion well to provide ultraviolet irradiation. A type 7620 ballasting control[13] was used with the lamp. Stirring was provided by a magnetic stirring bar.

Addition of Bromotrichloromethane to Vinyl Ethyl Ether.—A solution of 475 g. (2.4 moles) of bromotrichloromethane and 158 g. (2.2 moles) of vinyl ethyl ether was placed in the reaction vessel described above and irradiated at 0° with stirring for 12 hr. The unchanged material was stripped from the solution at reduced pressure and the remainder was fractionated to give a cut, b.p. 51° (0.7 mm.). Although this sample decomposed too rapidly to allow analysis and proper determination of its physical properties, it was assigned the structure $CCl_3CH_2CHBrOC_2H_5$ (I) on the basis of its reduction with lithium aluminum hydride to $CCl_3CH_2CH_2OC_2H_5$ and hydrolysis to $CCl_2{=}CHCHO$.

Addition of Dibromodifluoromethane to Vinyl Ethyl Ether.—A solution of 720 g. (3.45 moles) of dibromodifluoromethane and 144 g. (2.0 moles) of vinyl ethyl ether was treated as described above for 10.5 hr. The products were processed as described above to give 362 g. (83% conversion[14]) of $CF_2BrCH_2CHBrOC_2H_5$ (II). Decomposition of the compound by elimination of hydrogen bromide would account for the high carbon–hydrogen and low bromine analysis noted in Table II. Assignment of structure was based on reduction of the compound to $CF_2BrCH_2CH_2OC_2H_5$.

Addition of 1,2-Dibromo-2-chloro-1,1,2-trifluoroethane to Vinyl Ethyl Ether.—A solution of 600 g. (2.17 moles) of $CF_2BrCFClBr$ and 144 g. (2.0 moles) of vinyl ethyl ether was treated as before for 12 hr. The products were processed as described above. A few grams of product (apparent b.p. 71° at 1 mm.) was collected when the material in the distilling flask began to decompose at 85°. The structure $CF_2BrCFClCH_2CHBrOC_2H_5$ (III) was assigned to this compound on the basis of its reduction to $CF_2BrCFClCH_2CH_2OC_2H_5$.

Addition of Bromotrichloromethane, Dibromodifluoromethane, and 1,2-Dibromo-2-chloro-1,1,2-trifluoroethane to Vinyl 2,2,2-Trifluoroethyl Ether.—A solution of 397 g. (2.0 moles) of bromotrichloromethane and 200 g. (1.59 moles) of $CH_2{=}CHOCH_2CF_3$ was irradiated at 0° for 11 hr. as previously described. Unchanged material was stripped under reduced pressure and the remainder was fractionally distilled to give 470 g. (91% conversion) of $CCl_3CH_2CHBrOCH_2CF_3$ (IV).

A solution of 560 g. (2.68 moles) of dibromodifluoromethane and 126 g. (1.0 mole) of $CH_2{=}CHOCH_2CF_3$ was treated for 13 hr. and worked up as previously described. On fractionation, 241 g. (72% conversion) of $CF_2BrCH_2CHBrOCH_2CF_3$ (V) was obtained.

A solution of 700 g. (2.54 moles) of $CF_2BrCFClBr$ and 200 g. (1.59 moles) of $CH_2{=}CHOCH_2CF_2$ was irradiated for 13 hr. and worked up as before. Fractional distillation provided 457 g. (72% conversion) of $CF_2BrCFClCH_2CHBrOCH_2CF_3$ (VI).

Reaction of I with Lithium Aluminum Hydride.—A solution of 24 g. (0.63 mole) of lithium aluminum hydride in 350 ml. of anhydrous ethyl ether was added to crude $CCl_3CH_2CHBrOC_2H_5$ (I) remaining after stripping unchanged material from the addition of excess CCl_3Br to vinyl ethyl ether (2.0 moles) by the method previously described. The ether was not isolated before action with lithium aluminum hydride owing to its tendency to decompose during distillation. The reaction was carried out at 0° and was necessarily slow owing to the extremely vigorous reaction. After the addition of lithium aluminum hydride, the mixture was stirred an additional 1.5 hr. at room temperature, followed by the addition of 200 ml. of water. The mixture was extracted with ethyl ether, separated, and dried over anhydrous calcium chloride. Low boiling material was stripped, and the remainder was fractionated to give 208 g. of material, boiling range 55–64° (15 mm.). A gas chromatogram showed that this sample consisted of three components with the higher boiling material richer in the major component. An infrared absorption peak at 6.22 μ indicated an unsaturated impurity. The sample was washed with water, separated, dried, and refractionated with a 65-cm. column packed with protruded nickel packing to give chromatographically pure $CCl_3CH_2CH_2OC_2H_5$ (VII).

An assignment of structure was based on conversion of the compound to ethyl β-ethoxypropionate by ethanolic potassium hydroxide.

In a similar manner II, III, IV, V, and VI were reduced to the corresponding α,α-dihydro ethers.

Dehydrobromination of VIII.—A slurry of 9.5 g. (0.15 mole) of powdered potassium hydroxide and 50 ml. of mineral oil was heated to 100° and 23 g. (0.113 mole) of $CF_2BrCH_2CH_2OC_2H_5$ was added dropwise with vigorous stirring. The reaction products were stripped at reduced pressure into a cold trap. The crude material then was dried over calcium chloride and fractionated to give 4.5 g. (36% conversion) of $CF_2{=}CHCH_2OC_2H_5$ (XIII). An infrared spectrum of this compound showed a very strong absorption peak in the carbon–carbon double bond region at 5.73 μ.

Dehydrobromination of XI.—A slurry of 9.5 g. (0.152 mole) of powdered potassium hydroxide in 50 ml. of mineral oil was heated to 100°, and 32 g. (0.125 mole) of $CF_2BrCH_2CH_2OCH_2CF_3$ was added dropwise with vigorous stirring. The material was handled as before to give 25 g. of crude material which was dried and distilled over a 20° boiling range. An analytical sample of $CF_2{=}CHCH_2OCH_2CF_3$ (XV) was obtained using preparative scale gas chromatography. An infrared spectrum showed a strong, sharp absorption peak assigned to the $CF_2{=}CH-$ group at 5.72 μ. Conversion was 45%. In a similar manner XXI, $CF_2BrCH_2CH(CH_3)OC_2H_5$, was converted to $CF_2{=}CHCH(CH_3)OC_2H_5$ (XXII), which exhibited the band at 5.74 μ characteristic of the $CF_2{=}CH-$ group.

Dehalogenation of IX.—A mixture of 19.5 g. (0.30 mole) of powdered zinc, 0.5 g. of zinc chloride, and 100 ml. of absolute ethanol was heated to reflux and 60 g. (0.223 mole) of $CF_2BrCFClCH_2CH_2OC_2H_5$ was added with stirring over a 1-hr. period. The mixture was stirred at reflux an additional 2 hr., and the liquid was decanted, washed with water, and separated. The wash water was extracted with ethyl ether which was combined with the organic layer, dried, and fractionated to give 17 g. of material, b.p. 72–76°, and 4.5 g. of material, b.p. 78°. A vapor phase chromatogram revealed that the former contained 50% ethyl ether and 50% $CF_2{=}CFCH_2CH_2OC_2H_5$ (XIV), while the latter fraction consisted of approximately 90% $CF_2{=}CFCH_2CH_2OC_2H_5$. The high boiling fraction was purified by passing through a preparative scale gas chromatography column to give a chromatographically pure analytical sample, whose properties are given in the tables. An infrared spectrum of XIV exhibited a strong, sharp absorption peak at 5.54 μ, characteristic of the $CF_2{=}CF-$ group.[15,16] Conversion was 35%.

In a similar manner XII, $CF_2BrCFClCH_2CH_2OCH_2CF_3$, was dehalogenated to XVI, $CF_2{=}CFCH_2CH_2OCH_2CF_3$. An infrared spectrum exhibited a distinctive $CF_2{=}CF-$ absorption peak at 5.53 μ.

Reaction of II with Ethanol.—Absolute ethanol (300 ml.) was placed in a 1-l. three-necked flask fitted with stirrer, condenser, and dropping funnel. To the stirred ethanol was added 175 g. (0.62 mole) of $CF_2BrCH_2CHBrOC_2H_5$. Addition required 1 hr. and was accompanied by evolution of heat. The solution was

(11) Analyses by Galbraith Laboratories, Knoxville, Tenn.

(12) In most cases, no attempt was made to optimize conversions.

(13) Obtained from Englehard Hanovia, Inc., Newark, N. J.

(14) Conversion is defined as the moles of product divided by the moles theoretically obtainable.

(15) M. R. Lilyquist, Ph.D. dissertation, University of Florida, 1955.

(16) R. N. Haszeldine, *J. Chem. Soc.*, 4423 (1952).

stirred an additional 1.5 hr. at room temperature, washed thoroughly with water, and the crude product (150 g.) was separated, dried over Drierite, and fractionated to give 122 g. of material with boiling range 61–67° (14 mm.). An analytical sample was shown by a vapor phase chromatogram to contain one major and three minor components. The major component has been assigned the structure $CF_2BrCH_2CH(OC_2H_5)_2$ (XVII) on the basis of n.m.r. spectra for hydrogen and fluorine.

An infrared spectrum showed two strong, broad absorption peaks in the 9.0–9.5-μ region and no absorption in the carbonyl or carbon–carbon double bond regions. Conversion was approximately 75%.

In a similar manner III, $CF_2BrCFClCH_2CHBrOC_2H_5$, reacted with ethanol to give XVIII, $CF_2BrCFClCH_2CH(OC_2H_5)_2$. N.m.r. spectra for hydrogen and fluorine were consistent with the assigned structure.

Reaction of V with Trifluoroethanol.—Trifluoroethanol (100 ml.) and 58 g. (0.17 mole) of $CF_2BrCH_2CHBrOCH_2CF_3$ were combined and stirred at room temperature with slow evolution of heat for 16 hr. and at 75° for 6 hr. White fumes were evolved and the flask was etched, indicating elimination of hydrogen fluoride. After work-up and fractionation of the crude material, a center cut showed both carbonyl and carbon–carbon double bond absorption in its infrared spectrum.

The desired acetal was successfully prepared in the following manner. Trifluoroethanol (200 ml.) and 84 g. (0.25 mole) of the subject ether were combined and stirred for 48 hr. at room temperature. During this period, the flask was swept with nitrogen and was backed by a cold trap. The solution was washed with water, and the crude material (64 g.) was dried over Drierite and fractionated to give 17.5 g. (21% conversion) of $CF_2BrCH_2CH(OCH_2CF_3)_2$ (XIX).

An infrared spectrum showed a strong, broad peak from 8.9–9.3 μ. No carbonyl or carbon–carbon double bond absorption was observed.

Trifluoroethanol also reacted with VI, $CF_2BrCFClCH_2CHBrOCH_2CF_3$, to give the corresponding acetal XX.

Reaction of II with Methylmagnesium Bromide.—$CF_2BrCH_2CHBrOC_2H_5$ was prepared from 2.84 moles of vinyl ethyl ether and excess CF_2Br_2 and was used without distillation. The crude ether was placed in a three-necked flask fitted with an addition funnel, stirrer, and condenser and was cooled to 0°. Two moles of methylmagnesium bromide in ethyl ether was then added dropwise over a 1-hr. period. The reaction was very vigorous and necessitated continued cooling. After addition was complete, the mixture was stirred for 1 hr. at 0° and for 4 hr. at room temperature. The mixture was filtered, and the organic layer was separated, dried, and fractionated to give 80 g. (19% conversion based on the vinyl ethyl ether) of $CF_2BrCH_2CH(CH_3)OC_2H_5$ (XXI). An infrared spectrum showed no carbonyl or carbon–carbon double bond absorption.

Reaction of Trifluoroethanol with Methylacetylene.—An autoclave was charged with 200 g. (2.0 moles) of trifluoroethanol, 80 g. (2.0 moles) of methylacetylene, and 10 g. of potassium hydroxide and was heated at 225° for 18 hr. Unchanged methylacetylene (65 g.) was bled into a trap, and the remainder was fractionated to give 17 g. of material, b.p. 57–72°. A vapor phase chromatogram showed that this fraction consisted of three components, the major one being trifluoroethanol. The material was washed thoroughly with water, and the organic layer was separated, dried, and fractionated to give 1 g. of material, identified as $(CH_3)_2C(OCH_2CF_3)_2$.

N.m.r. spectra of hydrogen and fluorine were consistent with the proposed structure. Conversion, based on chromatographic analysis of the 57–72° cut, was approximately 10%.

Reaction of $CCl_3CH_2CH_2OC_2H_5$ with Ethanolic Potassium Hydroxide.—A solution of 80 g. (1.2 moles) of potassium hydroxide in 200 ml. of 95% ethanol was heated to reflux followed by the dropwise addition of 70 g. (0.37 mole) of $CCl_3CH_2CH_2OC_2H_5$. The mixture was stirred at reflux for 20 hr., decanted, and washed with water. The insoluble organic layer was separated, dried, and fractionated to give a single product, b.p. 66° (17 mm.); $n^{23}D$ 1.4059; d^{23} 0.960; MR_D calcd. for $C_2H_5OOCCH_2CH_2OC_2H_5$, 37.82; ME_D found, 37.48. Physical constants reported for ethyl β-ethoxy propionate are b.p. 67° (17 mm.), $n^{25}D$ 1.4070, d^{25} 0.949.

An infrared spectrogram was identical with that of an authentic sample.

Preparation of Vinyl 2,2,2-Trifluoroethyl Ether.—A solution of 50 g. of potassium hydroxide in 300 g. (3.0 moles) of trifluoroethanol was sealed in a 1.4-l. stainless steel autoclave, which was then charged with acetylene to a pressure of 300 p.s.i.g. The autoclave was heated with rocking at 135° for 5 hr. and at 150° for 5 hr. Distillation of the product mixture gave the desired ether, b.p. 40–42°, in approximately 90% conversion.

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Fluoro Compounds. II.[1] Reactions and Nuclear Magnetic Resonance Studies of Some Fluorobromo Esters

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Fluorobromination of several α,β-unsaturated esters has been carried out using hydrofluoric acid and N-bromoacetamide. In each case the fluorine atom appeared on the β-carbon and was more easily lost than the α-bromine substituent in reaction with potassium phthalimide. Proton and fluorine nuclear magnetic resonance studies were made on several fluorobromo compounds. The fluorobromo compound derived from dialkyl maleate has been assigned the *threo* configuration; the corresponding fumarate derivative has been assigned the *erythro* configuration. At higher temperatures these two fluorobromo derivatives undergo interconversion. Electron paramagnetic resonance data and deuterium-exchange experiments do not indicate either a free radical or a carbanion intermediate for this interconversion.

In recent years there has been considerable interest in fluorinated compounds, particularly as potential antimetabolites. Some time ago we undertook a project on the synthesis of α-fluoro-β-alanine,[2,3] fluoroaspartic acid, and other fluoroamino acids. A possible intermediate in the synthesis of α-fluoro-β-alanine appeared to be β-bromo-α-fluoropropionic ester. Henne and Fox[4] tentatively assigned such a structure for the product obtained from ethyl dibromopropionate by halogen

(1) Part I: A. K. Bose, K. G. Das, and T. M. Jacob, *Chem. Ind.* (London), 452 (1963).

(2) Recently isolated as a metabolic product of 5-fluorouracil: C. Heidelberger and K. L. Mukherjee, *J. Biol. Chem.*, **235**, 433 (1960).

(3) Synthesized by E. D. Bergmann and S. Cohen, *J. Chem. Soc.*, 4669 (1961).

(4) A. L. Henne and C. J. Fox, *J. Am. Chem. Soc.*, **76**, 479 (1954).

TABLE I

FLUOROBROMO ESTERS

Fluorobromo ester	B.p., °C. (mm.)	Yield, %	$n^{22}D$	Analysis, %
$CH_2FCHBrCOOCH_3$ (I)	70–72 (10)	50	1.4464	Calcd.: C, 25.94; H, 3.24; F, 10.27; Br, 43.24
				Found: C, 25.83; H, 3.21; F, 10.16; Br, 43.36
$C_6H_5CHFCHBrCOOC_2H_5$ (II)	110–112 (1)	60	1.5125	Calcd.: C, 48.00; H, 4.36; F, 6.90; Br, 29.09
				Found: C, 47.85; H, 4.36; F, 6.75; Br, 28.99
$CH_3OOCCHFCHBrCOOCH_3$ (III) (from dimethyl maleate)	108–110 (1)	55	1.4575	Calcd.: C, 29.63; H, 3.29; F, 7.81; Br, 32.92
				Found: C, 30.26; H, 3.53; F, 7.73; Br, 32.59
$CH_3OOCCHFCHBrCOOCH_3$ (IV) (from dimethyl fumarate)	105–107 (1)	58	1.4580	Calcd.: C, 29.63; H, 3.29; F, 7.81; Br, 32.92
				Found: C, 30.09; H, 3.47; F, 7.78; Br, 32.80
$C_2H_5OOCCHFCHBrCOOC_2H_5$ (V) (from diethyl maleate)	102–104 (1)	51	1.4550	Calcd.: C, 35.42; H, 4.43; F, 7.01; Br, 29.52
				Found: C, 35.71; H, 4.58; F, 6.78; Br, 29.45
$C_2H_5OOCCHFCHBrCOOC_2H_5$ (VI) (from diethyl fumarate)	100–102 (1)	55	1.4550	Found to be homogeneous by gas chromatography and n.m.r. spectroscopy

exchange. In a previous communication[1] we have shown that this compound is actually β-fluoro-α-bromopropionic ester and is, therefore, unsuitable as an intermediate for the synthesis of α-fluoro-β-alanine.[5]

Recently a new method[6] has been described for the fluorobromination of alkenes. We have used this method for preparing fluorobromo esters of several unsaturated esters and have attempted to replace the bromine with the phthalimido function to obtain fluoroamino acid derivatives. An added interest in these compounds arose from the fact that several of the fluorobromo derivatives could possibly have restricted rotation and show the phenomenon of rotational isomerism.[7]

Experimental

A. Fluorobromination. General Procedure.—A solution of 0.05 mole of the α,β-unsaturated ester in 50 ml. of a 1:1 mixture of dry tetrahydrofuran and dry dichloromethane was cooled to −80° in a polyethylene container. A solution of 2.5 moles of anhydrous hydrogen fluoride in 50 ml. of a 1:1 mixture of tetrahydrofuran and dichloromethane prepared at −80° was added, followed by the addition of 0.065 mole of N-bromoacetamide which was previously purified by vacuum desiccation to remove all free bromine. The mixture was stirred for 1 hr. at −80° and left at 0° for 18 hr.[6] A reddish brown solution was obtained, which was poured into an excess of 10% cold sodium carbonate solution. The dichloromethane layer was separated, and the aqueous layer was extracted with dichloromethane (20 ml.). The combined dichloromethane extract was washed with water (three 75-ml. portions) until neutral and dried over anhydrous magnesium sulfate; the solvent was removed under reduced pressure. The crude product (yield 55–70%) was purified by fractional distillation through a Vigreux column under reduced pressure. Old samples of N-bromoacetamide containing free bromine did not fluorobrominate in the presence of anhydrous hydrogen fluoride. After vacuum desiccation these samples were found to be good for the reaction.

The following α,β-unsaturated esters were fluorobrominated by the above procedure: (i) methyl acrylate, (ii) ethyl cinnamate, (iii) dimethyl maleate, (iv) dimethyl fumarate, (v) diethyl maleate, and (vi) diethyl fumarate. All the fluorobromo derivatives were characterized by gas chromatography and nuclear magnetic resonance spectra (see Table I). Fluorobromination of maleic anhydride failed.

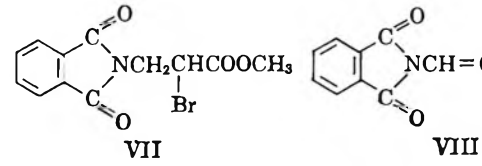
B. Some Reactions of Fluorobromo Esters. Action of Potassium Phthalimide on the Fluorobromo Derivatives of Ethyl Cinnamate (II).—A solution of the fluorobromo ester II (2.5 g.) in 20 ml. of anhydrous N,N-dimethylformamide or in 20 ml. of N,N-dimethylacetamide was stirred with dry powdered potassium phthalimide (1.8 g.) at room temperature for 2 days or at 70° for 1 hr. The reaction mixture was poured into 100 ml. of water. Phthalimide was quantitatively recovered.

The carbon tetrachloride layer was separated from the rest of the filtrate washed repeatedly with water, and dried over anhydrous sodium sulfate; the solvent was removed under reduced pressure. The liquid so obtained (1.9 g.) was purified by distillation under reduced pressure. This product was identified as ethyl α-bromocinnamate by comparison with an authentic sample[8,9] [identical retention time on a gas chromatography column (Perkin-Elmer "K" column) and identical n.m.r. spectra]. The corresponding acids[8,9] had the sample melting point and mixture melting point (131–132°).

Reaction between Methyl Fluorobromopropionate (I) and Potassium Phthalimide.—Methyl fluorobromopropionate reacted with potassium phthalimide in N,N-dimethylformamide at 70° to give a 70% yield of phthalimido ester free from fluorine. It was obtained as colorless crystals from methanol and had m.p. 91–95°.

Anal. Found: C, 50.54; H, 3.71; N, 5.08; Br, 19.44; F, 0.00.

This crystalline product was found to be a mixture of methyl α-bromo-β-phthalimidopropionate (VII) and methyl β-phthalimidoacrylate (VIII). The former was separated by chromatography over a Florosil column and identified with an authentic sample[10,11] by direct comparison and infrared spectroscopy. The acrylate derivative could not be isolated in analytically pure form; the infrared spectrum, however, indicated VII to be the contaminant.



VII VIII

Methyl α,β-dibromopropionate (2.46 g.) in 16 ml. of N,N-dimethylacetamide was stirred with potassium phthalimide (1.85 g.) for 4 days. The mixture was poured into ice water–chloroform. From the chloroform layer phthalimide (identified by melting point and infrared spectrum) was isolated (1.3 g.). Extraction of the water layer with chloroform gave 22 mg. of methyl α-bromo-β-phthalimidopropionate, m.p. 103.5–105°, which was identified by comparison with an authentic sample.[10,11]

Action of Potassium Phthalimide on Methyl Bromofluorosuccinate (III).—Methyl α-bromo-β-fluorosuccinate reacted with potassium phthalimide in N,N-dimethylformamide at 70° to give quantitative yields of phthalimide and a liquid product which contained much bromine and little fluorine.

Anal. Found: C, 45.47; H, 5.35; Br, 17.39; F, 2.05.

C. N.m.r. Studies on Fluorobromo Esters.—All the proton spectra were taken at 60 Mc. on a Varian Model DP-60 high resolution spectrometer using tetramethylsilane as an internal standard. Esters purified by repeated fractional distillation were

(5) Also see V. Tolman and K. Veres, *Collection Czech. Chem. Comm.*, **28**, 421 (1963).

(6) A. Bowers, *J. Am. Chem. Soc.*, **81**, 4107 (1959); C. H. Robinson, L. Finckenor, D. Gould, and E. P. Oliveto, *ibid.*, **81**, 2191 (1959).

(7) For example, see (a) P. M. Nair and J. D. Roberts, *ibid.*, **79**, 4565 (1957); (b) H. S. Gutowsky, G. G. Belford, and P. E. McMahon, *J. Chem. Phys.*, **36**, 3353 (1962).

(8) L. Suprin, *Ann. Chem.*, [12]**6**, 294 (1951).

(9) C. F. H. Allen and C. O. Edens, Jr., *Org. Syn.*, **25**, 92 (1949).

(10) S. Gabriel, *Chem. Ber.*, **41**, 242 (1908).

(11) A. Schöbert and H. Braun, *Ann. Chem.*, **542**, 274 (1939).

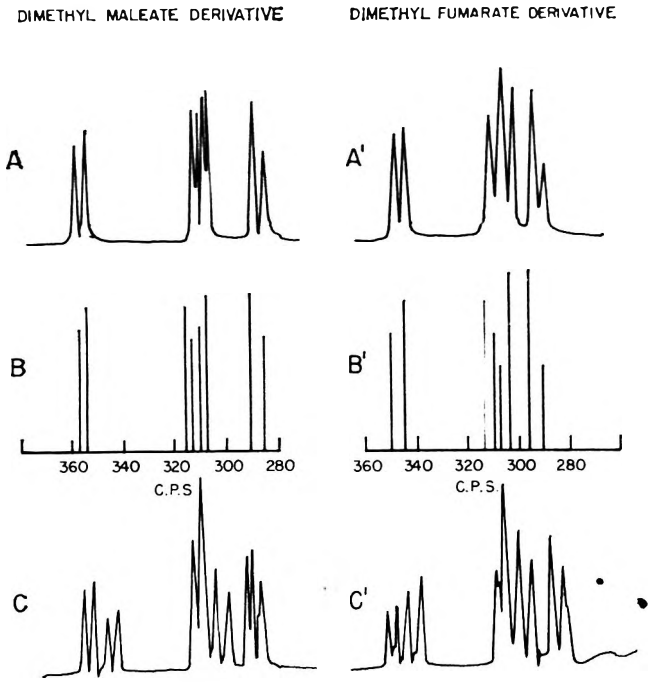


Fig. 1.—Proton nuclear magnetic resonance spectra: A and A', observed spectra at room temperature; B and B', calculated spectra; C and C', observed spectra upon heating the sample for 5 hr. at 150°.

placed in n.m.r. tubes which were then evacuated at room temperature and sealed. The fluorine spectra were obtained on the same instrument at 56.4 Mc., but no internal standard was used. All the systems which were studied were of the ABX type and were analyzed according to the procedure described by Pople, Schneider, and Bernstein.[12]

The coupling constants and chemical shifts reported in Table II were assigned on the basis of line positions as well as relative intensities with the assumption that the coupling constants are positive.

TABLE II

CHEMICAL SHIFTS AND COUPLING CONSTANTS FOR PROTON NUCLEAR MAGNETIC RESONANCE SPECTRA

No.	Fluorobromo derivative of	Chemical shifts, c.p.s.	Coupling constants, c.p.s.
1	Dimethyl maleate	ν_H = 333.19	$J_{FH\ (gem)}$ = 45.99
		$\nu_{H'}$ = 300.00	$J_{HH'}$ = 3.66
			$J_{FH'}$ = 23.69
2	Dimethyl fumarate	ν_H = 324.65	
		$\nu_{H'}$ = 298.55	$J_{FH\ (gem)}$ = 45.95
			$J_{HH'}$ = 4.62
			$J_{FH'}$ = 18.45
3	Diethyl maleate	ν_H = 328.36	$J_{FH\ (gem)}$ = 46.76
		$\nu_{H'}$ = 295.18	$J_{HH'}$ = 4.21
			$J_{FH'}$ = 23.44
4	Diethyl fumarate	ν_H = 320.06	$J_{FH\ (gem)}$ = 46.54
		$\nu_{H'}$ = 293.12	$J_{HH'}$ = 5.01
			$J_{FH'}$ = 17.50
5	Ethyl cinnamate	ν_H = 351.40	$J_{FH\ (gem)}$ = 45.61
		$\nu_{H'}$ = 275.00	J_{HH} = 9.38
			$J_{FH'}$ = 17.47

In the case of the dimethyl maleate derivative when the n.m.r. spectrum was run on the pure liquid, there was overlapping of peaks in the ABX portion of the spectrum. When, however, the spectrum was run in carbon tetrachloride solution, there was a clear separation between the sets of peaks, and assignment of transitions was possible without ambiguity. The assignments

(12) 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. 133.

TABLE III

FREQUENCIES IN CYCLES PER SECOND

Transition no.	Pure dimethyl maleate derivative (III)	Transition no.	Pure dimethyl fumarate derivative (IV)
8	358.75	8	350.17
6	355.12	6	345.59
7	313.45	4	309.94
4	312.20	2	305.39
5	309.79	7	304.43
2	308.51	5	299.81
3	289.02	3	29..32
1	285.35	1	286.64

to the different transitions, in accordance with the notation of Pople, Bernstein, and Schneider,[12] are shown in Fig. 1 and listed in Table III.

Temperature Studies on Fluorobromo Derivatives of Dimethyl Maleate and Dimethyl Fumarate.—A sample of freshly distilled fluorobromo ester (sealed in an n.m.r. tube as described above) was heated in a constant temperature bath at 150 ± 0.5° for about 30 min. After rapidly cooling the tube to room temperature, the spectrum was recorded. The sample was again heated at 150° for different periods (aggregating more than 5 hr.). New peaks (see Fig. 1) appeared, the intensities of which were found to increase with time; it was also noticed that only very little of the sample decomposed. This decomposition, however, did not interfere with the portion of the spectrum under study.

This experimental procedure was repeated using a freshly distilled sample of fluorobromo derivative of dimethyl fumarate. Again we observed the formation of new peaks the intensities of which increased with time (see Fig. 1).

We were able to identify the new peaks obtained in the spectrum of the dimethyl maleate derivative after heating as those of the dimethyl fumarate derivative. Similarly, the new peaks which appeared in the spectrum of dimethyl fumarate derivative after heating were identified with the frequencies of the dimethyl maleate derivative.

Similar results were obtained from the diethyl maleate and fumarate derivatives. These liquid samples had to be heated to 170° in order to have any appreciable change. In similar experiments with the fluorobromo derivative of ethyl cinnamate, extensive decomposition of the ester was found with etching of glass due to loss of hydrogen fluoride in preference to hydrogen bromide. The decomposition product was purified by short-path distillation and was identified as mainly α-bromocinnamate by n.m.r. spectrum and by comparison with an authentic sample.[8]

Fluorine Spectra.—The coupling constants obtained from the proton n.m.r. spectrum and the fluorine n.m.r. spectrum were in agreement. The fluorine spectrum was also used for studying the effect of temperature on the fluorobromo derivatives of maleates and fumarates, and results similar to those from the proton n.m.r. spectra were obtained.

Discussion

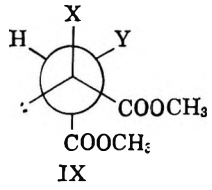
Orientation and Relative Reactivities of the Halogen Atoms in Fluorobromo Esters. A. Orientation.—The fluorobromination of acrylate and cinnamate esters was found to be a specific reaction leading to a single product as was evident from vapor phase chromatography and n.m.r. spectra. The appearance of the fluorine on the carbon atom β to the carboxyl group is to be expected on the basis of higher electronegativity of fluorine than that of bromine. During fluorobromination appreciable quantities of the maleate ester were converted into fumarate esters which remained mostly unchanged in the course of the halogenation.

B. Reactivity.—Methyl β-fluoro-α-bromopropionate reacted with potassium phthalimide in N,N-dimethylformamide or N,N-dimethylacetamide at room temperature for 2 days or at 70° for 1 hr. to give about 70% yield of the phthalimido ester. Methyl dibromopropionate and several other fluorobromo esters, how-

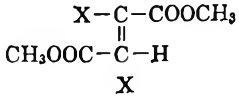
ever, gave phthalimide and the corresponding unsaturated α-bromo esters in high yield; contrary to expectation, the phthalimido ester was formed only in small quantities.

It is of interest to note that in the dehydrohalogenation of dimethyl maleate derivative in the presence of potassium phthalimide the product was a mixture of unsaturated bromo esters and fluoro esters. A quantitative analysis of this mixture was conveniently carried out by studying the n.m.r. spectrum of the total product. The vinyl protons in the bromo esters appeared as single peaks, whereas the vinyl protons of the unsaturated fluoro esters appeared as doublets. It was assumed that the doublet with the larger coupling constant (9.94 c.p.s.) corresponded to the *trans* ester. The *cis* ester showed the coupling constant of 3.14 c.p.s. It was estimated that the four unsaturated halo esters were present in the following approximate proportions: bromomaleate, 25%; bromofumarate, 36%; fluoromaleate, 16%; fluorofumarate, 23%.

In all probability the dehydrohalogenation is an ionic reaction. If it is a concerted process without involving a carbanion, then the molecule may have to arrange itself in conformation IX so that the two leaving groups and the carbons involved will all be in one plane, and the *trans* ester X will be favored. The



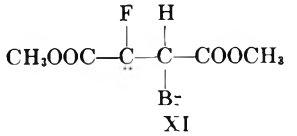
IX



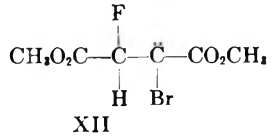
X

conventional reaction mechanism involving a carbanion would also favor the formation of the *trans* ester X. We have noted that the fluorobromo derivative from dimethyl melate produces more *trans* than *cis* ester in its reaction with potassium phthalimide. This would indicate the *threo* configuration for the starting fluorobromo ester. The same conclusion has been arrived at from a consideration of the stereochemistry of the addition of halogen to unsaturated compounds (see below).

In view of Bergmann's[13] work the formation of carbanion XI should be easier than the alternative carbanion XII. It might, therefore, be expected that the



XI

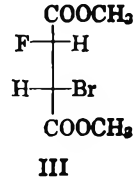


XII

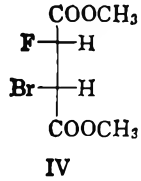
unsaturated fluoro ester would be formed in preference to the bromo ester. This is, however, contrary to our finding that the proportion of the bromo ester to the fluoro ester is 3:2.

In this connection it is interesting to note that Viehe, *et al.*,[14] have reported preferential loss of hydrogen bromide from bromofluoroethylene but hydrogen fluoride from chlorofluoroethylene on treatment with sodium amide.

Fluorobromo Derivatives of Dimethyl Maleate and Dimethyl Fumarate.—In general, the addition of bromine or chlorine to a double bond takes place in a *trans* fashion. Thus, the bromination of maleic and fumaric acids has been reported to lead to *meso*- and *dl*-α,α'-dibromosuccinic acids,[15] respectively. According to Terry and Eichelberger,[16] however, the salts of these acids add bromine both in the *trans* and *cis* manner. The stereochemistry of bromofluorination with hydrofluoric acid and N-bromoacetamide also appears to follow a *trans* course in steroids.[5,6] Assuming *trans* addition, one can assign the *threo* (III) and *erythro* (IV) configurations to the fluorobromo derivatives from dimethyl maleate and fumarate, respectively. Most probably both isomers can be expected to consist of rapidly interconverting mixtures of rotamers.



III



IV

Recently Bothner-By and Naar-Colin[17] and Anet[18] have studied the n.m.r. spectra of several symmetrical 2,3-disubstituted butanes. They have reported that the $J_{AA'}$ is higher in the *meso* isomer than in the *dl* isomer for the dibromo, the dichloro, and diphenyl derivatives. The diacetoxy butanes, however, are an exception to this pattern. Inspection of Table II shows that the fluorobromo derivative of a dialkyl fumarate (*erythro* configuration) has a higher $J_{AA'}$ than the corresponding maleate (*threo* configuration).

Bothner-By and Naar-Colin[17] and also Anet[18] have estimated the population of the three chief rotamers for both the *meso* and *dl* types of 2,3-disubstituted butanes on the basis of the assumptions that the rotamer, in which the methine protons are *trans*, has a large coupling constant, and the two gauche forms have small and equal coupling constants.

The $J_{AA'}$ values for the maleate and fumarate derivatives resemble the values reported for 2,3-diacetoxybutanes (*meso* isomer, 3.53 c.p.s.; *dl* isomer, 5.12 c.p.s.).[17] To rationalize the low value of $J_{AA'}$ for the *dl* isomer, Bothner-By and Naar-Colin have suggested mutual attraction of the two acetoxy groups. In the case of the fluorobromo derivative from fumaric ester, however, similar attraction is implausible. It is likely that the coupling constants and the equation used for estimating the relative contribution of rotamers are not valid—at least for the fluorobromo compounds.

It is interesting to note here that the replacement of the methyl ester group by an ethyl ester group changes the coupling constant noticeably (see Table II).

Gutowsky, Belford, and McMahon[7b] have studied 2,3-disubstituted butane systems by measuring the effect of temperature on $J_{AA'}$. In our own study we have found $J_{AA'}$ to be temperature dependent. (For the diethyl maleate derivative (III), $J_{HH'} = 4.21$ c.p.s. at room temperature and 4.70 c.p.s. at 102°.)

The study of the effect of temperature on the n.m.r. spectra of the fluorobromo derivatives established that a reversible interconversion of the *threo* and *erythro* iso-

(13) E. D. Bergmann and S. Szinal, *J. Chem. Soc.*, 1521 (1956).
(14) H. G. Viehe and E. Franchimont, *Chem. Ber.*, **95**, 321 (1962).
(15) A. McKenzie, *J. Chem. Soc.*, **101**, 1200 (1894).
(16) E. M. Terry and L. Eichelberger, *J. Am. Chem. Soc.*, **47**, 1077 (1925).
(17) A. Bothner-By and C. Naar-Colin, *ibid.*, **84**, 743 (1962).
(18) F. A. L. Anet, *ibid.*, **84**, 747 (1962).

mers of 2-fluoro-3-bromosuccinic acid esters takes place at higher temperatures. Such interconversion must involve the scission of a chemical bond and its regeneration in a different steric fashion.

Fluorine has been found to be an activating group. Bergmann[13] has shown that, on treatment with a base, fluoroacetic esters readily produce carbanions which can be alkylated. In view of this it appeared plausible that carbanion IX might be instrumental in the interconversion of the *threo* and *erythro* isomers. To test this possibility a sample of the dimethyl fumarate derivative and deuterated methanol (CH_3OD) was heated to 150–155° for 2 hr. The n.m.r. spectrum indicated the usual conversion of the *erythro* to the *threo* isomer, but no deuterium incorporation. It is evident, therefore, that a carbanion is not involved in the isomer interconversion. We have observed that hydrogen fluoride failed to add to bromomaleate and bromofumarate.

No etching of the n.m.r. tubes was observed during the heating experiments. Reversible elimination and addition of hydrogen fluoride is, therefore, unlikely to be involved in the interconversion of these esters.

A free-radical mechanism does not appear to be involved because e.p.r. spectra studies on the heated sample of the dimethyl maleate derivative failed to indicate any unpaired electrons. Moreover, if free radicals are formed, the n.m.r. spectrum at high temperature should have shown broadening of the peaks.[19] The proton n.m.r. peaks, however, were found to be sharp at all the temperatures studied. If, however, free radicals have very short life or are produced in small concentrations, our methods for the detection of free radicals may have been inadequate.

The mediation of a carbonium ion in the interconversion of the *threo* and the *erythro* epimers is possible. Further work will be necessary to get definitive evidence about the mechanism of interconversion of the isomeric fluorobromo esters.

Acknowledgment.—We wish to thank Dr. E. R. Malinowski and Professors P. Allen and J. van der Veen for helpful discussions, and R. Spanier for determining some of the n.m.r. spectra. This work was supported in part by a grant (CA-05079) from the National Cancer Institute of the U. S. Public Health Service.

(19) S. I. Weisman, C. R. Bruce, and R. E. Norberg, *J. Chem. Phys.*, **24**, 473 (1958).

Reactions of N-Bromosuccinimide and Indoles. A Simple Synthesis of 3-Bromooxindoles[1]

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N-Bromosuccinimide (NBS) in *t*-butyl alcohol converts 3-alkylindoles such as skatole, indole-3-acetic acid, and other indole-3-alkanoic acids to the corresponding oxindoles when a 1:1 mole ratio of NBS to indole is used. 3-Bromooxindoles are obtained with a 2:1 ratio of reactants. Oxindoles are intermediates in the formation of 3-bromooxindoles, but NBS does not attack oxindoles in dry alcohol. The hydrogen bromide evolved in oxindole formation in the first step must catalyze the formation of 3-bromooxindoles, probably by way of the enol form of the oxindole. Basic catalysis of 3-bromination of oxindoles by NBS can be effected also, but in neutral aqueous *t*-butyl alcohol 5-bromooxindoles are formed. In glacial acetic acid NBS effects bromination of the indole hetero ring. The reaction of indoles and NBS is the method of choice for the synthesis of oxindole-3-acetic acid and related compounds, as well as oxindole analogs of tryptamine and tryptophan. The reaction also provides the first simple and general route to 3-alkyl-3-bromooxindoles, stable intermediates which undergo facile replacement of the halogen by alcohols, water, and other nucleophiles. The mechanisms of oxindole formation and bromination are discussed. The ultraviolet and infrared absorption spectra of the bromoindoles are tabulated.

Interest in the products of chemical and enzymatic oxidations of indoles[2] prompted us to seek new methods for the synthesis of oxindoles and dioxindoles related to indole-3-acetic acid (IAA). Lawson and Witkop have shown that N-bromosuccinimide (NBS) can be used to convert indoles to oxindoles[3,4] and have drawn attention to the importance of the solvent in determining the nature of the products—nonaqueous media favoring bromine substitution of the hetero ring, aqueous media supporting oxindole formation.[5]

In the course of further studies on the effects of solvents, we have found that NBS in *t*-butyl alcohol is an excellent system for converting a variety of 3-alkylindoles to the corresponding oxindoles in one operation. Depending on the NBS–indole ratio, either simple oxindoles or 3-bromooxindoles can be obtained (eq. 1). The latter compounds are stable but reactive intermediates accessible for the first time by a simple and convenient procedure. Some of their reactions will be described in a forthcoming publication.[6] We have also studied the reactions of NBS and a variety of indoles in glacial acetic acid, in which substitution predominates.

Reactions in *t*-Butyl Alcohol.—The reactions of NBS and indoles in *t*-butyl alcohol are summarized in Table I.

(1) Presented before the Organic Division of the 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April, 1963.

(2) (a) R. L. Hinman and P. Frost, "Plant Growth Regulation," R. Klein, Ed., Iowa State University Press, Ames, Iowa, 1961, p. 205; (b) R. L. Hinman, C. Bauman, and J. Lang, *Biochem. Biophys. Res. Commun.*, **5**, 250 (1961).

(3) W. B. Lawson and B. Witkop, *J. Org. Chem.*, **26**, 263 (1961).

(4) *t*-Butyl hypochlorite has been used to transform members of the indole alkaloids to oxindoles by pathways analogous to those described here, but generally involving migration of an alkyl group from the 2-position [N. Finch and W. E. Taylor, *J. Am. Chem. Soc.*, **84**, 3871 (1962); J. Shavel and H. Zinnes, *ibid.*, **84**, 1320 (1962)].

(5) W. B. Lawson, A. Patchornik, and B. Witkop, *ibid.*, **82**, 5918 (1960).

(6) R. L. Hinman and C. P. Bauman, *J. Org. Chem.*, in press.

TABLE I

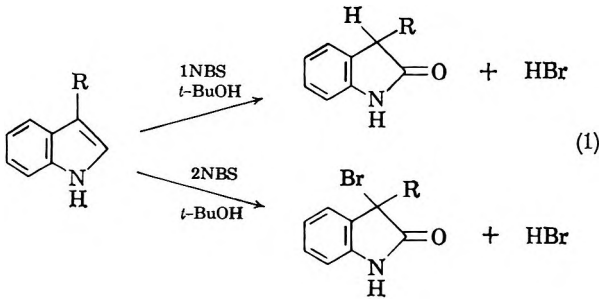
REACTIONS OF INDOLES WITH N-BROMOSUCCINIMIDE IN *t*-BUTYL ALCOHOL

Indole	Mole ratio of NBS indole	Solvent[a]	Product	% yield	Recrystn. solvent[b]	M.p., °C.	Reported m.p., °C.	Empirical formula	Anal., % Calcd. C	Calcd. H	Calcd. N	Calcd. Br	Found C	Found H	Found N	Found Br
Skatole	1	B[c]	3-Methyloxindole	26	W, A–H	124–125	123–124[d]	C_9H_9NO	73.43	6.17	9.52		73.21	6.27	9.56	
Indole-3-acetic acid	1	A[c]	Oxindole-3-acetic acid	42	A–B	145–146	147[e]	$C_{10}H_9NO_3$								
Indole-3-propionic acid	1	B[f]	Oxindole-3-propionic acid	52	A, W	169–170	169–170[g]	$C_{11}H_{11}NO_3$	64.38	5.40	6.82		64.62	5.57	6.92	
Indole-3-butyric acid	1	B[c]	Oxindole-3-butyric acid	50	A, B, M	170–171		$C_{12}H_{13}NO_3$	65.74	5.98	6.39	(219)[h]	65.58	5.93	6.38	(218)[h]
Indole-3-caproic acid	1.1	A[c]	Oxindole-3-caproic acid	4[i]	A	159.5–160.0		$C_{14}H_{17}NO_3$	67.97	6.93	5.67		68.02	7.30	5.43	
3-(β-Benzamidoethyl)-indole	1	B[f]	3-(β-Benzamidoethyl)-oxindole	35	A	195–197	194[j]	$C_{17}H_{16}N_2O_2$	72.83	5.75	10.00		72.56	5.78	10.16	
Tryptamine·HBr	1	B[k]	3-(β-Aminoethyl)oxindole hydrobromide	31	A–E, E	266–268 dec.		$C_{10}H_{13}BrN_2O$	46.70	5.09	10.90	31.08	46.55	5.22	10.68	31.20
N^{α}-Acetyltryptophan	1	C[c]	α-Acetamido(oxindole-3)-propionic acid	14	A–M	214.0–214.5	209–210[l]	$C_{13}H_{14}N_2O_4$	59.58	5.38	10.68		59.87	5.37	11.21	
			α-Acetamido(dioxindole-3)-propionic acid lactone	8	M–W	290–293 dec.	284 dec.[m]	$C_{13}H_2N_2O_4$	59.99	4.65	10.77		60.07	4.72	10.88	
Skatole	2	A[f]	3-Bromo-3-methyloxindole	42	A–B	143 dec.		C_9H_8BrNO	47.81	3.57	6.20	35.35	47.61	3.54	6.36	35.29
Indole-3-acetic acid	2	A[f]	3-Bromooxindole-3-acetic acid	75	A–B	151–152 dec.		$C_{10}H_8BrNO_3$	44.46	2.98	5.19	29.59	44.59	3.20	5.05	29.80
Indole-3-propionic acid	2	A[f]	3-Bronooxindole-3-propionic acid	44[n]												
Indole-3-butyric acid	2	A[f]	3-Bromooxindole-3-butyric acid	63	T–B	140–141 dec.		$C_{12}H_{12}BrNO_3$	48.34	4.06	4.70	26.80	48.54	4.04	4.63	26.60

[a] A, *t*-butyl alcohol; B, 95% *t*-butyl alcohol; C, 81% *t*-butyl alcohol. [b] A = acetone; B = benzene; E = absolute ethanol; H = hexane; M = methanol; T = tetrahydrofuran; W = water. [c] *t*-Butyl alcohol not purified before use. [d] Ref. 28. [e] Ref. 8. [f] *t*-Butyl alcohol dried over sodium sulfate and treated once with Darco G. [g] P. L. Julian and H. C. Printy, *J. Am. Chem. Soc.*, **75**, 5301 (1953). [h] Neut. equiv. [i] Result of one experiment; low yield probably a result of not purifying solvent. [j] Ref. 11b. [k] Treated twice with Darco before use. [l] Ref. 10b. [m] Ref. 10a. [n] Bromooxindole could not be crystallized; converted to dioxindole with dilute sulfuric acid; yield given is of dioxindole.

The synthesis of an oxindole by use of a 1:1 mole ratio of NBS and indole could be carried out in an open erlenmeyer flask at room temperature, and the course of the reaction was readily followed by the changes in the ultraviolet spectrum.[7] Reactions were usually complete as soon as all the NBS had dissolved. Although oxindoles were obtained when anhydrous *t*-butyl alcohol was used, the yields were improved considerably when 5% of water was added to the solvent, presumably because water is the source of the oxygen introduced at the 2-position. The addition of still more water tends to promote 5-bromination of the oxindole already formed. Moreover, for the synthesis of oxindole-3-acetic acid (OAA), dry conditions are preferable since rearrangement of oxindole-3-acetic acid to 3,4-dihydroquinolone-4-carboxylic acid is facilitated by a more polar medium.[8] When water was not added, however, purification of the solvent was usually required to remove an impurity which exerts a powerful effect on the product distribution between oxindoles and α-bromoindoles (see Experimental).

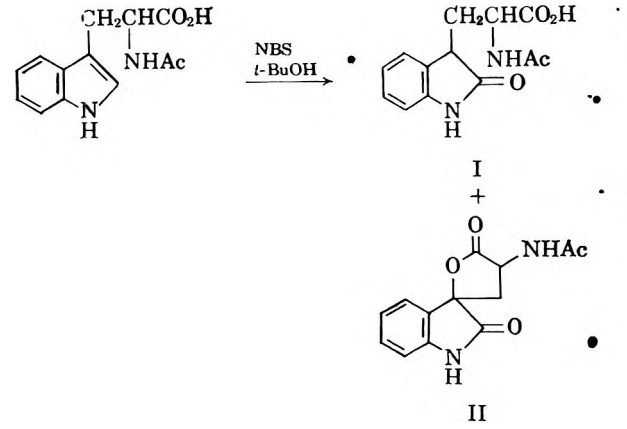
Although the yields are modest, the simplicity of the method recommends it over those reported previously for the conversion of indoles to oxindoles.[3,9] An at-



(1)

tractive application of the procedure was the synthesis of α-acetamidooxindole-3-propionic acid (I) from N^{α}-acetyltryptophan. The oxindolealanine, previously accessible only by multistep procedures,[10] was obtained in 14% yield (based on unrecovered starting material) along with the lactone of α-acetamidodioxindole-3-propionic acid (II), the latter apparently arising from the presence of the sodium bicarbonate added to increase the solubility of the starting material in the reaction medium (see col. 2).

The oxindole analog of tryptamine[11] was also synthesized by this method. Attack on the primary amino group was avoided by the addition of hydrogen bromide



prior to the reaction with NBS. Attempts to apply this technique to the synthesis of oxindole-3-alanine were unsuccessful.

The reaction of 2 moles of NBS with a 3-alkylindole *in aqueous media* leads to a 5-bromooxindole.[5] The oxindole, a modified acetanilide, is apparently brominated *para* to the acylamino group as rapidly as the latter is formed in the polar medium. In *t*-butyl alcohol, as used in the present work, the reaction follows a different path and 3-alkyl-3-bromooxindoles are formed (Table I). This procedure, which affords the first simple general route to 3-alkyl-3-bromooxindoles, is also simple to carry out. Reaction of the second mole of NBS is slower than the first, but the reaction is usually complete within 1–2 hr. after the NBS has been added. Since water promotes 5-bromination of oxindoles, the *t*-butyl alcohol was usually dried before use, in contrast to the practice of adding water when only 1 mole of NBS was used. Removal of impurities from the solvent was necessary for optimum results.

The 3-bromooxindoles were characterized by their elemental analyses, labile halogen (precipitate with alcoholic silver nitrate within 3 sec. at room temperature), typical oxindolic carbonyl and NH peaks in the infrared, and conversion to dioxindoles and 3-methoxyoxindoles by treatment with water and methanol, respectively (reactions which will be described in detail in a subsequent publication).[6]

In several experiments with indole-3-acetic acid both 3-bromooxindole-3-acetic acid and its *t*-butyl ester were obtained. The hydrogen bromide evolved during the reaction was probably responsible for the esterification, but we have been unable to effect direct esterification of the isolated acid under comparable conditions. Indole-3-propionic acid (IPA) was converted to the 3-bromooxindole, as indicated by the characteristic ultraviolet spectrum of the class,[7] but the product could not be obtained in solid form. It was characterized by hydrolysis under acidic conditions to a mixture of crystalline β-dioxindole-3-propionic acid and its lactone. By carrying out the reaction of indole-3-propionic acid and NBS in the presence of sodium bicarbonate, the lactone could be obtained directly.

t-Butyl hypochlorite and bromine in *t*-butyl alcohol were also examined as reagents for oxindole formation. From the reaction of a 2:1 mole ratio of *t*-butyl hypochlorite to skatole, no 3-chlorooxindole could be isolated. Only a very small amount of what was presumably 5-chloro-3-methyloxindole was obtained. Bromine and indole-3-butyric acid (IBA) (1:1 mole ratio)

(7) The marked differences between the ultraviolet spectra of alkylindoles [λ_{max} ~ 288 mμ (ε ~ 7000), see Table V] and the derived oxindoles [λ_{max} ~ 250 mμ (ε ~ 8000)] are well-known. The spectra of 3-bromooxindoles, which have not previously been recorded, show an unexpected difference from the parent oxindoles by having a double peak in the 220–230-mμ region and no observable maximum in the normal oxindolic region near 250 mμ. Thus, in 95% ethanol, 3-methyloxindole absorbs at λ_{max} 207, 249, and 278 (sh) mμ (ε 27,400, 8720, 1440), whereas 3-bromo-3-methyloxindole absorbs at λ_{max} 217, 229 (sh), and 310 mμ (ε 16,900, 13,400, and 940).

(8) P. L. Julian, H. C. Printy, R. Ketcham, and R. Doone, *J. Am. Chem. Soc.*, **75**, 5309 (1953).

(9) (a) W. E. Sumpter and F. M. Miller, "Heterocyclic Compounds with Indole and Carbazole Systems," Interscience Publishers, Inc., New York, N. Y., 1954, p. 134; (b) C. E. Dalgliesh and W. Kelly, *J. Chem. Soc.*, 3723 (1958).

(10) (a) P. L. Julian, E. E. Dailey, H. C. Printy, H. L. Cohen, and S. Hamashige, *J. Am. Chem. Soc.*, **78**, 3503 (1956); (b) J. W. Cornforth, R. H. Cornforth, C. E. Dalgliesh, and A. Neuberger, *Biochem. J.*, **48**, 591 (1951); (c) T. Wieland, O. Weiberg, and W. Dilger, *Ann.*, **592**, 69 (1955).

(11) (a) J. Harley-Mason and R. F. J. Ingleby, *J. Chem. Soc.*, 3639 (1958); (b) K. Freter, M. Weissbach, B. Redfield, S. Udenfriend, and B. Witkop, *J. Am. Chem. Soc.*, **80**, 983 (1958).

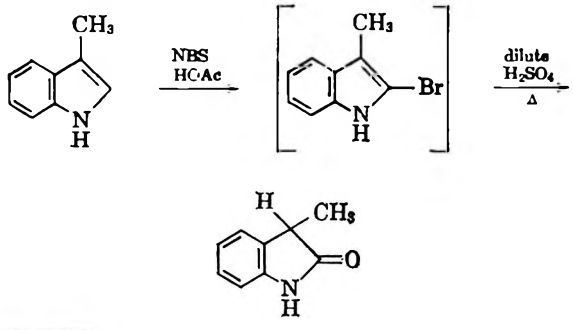
gave a low yield of oxindole-3-butyric acid. Bromine has been used more successfuly in aqueous acetic acid.[3]

Reactions in Acetic Acid.—To gain further insight into the effect of solvent on the reactions of indoles with NBS, a number of reactions were carried out in glacial acetic acid. As shown in Table II, NBS in this solvent at room temperature rapidly brominates indoles at an available position in the hetero ring. Indole itself gave a mixture of products which could not be identified.[12]

Although bromoindoles were the main products, oxindolic materials were invariably found also and recognized by their ultraviolet and infrared spectra. In view of the marked instability of the bromoindoles in the presence of acids, it seemed likely that the oxindolic material was formed by the action of hydrogen bromide evolved during the reaction. However, scrupulous drying of the acetic acid and work-up of the product by first pouring the reaction mixture into base did not eliminate the oxindoles. Since some 2,6-dibromoindole-3-butyric acid was isolated from the reaction of NBS with indole-3-butyric acid in *t*-butyl alcohol from which the main product (63%) was the 3-bromooxindole-3-butyric acid (Table I), it is apparent that substitution and oxidation are competitive reactions, and that the balance is shifted by the solvent, but that neither reaction is completely excluded.[13]

The simple bromoindoles were not very stable, undergoing gradual decomposition on standing, a process accelerated by acid or light.[12] When heated with acidic silver nitrate solution, a precipitate of silver bromide formed rapidly, but in the absence of acid, no precipitate formed, even on prolonged heating. The resistance of a presumed 2-bromolysergic acid diethylamide to reaction with silver oxide has been noted previously.[14] 2-Bromoskatole was recovered unchanged after 24 hr. in refluxing ethanolic potassium hydroxide solution.

The instability under acidic conditions of indoles substituted at the α-position by bromine and other related leaving groups has been used previously to obtain oxindoles.[5,11b,14] We have found that by simply adding sulfuric acid to the reaction mixture of NBS and a 3-alkylindole and refluxing, the 3-alkyloxindole can be obtained in one over-all operation, without isolation of the intermediate (eq. 2). Thus, oxindole-3-butyric



(2)

TABLE II

SUBSTITUTION REACTIONS OF N-BROMOSUCCINIMIDE WITH INDOLES[a]

Starting indole	Mole ratio of NBS-indole	Product indole	% yield	M.p., °C.	Recrystn. solvent[b]	Empirical formula	Anal., % Calcd. C	Calcd. H	Calcd. N	Calcd. Br	Found C	Found H	Found N	Found Br
3-Methyl	1	2-Bromo-3-methyl	45	88–90 dec.	A–W	C_9H_8BrN	51.48	3.84	6.67	38.06	51.54	4.00	6.71	37.89
2-Methyl	1[c]	3-Bromo-2-methyl	50	90–91 dec.[d]	B–H	C_9H_8BrN	51.48	3.84	6.67	38.06	51.55	3.79	6.77	37.98
1,2-Dimethyl	1[e]	3-Bromo-1,2-dimethyl	64	73–74 dec.	M	$C_{10}H_{10}BrN$	53.59	4.51	6.25	35.65	53.33	4.58	6.46	35.23
3-*n*-Propyl	1	2-Bromo-3-*n*-propyl	25[f] (crude)											
3-*n*-Propyl	2	2,6-Dibromo-3-*n*-propyl	[f]											
2-Bromo-3-methyl	1	2,6-Dibromo-3-methyl	48	99–101 dec.[g]	E–W									
Indole-3-butyric acid	1	2-Bromoindole-3-butyric acid	19	99–100	W	$C_{12}H_{12}BrNO_2$	51.08	4.28	4.96 (282)[h]	28.32	51.29	4.52	4.94	28.28 (280[h])
Indole-3-butyric acid	2	2,6-Dibromoindole-3-butyric acid	*i*	165–166 dec.	M–W	$C_{12}H_{11}Br_2NO_2$	39.92	3.07	3.88	44.27	39.99	3.21	4.20	44.32

[a] Solvent was glacial acetic acid, dried before use with triacetyl borate, except where noted otherwise. [b] A = acetic acid; B = benzene; E = ethanol; H = hexane; M = methanol; W = water. [c] Acetic acid not dried. [d] Terent'ev, Belenkii, and Yanovskaya [*Zh. Obshch. Khim.*, **24**, 1265 (1954)] report m.p. 86–87°. [e] Solvent *t*-butyl alcohol. [f] Product was an oil which could not be purified; identified by ultraviolet and infrared spectra and by hydrolysis to the corresponding oxindole. [g] Lit.[5] m.p. 100° dec. [h] Neut. equiv. [i] Isolated as a by-product from reactions in *t*-butyl alcohol.

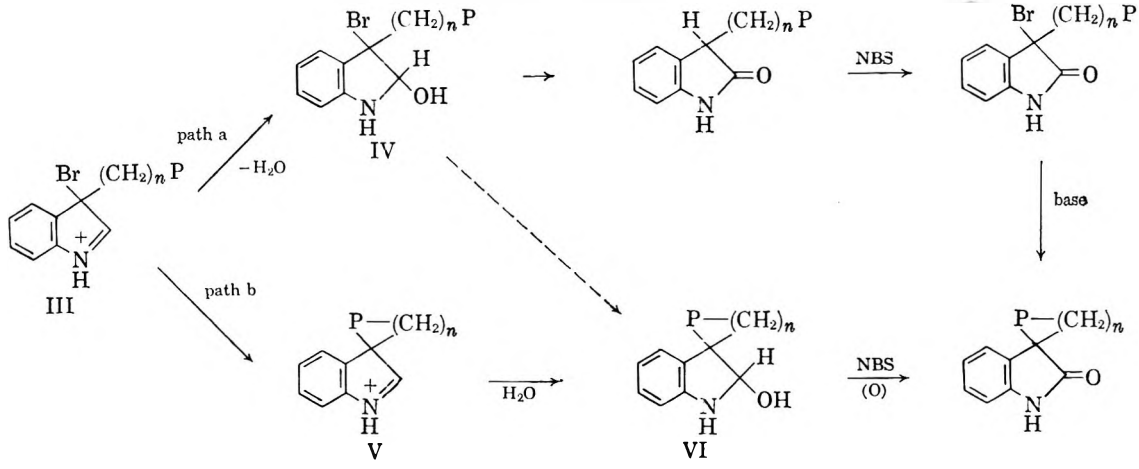
(12) Conversion of indole to 3-bromoindole by use of dioxane dibromide or pyridinium bromide perbromide has been reported [K. Piers, C. Meimaroglow, R. V. Jardine, and R. K. Brown, *Can. J. Chem.*, **41**, 2399 (1963)]. This method was particularly effective with pyridine as the solvent. From attempts to brominate skatole with NBS in 2,6-lutidine we were unable to obtain any pure product.

(13) Although the formation of 5-bromo-3-methyloxindole from skatole in aqueous acetic acid may be a result of hydrolysis of the α-bromoindole, it seems more likely that it arises by a change in reaction mechanism (see below).

(14) K. Freter, J. Axelrod, and B. Witkop, *J. Am. Chem. Soc.*, **79**, 3191 (1957).

CHART I

POSSIBLE PATHWAYS OF OXINDOLE FORMATION



acid was obtained in 41% over-all yield from indole-3-butyric acid and 3-methyloxindole was obtained in 26% yield from skatole. For simple conversion of an indole to an oxindole, however, the reaction with NBS in *t*-butyl alcohol is more convenient.

Although hydrolysis of α-bromoindoles takes place quite readily, introduction of a bromine into the aromatic ring has a very marked retarding effect. 2,6-Dibromoskatole underwent no perceptible hydrolysis during 2 hr. in a refluxing ethanolic solution, which was 1.1 *M* in sulfuric acid. With refluxing dioxane as solvent, as used by Witkop,[5] hydrolysis to the oxindole took place. With 2,6-dibromo-3-*n*-propylindole, only partial hydrolysis was effected during 19 hr. even in refluxing dioxane in which the sulfuric acid concentration was 4.5 *M*.

2,6-Dibromoindole-3-butyric acid behaved similarly. The decreased reactivity is probably the result of a decrease in the basicity of the ring system since 3-protonation[15] is undoubtedly the first step in hydrolysis.

Mechanisms of the Reactions.—Witkop has proposed[5] two pathways for the reaction of NBS and indoles in aqueous media which account for both the formation of oxindole derivatives from simple indoles such as skatole, and the formation of spirolactones of oxindoles which bear a polar group (P) on the side chain at the 3-position. The general form of this scheme is shown, with minor simplifying changes, in Chart I with the 3-bromoindolenine (III), the first species formed in the interaction of NBS and an indole, as an intermediate common to both.[16] When group P is a polar species in a polar medium, ring closure to the spirolactone must occur prior to formation of the amide function of the oxindole because the aqueous conditions employed would facilitate bromination of the benzene ring, rather than the 3-bromination required for lactone formation.[17]

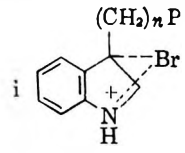
In *t*-butyl alcohol only pathway a appears to be applicable, since oxindoles are obtained from the reaction of 1 mole of NBS with 1 mole of indole even if the side chain at the 3-position bears a cyclizable carboxyl group. That ring closure by path b does not occur is understandable in view of the high acidity (from evolved hydrogen bromide) and low polarity of the medium which would repress ionization to the nucleophilic carboxylate ion. (In aqueous systems the carboxylate ion must be the active species rather than the undissociated carboxyl group, as formulated previously.[5])

By this scheme bromination rather than oxidation occurs in acetic acid because this solvent is not sufficiently nucleophilic to react with intermediate III. The pathway can be shifted by addition of more reactive nucleophiles. When skatole and NBS reacted in dry glacial acetic acid containing dry sodium acetate, 3-methyloxindole and other oxindolic or dioxindolic materials were obtained in 73% yield.[18] We have also observed a change over to oxindole formation when water was added to the acetic acid, as reported previously.[5,13]

Formation of a 3-bromooxindole from an indole must occur *via* bromination of an intermediate oxindole, a stepwise transformation which can be observed directly in the ultraviolet spectra[7] as each mole of NBS is added. The mode of conversion of oxindole to 3-bromooxindole is an interesting problem, however, since NBS in dry *t*-butyl alcohol did not attack 3-methyloxindole or oxindole-3-butyric acid over a period of a few hours, and, when 10% of water was added, only 5-bromooxindoles were formed.[19] The paradox was resolved when it was found that under dry conditions the addition of either hy-

(15) R. L. Hinman and E. B. Whipple, *J. Am. Chem. Soc.*, **84**, 2534 (1962).

(16) In the previously proposed reaction pathway[5] a bromonium ion (i) was proposed as the common intermediate. Hydration would then yield IV, but intramolecular displacement of bromine requires the formation



i

of a 2-bromoindoline which would, in turn or simultaneously, lose hydrogen bromide yielding V. In the absence of any data on the nature of the intermediates, it is more economical to consider III as the first-formed intermediate, common to both pathways.

(17) None of these pathways is completely specific. Under Witkop's conditions for synthesis of 5-bromodioxindole-3-propionic acid lactone in an acetonitrile–water system, buffered by acetate at pH 4,[5] we have found that some 3-bromination of oxindoles may occur, although 5-bromination is expected and preferred. A particularly sensitive test is provided by oxindole-3-acetic acid. Any 3-bromooxindole-3-acetic acid which is formed is rapidly converted in the aqueous medium to 3-methyleneoxindole,[2b,6] which is readily detected by its intense ultraviolet absorption. Only 5–10% of 3-bromination was observed by this method.

(18) 3-Methyloxindole made up only 12% of this mixture. Since the bromine in intermediates such as III would be easily displaced by reactive nucleophiles, the formation of dioxindoles would not be surprising.

(19) For a general review of the halogenation of oxindoles see ref. 9a, p. 140.

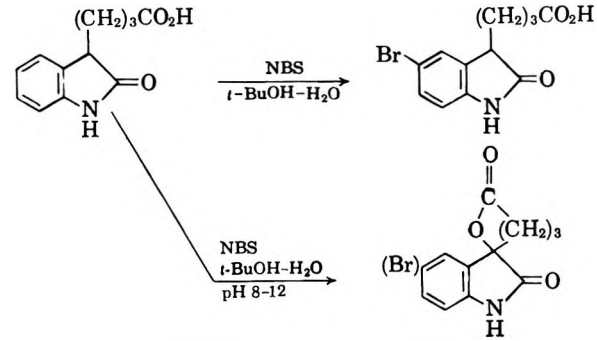
TABLE III

SPECTRAL CHARACTERISTICS OF BROMOINDOLES

No.	Compound	Ultraviolet λ_{max}, mμ (ε) in 95% ethanol			Infrared, μ (KBr) NH region	Infrared, μ (KBr) C=O region
1	2-Bromoskatole	223 (35,800)	277 sh	(7480)	2.98	
			282	(7780)		
			291	(6570)		
2	Skatole	223 (34,800)	276 sh	(5450)		
			282	(5860)		
			291	(4930)		
3	3-Bromo-2-methylindole	223 (33,700)	275 sh	(6980)	2.99	
			281	(7500)		
			289	(6670)		
4	2-Methylindole	220 (33,600)	272	(7140)		
			277	(7040)		
			288	(5360)		
5	3-Bromo-1,2-dimethylindole	227 (34,800)	277 sh	(6640)		
			283	(7440)		
			291 sh	(7080)		
6	1,2-Dimethylindole	223 (34,400)	276	(7200)		
			282	(7650)		
			291	(6420)		
7	2-Bromoindole-3-butyric acid	224 (35,700)	275–277 sh	(7750)	2.91	5.82
			283	(8200)		
			291	(6950)		
8	2,6-Dibromoskatole	230 (38,000)	286	(8370)	2.95 sh	5.89
			297 sh	(7300)	2.97	
9	2,6-Dibromoindole-3-butyric acid	229 (41,600)	286	(8780)	2.95	5.84
					3.00	5.96

drogen bromide or sulfuric acid promoted bromination of the 3-position. Moreover, molecular bromine substituted the 3-position without addition of acid under dry conditions (with water present, 5-bromooxindoles were formed). The 3-bromination of an oxindole is thus clearly analogous to α-bromination of a ketone, with acid required to produce the reactive enol form. In the reactions of NBS with indoles, the formation of hydrogen bromide in the first step provides the catalyst to make NBS an active brominating agent for the 3-position. Bromine would also be present because of the reaction: NBS + HBr ⇌ succinimide + Br_2.[20]

The analogy between oxindoles and ketones in halogenations also accounts for a number of reported instances of 3-halogenations of oxindoles which occur in aqueous media. Thus, simple indoles and N-alkyloxindoles react with hypohalites to yield 3,3-dihalooxindoles,[19] lysergic acid derivatives yield dioxindoles when treated with calcium hypochlorite,[21] and 3-alkyloxindoles have been converted to dioxindoles by alkaline hypoiodite.[10a,22] In these cases 3-halogenation of the oxindole takes place *via* the enolate ion formed under the basic conditions of the hypohalite reactions.[23] A good demonstration of the latter pathway was provided by the reaction of NBS with oxindole-3-butyric acid. Whereas 5-bromooxindole-3-butyric acid was obtained in 73% yield in 90% *t*-butyl alcohol containing no acidic or basic catalyst, in 80% *t*-butyl alcohol, brought to pH 8 or 12 by the addition of sodium hydroxide, a mixture of dioxindole-3-butyric acid lactone and 5-bromodioxindole-3-butyric acid lactone was obtained, along with oxindole-3-butyric acid. The lactones could only have been formed by prior bromination of the 3-position.[24] Halogenation of the benzene



ring can apparently compete successfully with 3-halogenation only in relatively polar media under acidic or near neutral conditions. 3-Halogenation of oxindoles by bromine in carbon tetrachloride[19] or chlorobenzene[25] are simply additional examples of the acid-catalyzed behavior observed in *t*-butyl alcohol.

(20) These results provide additional evidence in support of path b under Witkop's conditions. Moreover, in the use of bromoamides for cleavage of C-tryptophyl peptide bonds it has been pointed out that cleavage of C-oxindolealanine peptides occurs to a much smaller extent than does cleavage of the corresponding indole derivatives. The conditions used (aqueous acetate–formate buffer at pH 4) are those most likely to promote bromination of the oxindole's benzene ring. Even after deactivation of that ring by bromination, substitution of bromine at the 3-position would be slow because of the acid catalysis required. It is particularly interesting that, in 10 *M* lithium acetate at pH 4, N-bromoacetanilide is as effective in cleaving an oxindolealanine peptide bond as the corresponding one containing a tryptophan residue. Apparently 3-bromination occurs in this case, but it is not clear why these conditions favor it (*cf.* ref. 17).

(21) F. Troxler and A. Hofmann, *Helv. Chim. Acta*, **42**, 793 (1959).

(22) P. L. Julian, H. C. Printy, and E. E. Dailey, *J. Am. Chem. Soc.*, **78**, 3501 (1956).

(23) In the conversion of lysergic acid derivatives to dioxindoles,[21] an alternate though less attractive route would involve displacement by hydroxyl of the halogen of a reactive intermediate such as III prior to oxindole formation. Moreover, under basic conditions, oxindoles can be oxidized by air to dioxindoles (P. L. Julian, F. W. Meyer, and H. C. Printy, "Heterocyclic Compounds," Vol. 3, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1952, p. 241). What part this pathway plays in the media used for hypohalite oxidations is not known.

(24) The formation of dioxindole-3-propionic acid lactone from indole-3-propionic acid and NBS in the presence of bicarbonate may have occurred by this pathway or by path b of Chart I or both.

(25) E. Giovannini and P. Portmann, *Helv. Chim. Acta*, **31**, 1375 (1948).

Experimental[26]

Ultraviolet and infrared absorption spectra of the bromoindoles are listed in Table III, from which it is apparent that bromination effects little change in the ultraviolet spectrum of a methylindole. The spectra of all the oxindolic products have been determined and will be summarized and discussed with additional examples in a subsequent paper.[6]

Reactions in *t*-Butyl Alcohol.—These reactions were all performed in the same general manner, differing slightly only in the work-up procedure. The examples given below are illustrative of the method or are important because of the particular product or an unusual variation in method. The *t*-butyl alcohol was purified by the following general method (see further discussion below). A mixture of 7 g. of Darco G in 500 ml. of *t*-butyl alcohol, previously dried over sodium sulfate, was stirred for 10 min. at 50°. The mixture was filtered by gravity through a heated funnel. When water was added, purification was unnecessary (Table IV).

TABLE IV

EFFECT OF TREATMENT OF *t*-BUTYL ALCOHOL ON THE INDOLE–OXINDOLE TRANSFORMATION

Treatment of *t*-butyl alcohol[a]	*R* value[b]
None (used as supplied)	0.60
Darco (1X)[c]	1.84
Darco (2X)	3.06
Alumina (1X)[d]	1.98
1% water added	3.24
5% water added	3.10
Darco (1X), then 5% water added	3.22
Anhydrous Na_2SO_4[e]	1.40
Anhydrous Na_2SO_4, then Darco (1X)	2.14
Anhydrous Na_2SO_4, then 5% water added	3.15
$Na_2SO_4 \cdot 10H_2O$[e]	3.13

[a] All experiments were carried out with one batch of *t*-butyl alcohol (Matheson Coleman and Bell Cat. No. BX 1800). [b] *R* value = absorbance at 248 mμ/absorbance at 282 mμ for the reaction of 0.0025 mole each of IBA and NBS in 16.3 ml. of solvent. Spectra were obtained by diluting portions of the reaction mixture with *t*-butyl alcohol which had been dried and treated with Darco. [c] Darco G (1.5 g.)/100 ml. of solvent. [d] Alumina (1.5 g.)/100 ml. of solvent. [e] Sodium sulfate (15 g.)/100 ml. of solvent.

Oxindole-3-acetic Acid.—To a solution of 3.50 g. (0.02 mole) of indole-3-acetic acid in 130 ml. of *t*-butyl alcohol was added in small portions with stirring 3.56 g. (0.02 mole) of N-bromosuccinimide at 21–23°. After 2 hr. the solution was concentrated to a thick sirup under reduced pressure at room temperature, 30 ml. of water was added, and the mixture was extracted with three 40-ml. portions of ethyl acetate. The extract was washed with saturated salt solution, dried over sodium sulfate, and evaporated at room temperature. Residual ethyl acetate was entrained by repeated evaporation with acetone *in vacuo*. The residue was then taken up in 1.5 ml. of acetone and 25 ml. of benzene. Upon standing at −20° for several days, a cream-colored solid formed, which after recrystallization from an acetone–benzene mixture gave 1.61 g. (42%) of oxindole-3-acetic acid, m.p. 141–143°, which was obtained only by drying *in vacuo* for 1 hr. at 55°. The melting point could be raised to 145–146° by recrystallization from a mixture of acetone and benzene (lit.[8] m.p. 147°). The product was identified by its undepressed mixture melting point with an authentic specimen.[27]

3-Methyloxindole.—To a solution of 3.28 g. (0.025 mole) of skatole in 163 ml. of 95% *t*-butyl alcohol was added 4.45 g. (0.025 mole) of N-bromosuccinimide with stirring over a period of 19 min. The reaction mixture was kept under nitrogen and at a temperature of 20 ± 2°. After 2.5 hr. the solution was concentrated under reduced pressure at room temperature to a volume of a few milliliters, 30 ml. of water was added, and the mixture was extracted with three 25-ml. portions of ethyl acetate. The extract was washed with saturated salt solution, dried over sodium sulfate, and evaporated. The residue was crystallized from water and then from an acetone–hexane mixture. Less pure crops were recrystallized from a benzene–hexane mixture before recrystallization from an acetone–benzene mixture. Several crops of 3-methyloxindole were obtained from the last solvent mixture, totaling 0.94 g. (26%), m.p. 119–123° (lit.[28] m.p. 123–124°) An analytical sample melted at 124–125°.

3-(β-Benzamidoethyl)oxindole.—The procedure described for the preparation of 3-methyloxindole was followed with the exception that the residue from the ethyl acetate extract was crystallized from acetone. From 2.64 g. (0.01 mole) of 3-(β-benzamidoethyl)indole in 65 ml. of 95% *t*-butyl alcohol was obtained 0.97 g. (35%) of 3-(β-benzamidoethyl)oxindole, m.p. 194–197°. An analytical sample, m.p. 195–197°, was obtained by recrystallization from acetone.

3-(β-Aminoethyl)oxindole Hydrobromide.—To a solution of 3.20 g. (0.02 mole) of tryptamine in 130 ml. of 95% *t*-butyl alcohol was added 2.3 ml. (0.02 mole) of 48% hydrobromic acid followed by 3.56 g. (0.02 mole) of N-bromosuccinimide, which was added with stirring over a period of 16 min. The reaction mixture was kept under nitrogen and at a temperature of 21–23°. After 1 hr. the solution was concentrated under reduced pressure at room temperature to a thick sirup. The residual solvent was entrained by repeated evaporation with benzene. To the residue was added 50 ml. of benzene and 100 ml. of acetone. Pale pink crystals (1.45 g., m.p. 262–264° dec.) of 3-(β-aminoethyl)oxindole hydrobromide were filtered and washed with acetone. A semi-solid material, which also formed in the benzene–acetone mixture, was mixed with 10 ml. of absolute ethanol and 50 ml. of acetone yielding an additional 0.13 g. of product, m.p. 262–264° dec., giving a total yield of 1.58 g. (31%). An analytical sample, m.p. 266–268° dec., was obtained by recrystallization from absolute ethanol.

α-Acetamidodioxindole-3-propionic Acid and α-Acetamidooxindole-3-propionic Acid Lactone.—To a solution of 4.92 g. (0.02 mole) of N^{α}-acetyltryptophan and 1.68 g. (0.02 mole) of sodium bicarbonate in a mixture of 35 ml. of water and 150 ml. of *t*-butyl alcohol was added, with stirring at 25°, 3.56 g. (0.02 mole) of NBS. After 3 hr. the mixture was concentrated at room temperature, and to the sirupy residue was added a mixture of water and methanol. The white crystals which formed upon standing were filtered and recrystallized from a methanol–water mixture, yielding 0.41 g. of α-acetaminodioxindole-3-propionic acid lactone, m.p. 277–282° dec. (8%). An analytical sample, m.p. 290–293° dec., was obtained by recrystallization from a methanol–water mixture.

Concentration of the filtrate followed by the addition of a few milliliters of water gave two crops of N-acetyltryptophan (20%) and three crops of material which contained both indolic and oxindolic substances as indicated by the ultraviolet spectra. The filtrate was concentrated to a sirup, diluted with 25 ml. of water, and extracted with three 30-ml. portions of ethyl acetate. The ethyl acetate extract was evaporated at room temperature, and the residue was mixed with ether and a few milliliters of methanol. Two crops of oxindolic material (0.31 g., m.p. 192–202°) were obtained, followed by a crop of material melting at at 115–117°. The addition of acetone to the filtrate followed by cooling gave 0.38 g. of white crystals of α-acetaminooxindole-3-propionic acid, m.p. 209–210° dec. (9.2% based on unrecovered starting material). Recrystallization of the oxindolic material melting at 192–202° from methanol–ether gave four crops of the oxindole totaling 0.20 g., m.p. 202–212° (4.6% based on unrecovered starting material).

An analytical sample of α-acetamidooxindole-3-propionic acid, m.p. 214.0–214.5°, was obtained by recrystallization from an acetone–methanol mixture and then from acetone alone.

3-Bromo-3-methyloxindole.—To a solution of 5.2 g. (0.04 mole) of skatole in 260 ml. of *t*-butyl alcohol was added over a period of 1 hr. in small portions 14.2 g. (0.08 mole) of N-bromosuccinimide with stirring at 22–23°. After an additional 2 hr. the mixture was evaporated under reduced pressure at room temperature. After the addition of 50 ml. of anhydrous ether to the sirupy residue, the crystals of succinimide that formed were filtered and washed with 50 ml. of ether. A second crop of succinimide was removed by filtration. The filtrate was concentrated to about 50 ml. and cooled. A cream-colored solid

(26) Melting points and boiling points are uncorrected. Ultraviolet absorption spectra were determined with a Beckman DK-2 recording spectrophotometer, using quartz cells of 1-cm. light path. Infrared spectra were obtained with a Perkin-Elmer 21 recording spectrophotometer equipped with sodium chloride optics.

(27) The authors are indebted to Dr. Percy Julian for the sample of oxindole-3-acetic acid.

(28) L. Horner, *Ann.*, **548**, 117 (1941).

formed, which when recrystallized from ether, gave 2.1 g. of pale yellow crystals of 3-bromo-3-methyloxindole, m.p. 142–143° dec. Additional crops of product obtained from the mother liquor and from the recrystallization of the first crop afforded, after recrystallization from an acetone–benzene mixture, an additional 1.7 g. of product, m.p. 140–142° dec., giving a total yield of 3.8 g. (42%). Recrystallization from a chloroform–carbon tetrachloride mixture gave an analytical sample as pale yellow crystals, m.p. 142° dec. (decomposition gradual). The infrared spectrum (KBr) showed typical oxindolic features: NH band at 3.12 μ and double carbonyl band at 5.76 and 5.91 μ.

3-Bromooxindole-3-butyric Acid.—To a solution of 10.2 g. (0.05 mole) of indole-3-butyric acid in 325 ml. of anhydrous *t*-butyl alcohol, which had previously been treated with Darco G, was added in small portions 17.8 g. (0.10 mole) of N-bromosuccinimide with stirring over a period of 80 min. The reaction mixture was kept under nitrogen and at a temperature of 22–24°. After 5 hr. the mixture was evaporated under reduced pressure at room temperature. To the residue was added 125 ml. of anhydrous ether. The white crystals of succinimide that formed were filtered and washed with 125 ml. of ether. The filtrate was evaporated, and the residual ether was entrained by repeated evaporation with benzene until crystallization began. The cream-colored crystals (8.66 g., m.p. 137–138° dec.) of 3-bromooxindole-3-butyric acid were filtered and washed with benzene. Additional crops of the bromooxindole were obtained from the filtrate by the addition of peroxide-free tetrahydrofuran and benzene followed by concentration and cooling. Purification by recrystallization from a tetrahydrofuran–benzene mixture gave a total yield of 9.40 g. (63%), m.p. 138–142° dec. An analytical sample melted at 140–142° dec.

3-Bromooxindole-3-acetic Acid.—To a solution of 13.1 g. (0.075 mole) of indole-3-acetic acid in 490 ml. of anhydrous *t*-butyl alcohol, which had previously been treated with Darco G, was added in small portions 26.7 g. (0.15 mole) of N-bromosuccinimide with stirring under nitrogen over a period of 1 hr. at 21–23°. After an hour the mixture was concentrated at room temperature to a thick sirup which was then mixed with 200 ml. of anhydrous ether. White crystals of succinimide were removed by filtration and washed with 125 ml. of ether. After concentration of the filtrate to approximately 100 ml. and cooling, a second crop of succinimide was removed by filtration. The filtrate was evaporated at room temperature, and residual solvent was entrained by repeated evaporation with benzene *in vacuo* until the sirupy residue began to crystallize. The residue was then mixed with 150 ml. of benzene and 11.0 g. of pale chartreuse crystals of 3-bromooxindole-3-acetic acid, m.p. 152–153° dec. (melting point taken slowly), was obtained. Two additional crops of product totaling 2.22 g. (total yield 65%), m.p. 150–153° dec., were obtained. In another experiment, exhaustive work-up of the mother liquor, including recrystallizations from an acetone–benzene mixture, gave an additional 10% of product.

In some experiments a more soluble product was obtained by concentration of the mother liquors from the crystallizations of 3-bromooxindole-3-acetic acid. This white solid proved to be **t-butyl 3-bromooxindole-3-acetate**, which melted at 134–135° dec. after crystallization from a mixture of acetone and benzene.

Anal. Calcd. for $C_{14}H_{16}BrNO_3$: C, 51.55; H, 4.94; Br, 24.50; N, 4.29. Found: C, 51.97; H, 5.09; Br, 25.05; N, 4.46.

The ester was distinguished from the free acid in various stages of the work-up by the fact that in 95% ethanol the ultraviolet spectra of those samples containing primarily 3-bromooxindole-3-acetic acid changed rapidly toward that of 3-methyleneoxindole,[2b,6] while the spectra of those containing the ester did not change. Although ester formation occurred frequently, it did not seem to be reproducible. Moreover, attempts to prepare the *t*-butyl ester by reaction of the free acid and isobutylene[29] were completely unsuccessful. Evidence for ester formation was found in the ultraviolet spectra of the reaction mixtures, but in every case either unchanged acid was recovered or decomposition of the acid occurred forming insoluble material, apparently derived from 3-methyleneoxindole, the usual decomposition product of the acid.[2b,6]

Dioxindole-3-propionic Acid Lactone.—To a solution of 9.46 g. (0.05 mole) of indole-3-propionic acid and 4.20 g. (0.05 mole) of sodium bicarbonate in a mixture of 125 ml. of water and 325 ml. of *t*-butyl alcohol was added, with stirring at 21–23°, 17.8 g. (0.10 mole) of NBS in small portions over a period of 30 min. After 4 hr. 8.40 g. (0.10 mole) of sodium bicarbonate and 25 ml. of water were added, and the mixture was stirred for 16 hr. The mixture was concentrated to 200 ml., 200 ml. of water was added, and the mixture was extracted with three 150-ml. portions of ethyl acetate. The extract was washed with saturated salt solution, dried over sodium sulfate, and evaporated at room temperature. Residual ethyl acetate was entrained by repeated evaporation with benzene *in vacuo*. The sirupy residue was taken up in a mixture of benzene and methanol. White crystals which formed upon cooling were filtered and recrystallized from benzene and then from water, yielding 2.20 g. (22%) of dioxindole-3-propionic acid lactone, m.p. 132.5–133°. An analytical sample recrystallized from benzene melted at 134°.

Anal. Calcd. for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.90. Found: C, 64.98; H, 4.76; N, 6.82.

2-Bromoskatole.—To a solution of 3.28 g. (0.025 mole) of skatole in 40 ml. of anhydrous glacial acetic acid (previously dried with triacetyl borate) was added slowly with stirring a solution of 4.45 g. (0.025 mole) of N-bromosuccinimide in 170 ml. of glacial acetic acid. The reaction mixture, which was kept under nitrogen at 19–21°, was stirred for 2.5 hr. and then was neutralized to pH 7 with a solution of 136 g. of sodium hydroxide in 250 ml. of water with cooling in an ice bath under nitrogen. The cream-colored precipitate that formed was filtered by suction, washed with water several times, and then dried *in vacuo* over potassium hydroxide. The solid was sublimed by heating in a water bath at approximately 0.025 mm. The sublimate was 2.36 g. (45%) of a white solid, 2-bromoskatole, m.p. 88–90° dec. An analytical sample was prepared by crystallization from aqueous acetic acid. Crystallization without decomposition was successful only after sublimation.

The product underwent slow decomposition to a black solid at room temperature but could be preserved when stored under nitrogen in the dark at −20°.

2,6-Dibromoskatole.—To a solution of 2.10 g. (0.01 mole) of 2-bromoskatole in 30 ml. of anhydrous glacial acetic acid (previously dried with triacetyl borate) was added dropwise with stirring under nitrogen a solution of 1.78 g. (0.01 mole) of NBS in 70 ml. of anhydrous acetic acid. The mixture was stirred for 3 hr. at 18–20° and then was poured slowly with stirring and cooling into a mixture of 75 g. of sodium hydroxide and 50 g. of ice in 125 ml. of water. The cream-colored precipitate that formed was filtered by suction, washed with ice water until free of base, and dried *in vacuo* over potassium hydroxide. The solid was dissolved in 75 ml. of warm 95% ethanol, and water was added to the saturation point. Upon cooling, 1.09 g. of tan crystals of 2,6-dibromoskatole, m.p. 96–98° dec. (lit.[5] m.p. 100° dec.), was obtained. Concentration of the filtrate gave an additional 0.31 g., m.p. 99–101° dec.; total yield was 1.40 g. (48%).

3-Methyloxindole by Hydrolysis *in situ* of 2-Bromoskatole.—To a solution of 26.2 g. (0.20 mole) of skatole in 400 ml. of glacial acetic acid was added 35.6 g. (0.2 mole) of NBS over a period of 20 min. in an atmosphere of nitrogen. The solution was stirred for 1 hr. at 15–18°. Then 300 ml. of 5% sulfuric acid and 150 ml. of ethanol were added, and the mixture was refluxed under nitrogen for 2.25 hr. The mixture was concentrated *in vacuo* to 500 ml., diluted with 1 l. of water, and extracted with three 400-ml. portions of ether. The extract was neutralized by washing with dilute sodium hydroxide, washed with saturated salt solution, dried over sodium sulfate, and concentrated under reduced pressure. The residual oil was distilled *in vacuo*. The distillate (16.7 g., b.p. 127–150° at 0.55-mm. pressure) was recrystallized from benzene yielding 8.0 g. (28%) of 3-methyloxindole, m.p. 121–122° (lit.[28] m.p. 123–124°).

3-*n*-Propyloxindole by Hydrolysis of 2-Bromo-3-*n*-propylindole.—To a solution of 3.18 g. (0.02 mole) of 3-*n*-propylindole in 32 ml. of glacial acetic acid (previously dried with triacetyl borate) was added dropwise with stirring at 16–20° under nitrogen a solution of 3.56 g. (0.02 mole) of N-bromosuccinimide in 136 ml. of anhydrous glacial acetic acid. After 2 hr. the solution was poured slowly with stirring and cooling into a mixture of 120 g. of sodium hydroxide and 100 g. of ice in 200 ml. of water. The temperature of the mixture was not allowed to exceed 25°, and the mixture was kept under nitrogen during these operations. The solution was decanted from a brown tar that formed and then was extracted with 3 100-ml. portions of ethyl acetate. The extract, after drying over sodium sulfate, was evaporated at room

(29) A. L. McCloskey, G. S. Fonken, R. W. Kluiber, and W. S. Johnson, "Organic Syntheses," Coll. Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1963, p. 261.

temperature. A portion of the oily residue was placed in a sublimation apparatus, and at 90° and 0.025-mm. pressure 0.30 g. of a colorless sirup was collected on the Dry Ice-cooled condenser. The sirup, crude 2-bromo-3-*n*-propylindole, gave a negative test with alcoholic silver nitrate but gave a positive test when nitric acid was added followed by heating for 30 sec. The ultraviolet spectrum of the product showed λ_{max}^{EtOH} 224, 275 sh, 283, and 291 mμ. The infrared spectrum showed a strong band at 2.97 μ (indolic N–H). The presence of a medium strong band at 5.84 μ (C=O) indicated that the sirup was contaminated.

The remainder of the residual oil was distilled in a short-path distillation apparatus at about 90° and 0.04-mm. pressure. A total of 0.91 g. of oil was collected, but the product was contaminated by spattering of the residue. The total yield of crude 2-bromo-3-*n*-propylindole was 1.17 g. (25%). The product decomposed when an attempt was made to distil it by the conventional method.

The residue from the short-path distillation was mixed with 1.1 ml. of concentrated sulfuric acid, 2 ml. of water, and 20 ml. of 95% ethanol and was refluxed under nitrogen for 25 hr. The mixture was concentrated to a volume of 10 ml., water was added to the saturation point, and the mixture was extracted with ether. The ether layer, after washing with 1 *N* sodium bicarbonate and drying over sodium sulfate, was treated with Norit A and evaporated. The residue was extracted with two 50-ml. portions of hot water and then with 200 ml. of boiling water. A total of 0.18 g. of white crystals of 3-*n*-propyloxindole, m.p. 78.0–79.5°, was obtained from the combined aqueous extracts. An analytical sample, m.p. 81–82°, was obtained by recrystallization, first from hexane and then from water.

Anal. Calcd. for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 8.00. Found: C, 75.12; H, 7.43; N, 8.26.

2,6-Dibromo-3-*n*-propylindole.—To a solution of 4.0 g. (0.025 mole) of 3-*n*-propylindole in 40 ml. of anhydrous glacial acetic acid (previously dried with triacetyl borate) was added dropwise with stirring under nitrogen at 16–20° a solution of 8.9 g. (0.05 mole) of N-bromosuccinimide in 340 ml. of anhydrous glacial acetic acid over a period of 110 min. After 2 hr. the mixture was neutralized to pH 5 by pouring it under nitrogen into a liter of a solution containing an equivalent amount of sodium hydroxide cooled in a Dry Ice bath so that the temperature did not exceed 25°. The mixture was extracted with ethyl acetate and the extract, after drying, was concentrated to a thick sirup. Attempts to isolate the product by crystallization and by distillation failed. The ultraviolet spectrum of the reaction mixture showed absorption at 229 and 286 mμ, which suggested that a 2,6-bromoindole was present. An attempt to hydrolyze the dibromoindole by refluxing for 19 hr. with 30 ml. of 4.5 *M* sulfuric acid and 60 ml. of dioxane resulted in only partial hydrolysis, as indicated by the ultraviolet spectrum of the mixture. Only 8 mg. of a solid, m.p. 195–198°, was isolated. The ultraviolet spectrum, λ_{max}^{EtOH} 215, 251–257, and 289 mμ, and infrared spectrum, λ_{max}^{KBr} 3.02, 5.82, 5.95 μ, indicated that the product was impure 6-bromo-3-*n*-propyloxindole.

5-Chloro-3-methyloxindole from Reaction of *t*-Butyl Hypochlorite and Skatole.—To a solution of 5.28 g. (0.025 mole) of skatole in 165 ml. of *t*-butyl alcohol, which had been dried over sodium sulfate and treated with Darco, was added with stirring under nitrogen at 25–25° a solution of 5.44 g. (0.050 mole) of *t*-butyl hypochlorite in 25 ml. of purified *t*-butyl alcohol over a period of 40 min. After 4.33 hr. the solution was concentrated with mild warming to an oily residue, which was taken up in benzene and a small amount of acetone, and hexane was added to the saturation point. After a brown tarry material had been removed, two crops of a white solid were obtained, totaling 0.49 g., m.p. 182–198° (cloudy until approx. 225°). The solid was recrystallized from an acetone–benzene mixture, then from benzene, and then from a methanol–water mixture yielding 0.13 g. (2.8%) of product, presumably 5-chloro-3-methyloxindole, m.p. 201–203°. An analytical sample, m.p. 201–203°, was obtained by an additional recrystallization from a methanol–water mixture.

Anal. Calcd. for C_9H_8ClNO: C, 59.51; H, 4.44; N, 7.71; Cl, 19.52. Found: C, 59.29; H, 4.66; N, 7.61; Cl, 19.30.

Oxindole-3-butyric Acid (by Reaction of Indole-3-butyric Acid and Bromine).—To a solution of 4.06 g. (0.02 mole) of indole-3-butyric acid in 130 ml. of *t*-butyl alcohol which had been dried over calcium sulfate was added with stirring at 22–24° a solution of 3.20 g. (0.02 mole) of bromine in 30 ml. of anhydrous *t*-butyl alcohol over a period of 35 min. After 4 hr. the solution was concentrated at room temperature to an oily residue which was taken up in a mixture of benzene and ethyl acetate. The solution was washed with water three times and dried over calcium sulfate; then hexane was added to the saturation point. Upon standing, 0.12 g. of oxindole-3-butyric acid, m.p. 165–167°, was obtained. The addition of hexane to the filtrate caused a brown oil to form, which when separated and mixed with acetone gave three additional crops of product, totaling 0.16 g., m.p. 163–168° (total yield 6.4%).

5-Bromooxindole-3-butyric Acid.—A solution of 1.0 g. (4.6 mmoles) of oxindole-3-butyric acid and 0.81 g. (4.6 mmoles) of N-bromosuccinimide in 130 ml. of 90% *t*-butyl alcohol was stirred at room temperature for 2 days. The solution was concentrated *in vacuo* at room temperature to a thick sirup. After the addition of 15 ml. of water, the mixture was extracted with three 20-ml. portions of ethyl acetate. The extract was dried over sodium sulfate and evaporated; the residual oil was crystallized from a mixture of acetone and benzene. Two crops of crystals were obtained, which upon recrystallization from a benzene–ethyl acetate mixture gave several crops of crystals of 5-bromooxindole-3-butyric acid, m.p. 156–159°, totaling 1.0 g. (73%).

An analytical sample, m.p. 158°, was obtained by recrystallization twice from an ethyl acetate–benzene mixture and then twice from water.

Anal. Calcd. for $C_{12}H_{12}BrNO_3$: C, 48.34; H, 4.06; N, 4.70; Br, 26.80. Found: C, 48.45; H, 4.24; N, 4.91; Br, 26.67.

Oxindole-3-butyric Acid and N-Bromosuccinimide at pH 11–12.—To a solution of 1.1 g. (5.0 mmoles) of oxindole-3-butyric acid in a mixture of 5.3 ml. of 1 *N* sodium hydroxide and 20 ml. of *t*-butyl alcohol was added slowly with stirring 0.89 g. (5.0 mmoles) of N-bromosuccinimide. The pH of the solution dropped from 11–12 to 7–8 during the reaction time. After 2.5 hr., 30 ml. of water was added, and the solution was concentrated *in vacuo* at room temperature to about 60 ml. An oil formed which, after the addition of a few milliliters of ether followed by cooling and scratching, crystallized to give 0.57 g. of white crystals, m.p. 164–175°, the ultraviolet spectrum of which (λ_{max}^{EtOH} 259, 300 mμ) indicated it was probably a mixture of 5-bromodioxindole-3-butyric acid lactone and dioxindole-3-butyric acid lactone. Oxindole-3-butyric acid was recovered (24% crude) from the reaction mixture.

Reproducibility of Reactions in *t*-Butyl Alcohol. Effect of Impurities.—A thorough study of the reaction variables, prompted by difficulties in reproducing yields of oxindoles, revealed that the presence of an impurity in the *t*-butyl alcohol was responsible for increased yields of α-bromoindoles sufficient to make the product mixture exceedingly difficult to separate. The effectiveness of various methods of treating the solvent to promote oxindole formation alone are shown in Table IV.[30] It is evident that two treatments with Darco are sufficient to prepare the solvent for use in oxindole syntheses, although generally only one treatment was employed in preparative work. Alumina is also effective. The beneficial effects of either adding water or drying with sodium sulfate appear contradictory but may be accounted for by the promotion of addition of water[31] to the 3-bromoindolenine (III) in the former case, and by removal of some of the undesirable impurity by adsorption in the latter. Hydrated sodium sulfate may perform both functions.

The practical consequences of the results shown in Table IV are twofold. If the indole-to-oxindole transformation is desired, addition of water to the solvent will give satisfactory results without further purification. On the other hand, when the reaction of an indole with 2 moles of NBS is to be carried out for the synthesis of a 3-bromooxindole, treatment with Darco is the preferred method, since water facilitates bromination of the benzene ring and other reactions. Even the addition of 1% of water to the medium has a deleterious effect which is shown by the failure of the ultraviolet spectrum to take on the complete charac-

(30) The values of the ratio in Table IV vary from 0.6 to 3.2. The highest ratios observed have been about 3.5. The residual indolic absorption may have been due to starting material, unreacted because of wastage of NBS, or to α-bromoindoles. The isolation of 2,6-dibromoindole-3-butyric acid from almost all reactions of IBA with 2 moles of NBS indicates that the latter is the case and that the reaction in *t*-butyl alcohol never gives a completely clean-cut conversion to oxindole.

(31) Analysis of reaction mixtures by v.p.c. showed that enough water is formed from the *t*-butyl alcohol to account for oxindole formation. The water was not determined directly but was estimated from the amounts of *t*-butyl bromide and isobutylene which are readily separated on a polypropylene glycol column.

teristics of the 3-bromooxindole. [For oxindole formation alone, 1% of water appears to be as useful as 5% (Table IV), but no experiments on a preparative scale have been performed in the former.]

When a sample of *t*-butyl alcohol was distilled and the collected fractions were used as the reaction medium, the value of R decreased as the fraction number increased. Moreover, many commercial samples of the alcohol showed an anomalous absorption maximum at 236 mμ, and the peak became more intense in the later fractions. The presence of benzene obscures this peak, but, as the benzene is removed in the first fractions, the new absorption peak becomes visible. Treatment with Darco reduced the peak to a slight shoulder, and NBS had a similar effect. However, a second treatment with Darco had no further effect on the absorption spectrum even though the value of R increased further (Table IV), and treatment of *t*-butyl alcohol with NBS followed by distillation yielded solvent with the same R value as that observed before the NBS treatment. Moreover, many samples of *t*-butyl alcohol do not show this anomalous absorption but do give low R values. Whether the impurity absorbing at 236 mμ is responsible for the low R values is, therefore, a moot point at this time.

All attempts to concentrate the impurity by careful fractionation or to identify it by v.p.c. analysis have been unsuccessful. Samples of *t*-butyl alcohol rich in the impurity discharged the color of potassium permanganate and gave negative Beilstein tests for halogen and negative tests for thiophene. A number of substances suggested by the position of the absorption maximum or by the likelihood of their presence as contaminants of commercial *t*-butyl alcohol have been added to reaction mixtures of NBS and indole-3-butyric acid in small quantities, but without effect on the value of R. These included 2,5-dimethyl-2,4-hexadiene, diisobutylene, mesityl oxide, thiophene, and *n*-butyraldehyde.

The impurity is present in many, but not all, commercial samples of *t*-butyl alcohol, even those of the specially purified grade used in the analysis of corticosteroids (Matheson Coleman and Bell, Catalog No. BX 1800). From the lot analysis of the best samples, the impurity must be present in very small amounts (<0.1%). If this is the case, its effect on the product distribution is of a remarkable catalytic nature.

Preparation of Cyclic Siloxazanes

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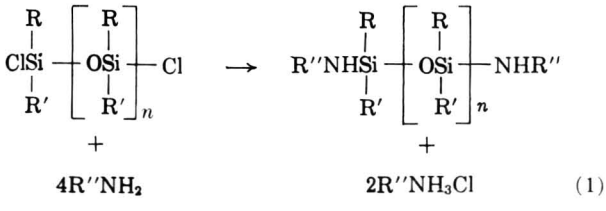
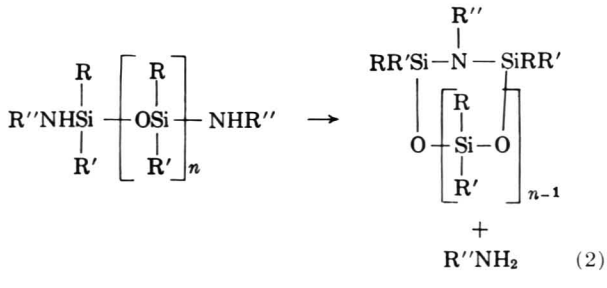
The preparation and characterization of a number of mixed cyclic siloxane–silazane compounds (*i.e.*, cyclic siloxazanes) is described.

This report describes the preparation and some properties of mixed cyclic silicon compounds having both siloxane and silazane bonds (*i.e.*, cyclic siloxazanes), which were of interest to us as intermediates for polymerization and condensation reactions. At the outset of this work, this class of compounds had not been isolated and characterized. Since then, Kruger and Rochow[1] have described the preparation and isolation of several of the compounds reported in this paper. The compounds prepared in this work are listed in Fig. 1 and their properties in Table I.

The general reactions for the preparation of the cyclic siloxazanes are indicated in eq. 1 and 2. Most of the



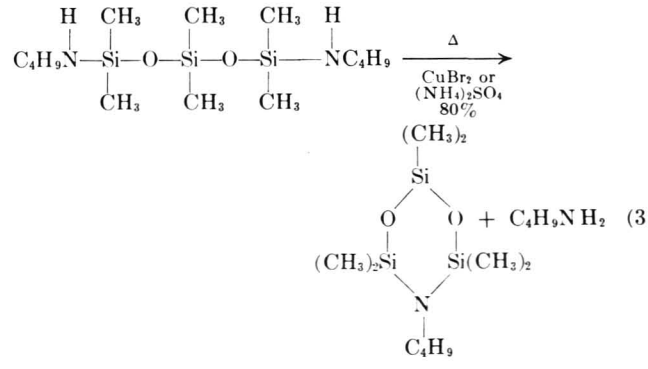
(1)



(2)

dichlorosiloxanes used in reaction 1 were prepared by the partial hydrolysis of the dialkyldichlorosilane followed by distillation to separate the individual members of the homologous series of materials formed. These products have been described previously.[2,3] The intermediate for the preparation of IX (1,5-dichloro-1,1,5,5-tetramethyl-3,3-diphenyltrisiloxane) was prepared by the condensation of diphenylsilanediol and dimethyldichlorosilane in pyridine–benzene solution.

The products of reaction 1 were not isolated when R'' was H, but the presence of these diaminosiloxanes in the crude reaction products was indicated in some cases by the NH_2 band splitting (near 3390 cm.$^{-1}$) in the infrared spectra. On heating, this splitting disappeared. When R'' was butyl, only the diaminosiloxane was formed, with no cyclization occurring even during the distillation of the product. In the presence of an acidic catalyst, however, cyclization and elimination of butylamine took place readily, as indicated in eq. 3 for the preparation of VII.



(3)

The yield of the low cyclic isolated varied from 21–81%. No attempt was made to optimize yields. Most of the reactions were run by passing ammonia into a moderately concentrated solution of the dichloropolysiloxane; this procedure might be expected to favor the formation of the larger cyclics and linear polymers at the

(1) C. R. Kruger and E. G. Rochow, *Angew. Chem.*, **74**, 491 (1962).

(2) W. I. Patnode and D. F. Wilcock, *J. Am. Chem. Soc.*, **68**, 358 (1946).

(3) W. H. Daudt and J. F. Hyde, *ibid.*, **74**, 386 (1952).

TABLE I

PROPERTIES OF CYCLIC SILOXAZANES

Compound	B.p., °C. (mm.)	M.p., °C.	% yield	% N Calcd.	% N Found	Mole wt.[g] Calcd.	Mole wt.[g] Found
I	35–37 (5)[a]		34	6.32	6.25	221.49	230
II	78–79 (10)[b]		51	4.74	5.0	295.65	304
III	81–83 (3)		37	3.79	4.0	369.81	380
IV	64–65 (0.1)		30	3.16	3.6	443.96	451
V	98–101 (14)[c]	38.5–39.5	44	9.51	9.3	294.67	280
VI	72–75 (0.1)		[d]	6.3	6.25	442.98	446
VII	78 (5)		80[e]	(30.36)[f]	(30.3)[f]	277.60	290
VIII	95–98 (0.25)		38	6.89	7.1	406.88	403
IX	119–135 (0.05)	99–100	81	4.06	4.1	345.62	338
X	169–172 (0.25)		43	3.5	3.5	400	411
X-A		113–115	...	3.5	3.7	400	396
XI	192–202 (0.15)		58	2.6	2.5	544	554
XII	200–206 (0.1)		42	5.18	5.5	542.93	544

[a] Compound I, $n^{20}D$ 1.4088; lit.[1] b.p. 151–151.5° (760 mm.), $n^{20}D$ 1.4068. [b] Compound II, $n^{20}D$ 1.4156; lit.[1] b.p. 190–191° (760 mm.), $n^{20}D$ 1.4151. [c] Lit.[1] b.p. 206–208° (760 mm.), 82–83° (9 mm.); m.p. 37°. [d] Isolated as a by-product in preparation of I. [e] Yield in cyclization reaction. [f] Silicon analysis. [g] Ebullioscopic in benzene.

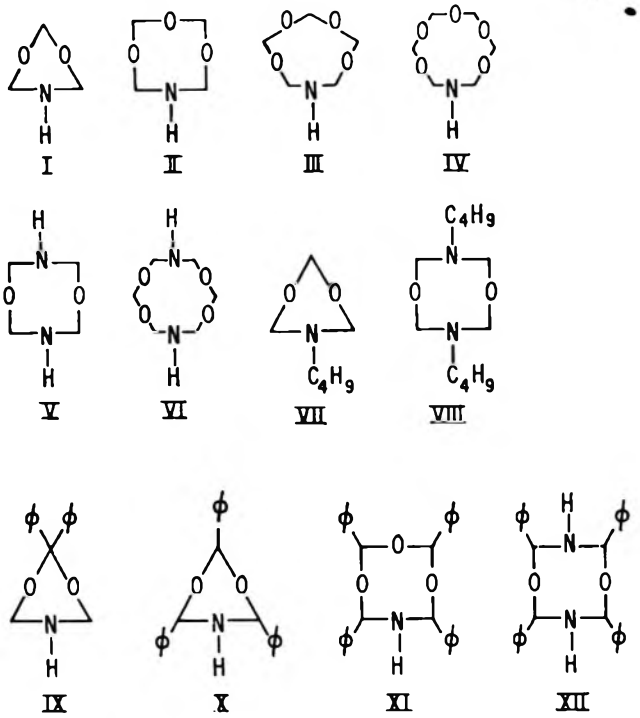
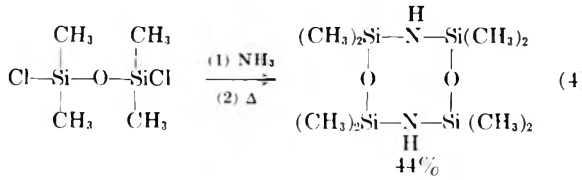


Fig. 1.—Cyclic siloxazanes prepared (corners represent silicon with dimethyl substitution except where replacement of one or both methyl groups by phenyl is indicated).

expense of low cyclics. In spite of this, reasonably good yields were obtained in some cases. However, none of the four-membered ring cyclics were isolated in reactions of ammonia or amine with dichlorodisiloxanes. In these reactions the eight-membered ring compound was the product isolated, as indicated in eq. 4 for the preparation of V.



(4)

Compounds X–XII were prepared as mixtures of stereoisomers. In the case of X, one of the pure isomers (X-A) was isolated and has been tentatively identified as the *meso* compound having methyl groups *cis* to each other (rather than the possible *trans–meso* or *trans–dl* configurations). This assignment was made by comparison of the infrared spectra of X-A and the liquid mixture of stereoisomers remaining after removal of X-A, with that of the two isomeric phenylmethyltrisiloxanes.[4] In the phenylmethylsiloxane trimers, the *cis* compound has a strong methyl absorption at 778 cm.$^{-1}$ which appears at 793 cm.$^{-1}$ in the *trans* isomer. Compound X-A has a strong methyl absorption at 770 cm.$^{-1}$ which correspondingly appears at 790 cm.$^{-1}$ in the liquid mixture of isomers of X remaining after removal of X-A. The proton magnetic resonance of X-A shows a slight splitting (*ca.* 1 cycle) and a 2:1 ratio of peak heights for the methyl hydrogen atoms, presumably as a result of configurational differences introduced by the adjacent nitrogen and oxygen atoms.

The infrared spectra of the products (Table II) are of interest. The silazane stretching and NH bending absorptions shift to longer wave lengths in the smaller rings in a manner analogous to the shift in siloxane stretching bands in small ring siloxane compounds.[5] The siloxane asymmetric stretching absorptions are different from cyclosiloxanes of the same ring size. This difference is due to the interruption of coupling between siloxane chain segments by the silazane linkage. Siloxazanes, therefore, have a siloxane stretching band with an absorption characteristic of a short siloxane chain held in the ring configuration rather than the absorption typical[5] of the analogous cyclosiloxane. Thus, for example, I and II have a siloxane stretching frequency split into two bands at 983 and 1022 cm.$^{-1}$ and at 1022 and 1069 cm.$^{-1}$, respectively, while the analogous hexamethylcyclotrisiloxane and octamethylcyclotetrasiloxane have only a single band at 1018 and 1075 cm.$^{-1}$, respectively.

Some qualitative comparisons were made of the relative hydrolytic stability of four of the cyclic siloxazanes and three cyclic silazanes. These observations were made by preparing 0.25 *M* solutions of the compounds in aqueous dimethylformamide (5% water) and observing the rate of disappearance of the silazane band in the infrared spectrum. The results are listed in Table III. It is apparent that the rates of hydrolysis differ by

(4) C. W. Young, P. C. Servias, C. C. Currie, and M. J. Hunter, *J. Am. Chem. Soc.*, **70**, 3758 (1948).

(5) A. Lee Smith, *Spectrochim. Acta*, **16**, 87 (1960).

TABLE II

INFRARED ABSORPTIONS OF CYCLIC SILOXAZANES

Compound	SiOSi stretch, cm.$^{-1}$	SiNSi[a] stretch, cm.$^{-1}$	NH bending,[a] cm.$^{-1}$
Hexamethylcyclotrisilazane		925	1158
Octamethylcyclotetrasilazane		941	1175
I	983 m, 1023 s	904	1147
II	1022 m, 1069 s	924	1176
III	1028 m, 1080 s	934	1180
IV	1020 sh, 1067 s, 1090 sh	939	1184
V	1059 s	947	1173
VI	1065 s, 1085 sh	945	1186
VII	1070 s	905	
VIII	1056 s	904	
IX	1015 s	898	1147
X	990 m, 1022 s	909	1157
XI	1078 s	927	1172
XII	1040 sh, 1072 s	941	1169

[a] See H. Kriegsmann and G. Englehardt, *Z. anorg. allgem. Chem.*, **310**, 321 (1961), for assignments of silazane infrared bands.

TABLE III

HYDROLYTIC STABILITY

Compound	Silazane stretching band position, cm.$^{-1}$	Rate of disappearance of silazane stretching band (solution allowed to stand at 25°)
Hexamethylcyclotrisilazane	925	Rapid loss during 1 hr.
IX	898	Rapid loss during 1 hr.
Octamethylcyclotetrasilazane	941	Rapid loss during 1 hr.
V	947	Slight loss in 13 hr.
XII	941	No change in 25 hr. Slight change after 7 days
VIII	904	No change in 7 days
Hexaphenylcyclotrisilazane	952	No change in 7 days

several orders of magnitude. Compounds having a phenyl substituent on the silicon atom adjacent to nitrogen, or a butyl substituent on the nitrogen atom, have improved stability.

Experimental[6]

The homologous dimethylsiloxanes chain-stopped with chlorine were prepared as described by Patnode and Wilcock,[2] and the phenylmethylsiloxanes chain-stopped with chlorine were prepared as described by Daudt and Hyde.[3]

Preparation of 1,5-Dichloro-1,1,5,5-tetramethyl-3,3-diphenyltrisiloxane.—Solid diphenylsilanediol (108.2 g., 0.5 mole) was added in portions during 1.5 hr. to a mixture of 129 g. (1.0 mole) of dimethyldichlorosilane, 79 g. (1.0 mole) of pyridine, and 1.5 l. of benzene contained in a 3-l. flask equipped with a stirrer and drying tubes to keep the temperature at 6–10°. The mixture was stirred overnight, being allowed to warm to room temperature. Pyridine hydrochloride was removed by filtration, the precipitate was washed with benzene, and the benzene was removed from the filtrate under reduced pressure. The residue was distilled through a short Vigreux column, and distillation was interrupted after the initial portion of product started distilling to remove sublimed pyridine hydrochloride. Distillation then was continued and there was collected 131.5 g. (66%) of product, b.p. 130–142° (0.3 mm.).

Condensation of Ammonia with Dichlorosiloxanes. General Procedure.—Ammonia was passed rapidly into benzene or ether solutions of the dichlorosiloxane with good stirring and with the mixture protected from moisture. The temperature was kept at 20–50° with cooling until ammonia absorption appeared to have stopped, and for 30 min. thereafter. The mixtures were filtered (protected from moisture), washed with fresh solvent, and the solvent was removed from the filtrate under reduced pressure. The residues then were distilled (X–XII were heated for an hour at 100° *in vacuo* to condense any unchanged silyl amine) under reduced pressure through a 3-ft. spinning band column.

Preparation of 3-*n*-Butyl-2,2,4,4,6,6-hexamethyl-1,5-dioxa-3-azacyclohexasilane (VII).[7]—The intermediate, 1,5-di-*n*-butylaminohexamethyltrisiloxane, was prepared by the addition of 58.5 g. (0.8 mole) of *n*-butylamine to a stirred mixture of 111 g. (0.4 mole) of 1,5-dichlorohexamethyltrisiloxane and 80.8 g. (0.8 mole) of triethylamine in 600 ml. of ether during 2 hr., with the temperature at 25–35°. The mixture was stirred for 2 hr. more and allowed to stand overnight. The product was filtered and washed with ether, the solvent was removed, and the residue was distilled under reduced pressure: 98.8 g. (70.6%) of product, b.p. 106–108° (1.0 mm.), was collected.

Cyclization of this diaminosiloxane to VII was carried out by slow distillation of 30.3 g. of this product from more than 0.5 g. of cupric bromide (or ammonium sulfate) in a 3-ft. spinning band column at 6 mm. using a liquid nitrogen trap to collect *n*-butylamine. There was obtained 19.5 g. (79%) of VII, b.p. 75–80° (6 mm.), which contained traces of lower boiling impurities (by v.p.c.) together with 6.0 g. of material in the trap. The product was redistilled for analysis and material with b.p. 78° (5 mm.) was collected.

Preparation of 3,7-Di-*n*-butyl-2,2,4,4,6,6,8,8-octamethyl-1,5-dioxa-3,7-diazacyclooctasilane (VIII).[8]—A mixture of 18.7 g. (0.064 mole) of V and 18.7 g. (0.256 mole) of *n*-butylamine together with 0.3 g. of copper bromide was refluxed for 17 hr. This reaction mixture then was distilled in the spinning band column, first removing 2.0 g. of material, b.p. 75° (atm.), lowering the pressure, and removing an additional 6.2 g. of material, b.p. 32° (132 mm.). Finally, the residue was distilled at 0.3 mm., and 9.9 g. of product, b.p. 88–98° (0.3 mm.), was collected. This material was about 90% pure (by v.p.c.), it was redistilled, and a sample of material, b.p. 95–98° (0.25 mm.), was collected for analysis.

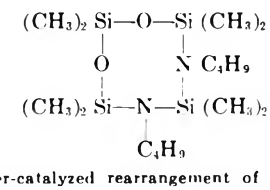
Isolation of *cis*-2,4,6-Trimethyl-2,4,6-triphenyl-1,5-dioxa-3-azacyclohexasilane (X-A).—Fifty grams of the semisolid reaction product X was twice recrystallized from cyclohexane (in the drybox) and the product dried at 60° *in vacuo* yielding 11.1 g. of white crystals, m.p. 113–115°. The n.m.r. spectra of this product was run as a 10% solution in deuteriochloroform.

Acknowledgment.—The authors wish to thank Dr. J. F. Brown, Jr., for interpretations of infrared spectra.

(6) Melting points are uncorrected and were taken on a Fisher-Johns apparatus. Infrared spectra were measured as 2% solutions in CS_2 on a Beckman Model IR7 spectrophotometer by Miss Dorothy McClung. N.m.r. absorption was recorded by Dr. C. M. Huggins with a 40-Mc. Varian high resolution spectrometer.

(7) These compounds are named using the oxa aza convention for organosilicon compounds [see *Chem. Eng. News*, **30**, 5517 (1952).

(8) One of the referees has suggested that VIII may contain the isomeric structure,



formed by a copper-catalyzed rearrangement of siloxane bonds. The possibility that this compound was present as an impurity in VIII cannot be ruled out, although the product isolated appeared to be essentially pure by analysis (9.3-min. retention time on a 2-ft. silicone rubber column programmed from 100–250° at 7.9°/min.). If the product isolated had the rearranged structure, we might expect to have observed a splitting of the siloxane band in the infrared spectrum.

Aromatic Peracids. The Effects of Solvent on the Ozone-Initiated Autoxidation of Benzaldehydes

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Received October 28, 1963

The yields of perbenzoic acids from the corresponding aldehydes are solvent dependent. In methyl or ethyl acetate solutions, perbenzoic acid was prepared in 90% yields at 98+% aldehyde consumption by the action of ozone and oxygen. In a like manner the 2-Cl, 4-Cl, 3-NO_2, and 4-NO_2 peracids were prepared in 83 to 60% yields.

Perbenzoic acid (I) has been known for years and its effectiveness as an epoxidizing agent is unquestioned. The preparation of I from benzoyl peroxide[2] is effective, but at the same time cumbersome and not readily applied to large-scale work. Jorissen and Van der Beek[3] reported the preparation of I in 65% yield by sunlight-initiated autoxidation of benzaldehyde (II) in carbon tetrachloride. More recently, Swern[4] reported a large-scale preparation of I in 40% yield by air oxidation of II in an acetone solution under ultraviolet irradiation.

The ozone-initiated oxidation of II has been documented by Briner[5] and co-workers, but their studies were directed more toward the effect of ozone as a catalyst than the preparation of I *per se*. Using carbon tetrachloride, *n*-hexane, and cyclohexane as solvents, they obtained at best a 25% yield of I, while the remainder of II was converted to benzoic acid (III).

The relatively low yields of I from II could result from the peracid forming a hemiacetal-type adduct with the aldehyde, such as are formed with the aliphatic aldehydes. Such a reaction would preclude any one-step, high yield perbenzoic acid synthesis as it does in the acetaldehyde–peracetic acid system. Phillips[6] and co-workers have described an elegant method of surmounting this problem in the case of peracetic acid, but an analogous preparation of I does not seem feasible owing to its high boiling point. On the other hand, it should be noted that there is no report of such an adduct being formed from I and II.

To determine whether I and II form an adduct, equimolar amounts were dissolved in ethyl acetate, cooled to −70°, and allowed to warm slowly in the beam of an infrared spectrophotometer with periodic scanning. The relative concentrations of I and II did not change as the sample warmed. Similarly, the room temperature spectrum of the mixture indicated no adduct formation. It was concluded, therefore, that, if any adduct formed,[7] it was not a major product as it is in the case of the aliphatics.

In order to determine if solvents could effect a change in the yield of I, a series of runs, using ozone as initiator, was made at 20–22°, with 0.25 moles of II as a 0.50 molar solution and constant oxygen–ozone feed rate. The results are listed in Table I.

The data clearly demonstrate the ability of methyl and ethyl acetates to promote the formation of high yields of I at high conversions of II. The effectiveness of these esters, particularly ethyl acetate, is seen in runs 1, 3, 7, and 10, wherein the yield of I increases with increasing amounts of ethyl acetate, the polar component of the solvent.

The effects of solvent on the consumption of ozone are listed in the last column of Table I. The apparent reactivity of the solvent toward ozone would be greatly suppressed in the presence of the more reactive II, but it would become significant at high conversions of II. Bearing in mind that the consumption of II is directly proportional to the rate of ozone input, it appears that there is some relation between the data in columns 4, 5, and 7 in Table I. Thus, a more reactive solvent results in a higher ozone consumption and a longer reaction time. The yield of I is independent of oxygen solubility, within the limits of the data in col. 6.

In view of the work of Van der Beek[8] and associates, who found only traces of 3- and 4-chloroperbenzoic acid when acetone solutions of the respective aldehydes were air oxidized in the presence of light, the process herein described was extended to various substituted benzaldehydes (Table II).

From the data in Table I it is seen that the yields are low in nonpolar solvents (*e.g.*, CCl_4) and in solvents which are relatively reactive toward ozone (*e.g.*, benzene). In general, the yields in ester solvents tend to be higher with decreasing aliphatic character and an increase in polar character. The yield in ethyl acetate is an exception to this generality, being higher than in methyl acetate, although the difference is not large. It is not possible to ascribe the high yield in the lower molecular weight esters to the polar nature of the solvent alone, since other polar solvents have not been investigated. However, it is thought that the relatively short reaction times obtained by the use of ozone and the presence of a solvent capable of minimizing the interaction of peracid with aldehyde combine to reduce the extent of reaction of I with II with a resulting increase in yield.

Experimental[9a]

Preparation of Perbenzoic Acid (I).—All reactions were carried out in an all-glass, 500-ml. cylindrical reactor having a central cold finger as well as an exterior cooling jacket. The distance between the cooling surfaces was 3/8 in. The reactor was equipped

(1) To whom inquiries should be directed.

(2) H. Gilman and A. H. Blatt, "Organic Syntheses," Coll. Vol. I, 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1948, p. 431.

(3) W. P. Jorissen and P. A. A. Van der Beek, *Rec. trav. chim.*, **45**, 245 (1926).

(4) D. Swern, T. W. Findley, and J. T. Scanlan, *J. Am. Chem. Soc.*, **66**, 1925 (1944).

(5) For a review, see E. Briner, *Advan. Chem. Ser.*, **21**, 184 (1959).

(6) B. Phillips, F. C. Frostick, Jr., and P. S. Starcher, *J. Am. Chem. Soc.*, **79**, 5982 (1957).

(7) In consideration of accuracy limits, the adduct cannot be present in concentrations exceeding ±3% of amount present. This experiment was carried out only in ethyl acetate. The results might differ significantly in other solvents.

(8) P. A. A. Van der Beek, *Rec. trav. chim.*, **51**, 411 (1932).

(9) (a) All melting points and boiling points are uncorrected. (b) SCFM is standard cubic feet per minute.

TABLE I

OXIDATION OF BENZALDEHYDE

Run no.[a]	Solvent	% yield of I at 99% conversion of II	Reaction time, hr.	Moles of O_3/mole of II consumed	Soly. of O_2, ml. of O_2/l. of solvent at 22°	Consumption of O_3 by solvent[b]
1	Ethylacetate (EA)	90	1.7	0.078	24	0 ± 0.5
2	EA/dichloromethane[c]	90	2.0	0.089	17	0
3	EA/carbontetrachloride[c]	87	1.7	0.061	23	0
4	Methyl acetate	85	1.1	0.037	21	0
5	Methyl propionate	83	1.7	0.102		
6	Methyl butyrate	80	1.7	0.104	24	
7	EA/carbontetrachloride[d]	77	1.5	0.068	23	0.5
8	Ethyl butyrate	72	2.7	0.113	23	6
9	Dichloromethane	72	3.0	0.136	13	7
10	Carbon tetrachloride	67	1.5	0.085	23	0.5
11	Butyl butyrate	64	4.7	0.207		
12	Isoamyl acetate	59	5.0	0.208	23	22
13	Chlorobenzene	57	4.1	0.224	15	58
14	Benzene	47	4.0	0.226		58

[a] Data is average of three runs, excepting run 2 which was made only once. [b] Solvent (100 ml.) was treated at 25° with O_3/O_2 at the rate of 0.2 mmole of O_3/min. and the concentration of O_3 in exit gas was determined after 6-min. equilibration time. The per cent decrease in the ozone concentration is reported. [c] 50 vol. % ethyl acetate. [d] 10 vol. % ethyl acetate.

TABLE II[a]

OXIDATION OF SUBSTITUTED BENZALDEHYDES

Substituted benzaldehyde	% yield of peracid	Reaction time,[b] hr.
4-CH_3	87	2
2-Cl	83	4
3-NO_2	73	7
4-Cl	72	2.5
4-NO_2	60	14

[a] 0.25 mole of aldehyde used as a 0.5 *N* ethyl acetate solution. [b] Time for 99% aldehyde consumption.

with a 1-in. glass frit in the bottom, a side sampling drain, a thermowell, and two top vents. The gas stream entered the reactor through the bottom frit and was vented through (in this order) a Dry Ice trap, a three-way stopcock, and two parallel 500-ml. scrubbers containing 5% potassium iodide solution. The ozone was prepared with a Welsbach T-23 generator.

A simplified apparatus used for preparative work consisted of a well-stirred, 2-l., baffled, round-bottom flask equipped with thermometer, gas dispersion tube, and sampling point.

A typical run was as follows. While purging with dry nitrogen, 203 g. of dry ethyl acetate and 26.9 g. of freshly distilled (under nitrogen) benzaldehyde were charged into the precooled reactor. While this mixture was being cooled to the reaction temperature of 20–22°, the ozone generator was purged with dry oxygen and finally adjusted at a gas flow of 0.055 SCFM[9b] containing 0.22 mmole of ozone per minute. At this point, the nitrogen purge was stopped and the oxygen–ozone stream was admitted into the reactor. At random time intervals during the run, the potassium iodide traps (wash bottles) were switched, removed, titrated with standard thiosulfate to starch end point, refilled with fresh 5% potassium iodide solution, and replaced, all in such a manner as to lose only a minimal amount of gas.[10]

The results of previous experiments indicated that the approximate time required to reach 98+% conversion was 1.4 hr.; hence, the reaction mixture was not sampled until this time period had elapsed. At this point, a 1-ml. aliquot was withdrawn through the side arm and the conversion of the aldehyde was determined by vapor phase chromatographic analysis. If the reaction had not reached at least 98.3% conversion, the flow was continued for a short time, depending on the extent of reaction, and the analysis was repeated. In this experiment the reaction was stopped after 91 min. The conversion was 99.6% of the aldehyde.

At this stage, the gas flow through the reactor was stopped, and the reactor was drained. The contents of the reactor, 229.7 g., were analyzed by the potassium iodide–thiosulfate procedure and found to contain 0.229 moles of I as peroxide. This corresponds to a 90% yield. The total ozone consumed was 18.6 mmoles, based on an input of 0.22 mmole/min. or 20 mmoles total minus 1.4 mmoles calculated from the titration of the contents of the potassium iodide scrubbers.

It should be noted that there is considerable latitude in reaction conditions, *i.e.*, 20 to 35°, 0.1 to 0.5 *M* aldehyde, and any ozone feed rate below that of the general procedure.

Analysis.—Since the standard sodium thiosulfate–potassium iodide method is not specific for peracids, an infrared method was used to confirm the titration data. Standard I was prepared from benzoyl peroxide, and the spectrum was determined. Subsequently, a fresh sample of I from the ozonator was analyzed both by titration and infrared. Typical results of triplicate determinations are shown in Table III.

TABLE III

EQUIVALENTS OF I FORMED

Thiosulfate	Infrared	Reaction solvent
0.404	0.405	Ethyl acetate
0.402	0.382	Ethyl acetate
0.073	0.077	Chlorobenzene

The vapor phase chromatographic analysis was carried out on a 5 ft. × 0.25 in. column of 20% Oronite NIW on 80–100-mesh Chromosorb-W at 160° and 15 p.s.i.g. of helium.

Effect of Temperature on the Benzaldehyde–Perbenzoic Acid Interactions.—To determine this effect, various amounts of benzoic acid, perbenzoic acid, and benzaldehyde were added to ethyl acetate and the solutions were cooled to Dry Ice temperatures. Infrared spectra were recorded at regular time intervals over the temperature range of −60 to 30°. The spectra were recorded with a Baird double beam instrument employing a Dry Ice-cooled cell equipped with a thermocouple. The cell was constructed with sodium chloride windows with a path length of 0.15 mm. Sample handling and recording operations were performed in a dry nitrogen atmosphere. Component concentrations were determined at the following wave lengths: perbenzoic acid, 11.35 μ; benzoic acid, 8.87 and 14.9 μ; benzaldehyde, 12.1 and 13.35 μ; and ethyl acetate, 5.30 and 10.9 μ. Standard blends of benzaldehyde and ethyl acetate without the two acids were scanned first under the above conditions to determine temperature effects upon analytical absorptions and cell path length. The resulting data on absorption variations were in agreement with the variations predicted on the basis of cell path length changes indicating that the absorptions were not temperature sensitive under these conditions.

(10) The loss of ozone-containing gas was that volume of gas in the line between the switching (3-way) valve and the surface of the potassium iodide solution in the scrubber—approximately 3 ml.

The blends of perbenzoic acid, benzoic acid, benzaldehyde, and ethyl acetate then were scanned at four 15-min. intervals over the indicated temperature range. The initial spectrum was recorded at −60° and the final one at 30°.

The absorptions of the two acids and benzaldehyde changed concomitantly with the changes of the ethyl acetate absorption and were perfectly consistent with the variations observed from the previous runs due to path length differences.

These results constituted unequivocal evidence that, between −60 and 30°, temperature has no effect upon the benzaldehyde–benzoic acid–perbenzoic acid equilibrium in ethyl acetate.

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The Synthesis and Cyclization of 2-(1-Naphthylmethyl)-2′-carboxybenzophenone[1,2]

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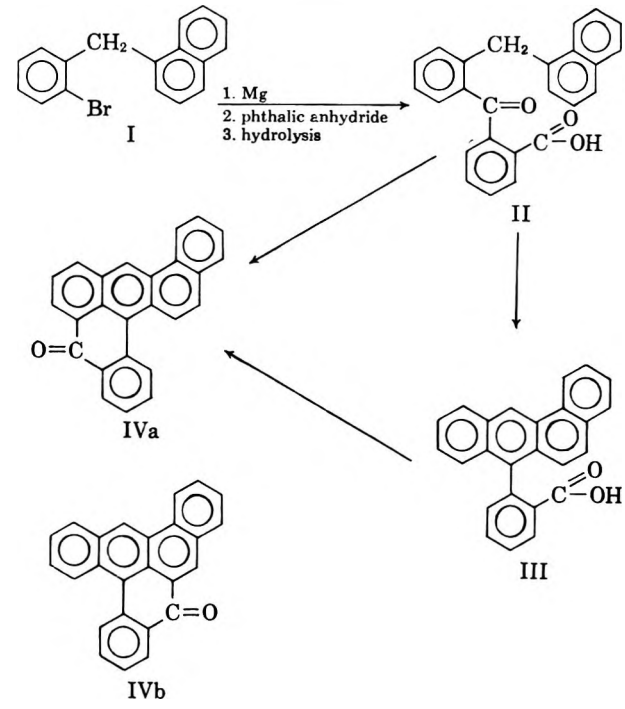
2-(1-Naphthylmethyl)-2′-carboxybenzophenone has been synthesized and cyclized to dibenzo[*hi,l*]chrysen-9-one under one set of conditions, and to 7-(2-carboxyphenyl)benz[*a*]anthracene under different conditions. One of the optically active forms of this acid has been isolated.

A study of the cyclization of 2-(1-naphthylmethyl)-2′-carboxybenzophenone (II) is interesting for several reasons. First, II might lose 1 mole of water to give 7-(2-carboxyphenyl)benz[*a*]anthracene (III). This should be resolvable into optically active forms owing to restricted rotation about the 7-1′ bond as a result of molecular overcrowding; it is of further interest because of its close relationship to 7-phenylbenz[*a*]anthracene.[4] Second, II might lose 2 moles of water to give dibenzo[*hi,l*]chrysen-9-one (IVa) and/or naphtho-[3,2,1-*fg*]naphthacen-9-one (IVb).

The keto acid (II) was prepared in satisfactory yield by the addition of the Grignard reagent of 2-(1-naphthylmethyl)bromobenzene[5] (I) to a boiling solution of phthalic anhydride in benzene (see Chart I). The structure of II was established by carbon–hydrogen analysis, neutralization equivalent titration, infrared spectrum, and by conversion to its methyl ester which was characterized by carbon–hydrogen analysis and by its infrared spectrum.

The keto acid (II) lost 1 mole of water when heated with a mixture of hydrobromic and acetic acids for 1 hr. to give 90% of 7-(2-carboxyphenyl)benz[*a*]anthracene (III).[6] It is interesting to note that when Bradsher and Vingiello[7] cyclized an analogous keto acid, 2-benzyl-2′-carboxybenzophenone, to 9-(2-carboxyphenyl)anthracene they obtained an 80% yield after 20 hr. of heating. The greater ease of aromatic cyclodehydration into the 2-position of the naphthyl system as compared with the phenyl system is consistent with a proposed mechanism for aromatic cyclodehydration.[8]

CHART I



The ease of cyclization of II to III was further illustrated when the reaction was accomplished in 60% yield by simply treating II with concentrated sulfuric acid for a few minutes at −40°.

The acid (III) was first isolated as an alcoholate as indicated by carbon, hydrogen analysis, neutralization equivalent titration, and gas chromatographic analysis. Heating *in vacuo* at 110° for 48 hr. gave the acid III.

The acid III should be optically active owing to restricted rotation about the 7-1′ bond, and preliminary experiments using brucine as a resolving agent confirm this.

On dehydration, III might be expected to give IVa and/or IVb. However, if one assumes that the reaction proceeds *via* an attack of the positive carboxylic acid carbon on an electron-rich ring position, one would predict ring closure at C-8 in preference to C-6. The calculation of the localization energies for the 7-(2-carboxyphenyl)benz[*a*]anthracene system (III) is com-

(1) The nomenclature used in this paper is that presented in the "Definitive Rules for Nomenclature of Organic Chemistry," *J. Am. Chem. Soc.*, **82**, 5545 (1960).

(2) Presented before the Division of Organic Chemistry at the Southeastern Regional Meeting of the American Chemical Society, Gatlinburg, Tenn., Nov., 1962.

(3) Abstracted from the M.S. thesis of E. J. Greenwood presented to the Virginia Polytechnic Institute, 1961.

(4) This compound, NSC #14080, showed slight activity against S-180 and L-1210 (private communication from the National Institutes of Health, Bethesda, Md.).

(5) For an improved method of preparation see P. Polss, Ph.D. dissertation, Virginia Polytechnic Institute, Blacksburg, Va., 1962.

(6) This compound, NSC #76322, which is currently being tested, showed activity against S-180 (private communication from the National Institutes of Health, Bethesda, Md.).

(7) C. K. Bradsher and F. A. Vingiello, *J. Org. Chem.*, **13**, 786 (1948).

(8) C. K. Bradsher and F. A. Vingiello, *J. Am. Chem. Soc.*, **71**, 1434 (1949).

plex and remains to be attempted. Since the attached phenyl ring would not contribute a mesomeric effect because of lack of conjugation due to steric inhibition of resonance,[9] it may be assumed that the localization energy values for III are nearly the same as those of the benz[*a*]anthracene system which are known.[10] The electron localization energy is smaller for position 8 than for position 6 and one might expect that III would give IVa. This reasoning is also applicable to the *frontier* electron density method,[11] and again one would predict ring closure at C-8 in preference to C-6.

Acid-catalyzed dehydration of III gave only one product. This fact was substantiated by gas chromatographic analysis. On the basis of elemental analysis, analysis of the trinitrofluorenone (TNF) adduct, and analysis of the reduction product $C_{25}H_{16}$, the compound could have been either IVa or IVb. An analysis of the infrared absorption spectrum of the compound made a choice possible. A detailed study of the infrared spectra of benz[*a*]anthracenes has been made.[12] Of interest here is the fact that the region between 790 and 850 cm.$^{-1}$ contains at least one strong band for all compounds except 5- and 6-substituted benz[*a*]anthracenes. The infrared spectrum of 7-(2-carboxyphenyl)benz[*a*]-anthracene (III) has two bands in this region which are located at 820 and 845 cm.$^{-1}$. If cyclization of III took place at C-6 to give IVb, these bands should disappear. Since the spectrum of the product still retained the bands in question, shifted slightly to 813 and 835 cm.$^{-1}$, it was assumed that cyclization took place at C-8 to give dibenzo[*hi,l*]chrysen-9-one (IVa).

The keto acid (II) was transformed to IVa with polyphosphoric acid and with liquid hydrogen fluoride. The cyclization of III to IVa was effected in 90% yield using liquid hydrogen fluoride and in 17% yield using 100% phosphoric acid.

The reduction of IVa, which failed using zinc dust and alkali, was effected using lithium aluminum hydride and aluminum chloride giving 9H-dibenzo[*hi,l*]-chrysene. This structure is consistent with the elemental analysis and the infrared spectrum, which reveals the absence of the carbonyl band at 1650 cm.$^{-1}$ found in the starting material (IVa) and the appearance of the adsorption band for aliphatic carbon–hydrogen linkages at 2900 cm.$^{-1}$.

Experimental[13,14]

2-(1-Naphthylmethyl)-2′-carboxybenzophenone (II).—The Grignard reagent, prepared from 1.64 g. (0.067 g.-atom) of magnesium and 20 g. (0.067 mole) of 2-(1-naphthylmethyl)bromobenzene[5] in ether, was added slowly to a boiling solution of 8.95 g. (0.061 mole) of phthalic anhydride in benzene. After acid hydrolysis and the usual work-up, the product was recrystallized twice from a 1:3 mixture of petroleum ether (b.p. 30–60°) and benzene to yield 11.4 g. (52%) of white feathery needles, m.p. 159–160°.

Anal. Calcd. for $C_{25}H_{18}O_3$: C, 81.95; H, 4.95. Found: C, 81.54; H, 5.09.

A 0.200-g. sample of this acid dissolved in ethanol required 5.4 ml. of 0.104 *N* sodium hydroxide for neutralization (bromthymol blue); neut. equiv. 356, calcd. neut. equiv. 366.

The infrared spectrum[15] of II revealed the acid carbonyl band at 1680 cm.$^{-1}$, the ketone carbonyl band at 1665 cm.$^{-1}$, and the carboxylic hydroxyl bands at 2660 and 2550 cm.$^{-1}$.

The methyl ester of II was prepared in 87% yield using methyl alcohol and sulfuric acid, m.p. 88–89°. Its infrared spectrum showed bands at 1730, 1360, and 1300 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{20}O_3$: C, 82.08; H, 5.30. Found: C, 82.09; H, 5.41.

7-(2-Carboxyphenyl)benz[*a*]anthracene (III) and Its Alcoholate.—A mixture of 0.50 g. of 2-(1-naphthylmethyl)-2′-carboxybenzophenone, 4 ml. of 48% hydrobromic acid, 1 ml. of water, and 15 ml. of glacial acetic acid was heated under reflux for 1 hr. Upon cooling to room temperature, white crystals formed. The product was filtered, washed with water, and recrystallized from ethanol giving an essentially quantitative yield of the alcoholate of III, m.p. 133–135°.

Anal. Calcd. for $C_{27}H_{22}O_3$: C, 82.21, H, 5.62. Found: C, 81.87; H, 5.65.

A 0.200-g. sample of this acid dissolved in ethanol required 5.3 ml. of 0.0972 *N* sodium hydroxide for neutralization (bromthymol blue); neut. equiv. 388, calcd. neut. equiv. 394. A g.p.c. analysis showed an ethyl alcohol peak.[16]

Heating the alcoholate *in vacuo* at 110° gave fine white crystals of III which melted at 199–200°.

Anal. Calcd. for $C_{25}H_{16}O_2$: C, 86.19; H, 4.63. Found: C, 86.12; H, 4.54.

The infrared spectrum showed the characteristic carboxylic acid absorption bands in the 1350–1450- and 1660–1740-cm.$^{-1}$ regions.

The ultraviolet spectrum, as would be expected, was very similar to that of benz[*a*]anthracene. A slight bathochromic shift was observed which can be attributed to the attached carboxyphenyl group.[17]

A 0.200-g. sample of III dissolved in ethanol required 5.8 ml. of 0.101 *N* sodium hydroxide for neutralization (bromthymol blue); neut. equiv. 341, calcd. neut. equiv. 348.

The methyl ester of III was prepared in 90% yield using diazomethane, m.p. 138–139°. Its infrared spectrum showed bands at 1730, 1260, and 1125 cm.$^{-1}$ characteristic of the ester group. The ultraviolet spectrum was similar to that of III.

Anal. Calcd. for $C_{26}H_{18}O_2$: C, 86.16; H, 5.01. Found: C, 85.72; H, 5.01.

Brucine, 9.52 g. (0.0241 mole), was added to a boiling solution of 8.4 g. (0.0241 mole) of 7-(2-carboxyphenyl)benz[*a*]anthracene (III) in 250 ml. of ethanol. The volume was reduced to 200 ml. and, on cooling to room temperature, 7.6 g. of salt crystallized. The salt was recrystallized five times from ethanol to give crystals with a constant specific optical rotation of $-10.77°$[18] in benzene.

Anal. Calcd. for $C_{48}H_{42}N_2O_6$: C, 77.61; H, 5.70; N, 3.77. Found: C, 77.39; H, 5.76; N, 3.88.

The brucine salt was decomposed with dilute hydrochloric acid. The optically active acid was recovered and recrystallized from ethanol to give white needles, m.p. 227–228°, which had a specific optical rotation of $+18.84°$ in benzene.

Dibenzo[*hi,l*]chrysen-9-one (IVa). A. From 2-(1-Naphthylmethyl)-2′-carboxybenzophenone (II).—(1) To 0.5 g. (0.0014 mole) of 2-(1-naphthylmethyl)-2′-carboxybenzophenone was added 5 ml. of 85% phosphoric acid. Phosphorus pentoxide was added until the mixture became pasty. The mixture was heated in a metal bath at 190–200° for 4.5 hr., and at 250° for an additional 1.25 hr. The mixture was worked up in the usual way and the resulting red crystals, 0.29 g. (64%), were recrystallized from benzene–ethanol giving red needles, m.p. 221–222°.

Anal. Calcd. for $C_{25}H_{14}O$: C, 90.89; H, 4.27. Found: C, 90.42; H, 4.53.

The infrared spectrum showed the carbonyl absorption band at 1650 cm.$^{-1}$ and peaks at 813 and 835 cm.$^{-1}$. These data are

(9) F. A. Vingiello and A. Borkovec, *J. Am. Chem. Soc.*, **77**, 3413 (1955).

(10) M. J. S. Dewar, *ibid.*, **74**, 3357 (1952).

(11) K. Fukui, T. Yonezawa, C. Nagata, and H. Shingu, *J. Phys. Chem.*, **22**, 1433 (1954).

(12) N. Fuson and M. L. Josien, *J. Am. Chem. Soc.*, **78**, 3049 (1956).

(13) Melting points were taken on a Fisher-Johns melting point block and are corrected.

(14) Analyses were performed by Geller Laboratories, Bardonia, N. Y.

(15) The infrared spectra of all solids were taken using the KBr disk method employing a Beckman Model IR-5 spectrophotometer.

(16) This analysis was performed by Mr. Jose Yanez using a Micro-Tek Model 2500R gas chromatograph with a 6 ft. × 1/4 in. column packed with 3.5% SE-30 on Gas-Chrom Z operated at a column temperature of 85°, inlet temperature of 305°, and using a hydrogen flame detector.

(17) The ultraviolet and visible spectra were taken with a Model 3000 Spectracord at a concentration of 10 mg./l. in 95% ethanol. The wavelength maxima for III are (in mμ) λ 222, 231, 259, 271, 281, 292, 321, 335, 352, and 365; and for IVa are λ 225, 249, 273, 312, 370, 405, 425, and 475.

(18) Optical measurements were made at 25° on a Rudolph Model No. 70 polarimeter using a 4-dm. jacketed tube.

consistent with structure IVa as are the ultraviolet and visible spectra.[17]

(2) The same product, IVa, was obtained in 85% yield when II was treated with anhydrous hydrogen fluoride at room temperature.

B. From 7-(2-Carboxyphenyl)benz[*a*]anthracene (III).—The same product, IVa, was obtained in 91% yield when III was treated with anhydrous hydrogen fluoride at room temperature.

Trinitrofluorenone Adduct of Dibenzo[*hi*,*l*]chrysen-9-one.—A hot solution of 0.048 g. of trinitrofluorenone in 15 ml. of ethanol was added to a hot solution of 0.050 g. of dibenzo[*hi*,*l*]chrysen-9-one in 15 ml. of benzene. On cooling, deep red crystals formed. Recrystallization from benzene–ethanol gave fine red needles, m.p. 201.5–202°.

Anal. Calcd. for $C_{38}H_{19}N_3O_8$: C, 70.69; H, 2.97; N, 6.51. Found: C, 70.73; H, 2.69; N, 6.35.

9H-Dibenzo[*hi*,*l*]chrysene.—A solution of 0.2 g. (0.0006 mole) of IVa and 0.081 g. (0.0006 mole) of aluminum chloride in 25 ml. of benzene was added slowly to a warm slurry of 0.029 g. (0.0008 mole) of lithium aluminum hydride and 0.100 g. (0.0008 mole) of aluminum chloride in 4 ml. of dry ether. After 20 min., the mixture was decomposed with 3 ml. of 6 *N* sulfuric acid and worked up in the usual way. The desired product, 0.11 g. (58%), was obtained as fine orange needles, m.p. 157–158°. Its infrared spectrum, in contrast to the spectrum of IVa, showed the absence of a carbonyl band at 1650 cm.$^{-1}$ and the appearance of the band for aliphatic carbon–hydrogen linkages at 2900 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{16}$: C, 94.90; H, 5.10. Found: C, 94.62; H, 5.31.

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Definition of "Inductive" Substituent Constants

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The definition of σ_I constants may conveniently be made by means of the equation $\sigma_{I,X} = m(pK_{a,X}) + c$, where $pK_{a,X}$ is that of a substituted acetic acid in water. In general, no steric effects are observed. Ionization constants of 2- or 3-substituted propanoic acids, substituted methylamines, 2-substituted ethylamines, and substituted methyl phosphonic acids in water and of acetic acids in 80% Methyl Cellosolve–water have also been examined as secondary reference series for the definition of σ_I constants. Data available in the literature have permitted the definition of more than 100 σ_I values.

The Hammett equation has been used extensively for the correlation of rate and equilibrium data and of certain physical properties with substituent effects. In its most general form the Hammett equation may be written

$$Q_X = \rho\sigma_X + Q_H \qquad (1)$$

where Q is the quantity correlated, σ is a constant representing the electrical effect of the X substituent, ρ is the slope, and Q_H is the intercept. The nature of the substituent constant σ_X appears to depend upon the hybridization state of the carbon atom to which the substituent is bonded. The electrical effect of a substituent X bonded to an sp^3 hybridized carbon atom is best represented by the σ_I constants.[1] These constants were originally defined by Taft[1a] from the equation

$$\sigma_I = \left[\log\left(\frac{k}{k^0}\right)_{OH^-} - \log\left(\frac{k}{k^0}\right)_{H^+}\right]/6.23 \qquad (2)$$

where OH^- and H^+ denote the base- and acid-catalyzed hydrolyses of esters, and k and k^0 are the rates of reaction of the substituted and unsubstituted compounds, respectively. This definition is inconvenient in that it requires two measurements to define a new value of σ_I, and also suffers from the difficulty of obtaining reliable and reproducible rate measurements in different laboratories. The choice of this approach to the definition of σ_I values by Taft[1b] was due to an attempt to eliminate steric effects. The steric effect in both acid- and base-catalyzed hydrolyses of esters is believed to be the same, as the transition states proposed for these reactions differ only by a proton, and of course the steric requirements for a proton must be quite small.

Our need for a convenient source of new σ_I values has led us to consider the alternative definition of σ_I constants in terms of the equation

$$\sigma_{I,X} = b(pK_{a,X}) + d \qquad (3)$$

where b is the slope of the regression line which minimizes deviation on the pK_a values and d is the intercept of this line and where the σ_I values are defined in terms of the pK_a values of the corresponding substituted acetic acids. There is nothing new in this proposal; that substituent effects are "inductive" in nature has been suggested many times before.[2] Taft's definition is based on the assumption that in addition to the polar effects of a substituent in an aliphatic compound there is also a significant steric effect which must be accounted for. If this steric effect is not significant (or, at most, rarely significant), then eq. 3 constitutes a more convenient definition. The advantages of such a definition are threefold. First, only one measurement suffices to define a new value of σ_I; second, the pK_a values may be more reliably and reproducibly determined; third, the definition of σ_I values would now be directly comparable to that of the Hammett[3a,b] substituent constants.

To determine whether such a definition is justifiable, pK_a values of substituted acetic acids in water at 18 and at 25° generally taken from the compendium of

(1) (a) R. W. Taft, Jr., and I. C. Lewis, *J. Am. Chem. Soc.*, **80**, 2436 (1958); (b) R. W. Taft, Jr., *J. Phys. Chem.*, **64**, 1805 (1960); (c) R. W. Taft, Jr., E. Price, I. R. Fox, I. C. Lewis, K. K. Anderson, and G. T. Davis, *J. Am. Chem. Soc.*, **85**, 709 (1963).

(2) G. E. K. Branch and M. Calvin, "Theory of Organic Chemistry," Prentice-Hall, New York, N. Y., 1941, p. 217.

(3) (a) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940; (b) H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953); (c) R. W. Taft, Jr., "Steric Effects in Organic Chemistry," M. S. Newman, John Wiley and Sons, Inc., New York, N. Y., 1956.

TABLE I

DATA USED IN CORRELATIONS[a-c]

Series	Temp., °C.	$K \times 10^5$ (X)
1a	5	1.700 (H), 1.305 (Me), 1.574 (Et), 20.82 (AcNH), 18.69 (EtCONH), 12.28 (H_2NCONH), 359.20 (CN),[d] 28.97 (MeO)
1b	10	1.729 (H), 1.326 (Me), 1.576 (Et), 21.09 (AcNH), 18.95 (EtCONH), 12.60 (H_2NCONH), 357.45 (CN),[d] 28.58 (MeO)[e]
1c	15	1.745 (H), 1.336 (Me), 1.569 (Et), 278.9 (F), 143.0 (Cl), 133.31 (Br), 71.90 (I), 21.25 (AcNH), 19.13 (EtCONH), 12.90 (H_2NCONH), 352.93 (CN),[d] 28.15 (MeO)[e]
1d	18	1.734 (H), 1.32 (Me), 1.53 (Et), 129 (Br), 70 (I), 14.6 (OH)
1e	20	1.753 (H), 1.338 (Me), 1.592 (Et), 268.4 (F), 139.4 (Cl), 129.63 (Br), 69.46 (I), 22.02 (AcNH), 19.21 (EtCONH), 13.22 (H_2NCONH), 346.94 (CN),[d] 27.60 (MeO)[e]
1f	25	1.754 (H), 1.336 (Me), 1.515 (Et), 259.6 (F), 135.9 (Cl), 125.30 (Br), 66.80 (I), 338.76 (CN),[d] 4.927 (Ph),[f] 2.166 ($PhCH_2$),[f] 14.76 (OH), 26.89 (MeO),[d] 21.39 (AcNH)
1g	30	1.750 (H), 1.326 (Me), 1.484 (Et), 249.0 (F), 130.79 (Cl), 120.78 (Br), 64.06 (I), 329.78 (CN),[d] 21.23 (AcNH), 19.02 (EtCONH), 13.38 (H_2NCONH), 26.10 (MeO)[e]
1h	35	1.728 (H), 1.310 (Me), 1.439 (Et), 237.9 (F), 125.94 (Cl), 115.88 (Br), 61.26 (I), 319.52 (CN),[d] 20.99 (AcNH), 18.82 (EtCONH), 13.39 (H_2NCONH), 25.14 (MeO)[e]
1i	40	1.703 (H), 1.284 (Me), 1.395 (Et), 20.68 (AcNH), 18.58 (EtCONH), 13.33 (H_2NCONH), 308.51 (CN),[d] 24.40 (MeO)[e]
1j	45	1.670 (H), 1.257 (Me), 1.347 (Et), 20.21 (AcNH), 18.19 (EtCONH), 13.17 (H_2NCONH), 296.40 (CN),[d] 23.37 (MeO)[e]
1k	50	1.633 (H), 1.229 (Me), 1.302 (Et), 19.67 (AcNH), 17.77 (EtCONH), 12.95 (H_2NCONH), 14.16 (OH), 22.34 (MeO)[e]
2a	18	1.32 (H), 1.44 (Me), 1.56 (Et), 1.62 (Pr), 1.32 (Cl), 107 (Br), 78 (I), 13.8 (OH)
2b	25	1.336 (H), 1.42 (Me), 13.87 (OH), 19.27 (AcNH), 12.81 (H_2NCONH)
3a	18	1.32 (H), 1.53 (Me), 1.51 (Et), 1.43 (Pr), 1.456 (*i*-Pr), 1.63 (*t*-Bu), 8.0 (Cl), 10.2 (Br), 8.2 (I), 2.0 (C_2H_3)
3b	25	1.336 (H), 1.515 (Me), 1.44 (Et), 2.166 (Ph), 3.588 (AcNH), 3.256 (H_2NCONH)
		$-pK_a^a$ (X)
4	25	7.33 (*i*-Pr), 7.30 $H(CH_2)_6$, 5.78 (OH), 5.04 (Cl), 6.73 (Ph)
5	25	10.624 (H),[h] 10.631 (Me),[h] 10.568 (Et),[h] 10.640 (Pr),[h] 9.49 (CH_2CH_3),[i] 9.37 (Ph),[j] 9.830 ($PhCH_2$),[j] 5.34 (CN),[k] 7.93 ($CONH_2$)[l]
6	25	10.631 (H),[h] 10.568 (Me),[h] 10.640 (Et),[h] 9.830 (Ph),[j] 9.498 (OH),[h] 9.20 (OMe),[m] 10.20 ($PhCH_2$)[j]
7[n]	25	2.38 (H), 2.43 (Me), 2.49 (Et), 1.40 (Cl), 1.14 (Br), 1.30 (I), 1.91 (OH), 1.85 (Ph)
8[o]	25	7.74 (H), 8.05 (Me), 8.18 (Et), 6.30 (Cl), 6.52 (Br), 6.72 (I), 7.15 (OH), 7.4 (Ph)

[a] All data in water unless otherwise noted. [b] All data from ref. 4 unless otherwise noted; values chosen are those given by ref. 4 as very reliable or reliable: [c] Series 1a–k are substituted acetic acids, series 2a and b are 2-substituted propanoic acids, series 3a and b are 3-substituted propanoic acids. [d] F. S. Feates and D. J. G. Ives, *J. Chem. Soc.*, 2798 (1956). [e] E. J. King, *J. Am. Chem. Soc.*, **82**, 3575 (1960). [f] E. J. King and J. E. Prue, *J. Chem. Soc.*, 275 (1961). [g] W. Simon, G. H. Lyssy, A. Morikofer, and E. Heilbronner, "Zusammenstellung von scheinbaren Dissoziations Konstanten im Losungsmittelsystem Methylcellosolve–Wasser," Vol. I, Juris-Verlag, Zurich, 1959; P. F. Sommer and W. Simon, *ibid.*, Vol II, 1961. [h] R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959, p. 65. [i] G. Girault-Vexlearschi, *Bull. soc. chim. France*, 589 (1956). [j] W. H. Carothers, C. F. Bickford, and G. J. Hurwitz, *J. Am. Chem. Soc.*, **49**, 2908 (1927). [k] G. W. Stevenson and D. Williamson, *ibid.*, **80**, 5943 (1958). [l] M. Zieff and J. T. Edsall, *ibid.*, **59**, 2245 (1937). [m] R. J. Bruehlman and F. H. Verhoek, *ibid.*, **70**, 1407 (1948). [n] pK_{a_1} value. [o] pK_{a_2} value.

Kortum, Vogel, and Andrussow[4] were correlated with the σ_I values given by Taft.[1b] From the series at 25°, σ_I constants were calculated for the EtCONH and H_2NCONH groups (these values are reported in Table II). These constants were then used in conjunction with those of Taft to correlate pK_a values of substituted acetic acids at other temperatures ranging from 5 to 50°. The pK_a values in water at temperatures from 5 to 50° in 5° intervals were considered by Kortum, *et al.*, to be very reliable while those at 18° were considered reliable.

The pK_a values used in the correlation are given in Table I. The values of σ_I which were accepted as standard and used in the correlations are given in Table II.

TABLE II

PRIMARY σ_I VALUES

X	σ_I	X	σ_I	X	σ_I
Et	−0.05	F	0.52	OH	0.25
Me	−0.05	Cl	0.47	MeO	0.25
H	0.00	Br	0.45	NHAc	0.28
$PhCH_2$	0.04	I	0.39	CN	0.58
Ph	0.10	*t*-Bu	−0.07	EtCONH	0.25[a]
				H_2NCONH	0.21[a]

[a] From Table V.

(4) G. Kortum, W. Vogel, and K. Andrussow, *Pure Appl. Chem.*, **1**, 190 (1961).

Results

The results of the correlations are given in Table III together with values of b and d for use in eq. 3. The

TABLE III

RESULTS OF CORRELATIONS

Series	ρ	r[a]	s[b]	Q_H	b	d	n[c]
1a	−3.869	0.994	0.0940	4.681	−0.2556	1.213	8
1b	−3.860	0.995	0.0892	4.676	−0.2565	1.214	8
1c	−3.938	0.997	0.0733	4.678	−0.2523	1.191	12
1d	−3.905	0.997	0.0809	4.700	−0.2544	1.197	6
1e	−3.917	0.997	0.0671	4.676	−0.2539	1.189	12
1f	−3.950	0.996	0.0806	4.712	−0.2512	1.186	13
1g	−3.875	0.998	0.0618	4.682	−0.2568	1.204	12
1h	−3.857	0.998	0.0588	4.688	−0.2582	1.217	12
1i	−3.816	0.997	0.0676	4.693	−0.2605	1.231	8
1j	−3.808	0.997	0.0652	4.703	−0.2611	1.236	8
1k	−3.843	0.994	0.0699	4.726	−0.2568	1.233	8
2a	−3.871	0.994	0.105	4.709	−0.2554	1.205	8
2b	−3.732	0.988	0.100	4.753	−0.2618	1.247	5
3a	−1.607	0.982	0.0734	4.776	−0.6003	2.981	10
3b	−1.306	0.972	0.0490	4.796	−0.7241	3.477	6
4	−4.646	0.993	0.132	7.13	−0.2124	1.517	5
5	−8.570	0.997	0.156	10.29	−0.1159	1.192	9
6	−4.388	0.970	0.155	10.42	−0.2145	2.239	7
7	−2.325	0.962	0.160	2.32	−0.3979	0.9630	8
8	−3.125	0.987	0.121	7.87	−0.3120	2.459	8

[a] Correlation coefficient. [b] Standard deviation. [c] Number of points in series.

TABLE IV

CALCULATED σ_I VALUES

X	pK_a[a]	σ_I[b]	Series[c]	X	pK_a[a]	σ_I[b]	Series[c]
CH_2Cl	4.10	0.15	1d	CH_2Br	3.991	0.18	1d
CH_2I	4.086	0.16	1d	EtO	3.652	0.27	1d
Me_2COHCH_2	4.873	−0.04	1d	$MeCHOHCH_2$	4.686	−0.01	1d
$PhCH_2SCH_2$	4.463	0.06	1d	$PhCH_2CH_2S$	3.7945	0.23	1d
PhCHOH	4.40	0.08	1d	$C_2H_3CH_2$	4.70	0.00	1d
i-Pr	4.770	−0.02	1d	Pr	4.821	−0.03	1d
Bu	4.845	−0.04	1d	*i*-Bu	4.8368	−0.03	1d
s-Bu	4.836	−0.03	1d	*t*-$BuCH_2$	4.788	−0.02	1d
i-Pr	4.8348	−0.04	1e	Pr	4.7673	−0.02	1e
EtO_2CNH	3.66	0.26	1e	HCONH	3.43	0.32	1e
CCl_3CH_2	4.21[d]	0.12	1e	$CCl_3CH_2CH_2$	4.52[e]	0.04	1e
$Cl_2C{=}CH$	4.04[d]	0.16	1e	$Cl_2C{=}CHCH_2$	4.57[e]	0.03	1e
CO_2^-	5.39513[d]	−0.17	1f	EtCONH	3.7176	0.25	1f
H_2NCONH	3.8758	0.21	1f	$AcNHCH_2$	4.4452	0.07	1f
C_2H_3	4.3521	0.09	1f	H_2NCO	3.6413	0.27	1f
H_2NCOCH_2	4.5388	0.05	1f	$C_2H_3CH_2$	4.6747	0.01	1f
PhO	3.171	0.39	1f	1-$C_{10}H_7$	4.2362	0.12	1f
2-$C_{10}H_7$	4.259	0.12	1f	HC_2	3.32[g]	0.35	1f
HC_2CH_2	4.21[g]	0.13	1f	SO_3^-	4.20[h]	0.13	1f
SH	3.68[i]	0.26	1f	NO_2	1.68[i]	0.76	1f
$MeSO_2$	2.36[i]	0.59	1f	PhS	3.52[i]	0.30	1f
MeS	3.72[i]	0.25	1f	EtS	3.74[i]	0.25	1f
i-PrS	3.72[i]	0.25	1f	PrS	3.77[i]	0.24	1f
BuS	3.91[i]	0.23	1f	Ph_3CS	4.30[i]	0.11	1f
$PhCH_2S$	3.73[i]	0.25	1f	Bu	4.857	−0.03	1f
i-Bu	4.845	−0.03	1f	*t*-Bu	4.998[j]	−0.07	1f
MeCH=CH—	4.507	0.05	1f	EtCH=CH	4.516	0.05	1f
$MeCH{=}CHCH_2$	4.719	0.00	1f	$Me_2C{=}CH$	4.600	0.03	1f
$BuCH_2$	4.893	−0.04	1f	$BuCH_2CH_2$	4.8945	−0.04	1f
$Bu(CH_2)_3$	4.959	−0.06	1f	cy-C_6H_{11}	4.801	−0.02	1f
CF_3	3.063	0.42	1f	cy-C_5H_9O	3.699	0.26	1f
cy-$C_6H_{11}O$	3.538	0.30	1f	cy-$C_6H_{10}S$	3.488	0.31	1f
cy-$C_6H_{11}Se$	3.187	0.38	1f	Me_3Si	5.22	−0.13	1f
Me_3SiCH_2	4.907	−0.05	1f	$PhMe_2Si$	5.27	−0.14	1f
AsO_3H^-	4.670	0.01	1f	ONO_2	2.26[k]	0.62	1f
Me_3N^+	1.83[i]	0.73	1f	EtO_2C	3.35[i]	0.34	1f
MeO_2C	3.35[l]	0.34	1f	$PhSO_2$	2.44[i]	0.57	1f
PhSO	2.66[i]	0.52	1f	SCN	2.523[m]	0.58	1f
N_3	3.03	0.42	1f	PrO	3.65[i]	0.27	1f
BuO	3.66[i]	0.27	1f	*s*-BuO	3.67[i]	0.26	1f
i-PrO	3.69[i]	0.26	1f	CO_2H	3.14764[f,n]	0.39	1f
CH_2CN	3.991	0.18	1f	CH_2CF_3	4.156	0.14	1f
$CH_2C_3F_7$	4.18	0.14	1f	$SiMe_2OSiMe_3$	5.22	−0.13	1f
3-Indolyl	4.75[o]	−0.01	1f	2-Thienyl	3.89[f]	0.21	1f
BzNH	3.66[q]	0.27	1f	Ac	3.58	0.29	1f
PhNHCO	3.717[m]	0.25	1f	$PhNHCOCH_2$	4.701[m]	0.00	1f
CH_2OH	4.507[m]	0.05	1f	CH_2OMe	4.461[r]	0.07	1f
$PhCH_2CH_2$	4.757	−0.01	1f	$Me_2C{=}NO$	3.56[s]	0.29	1f
CH_2CO_2Me	4.029[t]	0.17	1f	$PhSO_2NH$	3.461[u]	0.32	1f
CH_2SH	4.32[r]	0.10	1f	$Me_3Si(CH_2)_2$	4.886	−0.04	1f
$MeSi(CH_2)_3$	4.963	−0.06	1f	$H_2NCO(CH_2)_2$	4.600	0.03	1f
$H_2NCO(CH_2)_3$	4.629	0.02	1f	cy-$C_6H_{11}CH_2O$	3.903	0.21	1f
cy-$C_6H_{11}CH_2$	4.910	−0.05	1f	cy-$C_6H_{11}(CH_2)_4$	4.951	−0.06	1f
Me_2NH^+	1.95	0.70	1f	$MeNH_2^+$	2.35	0.60	1f
NH_3^+	2.3503	0.60	1f	$EtNH_2^+$	2.34	0.60	1f
$PrNH_2^+$	2.35	0.60	1f	$BuNH_2^+$	2.35	0.60	1f
i-$BuNH_2^+$	2.35	0.60	1f	H_3NO^+	2.87[s]	0.47	1f
PhNAc	3.914[m]	0.22	1f	Pr	4.8511	−0.04	1g
i-Pr	4.7945	−0.03	1g	MeCHOH	4.648	0.02	2a
SeCN	2.551[w]	0.58	2b	SCN	2.441[x]	0.61	2b
$SCONH_2$	3.487[x]	0.33	2b	SO_2Me	2.44	0.61	2b
SO_2Et	2.448	0.60	2b	SO_2Pr	2.507	0.59	2b
SO_2-*i*-Pr	2.522	0.59	2b	cy-$C_6H_{11}O$	3.638	0.29	2b
1-$C_{10}H_7NAc$	3.693[m]	0.26	2b	2-$C_{10}H_7NAc$	3.627[m]	0.27	2b
2-Furyl	6.97[y]	0.04	4	2-Thienyl	6.43	0.15	4
2-Thienylmethyl	6.91[y]	0.05	4	3-Indolyl	7.14[k]	0.00	4
				1-$C_{10}H_7CH_2$	6.81[y]	0.07	4
CF_2H	7.52[f]	0.32	5	$Ph(CH_2)_2$	10.201[z]	0.01	5

TABLE IV (*Continued*)

X	pK_a[a]	σ_I[b]	Series[c]	X	pK_a[a]	σ_I[b]	Series[c]
CO_2^-	9.7796	0.06	5	$CH_2CO_2^-$	10.2350	0.01	5
$CH_2NH_3^+$	7.149[aa,j]	0.36	5	CH_2NH_2	9.627[aa,e]	0.08	5
$Ph(CH_2)_3$	10.394[z]	−0.01	5	$Ph(CH_2)_4$	10.486[z]	−0.02	5
cy-C_6H_{11}	10.49[bb]	−0.02	5	HC_2	8.15[bb]	0.25	5
PhCHMe	9.80[bb]	0.06	5	$H(CH_2)_7$	10.57[bb]	0.03	5
t-Bu	10.24[bb]	0.01	5	CH_2OH	9.498[aa]	0.09	5
CO_2Me	7.66[cc]	0.30	5	CH_2CO_2Et	9.13[cc]	0.13	5

[a] All data in water; all pK_a values from ref. 4 unless otherwise noted. [b] σ_I values in which the hundredths place is upper case are calculated from reliable thermodynamic pK_a values using those series in Table III for which correlation is significant at the 99.9% confidence level. [c] Series from which σ_I was calculated; numbers refer to Table I. [d] A. N. Nesmeyanov, L. I. Zakharkin, and R. K. Friedlina, *Izv. Akad. Nauk. SSSR, Otdel. Khim. Nauk.*, 40 (1955). [e] Includes statistical factor 2. [f] Includes a statistical factor of 0.5. [g] G. H. Mansfield and M. C. Whiting, *J. Chem. Soc.*, 4761 (1956). [h] R. P. Bell and G. A. Wright, *Trans. Faraday Soc.*, **57**, 1377 (1961). [i] H. C. Brown, D. H. McDaniel, and O. Hafliger, "Determination of Organic Structures by Physical Methods," Vol. 1, Academic Press, New York, N. Y., 1955. [j] L. Otros, F. Sirokman, and O. Gall, *Univ. Szegediensis Acta Phys. Chem.*, [N.S.]**4**, 131 (1958). [k] K. S. McCallum and W. D. Emmons, *J. Org. Chem.*, **21**, 367 (1956). [l] W. D. Treadwell and E. Wettstein, *Helv. Chim. Acta*, **18**, 204 (1935). [m] W. Ostwald, *Z. physik. Chem.* (Leipzig), **3**, 241 (1889). [n] S. N. Das and D. J. G. Ives, *Proc. Chem. Soc.*, 373 (1961). [o] P. E. Pilet and M. A. Athanasiades-Mercantori, *Phyton Ann. rei Botan.*, **8**, 210 (1959). [p] E. Imoto and R. Motoyama, *Bull. Naniwa Univ.*, **2A**, 127 (1954). [q] E. Larrson, *Z. anorg. Chem.*, **155**, 247 (1926). [r] M. H. Palomaa, *Ann. Acad. Sci. Fennicae*, [A]**3**, 15 (1912). [s] E. Borek and H. T. Clarke, *J. Biol. Chem.*, **125**, 483 (1938). [t] J. Walker, *J. Chem. Soc.*, **61**, 705 (1892). [u] J. M. Loven, *Z. Physik. Chem.* (Leipzig), **19**, 456 (1896). [v] H. Borsook, E. L. Ellis, and H. M. Huffman, *J. Biol. Chem.*, **117**, 281 (1937). [w] A. Fredga, *J. prakt. Chem.*, [2]**123**, 129 (1929). [x] A. Fredga, *ibid.*, [2]**123**, 110 (1929). [y] In 80% Methyl Cellosolve–water; see footnote. *g*, Table I. [z] Footnote *j*, Table I. [aa] Footnote *h*, Table I. [bb] Footnote *i*, Table I. [cc] J. T. Edsall and M. H. Blanchard, *J. Am. Chem. Soc.*, **55**, 2337 (1933).

values of *b* and *d* permit the calculation of new σ_I constants.

As is shown by the correlation coefficients (r) and the standard deviations (s), the correlations are excellent. The success of these correlations demonstrates the absence of any steric effect. The results obtained are possible only if any steric effect which existed were constant throughout the series. A glance at the substituents involved in the series correlated suffices to show enormous variation in bulk and shape. Under these circumstances no constant steric effect is possible. Thus no steric effect whatsoever seems to be present in these series. The results justify definition of σ_I constants by eq. 3. A number of σ_I constants have been calculated from pK_a values extant in the literature. The pK_a values used and the σ_I values obtained are given in Table IV. Preferred values of the σ_I constants are given in Table V. Comparisons have been made with values given by Taft or values obtained from these equations.

$$\sigma_I = [(3\sigma_m - \sigma_p)/2] \quad (4)$$

$$\sigma_I = \sigma^*/6.23 \quad (5)$$

In general, the agreement is good, when comparison is made with the values obtained from eq. 4 and 5 or those quoted by Taft for reactivities in weakly protonic solvents. The values obtained by Taft and co-workers[1c] from F^{19} shielding parameters in weakly protonic solvents show fair agreement. In order more effectively to compare these $\sigma_{I,F^{19}}$ values with the σ_{I,pK_a} values in Table V, we have correlated the latter with the former (slope = 0.77, intercept = 0.08, r = 0.953, s = 0.07, n = 17). There is apparently a difference in scale between the two sets of σ_I values.

Supplementary Series for the Definition of σ_I.—We have examined the possibility of using series other than substituted acetic acids in water as a means of obtaining σ_I values. The series studied include ionization constants of 2-substituted propanoic acids in water at 18 (series 2a) and 25° (series 2b); 3-substituted propanoic acids in water at 18 (series 3a) and 25° (series 3b); substituted acetic acids in 80% Methyl Cellosolve–water at 25° (series 4); substituted methylamines in water at 25° (series 5); 2-substituted ethylamines in water at 25° (series 6); and the first and second ionization constants of substituted methylphosphonic acids in water at 25° (series 7 and 8, respectively). Correlations were made using the primary σ_I constants given in Table II and in some cases σ_I constants from Table V which are believed accurate to the hundredth place. Among the requirements that a series must meet to be useful in the determination of σ_I values is that ρ have a large value; thus the series will reflect small differences in substituent effect. By this criterion, series 2a, 2b, 4–6, and 8 should be useful in the evaluation of σ_I constants. A more important criterion is a high level of correlation for the series. We have arbitrarily considered the 99.9% confidence level to represent the degree of correlation necessary for the definition of σ_I values, and the 99% confidence level for their estimation. Defined values are considered reliable in the hundredths place, estimated values are considered reliable in the tenths place. On this basis, of the supplementary series examined, series 2a and 5 may be used to define σ_I constants and all other supplementary series may be used to estimate σ_I values. Only those thermodynamic ionization constants considered by Kortum, Vogel, and Andrussow to be very reliable, together with more recent values obtained by the same careful techniques, were used to define σ_I constants.

Limitations of the Definition of σ from Eq. 3.—There is one obvious limitation on the method and that is the comparatively large error in measuring the pK_a values of fairly strong acids (pK_a less than 2). This problem is lessened by the fact that choice of one of the supplementary series will usually give a substituted acid in the range of conveniently measured pK_a.

Another more serious limitation is intramolecular hydrogen bonding between substituent and carboxyl group. Thus the thermodynamic functions of K_1 and K_2 for malonic acid have been interpreted as an indication of an intramolecular hydrogen bond. The value of K_1 does cause some decrease in correlation when the σ_I value of 0.30 suggested by Taft for the carboxyl group

TABLE V

PREFERRED σ_I VALUES

	This work	Reactivities	Taft F^{19} shielding	Eq. 4	Eq. 5
Alkyl and Cycloalkyl					
i-Pr	−0.03				−0.03
Pr	−0.03				−0.02
Bu	−0.04				−0.02
i-Bu	−0.03				−0.02
s-Bu	−0.03				−0.03
t-Bu	−0.07				
t-$BuCH_2$	−0.02				−0.03
$BuCH_2$	−0.04				
$Bu(CH_2)_2$	−0.04				
$Bu(CH_2)_3$	−0.06				
Cyclohexyl	−0.02				
Vinyl, Ethynyl, Aryl, and Heteroaryl					
C_2H_3	0.09	0.05	0.01		
2,2-MeC_2H	0.03				
trans-2-$Me_2C_2H_2$	0.05			0.05	
trans-2-EtC_2H_2	0.05				
$C_2H_3CH_2$	0.00				
trans-2-$MeC_2H_2CH_2$	0.00				−0.02
HC_2	0.35				
HC_2CH_2	0.13				
1-$C_{10}H_7$	0.12				
2-$C_{10}H_7$	0.12				
1-$C_{10}H_7CH_2$	0.07				
$Ph(CH_2)_2$	−0.01				
$Ph(CH_2)_2$	−0.01				
$Ph(CH_2)_4$	−0.02				
2-Thienyl	0.21				
2-Furyl	0.04				
3-Indolyl	−0.01				
2-Thienylmethyl	0.05				
Haloalkyl and Halovinyl					
CF_3	0.42	0.41	0.41		0.37
CF_3CH_2	0.14				
$C_3F_7CH_2$	0.14				
CCl_3CH_2	0.12				
$CCl_3(CH_2)_2$	0.04				
CF_2H	0.32				
CH_2Cl	0.15	0.17	0.14		0.17
CH_2Br	0.18				0.16
CH_2I	0.16				0.14
2,2-Cl_2C_2H	0.16				
2,2-$Cl_2C_2HCH_2$	0.03				
Oxyalkyl					
$HOCH_2$	0.05	0.10	0.01		
$MeOCH_2$	0.07				
$MeCHOHCH_2$	−0.01				
Me_2COHCH_2	−0.04				
MeCHOH	0.02				
PhCHOH	0.08				
Other Substituted Alkyl					
$NCCH_2$	0.18	0.23	0.24		0.21
$PhNHCOCH_2$	0.00				
H_2NCOCH_2	0.05				
H_2NCH_2	0.08				
$AcNHCH_2$	0.07				
MeO_2CCH_2	0.17				
EtO_2CCH_2	0.13				
$HSCH_2$	0.10				
$PhCH_2SCH_2$	0.06				
Me_3SiCH_2	−0.05	−0.11	−0.07		−0.14
Carbonyl					
Ac	0.29	0.28	0.23		
CO_2Me	0.34	0.30			
CO_2Et	0.34	0.30	0.21		
$CONH_2$	0.27			0.24	
PhNHCO	0.25				
Aza					
EtOCONH	0.32				
HCONH	0.26				
EtCONH	0.25				
BzNH	0.27		0.21	0.29	
H_2NCONH	0.21				
PhNAc	0.22				
1-$C_{10}H_7NAc$	0.26				
2-$C_{10}H_7NAc$	0.27				
$PhSO_2NH$	0.32				
Oxa					
EtO	0.27			0.27	
PrO	0.27	0.28			
i-PrO	0.26				
BuO	0.27	0.31			
s-BuO	0.26				
Cy-pentyloxy	0.26				
Cy-hexyloxy	0.29				
PhO	0.39	0.38	0.37	0.38	
O_2NO	0.62				
$Me_2C{=}NO$	0.29				
Thia					
SH	0.26	0.25	0.18		
MeS	0.25	0.19	0.14		
EtS	0.25				
PrS	0.24				
i-PrS	0.25	0.25			
BuS	0.23				
Cyclohexyl-S	0.31				
$PhCH_2S$	0.25				
$Ph(CH_2)_2S$	0.06				
Ph_3CS	0.11				
PhS	0.30				
NCS	0.55				
$H_2N(CO)S$	0.33				
Sulfonyl					
$MeSO_2$	0.59	0.59		0.54	
$EtSO_2$	0.60				
$PrSO_2$	0.59				
i-$PrSO_2$	0.59				
$PhSO_2$	0.57				
Other					
Me_3Si	−0.13	−0.12			
$PhMe_2Si$	−0.14				
$Me_3SiOSiMe_2$	−0.13				
N_3	0.42				
PhSO	0.52				
Cyclohexyl-Se	.38				
SeCN	0.58				
Ionic					
CO_2^-	−0.17		−0.35	−0.15	
AsO_3H^-	0.01				
SO_3^-	0.13		0.25	0.03	
Me_3N^+	0.73	0.92	0.93		
Me_2NH^+	0.70				
$MeNH_2^+$	0.60				
NH_3^+	0.60	0.60	0.58		
$CH_2CO_2^-$	0.01				
$CH_2NH_3^+$	0.36	0.25	0.25		
$EtNH_2^+$	0.60				
$PrNH_2^+$	0.60				
$BuNH_2^+$	0.60				
i-$BuNH_2^+$	0.60				

is used. The values of r and s obtained for the series at 25° which includes the pK_{a_1} of malonic acid (correlated by a statistical factor of 0.5) are 0.989 and 0.131, respectively, slightly worse than those given in Table III for the series omitting this point. The value of σ_I calculated for the CO_2H group on the basis of series 1f is 0.39. This value seems somewhat high. The use of eq. 3 gives a value of 0.33. The carbomethoxy and carbethoxy groups have σ values of 0.34 and 0.34, respectively (Table IV). Presumably, the value of σ_I will be about the same as the values for CO_2Me and CO_2Et.

Effect of Temperature on the Reaction Constant.—The values of ρ obtained for series 1a–k permit a test of the relationship

$$\rho = \frac{m}{T} + c \qquad (6)$$

which has been proposed by a number of authors, and most recently by Hepler.[5] Correlation of the ρ values for series 1a–k with eq. 6 gives very poor results (r = 0.579, t = 2.129, n = 11). The ρ values seem by inspection more likely to fit a parabolic relationship. This is in accord with the observation that ionization constants of aliphatic carboxylic acids fit the parabolic equation

$$\log K = \log K_m - p(T - T_m)^2 \qquad (7)$$

where K_m is the maximum value of K, occurring at the maximum temperature T_m.[6] Thus, for these series of ionization constants, eq. 6 is not obeyed.

(5) L. Hepler, *J. Am. Chem. Soc.*, **85**, 3089 (1963).

(6) R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959, p. 69.

Solvolysis of Substituted γ-Butyrolactones and δ-Valerolactones

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Methyl substitution of γ-butyrolactone results in a reduction of the equilibrium constants for hydrolysis. This is due to a combination of the enhancement of the rate of ring closure and reduction in the ease of ring opening by substitution, the first factor being the more important. The results for the δ-valerolactones confirm these findings.

A previous publication[2] reported the influence of methyl substitution on the rate of saponification of γ-butyrolactone in 92.3% ethanol–water. Shechter and co-workers[3] have carried out similar studies in 50% dimethoxyethane–water and also have measured the basic hydrolysis of several δ-valerolactones. This paper reports measurements of the equilibrium constants of substituted γ-butyro- and δ-valerolactones in acid solution. The values of the rate constants of acid-catalyzed hydrolysis of γ-butyrolactone and γ-methylbutyrolactone (where the equilibrium constants were sufficiently large) and of the δ-valerolactones were determined also (see Tables I and II).

TABLE I

HYDROLYSIS OF BUTYROLACTONES[a]

Butyrolactone	25°, l. mole^{-1} min.$^{-1}$ $K_H \times 10^2$	25°, l. mole^{-1} min.$^{-1}$ $k_H \times 10^2$	0°, l. mole^{-1} min.$^{-1}$ $K_H \times 10^2$	0°, l. mole^{-1} min.$^{-1}$ $k_H \times 10^2$
	34.7 (37.2)	2.20 (1.40)	21.9	0.211
α-Methyl-	2.45 (4.9)	(1.0)		
β-Methyl-	4.81			
γ-Methyl-	7.81	1.58 (1.0)	7.46	0.184
α,α-Dimethyl-	<1			
β,β-Dimethyl-	<1			
γ,γ-Dimethyl-	2.8 (1.8)	(0.8)		

[a] Present work, in 0.025 *M* hydrochloric acid; values in parenthesis in 1 *N* nitric acid from H. Sibelius, Inaugural dissertation, Lund, 1927, quoted by W. Hückel ["Theoretical Principles of Organic Chemistry," Vol. II, Elsevier, New York, N. Y., 1958, p. 895] as equilibrium constants for cyclization ($1/K_H$).

TABLE II

HYDROLYSIS OF VALEROLACTONES[a]

Valerolactone	K_H	k_H
	16.3 (10.0)	2.16 (2.38)
β-Methyl-	0.92	1.92
δ-Methyl-	2.64 (3.72)	1.16 (2.07)
β,β-Dimethyl-	0.090	0.734
δ,δ-Dimethyl-	2.31 (3.0)	0.125 (0.155)

[a] All data at 25°, l. mole^{-1} min.$^{-1}$; present work in 0.020 *M* hydrochloric acid; values in parenthesis in 1 *N* nitric acid from H. Sibelius, Inaugural dissertation, Lund, 1927, quoted by W. Hückel ["Theoretical Principles of Organic Chemistry," Vol. II, Elsevier, New York, N. Y., 1958, p. 895] as equilibrium constants for cyclization ($1/K_H$).

In general, substitution, particularly *gem*-disubstitution, increases the rate of ring formation.[4] However, cyclization reactions are usually irreversible, and lactonization is the only simple example of such reactions which are reversible. Here alkylation can effect both the forward and reverse reactions.

γ-Butyrolactones.—The equilibrium constants for hydrolysis (K_H) of the γ-butyrolactones (Table I; K_H = [A]/[L] for L + (H_2O) ⇌ A) decrease with methyl substitution in the order H ≫ γ-CH_3 > β-CH_3 > α-CH_3 ~ γ,γ-$(CH_3)_2$ ≫ α,α-$(CH_3)_2$ ~ β,β-$(CH_3)_2$, the last two lactones being essentially unhydrolyzed. *gem*-Dialkyl effect favoring the cyclized product has been explained[4] as being due to a combination of a favorable enthalpy effect, since the number of gauche interactions in the ring compound is less than in the open-chain derivative, and an entropy effect resulting from increased restriction to internal rotation in the acyclic compound on chain branching. For γ-hydroxy-

(1) The Puerto Rico Nuclear Center is operated for the Atomic Energy Commission by the University of Puerto Rico.

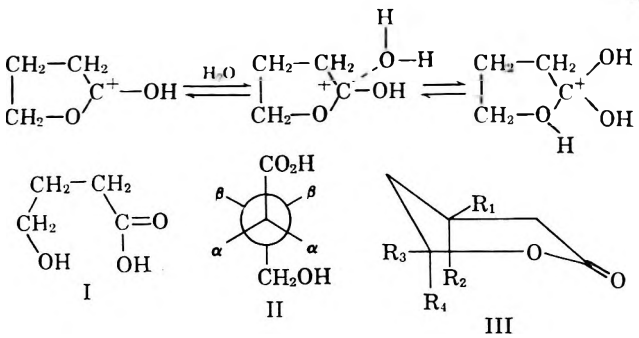
(2) O. H. Wheeler and D. S. Gamble, *J. Org. Chem.*, **26**, 3221 (1961).

(3) (a) H. Shechter, private communication; (b) C. A. Matussak, thesis, Ohio State University, 1957; (c) T. J. Dougherty, thesis, Ohio State University, 1959.

(4) N. L. Allinger and V. Zalkow, *J. Org. Chem.*, **25**, 701 (1960).

butyric acid (I), substitution on the δ- or β-positions by interfering with either the methylene hydroxy or carboxyl group (II) will favor cyclization. In the cyclized product, the methyl groups can be accommodated in a near-planar five-membered ring without seriously increasing the nonbonded interactions.[5] In the case of γ-substitution, interference with the carboxyl group is much less since the β-methylene group is interposed. The experimental order of equilibrium constants is that expected on the basis of the effects of ring stabilization.

The acid-catalyzed hydrolysis of γ-butyrolactone proceeds by acyl-oxygen fission[6] (AAc2 mechanism), and the most probable mechanism would seem to be a rapid protonation of the carbonyl oxygen atom, followed by a slow attack of a water molecule on the protonated carbonyl carbon atom with rapid ring opening.[7] These reactions are reversible, and the slow step in the acid-catalyzed lactonization is probably the attack of the hydroxyl oxygen atom on the carbon atom of the protonated carboxylic acid group.[8]



The alkaline hydrolysis of γ-butyrolactone[2] is retarded by alkyl substitution, although the over-all rate decrease is only a factor of 4. The transition state for acid hydrolysis only differs from that for alkaline hydrolysis by possesing two additional hydrogen atoms and should have similar steric requirements.[9] Hence the methyl substituted γ-butyrolactones should undergo acid-catalyzed hydrolysis at a slightly slower rate than the parent compound, and γ-methyl-γ-butyrolactone hydrolyzed at 25° at a rate 0.72 that of γ-butyrolactone (k_H, Table I; the ratio in basic hydrolysis was 0.87[2]). Thus the large differences in the equilibrium constants must be due to enhanced rates of cyclization. It can be concluded that alkylation facilitates ring formation *by both increasing the rate of cyclization and decreasing the rate of ring opening, and that the former is the principal effect.* This results from changes in the enthalpy and entropy of activation,[4] paralleling the changes in the equilibrium thermodynamic constants, and has similar origins.

The values of the energy of activation calculated from the Arrhenius equation were found to be 15.3 and 13.9 kcal./mole for γ-butyro- and γ-methyl-γ-butyrolactone, respectively. These are somewhat smaller than previously reported data in stronger acid solution (16.8 kcal./mole for γ-butyrolactone in 1 *N* hydrochloric acid,[10a] and 16.7 kcal./mole for γ-methyl-γ-butyrolactone in 0.1 *N* hydrochloric acid[10b]).

δ-Valerolactones.—The equilibrium constants for hydrolysis of the δ-valerolactones were all decreased by substitution, in the order H >> δ-CH_3 ~ δ,δ-$(CH_3)_2$ > β-CH_3 >> β,β-$(CH_3)_2$. In the open-chain hydroxy acid, β-methyl groups will interfere with carboxylic acid group as in the corresponding γ-hydroxybutyric acid. δ-Substitution, however, will exert less interference, in accordance with the observed order.

The acid-catalyzed hydrolysis of δ-valerolactones presumably follows a similar mechanism to that of γ-butyrolactone, in which the rate-determining step is the attack of a water molecule on the protonated lactone.[7,8] Alkyl substituents near the reaction center will retard this reaction, and such retardation of ring opening has been found in substituted glutaric anhydrides.[11]

The rate constants for hydrolysis of the valerolactones (k_H see Table II) were decreased also by substitution. β-Substitution generally reduces the rates of ring opening.[4,12] However, in this case the over-all reduction in rate for all the lactones was only 1:17 and cannot entirely account for the large differences in the equilibrium constants. In particular, a small rate reduction (1:1.1) occurred for the β-methyl lactone (III, R_1 = CH_3; R_2, R_3, R_4 = H) and a further, slightly, larger reduction for the β,β-dimethyl lactone (III, R_1, R_2 = CH_3; R_3, R_4 = H). Similar results were found for 3-methyl- and 3,3-dimethylglutaric anhydride,[11b] which bear a similar stereochemical relation to the lactones. The large decreases in the values of K_H must thus be due to increases in the rate constants for lactonization (k_L) (K_H = [A]/[L] = k_H/k_L). The smaller rate constant for hydrolysis of δ,δ-dimethyl-δ-valerolactone (III, R_1, R_2 = H; R_3, R_4 = CH_3) probably arose from steric hindrance to approach of a water molecule.

The six-membered (valero-) lactones hydrolyze faster (by *ca.* 100 times; *cf.* Tables I and II) than the corresponding five-membered (butyro-) lactones.[13] This has been attributed to I-strain,[14a] since reactions involving a change in coordination number of 3 to 4 (sp^2 to sp^3 hydrid) proceed more rapidly for six-membered rings.[11a] In addition, the equilibrium constants for hydrolysis of the δ-valerolactones are much larger (again by *ca.* 100 times). However, the rate constants, for lactonization (k_L) are similar (6.35 × 10^{-2} and 13.3 × 10^{-2} l. $mole^{-1}$ $min.^{-1}$, for γ-hydroxybutyric and δ-hydroxyvaleric acid, respectively). The closure of a six-membered ring requires the bringing together of the ends of a longer chain and results in a greater loss of entropy.[14b] On the other hand, the transition state for lactonization of γ-hydroxybutyric acid (*cf.* II) is more strained than the corresponding transition state leading

(5) *Cf.* substituted cyclopentanones, O. H. Wheeler and E. E. Granell de Rodriguez, *J. Org. Chem.*, **29**, 718 (1964).

(6) F. A. Long and L. Friedman, *J. Am. Chem. Soc.*, **72**, 3692 (1950).

(7) A. S. Osborn and E. Whalley, *Trans. Faraday Soc.*, **58**, 2144 (1962).

(8) A referee has indicated that γ,γ-dimethyl-γ-valerolactone and δ,δ-dimethyl-δ-valerolactone may hydrolyze *via* oxygen-alkyl cleavage forming a tertiary carbonium ion (AAL1 mechanism).

(9) *Cf.* J. Hine, "Physical Organic Chemistry," 2nd Ed., McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p. 95.

(10) (a) F. D. Coffin and F. A. Long, *J. Am. Chem. Soc.*, **74**, 5767 (1952); (b) H. S. Taylor and H. W. Close, *J. Phys. Chem.*, **29**, 1085 (1925).

(11) (a) T. C. Bruice and U. K. Pandit, *J. Am. Chem. Soc.*, **82**, 5858 (1960); (b) O. H. Wheeler and M. A. Almeida, *J. Org. Chem.*, **27**, 2448 (1962).

(12) H. K. Hall, Jr., M. K. Brandt and R. M. Mason, *J. Am. Chem. Soc.* **80**, 6320 (1958).

(13) *Cf.* F. Huisgen and H. Ott, *Tetrahedron*, **6**, 253 (1959).

(14) (a) H. C. Brown, J. H. Brewster, and H. Shechter, *J. Am. Chem. Soc.*, **76**, 467 (1954); (b) the formation of cyclopentane from *n*-pentane is favored by some 8 e.u. over the formation of cyclohexane from *n*-hexane, at 25° in the gas phase [C. W. Beckett, K. S. Pitzer, and R. Spitzer, *ibid.*, **69**, 2490 (1947)].

to the six-membered lactone. The ring closure of the monophenyl ester of succinic acid is 230 times as rapid as the glutaric ester,[11a] but this has been attributed to anchimeric assistance from the carboxylate anion.

Experimental

Lactones.—δ-Valerolactone was obtained by depolymerizing its commercially available polymer by distilling with red lead.[15] β-Methyl-δ-valerolactone was a commercial sample (Aldrich Chemical Co.). β,β-Dimethyl-δ-valerolactone was prepared by reduction of β,β-dimethylglutaric anhydride with sodium in ethanol.[16] δ,δ-Dimethyl-δ-valerolactone was prepared by reaction of glutaric anhydride with 2 equiv. of methylmagnesium iodide.[17] The physical constants of the valerolactones are given in Table III. The γ-butyrolactones were those used in a previous study.[2]

TABLE III

PHYSICAL CONSTANTS OF VALEROLACTONES[a]

Valerolactone	B.p., °C. (mm.)	$n^{25}D$
δ-	65 (3 mm.) [88 (4 mm.)][b]	1.4527 [1.4568[20]][b]
β-Methyl-	77 (8 mm.) [110–111 (15 mm.)][c]	1.4482 [1.4495][c]
δ-Methyl-	95 (9 mm.) [113 (20 mm.)][b]	1.4508 [1.4589[20]][d]
β,β-Dimethyl-	110 (10 mm.) [118–120 (20 mm.)][e]	1.4480
δ,δ-Dimethyl-	96 (5 mm.) [90 (3 mm.)][b]	1.4475 [1.4497[20]][b]

[a] Lit. values in brackets. [b] Ref. 18. [c] R. I. Longley, Jr., and W. S. Emerson, *Org. Syn.*, **35**, 87 (1955). [d] Ref. 19. [e] H. N. Rydon, *J. Chem. Soc.*, 594 (1936).

δ-Methyl-δ-valerolactone.—Ethyl acetoacetate (60 g.) was added to dry ethanol (200 ml.) containing sodium (6.5 g.), and ethyl β-bromopropionate (51 g.) in ethanol (50 ml.) then was added dropwise with stirring. The solution was heated to reflux for 4 hr. and worked up to give diethyl δ-acetoxyglutarate (25 g.), b.p. 138–142° (9 mm.), $n^{25}D$ 1.4361. The ester was refluxed with concentrated hydrochloric acid (250 ml.) for 6 hr. giving 5-ketohexanoic acid (25 g.), b.p. 125–130° (9 mm.), $n^{25}D$ 1.4367. The acid (10 g.) was dissolved in 5% sodium hydroxide (100 ml.) and treated with sodium borohydride (1 g.) in water (10 ml.). The solution was left at room temperature overnight, acidified with concentrated hydrochloric acid, saturated with salt, and extracted continuously with ether to give the lactone, b.p. 95° (9 mm.), $n^{25}D$ 1.4508 (lit. b.p. 113° at 20 mm.[18], $n^{20}D$ 1.4589[19]).

Equilibrium Constants.—The lactone (*ca.* 0.5 g.) was dissolved in 0.025 *M* hydrochloric acid (50 ml.) and immersed in a constant temperature bath at 25.0 ± 0.1° for up to 5 days. Aliquots were withdrawn, diluted with ice–water (20 ml.), and titrated with 0.02 *N* sodium hydroxide, using rapid magnetic stirring to avoid saponification of the lactone. Reproducible results were readily obtained.[20] Some samples were treated with an excess of sodium hydroxide, left at room temperature overnight, and back titrated with hydrochloric acid to determine the purity of the lactone.

Rate Constants.—The kinetic runs were carried out in the same manner by titrating aliquots at intervals of 10 to 60 min. Several aliquots were also left for 3 to 5 days to measure the equilibrium point. The pseudo first-order rate constants were determined from the slope of the linear plot of ln $(\chi_e - \chi)$ against time, using the kinetic relation,[21] $k't = (\chi_e/a) \ln [\chi_e/(\chi_e - \chi)]$, where a is the initial concentration of lactone, χ_e is the equilibrium concentration of liberated acid, and χ is the concentration of liberated acid at any time t. The rate constants (k_H) are expressed (Tables I and II) as second-order rate constants independent of the concentration of acid catalyst (see Table I; $k_H = k'_H/[H^+]$[18]).

Acknowledgment.—This work was financed in part by a grant from the National Science Foundation.

(15) H. K. Hall, Jr., M. K. Brandt, and R. M. Mason, *J. Am. Chem. Soc.*, **80**, 6420 (1958).
(16) S. S. G. Sicar, *J. Chem. Soc.*, 898 (1928); A. Burger and A. Hafstetter, *J. Org. Chem.*, **24**, 1290 (1959).
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(20) *Cf.* F. A. Long, W. F. McDevit, and F. B. Dunkle, *J. Phys. Chem.*, **55**, 813 (1951).
(21) K. J. Laidler, "Chemical Kinetics," McGraw-Hill Book Co., Inc., New York, N. Y., 1950, p. 19.

Lactam Formation through Aminolysis of α-Amino-γ-butyrolactone. 2-Amino-4-hydroxybutyramides and 1-Aryl 3-Aminopyrrolidin-2-ones

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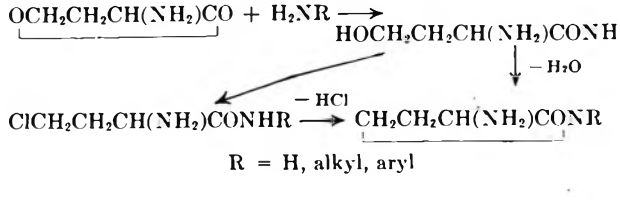
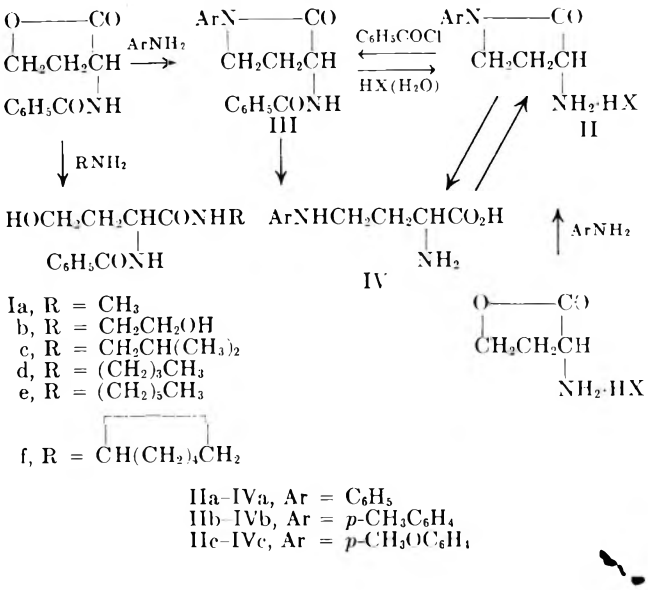
Reactions of α-amino- or α-benzamido-γ-butyrolactone with amines, leading to 1-aryl 3-amino- or 1-aryl 3-benzamidopyrrolidin-2-ones, or to α-benzamido-γ-hydroxybutyr-N-alkyl amides, are described. A mechanism is postulated for direct conversion of α-amino-γ-butyrolactone into 1-aryl 3-aminopyrrolidin-2-one, based on an unfavorable equilibrium for γ-hydroxybutyr-N-aryl amide formation and on irreversible oxygen–alkyl fission to α-amino-γ-arylaminobutyric acid, followed by direct γ-lactamization. Experiments using γ-butyrolactone and δ-valerolactone with aromatic amines demonstrate the dependence of reaction rate and of cyclization on the ring stability of starting and resulting compounds. Cyclization of γ-reactive butyr-N-alkyl amides to a lactonic, iminolactonic, or lactamic (γ-aminating) ring, determined by salt formation ability as well as by ring stability, is studied.

α-Amino-γ-butyrolactone (homoserine lactone) derivatives have been used for γ-amination by O-alkyl fission[1-3] or by γ-halogenation and appropriate subsequent amination.[1,3] In the present work, the application of homoseryl amides as possible intermediates in the γ-amination of α-amino-γ-butyrolactone was studied. Cyclization of such amides into α-amino-γ-butyrolactams in an intramolecular reaction or, indirectly, following γ-halogenation, was examined. The reactions in question might be formally postulated.



(1) M. Frankel, Y. Knobler, and T. Sheradsky *Bull. Res. Council Israel*, **7A**, 173 (1958)
(2) G. Talbot, R. Gaudry, and L. Berlinguet, *Can. J. Chem.*, **36**, 593 (1958).
(3) T. Sheradsky, Y. Knobler, and M. Frankel, *J. Org. Chem.*, **26**, 1482 (1961).

SCHEME I



α-Amino- and α-acylamido-γ-butyrolactone gave with primary aliphatic amines the expected homoseryl amides even at room temperature. With aromatic amines, no reaction was observed at room temperature, and the products obtained at the boiling point of the corresponding amine were 1-aryl 3-aminopyrrolidin-2-ones (IIa,b,c) and 1-aryl 3-benzamidopyrrolidin-2-ones (IIIa,b,c), respectively.

Benzoylation of the α-amino-γ-lactams (aminopyrrolidinones) II gave the formerly obtained α-benzamido-γ-lactams III, which also were debenzoylated to the aminolactams II by refluxing in 12% hydrochloric acid. In addition, the aminolactams II were characterized by their monopicrates and by their α-carbamido or α-phenylthiocarbamido derivatives.

Attempts to cleave the α-amino-γ-aryl butyrolactams (II) by heating in reflux concentrated hydrochloric, hydrobromic, or sulfuric acid, as well as in aqueous or alcoholic alkali, failed to yield the open α-amino-γ-arylaminobutyric acids, and the starting lactams were recovered. However, the ring fission of the lactams II and III to the acids IVa,b,c, was achieved by hydrolysis with barium hydroxide at 180–200° under a pressure of 12–15 atm. Monopicrates of the α-amino-γ-arylaminobutyric acids (IV) and their ethyl ester dihydrochlorides were prepared. (See Scheme I.)

The γ-N-arylated α,γ-diaminobutyric acids (IV) were cyclized to the α-amino-γ-N-aryl butyrolactams (II) by heating in the respective aromatic amine at reflux temperature without or in the presence of one equivalent of the amine hydrochloride, *i.e.*, under the same conditions as used during formation of the pyrrolidin-2-ones II.

The easy cyclization of the diamino acids IV suggests a formulation of the mechanism for the conversion of the lactones (a) into the lactams (d) *via* O-alkyl fission of the starting lactone (see Scheme II).

The course of the reaction of α-amino-γ-butyrolactone with a primary amine (and probably with other nucleophiles, too) depends upon the position of the equilibrium between the lactone (a) and the products of its O-acyl fission (b or b'). With the strongly basic aliphatic amines, the equilibrium lies far toward the γ-hydroxyamides (b), even at room temperature. On the other hand, with aromatic amines, presumably because of their low basicity and appreciable steric hindrance intensified by retarded C–N rotation, the lactone (a) is the favored side of the equilibrium. For example, α-amino-γ-butyrolactone as well as α-benzamido-γ-butyrolactone were recovered after heating in excess aniline (100°) for the same time period required for lactam formation at 170° (2 hr.). At reflux temperature an irreversible γ-aminolytic cleavage of the lactone (a) took place with aromatic amines, even though this reaction is considered to be slower and to need more drastic conditions[3] than the O-acyl fission. The intermediary α-amino- or α-benzamido-γ-arylaminobutyric acid (c') is unstable at the reflux temperature of the aromatic amine, undergoing the easy cyclization of a γ-arylaminobutyric acid. This cyclization proved to proceed much faster than the O-alkyl fission, and only pyrrolidin-2-one (γ-lactam, d) appeared as the end product.

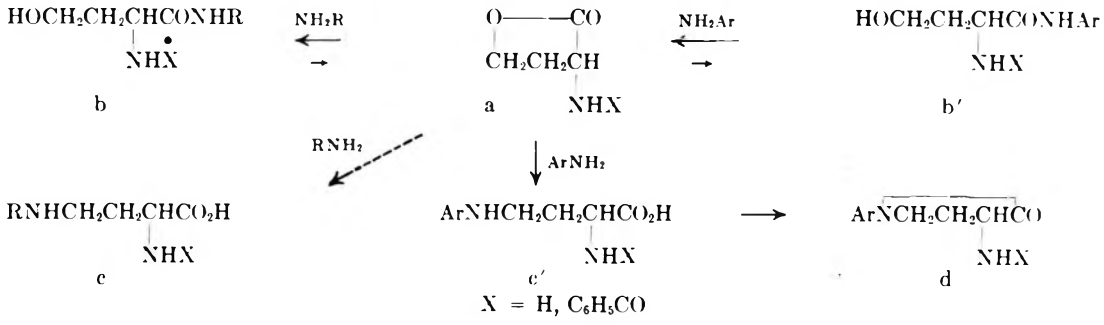
Additional evidence for the above postulated mechanism for γ-lactam formation through γ-aminolytic cleavage, and not through a γ-hydroxybutyr-N-aryl amide, is provided by cyclization of γ-hydroxybutyranilide. After heating in an excess of aniline for 2 hr. at reflux temperature, a small amount of the starting γ-hydroxybutyranilide and almost all of the amine, including that derived from the amide, was recovered; γ-butyrolactone was formed, but no 1-aryl pyrrolidin-2-one was detected.

That the difference in the course of the reaction depends on the alkylic or arylic character of the amine as well as on reaction time has not been considered previously. The formation of N-aryl pyrrolidin-2-ones could be assumed to proceed through γ-hydroxybutyr-N-aryl amides (and not by the γ-alkylic amination postulated above) because their preparation from γ-lactones and aromatic amines was performed under the extremely drastic conditions necessary for the cyclization of γ-hydroxy-N-alkyl amides, *i.e.*, at 215–300°[4,5] under pressure. The γ-hydroxy-N-alkyl amides have been isolated during the process of N-alkyl lactam formation. Thus, γ-lactamization may be considered to consist of dehydration achieved at highly elevated temperatures. However, γ-lactamization of γ-hydroxy-N-alkyl amides involves reversibility to γ-lactones (before irreversible O-alkyl fission); the drastic conditions in the presence of the aliphatic amine are required to force the thermal shift of the equilibrium back to the γ-lactone. The existence of this unfavored side of the equilibrium was demonstrated experimentally: α-carbobenzoxyamino-γ-butyrolactone was isolated after heating α-carbobenzoxyamino-γ-hydroxybutyr-N-benzylamide for several hours in boiling *o*-dichlorobenzene.

The γ-hydroxyamide–γ-butyrolactone equilibrium also was shown by heating α-benzamido-γ-hydroxybutyr-N-alkyl amides in boiling aniline. Fractions of the starting γ-hydroxyamide, of the intermediary α-benzamido-γ-butyrolactone, and of the resulting γ-lactam IIIa were isolated. Since γ-N-alkyl lactam could not be detected, direct lactamization of the γ-hydroxy-N-alkyl amide should not be considered. The formation of 1-phenyl-3-benzamidopyrrolidin-2-one

(4) E. Spaeth and J. Lintner, *Ber.*, **69**, 2727 (1936).
(5) W. Reppe, *Ann.*, **596**, 163 (1955).

SCHEME II



(IIIa) proceeds *via* lactonization and subsequent O-alkyl fission to the γ-arylamino acid.

Additional support for the interpretation of properties and reactions of γ-hydroxyamides and γ-lactams is provided by reference to δ-hydroxyvaleramide, δ-valerolactam, or δ-valerolactone equilibrium, as well as to the stability of homologous rings.

Easy preparation of δ-lactam from δ-hydroxyamide would be expected on the basis of gained stabilization energy contributed by nitrogen carbonyl interaction, giving rise to an *endo* double bond in the six-membered ring.[6] But δ-lactam formation, too, proceeds through an intermediary lactone and, subsequently, through a δ-aminovaleric acid. The δ-lactone–δ-hydroxyamide equilibrium, however, lies much more in favor of the hydroxyamide than the γ-lactone–γ-hydroxyamide one, in accordance with the known instability of δ-valerolactone (*exo* doubly bonded six-membered ring[6]). Therefore, enhanced O-acyl fission of once formed δ-lactone, facilitated by conversion of the trigonal atom of the six-membered ring to a tetrahedral one, might be expected through the intermediary addition compound with ammonia or amine, $\overline{OCH_2CH_2CH_2CH_2C(NH_2)OH}$. In fact, δ-valerolactone was obtained by Strojny, White, and Strojny[7] only by pyrolysis of δ-hydroxyvaleramide and removal of ammonia from the equilibrium.

γ-Butyrolactone is stable enough not to undergo effective O-acyl fission with aromatic amines even at reflux temperature; *e.g.*, after heating for 2 hr. in boiling aniline almost all of the amine and a small amount of the γ-lactam were isolated. By prolonged heating in aniline, γ-butyrolactone suffered slow irreversible γ-aminolytic cleavage to give N-phenylpyrrolidin-2-one. In contrast to that, δ-lactone–δ-hydroxyamide equilibrium lies in favor of the hydroxyamide even with aromatic amines. Heating δ-valerolactone with aniline, anisidine, or toluidine for 2 hr. at reflux temperature of the aromatic amine yielded the respective δ-hydroxy-N-aryl amide. Also, prolonged heating of δ-hydroxyvaler-N-aryl amides under the same conditions did not lead to detectable formation of N-aryl δ-lactam, and the δ-hydroxyamides were recovered. This fact emphasizes the importance of the stability of the intermediate lactone for the performance of subsequent aminolytic O-alkyl fission leading to γ-lactamization.

In addition to the stability of the γ-lactone intermediate (*exo* doubly bonded five-membered ring[6]), gain in stabilization may be expected by cyclization of the γ-arylamino acids to 1-aryl pyrrolidin-2-ones. Unsubstituted and N-alkylated γ-lactams are known to be less stable than the γ-aryl lactams owing to a strong nitrogen carbonyl interaction which gives rise to two adjacent trigonal atoms in the ring.[8] In the 1-aryl pyrrolidin-2-ones, however, nitrogen–aryl interaction should contribute to an exocyclic doubly bonded structure. This stabilization is reflected in the above-mentioned resistance of N-aryl pyrrolidin-2-ones to hydrolysis. Also, Bose and Manhas,[9] by utilizing N-ω-halogenoacylaminomalonic acid esters by the method of Sheehan and Bose,[10] showed that formation of five-membered N-phenyllactams tends to occur preferentially.

When α-amino-γ-butyrolactone hydrochloride and 2,4-dinitroaniline were used, no reaction occurred and both compounds were recovered. This base, as well as 4-nitroaniline, were too weak to react sufficiently to give the amide or the irreversible γ-aminobutyric intermediate. It was reported[11] that acidic catalysis facilitated the formation of some γ-dichlorophenylaminobutyr-N-dichloroanilide (14%) from γ-butyrolactone and 2,4-dichloroaniline. 1-Phenylpyrrolidin-2-one could also be obtained with a similar catalyst.[11]

The reaction of α-benzamido-γ-butyrolactone with a series of primary aliphatic amines was carried out at room temperature to yield the corresponding α-benzamido-γ-hydroxybutyr-N-alkyl amide (Ia–f), and these were not changed when heated at the boiling point of the amine for 2 hr.

Two possible cyclizations of γ-hydroxy-N-alkyl butyramide to γ-lactam or to γ-lactone may be considered. An attack on the slightly polarized γ-carbon atom by amidic or imidic nitrogen is quite unexpected, and no intramolecular dehydration could take place. Moreover, no effective stabilization energy can be gained with formation of the *endo* doubly bonded γ-lactam. The easier attack by γ-hydroxylic oxygen on the carbonylic or hydroxyimidic carbon would lead to expulsion of the amine and to formation of γ-lactone. The replacement of the more basic amine by γ-hydroxyl oxygen must, however, be readily reversible, and γ-hydroxyamide would be the kinetic product. Nevertheless, γ-lactone is the thermodynamically stable product, and its formation from a γ-hydroxyamide could be demonstrated as shown above, in a diluted solution. It was already mentioned that elevation of temperature to 250–300° should favor reversibility to γ-lactones and

(6) H. C. Brown, J. H. Brewster, and H. Schechter, *J. Am. Chem. Soc.*, **76**, 467 (1954).

(7) R. A. Strojny, H. C. White, and E. J. Strojny, *J. Org. Chem.*, **27**, 1241 (1962).

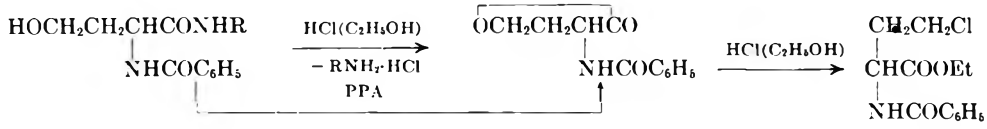
(8) H. K. Hall, Jr., *J. Am. Chem. Soc.*, **80**, 6404 (1958).

(9) A. K. Bose and M. S. Manhas, *J. Org. Chem.*, **27**, 1244 (1962).

(10) J. C. Sheehan and A. K. Bose, *J. Am. Chem. Soc.*, **72**, 5158 (1950).

(11) H. Meerwein, P. Borner, O. Fuchs, H. J. Sasse, H. Schrodt, and J. Spille, *Ber.*, **89**, 2060 (1956).

SCHEME III



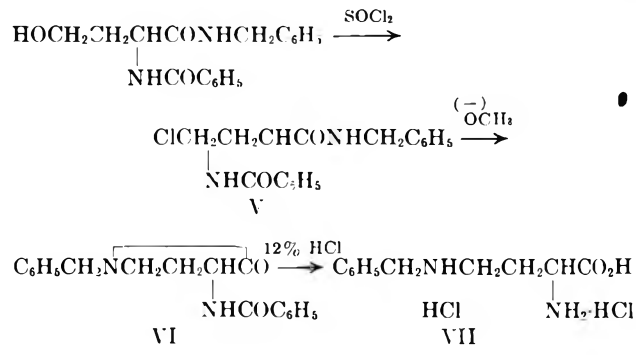
subsequent lactamization, but formation of γ-lactone was ascertained also below 200° even in the presence of excess aliphatic amine used as solvent. Since small amounts of γ-lactone are present, the irreversible γ-aminolytic cleavage proceeds slowly.

Heating of α-benzamido-γ-hydroxybutyr-N-benzylamide in a sevenfold excess of benzylamine under reflux for 35 hr. resulted in 1-benzyl-3-benzamidopyrrolidin-2-one (identical with the product obtained by the procedure described below). Heating of γ-butyrolactone in benzylamine as above leads at first to γ-hydroxybutyr-N-benzylamide (m.p. 72°), but very prolonged treatment (up to a week) yielded increasing amounts (up to 75%) of 1-benzyl-pyrrolidin-2-one (b.p. 148 at 5 mm.).

Reversible O-acyl fission of γ-lactone during cyclization of γ-hydroxyamide by the expelled aliphatic amine can be avoided by neutralization of the base. Lactonization of this kind is illustrated in reactions of γ-hydroxyamides (I) in ethanolic hydrogen chloride or in polyphosphoric acid (PPA). Saturation of an ethanolic solution of α-benzamido-γ-hydroxybutyr-N-alkyl amide (I) with hydrogen chloride under gentle refluxing (2 hr.) results in formation of α-benzamido-γ-halogenobutyric acid ethyl ester, the same product obtained from α-benzamido-γ-butyrolactone in ethanolic hydrogen chloride. α-Benzamido-γ-butyrolactone was obtained from γ-hydroxyamides by heating in polyphosphoric acid (100°).

Competing cyclization of lactamic or lactonic type can also be expected after γ-halogenation of γ-hydroxyamides (I). γ-Halogenobutyr-N-alkyl amides can cyclize to N-alkyl pyrrolidin-2-ones, and, here, iminolactone hydrochloride (2-alkyl iminotetrahydrofuran hydrochloride, $\overline{OCH_2CH_2CH_2C{=}NR}\cdot HCl$, prepared by Stirling[12]) is the competing product. Without addition of a base, the reaction should result in a preponderance of iminolactone due to increased stabilization by its *exo* double bond and to the thermodynamically favored salt formation. Laliberté and Berlinguet,[13] for example, isolated an N-alkyl imino-γ-lactone hydrochloride from an analogous γ-halogeno-α-alkylaminobutyr-N-alkyl amide. In the presence of a strong base, which promotes the reactivity of nitrogen by proton removal from the amidic group[14] and eliminates iminolactone salt formation, cyclization results to give N-alkyl pyrrolidin-2-one. The role of the strong base may be demonstrated in a reaction similar to those of Stirling,[12] *i.e.*, in the cyclization of γ-chlorobutyranilide. Heating in the presence of sodium carbonate (in ethanol–water) for 2 hr. results in two products, 1-phenylpyrrolidin-2-one and γ-hydroxybutyranilide; lactamization in the presence of the weaker base is slower and accompanied by γ-hydroxylation.

SCHEME IV



In practice, α-benzamido-γ-chlorobutyr-N-benzylamide (V) was prepared from γ-hydroxy-N-benzylamide[3] with thionyl chloride, and γ-lactamization to give 1-N-benzyl-3-benzamidopyrrolidin-2-one (VI) was carried out with the aid of sodium methoxide. The 1-N-benzylpyrrolidinone (VI) was used as a model substance because of its easily removable benzylic group. Hydrolysis of α-amino-γ-N-alkyl lactam (VI) with 12% hydrochloric acid yielded α-amino-γ-N-benzylaminobutyric acid dihydrochloride (VII).

Experimental

General Procedure for the Preparation of α-Benzamido-γ-hydroxybutyr-N-alkyl Amides (I, Listed in Table I).—α-Benzamido-γ-butyrolactone[15] (4.1 g., 0.02 mole) was dissolved with shaking in a fivefold excess of the respective amine. The mixture solidified within a few minutes. After standing at room temperature for 2–3 days, ether and petroleum ether (b.p. 40–60°) were added, and the precipitate was crystallized from ethanol.

1-Phenyl-3-aminopyrrolidin-2-one Hydrochloride (IIa).—α-Amino-γ-butyrolactone hydrochloride[16] (4.1 g., 0.03 mole) was heated in aniline (19.5 g., 0.21 mole) and kept under reflux for 2 hr. The solution was cooled, ether was added, and a crude product precipitated. Crystallization from absolute ethanol gave 6.2 g. (97%) of the γ-phenyllactam hydrochloride (IIa), m.p. 225°. The infrared spectrum showed no absorption in the 6.4–6.6-μ range (γ-lactam); λ_{max}^{Nujol} 5.95 (γ-lactam C=O), 3.03–3.13 (NH_3^+), 3.6–4.2 μ (NH_3^+).

Anal. Calcd. for $C_{10}H_{13}ClN_2O$: C, 56.5; H, 6.2; Cl, 16.7; N (Kj.),[17] 13.2; N (V. Sl.),[17] 6.6. Found: C, 55.8; H, 6.3; Cl, 16.9; N (Kj.), 13.15; N (V. Sl.), 6.5.

When the same reactants were heated as above for 0.5 hr. or for 1 hr., only a small amount of the resulting γ-lactam (IIa) could be obtained.

1-*p*-Tolyl-3-aminopyrrolidin-2-one Hydrochloride (IIb).—*p*-Toluidine (16.1 g., 0.15 mole) was heated to melting, α-amino-γ-butyrolactone hydrochloride (4.1 g., 0.03 mole) was added, and the solution was refluxed for 2 hr. The mixture solidified upon cooling. It was washed with many portions of ether in order to remove all the amine. The residue was crystallized twice from ethanol–ether yielding 5.65 g. (83%) of the γ-tolyllactam hydrochloride (IIb), m.p. 245°; λ_{max}^{Nujol} 3.00–3.28 (NH_3^+), 3.8–4.3 (NH_3^+), 5.75 μ (γ-lactam C=O), second amide band absent (γ-lactam).

(12) C. J. M. Stirling, *J. Chem. Soc.*, 255 (1960).
(13) R. Laliberté and L. Berlinguet, *Can. J. Chem.*, **40**, 1960 (1962).
(14) H. W. Heine, P. Love, and J. L. Bove, *J. Am. Chem. Soc.*, **77**, 5420 (1955).
(15) M. Frankel and Y. Knobler, *ibid.*, **80**, 3147 (1958); Y. Knobler and M. Frankel, *J. Chem. Soc.*, 1629 (1958).
(16) M. Frankel, Y. Knobler, and T. Sheradsky, *ibid.*, 3642 (1959).
(17) Kj. stands for Kjeldahl; V. Sl. for Van Slyke.

TABLE I

α-BENZAMIDO-γ-HYDROXYBUTYR-N-ALKYL AMIDES (I)

$HOCH_2CH_2CH(NHCOC_6H_5)CONHR$

R	M.p., °C.	Yield, %	Formula	% C Calcd.	% C Found	% H Calcd.	% H Found	% N Calcd.	% N Found
CH_3[a]	152	76	$C_{12}H_{16}N_2O_3$	61.0	61.2	6.8	6.9	11.8	11.7
CH_2CH_2OH	151	58	$C_{13}H_{18}N_2O_4$	58.7	58.3	6.8	7.1	10.5	10.4
$CH_2CH(CH_3)_2$	142	83	$C_{15}H_{22}N_2O_3$	65.0	64.1	7.9	7.8	10.1	10.1
$(CH_2)_3CH_3$	119	79	$C_{15}H_{22}N_2O_3$	65.0	64.3	7.9	7.6	10.1	9.9
$(CH_2)_5CH_3$	116	80	$C_{17}H_{26}N_2O_3$	66.6	66.3	8.5	8.4	9.1	9.2
$CH(CH_2)_4CH_2$	173	75	$C_{17}H_{24}N_2O_3$	67.1	66.8	7.9	7.9	9.2	9.0

[a] Aqueous methylamine (33%) was used.

TABLE II

1-ARYL 3-BENZAMIDOPYRROLIDIN-2-ONES (III)

$ArNCH_2CH_2CH(NHCOC_6H_5)C{=}O$

Ar	M.p., °C.	Yield, %	Formula	% C Calcd.	% C Found	% H Calcd.	% H Found	% N Calcd.	% N Found
C_6H_5	209	57	$C_{17}H_{16}N_2O_2$	72.9	72.8	5.7	5.9	10.0	10.0
p-$CH_3C_6H_4$	211	78	$C_{18}H_{18}N_2O_2$	73.4	73.5	6.2	6.1	9.5	9.8
p-$CH_3OC_6H_4$	216	75	$C_{18}H_{18}N_2O_3$	69.6	69.1	5.8	5.7	9.0	8.9

TABLE III

1-ARYL 3-CARBAMOYLAMINOPYRROLIDIN-2-ONES

$ArNCH_2CH_2CH(NHCONH_2)C{=}O$

Ar	M.p., °C.	Yield, %	Formula	% C Calcd.	% C Found	% H Calcd.	% H Found	% N Calcd.	% N Found
C_6H_5	310	56	$C_{11}H_{13}N_3O_2$	60.0	60.3	6.0	5.6	19.2	18.7
p-$CH_3C_6H_4$	312	43	$C_{12}H_{15}N_3O_2$	61.8	62.0	6.5	6.6	18.1	18.2
p-$CH_3OC_6H_4$	315	46	$C_{12}H_{15}N_3O_3$	57.8	57.3	6.1	6.1	16.9	16.4

Anal. Calcd. for $C_{11}H_{15}ClN_2O$: C, 58.3; H, 6.7; Cl, 15.6; N (Kj.), 12.4; N (V. Sl.), 6.2. Found: C, 55.6; H, 6.7; Cl, 15.8; N (Kj.), 11.9; N (V. Sl.), 5.9.

1-*p*-Tolyl-3-aminopyrrolidin-2-one hydrobromide was prepared as above, using α-amino-γ-butyrolactone hydrobromide[16] (5.4 g., 0.03 mole). The *p*-tolyl-γ-lactam hydrobromide, 4.9 g. (60%), melted at 230°.

Anal. Calcd. for $C_{11}H_{15}BrN_2O$: N, 10.3; Br, 29.5. Found: N, 9.7; Br, 30.6.

1-*p*-Anisyl-3-aminopyrrolidin-2-one hydrochloride (IIc) was prepared as described for IIb, using *p*-anisidine (18.4 g., 0.15 mole). *p*-Anisyllactam hydrochloride (IIc), 3.3 g. (45%), melted at 240°; λ_{max}^{Nujol} 2.8–3.0 (NH_3^+), 3.6–4.1 (NH_3^+), 5.9 μ (γ-lactam C=O), second amide band absent (γ-lactam).

Anal. Calcd. for $C_{11}H_{15}ClN_2O_2$: C, 54.4; H, 6.2; Cl, 14.6; N (Kj.), 11.5; N (V. Sl.), 5.7. Found: C, 54.5; H, 6.0; Cl, 14.6; N (Kj.), 11.8; N (V. Sl.), 5.6.

1-*p*-Anisyl-3-aminopyrrolidin-2-one hydrobromide was prepared as above, starting with α-amino-γ-butyrolactone hydrobromide (5.4 g., 0.03 mole); *p*-anisyllactam hydrobromide, 3.4 g. (40%), had m.p. 215°.

Anal. Calcd. for $C_{11}H_{15}BrN_2O_2$: N (Kj.), 9.7; N (V. Sl.), 4.8; Br, 27.8. Found: N (Kj.), 9.6; N (V. Sl.), 4.6; Br, 27.8.

General Procedure for the Preparation of 1-Aryl 3-Benzamidopyrrolidin-2-ones (III, Listed in Table II).—α-Benzamido-γ-butyrolactone[15] (4.1 g., 0.02 mole) was heated under reflux for 1 hr. in a fivefold excess of the respective aromatic amine. After cooling, ether and petroleum ether were added and the precipitate was crystallized from ethanol.

1-Aryl 3-Carbamoylaminopyrrolidin-2-ones.—The procedure below is general for the preparation of carbamoyl derivatives of 1-aryl 3-aminopyrrolidin-2-ones (II), listed in Table III.

1-Aryl 3-aminopyrrolidin-2-one hydrochloride (0.008 mole), potassium isocyanate (3.2 g., 0.04 mole), triethylamine (0.808 g., 0.008 mole), and glacial acetic acid (1.2 g., 0.02 mole) were added to 100 ml. of dry dichloromethane. The mixture was stirred at room temperature for 12 hr. Insoluble material was filtered, and the partially precipitated product was taken into ethanol and crystallized on concentration of the solution. Additional crops were obtained by concentration of the dichloromethane mother liquor.

1-Aryl 3-Phenylthiocarbamoylaminopyrrolidin-2-ones.—This procedure is general for the preparation of phenylthiocarbamoyl derivatives of 1-aryl 3-aminopyrrolidin-2-ones (II) listed in Table IV.

1-Aryl 3-aminopyrrolidin-2-one hydrochloride (II, 0.01 mole) was dissolved in 50 ml. of a pyridine–water mixture (1:1); the solution was brought to pH 9–10 by adding 2 *N* sodium hydroxide. Phenyl isothiocyanate (3 ml.) was added gradually with cooling (ice–salt bath), and after a few minutes a heavy precipitate separated. The crude product was washed with water and with petroleum ether and crystallized from benzene–petroleum ether.

Picrates of 1-Aryl 3-Aminopyrrolidin-2-ones (II).—A saturated solution of picric acid in ethanol was added to 1-aryl 3-aminopyrrolidin-2-one hydrochloride (II); the mixture was heated until dissolution and then for a few minutes more. After cooling, the precipitated picrate was collected and recrystallized from ethanol (see Table V).

Benzoylation of 1-Aryl 3-Aminopyrrolidin-2-one Hydrochlorides (II).—α-Amino-γ-lactam hydrochloride (IIa,b,c, 0.005 mole) was dissolved in 2 *N* sodium hydroxide (0.20 g., 0.005 mole) and, to the cooled solution, benzoyl chloride (2.1 g., 0.015 mole) was added in portions during 0.5 hr. The precipitate was washed with water and crystallized from ethyl acetate. These compounds, prepared from the aminolactams (II), were identical with the benzamidolactams (IIIa,b,c), as proved by mixture melting point, infrared spectrum, and elemental analysis.

Attempted Hydrolysis of 1-Aryl 3-Benzamidopyrrolidin-2-ones (II) with Mineral Acids.—α-Benzamido-γ-lactam (IIIa,b,c, 0.005 mole) was heated in refluxing 20% aqueous hydrochloric acid (20 ml.) for 2 hr. The mixture was filtered, and the filtrate was evaporated *in vacuo*. The residue was washed with ether and crystallized from ethanol–ether. Its identity with aminolactam hydrochloride (IIa,b,c) was proved by mixture melting point, infrared spectrum, and elemental analysis.

The same products also were obtained after prolonged refluxing as above.

TABLE IV

1-ARYL 3-PHENYLTHIOCARBAMOYLAMINOPYRROLIDIN-2-ONES

$ArNCH_2CH_2CH(NHCSNHC_6H_5)—C=O$

Ar	M.p., °C.	Yield, %	Formula	% C Calcd.	% C Found	% H Calcd.	% H Found	% N Calcd.	% N Found	% S Calcd.	% S Found
C_6H_5	192	98	$C_{17}H_{17}N_3OS$	65.6	65.8	5.5	5.7	13.5	12.9	10.3	10.3
p-$CH_3C_6H_4$	218	95	$C_{18}H_{19}N_3OS$	66.6	66.5	5.9	6.1	12.9	12.4	9.9	9.4
p-$CH_3OC_6H_4$	212	89	$C_{18}H_{19}N_3O_2S$	63.3	63.4	5.6	5.6	12.3	12.4	9.4	9.2

TABLE V

PICRATES OF 1-ARYL 3-AMINOPYRROLIDIN-2-ONES (II)

$ArNCH_2CH_2CH[NH_2\cdot HOC_6H_2(NO_3)_3]C=O$

Ar	M.p., °C.	Formula	% N Calcd.	% N Found
C_6H_5	243–245	$C_{16}H_{15}N\ O_{11}$	15.5	15.6
p-$CH_3C_6H_4$	250–255	$C_{17}H_{17}N_5O_{11}$	15.0	15.2
p-$CH_3OC_6H_4$	238–240	$C_{17}H_{17}N_5O_{12}$	14.5	14.5

2-Amino-4-arylaminobutyric Acids (IV).—General procedure for the barium hydroxide hydrolytic cleavage of 1-aryl 3-amino- and of 1-aryl 3-benzamido-pyrrolidin-2-ones (II and III) to yield the respective 2-amino-4-arylaminobutyric acids.

1-Aryl 3-aminopyrrolidin-2-one hydrochloride (II, 0.01 mole) or 1-aryl 3-benzamidopyrrolidin-2-one (III, 0.01 mole) and $Ba(OH)_2\cdot 8H_2O$ (10 g., 0.03 mole) were shaken in 100 ml. of water in an autoclave at 200° (12–15 atm.) for 0.5 hr. Shaking was continued for an additional hour without heating. Barium hydroxide and barium carbonate were filtered off and ammonium carbonate (4.5 g.) was added to the filtrate. Precipitated barium carbonate was removed by filtration and the filtrate was concentrated *in vacuo* until partial precipitation of the acid took place. Additional crops separated upon cooling. The 2-amino-4-arylaminobutyric acids (IV) were crystallized from concentrated hot aqueous solutions. Melting points and analytical values are listed in Table VI.

Cyclization of 2-Amino-4-arylaminobutyric Acids (IV). 1-Phenyl-3-aminopyrrolidin-2-one Hydrochloride (IIa).—2-Amino-4-phenylaminobutyric acid (IVa, 0.3 g., 0.0015 mole) was heated in aniline (6.5 g., 0.07 mole) for 0.5 hr. at reflux temperature. One equivalent of aniline hydrochloride (0.19 g., 0.0015 mole) was added, followed by an excess of ether. The crude product was crystallized from ethanol–ether. The 1-phenyl-3-aminopyrrolidin-2-one (IIa) obtained, 0.23 g. (72%), melted at 225°. None of the starting 2-amino-4-arylaminobutyric acid could be recovered.

Anal. Calcd. for $C_{10}H_{13}N_2O$: N (Kj.), 13.2. Found: N (Kj.), 12.9.

The corresponding γ-aryl amino-α-aminolactam hydrochlorides were obtained by a similar procedure from the parent acids, when heated in the respective amine. This aminolactam salt was identical with the 1-aryl 3-aminopyrrolidin-2-one hydrochloride prepared from α-amino-γ-butyrolactone hydrochloride and the aromatic amine (proved by mixture melting point and infrared analysis).

1-*p*-Tolyl-3-aminopyrrolidin-2-one hydrochloride (IIb) had m.p. 245°.

Anal. Calcd. for $C_{11}H_{15}ClN_2O$: N (Kj.), 12.4. Found: N (Kj.), 12.4.

TABLE VI

2-AMINO-4-ARYLAMINOBUTYRIC ACIDS (IV)

$ArNHCH_2CH_2CH(NH_2)CO_2H$

Starting lactam	Ar	Formula	% C Calcd.	% C Found	% H Calcd.	% H Found	% N (Kjeldahl) Calcd.	% N (Kjeldahl) Found	% N (Van Slyke) Calcd.	% N (Van Slyke) Found	M.p., °C.[a]	Yield, %	R_f[b]	Equiv. wt.[c] Calcd.	Equiv. wt.[c] Found
IIa	C_6H_5	$C_{10}H_{14}N_2O_2$	61.8	61.1	7.3	7.2	14.4	14.0	7.2	7.1	240	76.5	0.31	194.2	193.5
IIIa				61.7		7.6		13.8		7.0	245	72.0			
IIb	p-$CH_3C_6H_4$	$C_{11}H_{16}N_2O_2$	63.4	63.2	7.7	7.6	13.4	12.9	6.7	6.6	255	45.0	0.32	208.3	207.3
IIIb				63.5		7.5		13.1		6.9	255	50.0			
IIc	p-$CH_3OC_6H_4$	$C_{11}H_{16}N_2O_3$	58.9	58.2	7.2	7.5	12.5	12.0	6.2	5.9	225	40.0	0.33	224.3	225.0
IIIc				58.5		7.0		12.4		5.9	230	42.0			

[a] The acid melted with decomposition. [b] Butanol–water–acetic acid solution (4:1:1); spots detected by ninhydrin; t.l.c., Kieselgel G. Identical R_f values (±0.01) and equivalent weights (±0.1) were obtained for the acids IV, derived from α-amino-γ-lactams II or α-benzamido-γ-lactams III. [c] The determinations were carried out with a solution of 0.01 *N* $Ba(OH)_2\cdot 8H_2O$, by formol titration according to A. I. Vogel ["Quantitative Organic Analysis," Longmans, Green and Co., New York, N. Y., 1958, p. 409].

Picrates of 2-Amino-4-arylaminobutyric Acids (IV).—The picrates of the amino acids IV, listed in Table VII, were obtained as described for those of the aminolactams II.

TABLE VII

PICRATES OF 2-AMINO-4-ARYLAMINOBUTYRIC ACIDS (IV)

$ArNHCH_2CH_2CHCO_2H$

$NH_2\cdot HOC_6H_2(NO_3)_3$

Ar	M.p., °C.	Formula	% N Calcd.	% N Found
C_6H_5	238	$C_{16}H_{17}N_5O_{12}$	14.9	15.1
p-$CH_3C_6H_4$	246	$C_{17}H_{19}N_5O_{12}$	14.4	14.6
p-$CH_3OC_6H_4$	240	$C_{17}H_{19}N_5O_{13}$	14.0	14.0

2-Amino-4-arylaminobutyric Acid Ethyl Ester Dihydrochlorides.—2-Amino-4-arylaminobutyric acid (IV, 0.3 g.) was dissolved in a solution of 25% hydrogen chloride in ethanol (50 ml.) and left at room temperature for 24 hr. The solvent was evaporated *in vacuo*, and the residue was dissolved as above; this operation was repeated again. The residue was dissolved in ethanol, purified with charcoal, and precipitated by additon of dry ether. The products were crystallized twice from ethanol–ether. The ester dihydrochlorides of the acids (IV) thus obtained are listed in Table VIII.

1-*p*-Anisyl-3-aminopyrrolidin-2-one hydrochloride (IIc) had m.p. 240°.

Anal. Calcd. for $C_{11}H_{15}ClN_2O_2$: N (Kj.), 11.5. Found: N (Kj.), 11.5.

Attempted Reaction of α-Amino-γ-butyrolactone Hydrochloride with Aniline at 100°.—α-Amino-γ-butyrolactone hydrochloride (1.4 g., 0.01 mole) was heated with aniline (6.5 g., 0.07 mole) at 100° (water bath) for 2 hr. After cooling, ether was added and the starting material was recovered (1.2 g., 88%), m.p. 208°.

Anal. Calcd. for $C_4H_8ClNO_2$: N, 10.1. Found: N, 9.9.

The infrared spectrum was identical with that of the starting hydrochloride.

Likewise, α-benzamido-γ-butyrolactone was recovered after similar treatment by precipitation with petroleum ether.

Behavior of γ-Hydroxybutyranilide in Boiling Aniline.—γ-Hydroxybutyranilide (0.6 g., 0.0034 mole) was heated in aniline (1.86 g., 0.02 mole) for 2 hr. under reflux. After cooling, ether and petroleum ether were added; 0.1 g. (16%) of the recovered γ-hydroxyanilide crystallized in the cold overnight. The hydroxyamide was identified by melting point, infrared spectrum, and elemental analysis.

TABLE VIII

2-AMINO-4-ARYLAMINOBUTYRIC ACID ETHYL ESTER DIHYDROCHLORIDES

$ArNHCH_2CH_2CHCOOC_2H_5$
HCl
$NH_2 \cdot HCl$

Ar	M.p., °C.	Yield, %	Formula	% C Calcd.	% C Found	% H Calcd.	% H Found	% N Calcd.	% N Found	% Cl Calcd.	% Cl Found	% OC_2H_5 Calcd	% OC_2H_5 Found
C_6H_5	158	56	$C_{12}H_{20}Cl_2N_2O_2$	48.8	48.8	6.8	6.9	9.5	8.9	24.0	24.1	15.3	15.5
p-$CH_3C_6H_4$	132	45	$C_{13}H_{22}Cl_2N_2O_2$	50.5	50.3	7.2	6.9	9.0	8.7	22.9	22.9	14.5	14.9
p-$CH_3OC_6H_4$	160	42	$C_{13}H_{22}Cl_2N_2O_3$	48.0	47.5	6.8	6.8	8.6	7.9	21.8	21.8	13.8	13.9[a]

[a] Additional value for the p-methoxyanisyl group. Calcd.: OCH_3, 9.5. Found: OCH_3, 9.4.

Hydrogen chloride was passed through the ether–petroleum ether solution, and aniline hydrochloride (2.75 g.) was isolated. The amount of the amine hydrochloride includes the starting aniline (0.02 mole) and the equivalent derived from the cleaved γ-hydroxyanilide (0.0028 mole). γ-Butyrolactone, which remained after evaporation of ether–petroleum ether, could be ascertained by hydroxamic acid test and by its refractive index.

Lactonization of α-Carbobenzoxyamino-γ-hydroxybutyr-N-benzylamide.—α-Carbobenzoxyamino-γ-hydroxybutyr-N-benzylamide[3] (0.5 g., 0.0145 mole) was heated in 50 ml. of *o*-dichlorobenzene for 12 hr. under reflux. After precipitation with petroleum ether, α-carbobenzoxyamino-γ-butyrolactone, 0.23 g. (67%), m.p. 110°,[15] was filtered off and showed λ_{max}^{Nujol} 5.65 μ (γ-lactone C=O).

Anal. Calcd. for $C_{12}H_{13}NO_4$: N, 6.0. Found: N, 6.2.

The starting γ-hydroxyamide could be recovered when heated only for 1 hr. in *o*-dichlorobenzene. After 6 hr., mixtures of γ-hydroxyamide and γ-lactone were obtained.

Treatment of α-Benzamido-γ-hydroxybutyr-N-alkyl Amide with Aniline.—γ-Hydroxy-N-methylamide (Ia, 0.7 g., 0.003 mole) was heated in boiling aniline (3 ml.) for 2 hr. After cooling, ether was added and a precipitate was filtered off. The solid, 0.25 g., (30%) was identical with 1-phenyl-3-benzamidopyrrolidin-2-one (IIIa), as proved by mixture melting point and infrared spectrum. By concentration and further crystallization from ether–petroleum ether, fractions of the starting γ-hydroxyamide (Ia) and of α-benzamido-γ-butyrolactone could be separated and identified as above.

With γ-hydroxy-N-hexylamide (Ie), lactonization was much slower and most of the starting amide was recovered. The first fraction (from ether–petroleum ether) contained a small amount of the γ-lactam (IIIa) and α-benzamido-γ-butyrolactone.

By heating the same γ-hydroxy-N-alkyl amides for 12–15 hr. in an excess of boiling aniline, the formation of γ-lactam (subsequently to γ-lactonization) was increased greatly with respect to both amides. N-Methylamide (Ia) afforded γ-lactam (IIIa) in almost quantitative yield, and the more inhibited N-hexylamide yielded 60% of the lactam (IIIa).

δ-Hydroxyvaler-N-*p*-anisidide.—δ-Valerolactone (5 g., 0.05 mole) and *p*-anisidine (30.8 g., 0.25 mole) were heated under reflux for 2 hr. The reaction mixture solidified upon cooling. Petroleum ether was added and the crude product was crystallized from benzene–petroleum ether. The *p*-anisidide, 10 g. (90%), melted at 105°.

Anal. Calcd. for $C_{12}H_{17}NO_3$: C, 64.6; H, 7.7; N, 6.3. Found: C, 64.3; H, 7.5; N, 6.4.

δ-Hydroxyvaler-N-*p*-toluidide was prepared like *p*-anisidide was from *p*-toluidine (5.4 g., 0.05 mole) and δ-valerolactone (1 g., 0.01 mole). The *p*-toluidide, 2 g. (96%), melted at 115°.

Anal. Calcd. for $C_{12}H_{17}NO_2$: C, 69.5; H, 8.3; N, 6.8. Found: C, 69.5; H, 8.1; N, 7.1.

δ-Hydroxyvaler-*p*-toluidide did not change after heating in an excess of *p*-toluidine for 6–12 hr. at reflux temperature of the solvent.

δ-Hydroxyvaleranilide.—δ-Valerolactone (2.5 g., 0.025 mole) and aniline (11.6 g., 0.125 mole) were heated under reflux for 2 hr. The excess aniline was removed under reduced pressure and the residue was dissolved in ethyl acetate. The solution was clarified with charcoal and a semisolid was precipitated by addition of petroleum ether. It crystallized on storage in the cold for 2–3 days. The δ-hydroxyamide, 3.9 g. (80%), melted at 68–70°.

Anal. Calcd. for $C_{11}H_{15}NO_2$: C, 68.4; H, 7.8; N, 7.2. Found: C, 67.7; H, 7.8; N, 7.0.

δ-Hydroxyvaleranilide did not change after heating for 6–12 hr. in an excess of aniline under reflux.

The three δ-hydroxyvaler-N-aryl amides showed characteristic bands in the infrared spectrum indicating hydroxyl and monosubstituted aromatic amide groups: λ_{max}^{Nujol} 2.9–3.0, 9.4 (–OH); 6.0, 6.5 (CO–NH); 13.3, 14.4 μ (aromatic monosubstituted).

Reactions of γ-Butyrolactone and Aniline.—γ-Butyrolactone (25.8 g., 0.3 mole) and aniline (139.5 g., 1.5 mole) were heated under reflux (150–170°) for nearly 18 hr. with protection against moisture. Aniline and unchanged γ-butyrolactone were distilled under reduced pressure. The semisolid residue was crystallized from petroleum ether, yielding 1-phenylpyrrolidin-2-one, 3.85 g., (8.0%), m.p. 68°. Heating at 150–170° for 72 hr. yielded 35% of the γ-lactam, and for 100 hr., 80%. Heating of the same amounts of γ-butyrolactone and aniline for 120 hr. in the presence of excess water (6 ml.), at lower reflux temperature (120–130°) yielded 60% of the γ-lactam.

Anal. Calcd. for $C_{10}H_{11}NO$: N, 8.7. Found: N, 8.5.

Heating the same quantities of reactants for 2 hr. yielded minimal amounts of N-phenylpyrrolidin-2-one. Spaeth[4] obtained 55% yield at 215° (12 hr.); the high yield (85%) according to Meyer and Vaughan[18] is determined by prolongation of heating time and by elevation of temperature toward the end of the reaction.

Attempted Reaction of α-Amino-γ-butyrolactone Hydrochloride with *p*-Nitroaniline.—α-Amino-γ-butyrolactone hydrochloride (4.1 g., 0.03 mole) and *p*-nitroaniline (20.7 g., 0.15 mole) in 150 ml. of nitrobenzene were heated under reflux for 2 hr. After removal of nitrobenzene by steam distillation, *p*-nitroaniline (19.6 g., 95%), m.p. 148°, was recovered.

Reaction of α-Benzamido-γ-hydroxybutyr-N-alkyl Amide in Ethanolic Hydrogen Chloride. α-Benzamido-γ-chlorobutyric Acid Ethyl Ester.—α-Benzamido-γ-hydroxybutyr-N-hexylamide (Ie) (1.5 g., 0.005 mole) was dissolved in 60 ml. of ethanol, and dry hydrogen chloride was passed through the solution for 2 hr., the temperature being kept near boiling. The mixture was left overnight, a small quantity of inorganic material was filtered off, and the γ-chloro ester was precipitated from the cooled ethanolic solution by portionwise addition of water. The product (0.8 g., 60%) melted at 63°, lit.[19] m.p. 67°.

Anal. Calcd. for $C_{13}H_{16}ClNO_3$: N, 5.2; OC_2H_5, 16.7. Found: N, 5.8; OC_2H_5, 16.3.

The same γ-chloro ester (identified by mixture melting point and infrared spectrum) was obtained when α-benzamido-γ-hydroxybutyramide or N-methylamide (Ia) were heated as described above for N-hexylamide.

Lactonization of γ-Hydroxybutyr-N-alkyl Amide in Polyphosphoric Acid.—α-Benzamido-γ-hydroxybutyr-N-benzylamide (1.6 g., 0.005 mole) in 30 ml. of polyphosphoric acid (from British Drug Houses, 80% P_2O_5) was heated at 100° for 4 hr. The mixture was poured into 100 ml. of ice-water, and the water solution was extracted with chloroform. The chloroform extract was washed first with aqueous sodium bicarbonate and then with water, and dried over anhydrous sodium sulfate. The solution was concentrated and the residue crystallized from ethanol–ether yielding a product, 0.6 g. (58%), melting at 142°. The latter was identified as α-benzamido-γ-butyrolactone by mixture melting point and infrared spectrum.

The same results were obtained with α-benzamido-γ-hydroxybutyr-N-methylamide (Ia) and -N-hexylamide (Ie) with polyphosphoric acid.

γ-Chlorobutyranilide.—γ-Chlorobutyryl chloride (14.1 g., 0.1 mole) was added with stirring to a solution of aniline (9.3 g., 0.1 mole) in dioxane–water (4:1, 100 ml.), and the solution was neutralized with 5% sodium bicarbonate. The precipitated oil was crystallized from benzene–petroleum ether yielding 13.8 g. (70%) of the γ-chloroanilide, m.p. 68–70°.

(18) W. L. Meyer and W. R. Vaughan, *J. Org. Chem.*, **22**, 1554 (1957).

(19) E. P. Painter, *J. Am. Chem. Soc.*, **69**, 232 (1947).

Anal. Calcd. for $C_{10}H_{12}ClNO$: N, 7.1; Cl, 17.9. Found: N, 7.0; Cl, 17.6.

γ-Hydroxybutyranilide.—γ-Chlorobutyranilide (3.9 g., 0.02 mole) was heated in a solution of sodium carbonate (10.6 g., 0.01 mole) in 150 ml. of 33% ethanol until it dissolved. The solution was refluxed for 2 hr. with stirring and, after storage overnight in the cold (0°), sodium carbonate was filtered off and the filtrate was evaporated to dryness under reduced pressure. The solid residue was taken into hot benzene, and the benzene solution was concentrated to a semisolid. Petroleum ether was added, and the precipitate, obtained after storage in the cold (0°) overnight, was recrystallized from benzene–petroleum ether. The γ-hydroxybutyranilide thus obtained, 0.6 g. (17%), melted at 74–75°; λ_{max}^{Nujol} 3.0, 3.1, 3.15 (OH, NH-secondary amide); 6.0, 6.5 (CO–NH); 13.0–13.7, 14.4 μ (monosubstituted aromatic).

Anal. Calcd for $C_{10}H_{13}NO_2$: N, 7.8. Found: N, 7.6.

Evaporation of the petroleum ether precipitation solvent left 1.1 g. (34%) of 1-phenylpyrrolidin-2-one, identified by mixture melting point and infrared spectrum.

α-Benzamido-γ-chlorobutyr-N-benzylamide (V).—α-Benzamido-γ-hydroxybutyr-N-benzylamide (3.2 g., 0.01 mole) was dissolved with cooling (ice–salt bath) in 10 ml. of thionyl chloride. The reaction mixture was stirred, brought to room temperature, and then heated to boiling. After cooling, ether and petroleum ether were added. The separated oil was washed with water and dissolved in ethanol. The product was precipitated by addition of water and crystallized from ethanol, yielding 2.8 g. (85%), m.p. 168°.

Anal. Calcd. for $C_{18}H_{19}ClN_2O_2$: C, 65.3; H, 5.8; N, 8.5; Cl, 10.7. Found: C, 65.5; H, 5.4; N, 8.5; Cl, 11.0.

α-Benzamido-γ-chlorobutyr-N-cyclohexylamide was prepared as above (52%), m.p. 195°.

Anal. Calcd. for $C_{17}H_{23}ClN_2O_2$: C, 63.3; H, 7.2; N, 8.7; Cl, 11.0. Found: C, 64.0; H, 6.8; N, 8.5; Cl, 10.6.

1-Benzyl-3-benzamidopyrrolidin-2-one (VI).—α-Benzamido-γ-chlorobutyr-N-benzylamide (1.6 g., 0.005 mole) was dissolved in 50 ml. of 1 *N* methanolic sodium methoxide and heated for 4 hr. at reflux. The solvent was evaporated, and the residue was washed with water and crystallized from ether–petroleum ether. The product, 1.2 g. (80%), m.p. 160°, was identified by mixture melting point and infrared spectrum.[3]

α-Amino-γ-N-benzylaminobutyric Acid Dihydrochloride (VII).—1-Benzyl-3-benzamidopyrrolidin-2-one (1 g., 0.0034 mole) was heated in 25 ml. of 20% aqueous hydrochloric acid. After cooling, benzoic acid was filtered, and the solution was washed with ether and evaporated. The semisolid residue was crystallized twice from ethanol–ether yielding the product, 0.5 g. (52%), m.p. 185–188°.

Anal. Calcd. for $C_{11}H_{18}Cl_2N_2O_2$: C, 47.0; H, 6.5; N (Kj.), 10.0; N (V. Sl.), 5.0. Found: C, 47.4; H, 6.5; N (Kj.), 10.1; N (V. Sl.), 5.3.

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Organic Polysulfides.[1] IV. Synthesis of Bis(triphenylmethyl) Polysulfides

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Bis(triphenylmethyl) penta-, hexa-, hepta-, and octasulfides were obtained in crystalline state by condensation of the triphenylmethyl hydrodi- or hydrotrisulfide with sulfur di- or monochloride, respectively. For comparison, the bis(triphenylmethyl) mono-, di-, tri-, and tetrasulfides were prepared also by the ordinary methods. The ultraviolet absorption spectra of a series of these polysulfides were measured. No anomaly was observed among the spectra as the number of sulfur atoms increased from one to eight.

In a previous paper,[2] dibenzyl and dibenzhydryl penta- and hexasulfides were prepared by condensation of the corresponding aralkyl hydrodisulfides with sulfur di- and monochloride, respectively.

$$2RSSH + SCl_2 \longrightarrow RSSSSSR \quad (1)$$

$$2RSSH + S_2Cl_2 \longrightarrow RSSSSSSR \quad (2)$$

The corresponding mono-, di-, tri-, and tetrasulfides were prepared also to compare some properties of each series of polysulfides from mono- to hexasulfide. All the results obtained there supported linear sulfur linkages of the polysulfides.

Alkyl hydrotrisulfides, RSSSH, were prepared by Böhme and Zinner[3] as indicated in eq. 3–5, where R represents methyl, ethyl, or benzyl group. In the present paper, this method was applied to prepare triphenylmethyl hydrotrisulfide. Bis(triphenylmethyl) hepta- and octasulfides were prepared by condensation of 2 moles of triphenylmethyl hydrotrisulfide and 1 mole of sulfur di- and monochlorides, respectively. The synthetic method is indicated in eq. 3–7, where R represents the triphenylmethyl group.

$$2CH_3COSH + 2Cl_2 \longrightarrow CH_3COSSCl + CH_3COCl + 2HCl \quad (3)[4]$$

$$CH_3COSSCl + RSH \longrightarrow CH_3COSSSR + HCl \quad (4)[4]$$

$$CH_3COSSSR + C_2H_5OH \longrightarrow RSSSH + CH_3COOC_2H_5 \quad (5)[3]$$

$$2RSSSH + SCl_2 \longrightarrow RSSSSSSSR + 2HCl \quad (6)$$

$$2RSSSH + S_2Cl_2 \longrightarrow RSSSSSSSSR + 2HCl \quad (7)$$

As reported in part I for dibenzyl and dibenzhydryl compounds, bis(triphenylmethyl) penta- and hexasulfides were prepared according to eq. 1 and 2, respectively. The bis(triphenylmethyl) mono-, di-, tri-, and tetrasulfides also were prepared to obtain a series of polysulfides from mono- to octasulfide. All of the polysulfides were obtained in the crystalline state, although dibenzyl and dibenzhydryl hexasulfides could not be obtained in the crystalline state but only in the oily state as reported in a previous paper.

Table I indicates melting points, color, yields, and analytical data of these compounds.

The ultraviolet absorption spectra (Fig. 1) were measured in chloroform solution between 240 and 380 mμ. The strong absorption band with a maximum between 240 and 250 mμ may be ascribed to triphenylmethyl group. The broad absorption band in the range of 290–330 mμ is probably due to linear S–S linkages in the polysulfides, because ultraviolet absorption spectra[2] of dibenzyl and dibenzhydryl polysulfides indicate the similar broad band in the same region. Figure 1 shows that, as the number of sulfur atoms in these polysulfides increases, the absorbance becomes

(1) Part III: T. Nakabayashi and J. Tsurugi, *J. Org. Chem.*, **26**, 2482 (1961).

(2) J. Tsurugi and T. Nakabayashi, *ibid.*, **24**, 807 (1959).

(3) H. Böhme and G. Zinner, *Ann.*, **585**, 142 (1954).

(4) H. Böhme and M. Clement, *ibid.*, **576**, 61 (1952).

TABLE I

MELTING POINTS, COLOR, YIELDS, AND ANALYTICAL DATA OF BIS(TRIPHENYLMETHYL) POLYSULFIDES

Compound	Yield, %[a]	Color	M.p., °C.	Calcd., % C	Calcd., % H	Calcd., % S	Found, % C	Found, % H	Found, % S
Monosulfide	29	White	165 (182 dec.)[b]	87.99	5.83	6.18	87.32	5.75	6.1
Disulfide	70	White	155 dec. (155 dec.)[b]	82.87	5.49	11.64	83.79	5.74	11.3
Trisulfide	74	Faintly yellow	147–148.5	78.31	5.19	16.51	78.05	5.00	16.6
Tetrasulfide	81	Faintly yellow	146–148	74.22	4.92	20.86	74.17	5.13	20.5
Pentasulfide	56	Faintly yellow	146–147	70.54	4.68	24.78	70.38	4.59	24.5
Hexasulfide	82	Faintly yellow	146–147	67.21	4.45	28.33	67.05	4.58	28.9
Heptasulfide	54	Faintly yellow	136–137	64.18	4.25	31.57	64.63	4.37	30.9
Octasulfide	52	Yellow	43–47 dec.	61.41	4.07	34.52	60.62	4.00	34.7

[a] Yields calculated on the basis of the thiol, hydrodisulfide, or hydrotrisulfide. [b] D. Vorländer and E. Mittag, *Chem. Ber.*, 52, 413 (1919).

more intense, and the displacement toward the longer wave length occurs as in the dibenzyl and dibenzhydryl polysulfides.[2] No anomaly was observed among the curves of a series of polysulfides as the number of sulfur atoms increases from one to eight. If the higher polysulfides have any coordinate sulfur atoms in branches, their spectrum would differ from that of the linear one. It is concluded that the polysulfides thus prepared have suffered no rearrangement of sulfur atoms and, therefore, have linear sulfur chains.

It is well-known that primary and secondary thiols are readily oxidized by iodine to the corresponding disulfides. On the other hand, tertiary thiols[5,6] were reported to react with iodine to form sulfenyl iodide.

$$t\text{-RSH} + I_2 \longrightarrow \text{RSI} + \text{HI}$$

However, preliminary work in the present study showed that triphenylmethanethiol did not consume iodine in ethanol. This fact is ascribed to a steric effect, the bulky triphenylmethyl group of triphenylmethanethiol hindering the attack of the iodine molecule. In contrast to triphenylmethanethiol, triphenylmethyl hydrodi- and trisulfides were oxidized readily by the same method to the tetra- and hexasulfides.

Figure 2 shows the relation between the melting point and the number of sulfur atoms in three series of aralkyl polysulfides. The melting points of the dibenzyl- and dibenzhydryl polysulfides were reported in a previous paper[2] and are cited here.

A similar relation is observed between melting point and number of sulfur atoms of benzyl and benzhydryl series, although the increase of melting temperature of dibenzhydryl disulfide is more prominent than that of dibenzyl disulfide. As the sulfur chain of the bis(triphenylmethyl) series increases from one to seven, only a gradual decrease of melting temperature is observed in contrast to the benzyl and benzhydryl series. Figure 2 also shows that the melting temperatures of dibenzyl and dibenzhydryl hexasulfides and of bis(triphenylmethyl) octasulfide decrease suddenly. This sudden decrease as well as the anomalously high melting temperatures of dibenzyl and dibenzhydryl disulfides cannot be interpreted at the present time. Paucity of knowledge on conformations both in the solid and in the liquid state and on possible rotation about S–S bonds of the polysulfides prevents detailed discussion of the results indicated in Fig. 2.

(5) H. Rheinboldt and E. Motzkus, *Chem. Ber.*, **72**, 657 (1939).
(6) I. M. Kolthoff and W. E. Harris, *Anal. Chem.*, **21**, 963 (1949).

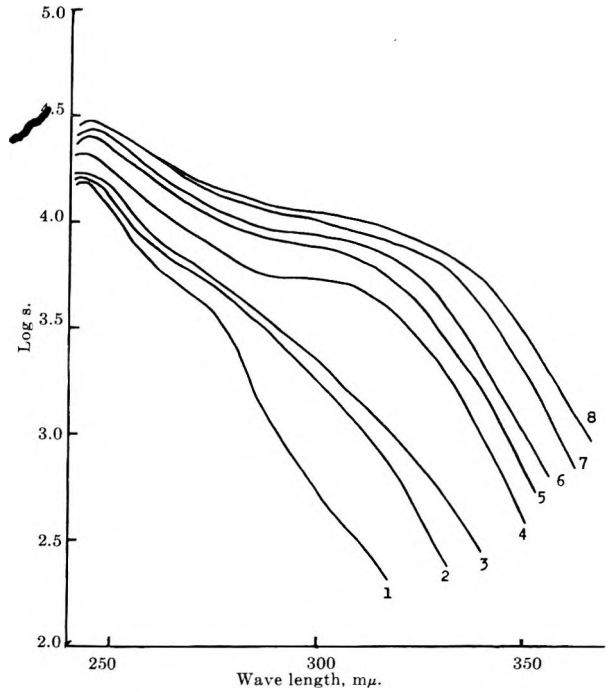

Fig. 1.—Ultraviolet absorption spectra of bis(triphenylmethyl) polysulfides in chloroform solution: 1, mono-; 2, di-; 3, tri-; 4, tetra-; 5, penta-; 6, hexa-; 7, hepta-; and 8, octasulfide.

Experimental

Acetyl sulfenyl chloride,[4] acetyl disulfide,[4] and triphenylmethanethiol[7] were prepared by methods in the literature. All the solvents used here were purified and dried by conventional methods. Sulfur di- and monochlorides were distilled directly before use.

Acetyl Triphenylmethyl Disulfide.—A solution of 82 g. (0.297 mole) of triphenylmethanethiol in a mixture of ether and benzene was added dropwise with stirring in a stream of nitrogen to a solution of 41 g. (0.371 mole) of acetyl sulfenyl chloride in ether. The temperature was kept below 5° by cooling during the reaction. After standing for 2 hr., the mixture was washed with water and aqueous sodium bicarbonate solution, and dried with anhydrous sodium sulfate. After evaporating the solvent, 89 g. (0.254 mole) of white crystals remained which were recrystallized from a mixture of ether and petroleum ether, m.p. 82–82.5° (85%).

Anal. Calcd. for $C_{21}H_{18}OS_2$: S, 18.30. Found: S, 18.10.

Acetyl Triphenylmethyl Trisulfide.—Triphenylmethanethiol was coupled with acetyl disulfide chloride ($CH_3COSSCl$) by the same procedure as for acetyl triphenylmethyl disulfide. A solution of 28 g. (0.101 mole) of triphenylmethanethiol in a mixture of ether (200 ml.) and benzene (70 ml.) was added to 17 g. (0.119 mole) of acetyl disulfide chloride in ether (50 ml.). The yield of white crystals which melted at 127–128° was 33 g. (0.863 mole,

(7) N. Kharasch and H. R. Williams, *J. Am. Chem. Soc.*, **72**, 1843 (1950).

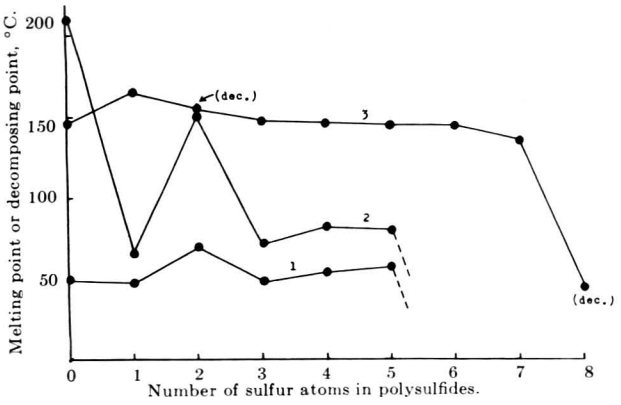

Fig. 2.—Relation between melting point and number of sulfur atoms of polysulfides: 1, dibenzyl; 2, dibenzhydryl; and 3, bis-(triphenylmethyl) series. Melting points of dibenzyl, *sym*-tetraphenylethane, and hexaphenylethane cited from the literature (I. Heilbron and H. M. Bunbury, "Dictionary of Organic Compounds," Oxford University Press, New York, N. Y., 1953).

85%). Recrystallization from a mixture of benzene and ether gave white crystals, m.p. 127.5–128.5°.

Anal. Calcd. for $C_{21}H_{18}OS_2$: S, 25.15. Found: S, 24.7.

Triphenylmethyl Hydrodisulfide.—Ten grams (28.5 mmole) of acetyl triphenylmethyl disulfide and 70 ml. of a mixture of benzene–ethanol (3:4 by vol.) were placed in a four-necked flask equipped with a dropping funnel, thermometer, nitrogen inlet tube, and reflux condenser, the top of which was protected with a calcium chloride tube. In a stream of nitrogen, 25 ml. of dry 5 *N* ethanolic hydrogen chloride was added to the contents of the flask, which was kept at 25–30°. The crystals of acetyl triphenylmethyl disulfide disappeared completely after 4–5 hr. After standing at room temperature, white crystals of triphenylmethyl hydrodisulfide separated from the solution. By evaporating under reduced pressure the solvent and the ethyl acetate which were formed during the reaction, 8 g. (25.9 mmoles, 91%) of a crude product (m.p. 110–114°) was obtained which was recrystallized from a mixture of benzene and ether. This compound had m.p. 114–116° and was easily oxidized by ethanolic iodine to the corresponding tetrasulfide (m.p. 146–148°), which was identified by mixture melting point with a sample prepared from the thiol and sulfur monochloride.

Triphenylmethyl Hydrotrisulfide.—Six grams (15.7 mmoles) of acetyl triphenylmethyl trisulfide in a mixture of benzene (50 ml.) and absolute ethanol (60 ml.) was treated with 15 ml. of dry 5 *N* ethanolic hydrogen chloride. After evaporating the solvent and ethyl acetate, 3 g. (8.8 mmoles, 56%) of the white solid was obtained and recrystallized from a mixture of ether and petroleum ether. This compound, m.p. 65–69°, should be stored in a refrigerator under an inert gas atmosphere. The compound was oxidized by ethanolic iodine to the hexasulfide, which was identified by mixture melting point with an authentic sample described later.

Bis(triphenylmethyl) Monosulfide.[8]—This compound was prepared by condensation of triphenylmethanethiol with triphenylmethyl chloride, was recrystallized from chloroform–ethanol, and had m.p. 165°, lit.[8] m.p. 182° dec.

Bis(triphenylmethyl) Disulfide.[8]—By the same method described in the literature, the disulfide was prepared by condensation of triphenylmethyl sulfenyl chloride with triphenylmethanethiol and was recrystallized from a mixture of benzene–petroleum ether. This compound should be recrystallized with the utmost care, because of its instability to heat or moisture.

Bis(triphenylmethyl) Trisulfide.—To a solution of 5.5 g. (19.9 mmoles) of the triphenylmethanethiol in ether (100 ml.) with cooling and stirring was added dropwise in a stream of nitrogen 1.1 g. (10.1 mmoles) of sulfur dichloride (b.p. 58.5–60°) in 30 ml. of ether at room temperature. After the evolution of hydrogen chloride gas, the solvent was evaporated under reduced pressure. The residue gave 4.3 g. (7.4 mmoles) of crude crystals (m.p. 143–145°) which were recrystallized from a mixture of benzene–petroleum ether.

Bis(triphenylmethyl) Tetrasulfide.—Sulfur monochloride (b.p. 136–137°) was used in place of sulfur dichloride in the above preparation. The crude crystals were recrystallized from a mixture of chloroform–ethanol.

Bis(triphenylmethyl) Pentasulfide.—To a solution of 2.2 g. (7.1 mmoles) of triphenylmethyl hydrodisulfide in a mixture of ether (50 ml.) and benzene (10 ml.) with stirring at room temperature was added dropwise an equivalent amount (0.4 g., 3.9 mmoles) of sulfur dichloride in a stream of nitrogen. After the solvent was evaporated under reduced pressure, 1.3 g. (2.0 mmoles) of the crude product was recrystallized from a mixture of chloroform–ethanol.

Bis(triphenylmethyl) Hexasulfide.—Sulfur monochloride (0.7 g., 5.2 mmoles) was added dropwise to triphenylmethyl hydrodisulfide (3.1 g., 10.1 mmoles) as for the pentasulfide. After evaporating the solvent, the crude compound was obtained in crystalline state and recrystallized from the same solvent mixture.

Bis(triphenylmethyl) Heptasulfide.—To a solution of triphenylmethyl hydrotrisulfide (1.6 g., 4.7 mmoles) in 60 ml. of ether was added slowly 0.23 g. (2.2 mmoles) of sulfur dichloride in 20 ml. of the same solvent. After evaporating the solvent under reduced pressure and adding a small amount of petroleum ether to the solution, cooling gave 0.9 g. (1.3 mmoles) of crude crystals. Recrystallization from a mixture of benzene and petroleum ether gave pure compound.

Bis(triphenylmethyl) Octasulfide.—The synthetic procedure was the same as for the heptasulfide. From 1.4 g. (4.1 mmoles) of triphenylmethyl hydrotrisulfide and 0.3 g. (2.2 mmoles) of sulfur monochloride, 0.8 g. (1.1 mmoles) of crude product was obtained as a yellow solid which was recrystallized from a mixture of ether and petroleum ether in a Dry Ice bath; it decomposed at 43–47° with evolution of gas.

Ultraviolet Absorption Measurements.—The ultraviolet absorption spectra were determined with a Hitachi EPU-2 spectrophotometer, using chloroform as the solvent.

(8) D. Vorländer and E. Mittag, *Chem. Ber.*, **52**, 413 (1919).

Ketenes. II. Cycloaddition of Dialkyl Ketenes to Vinyl Ethers[1]

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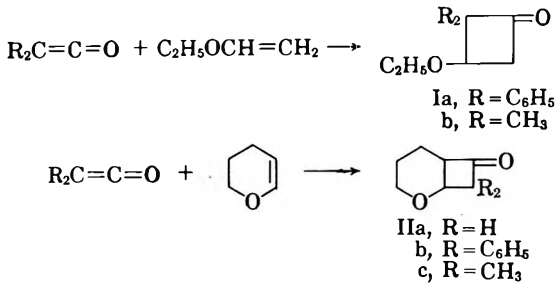
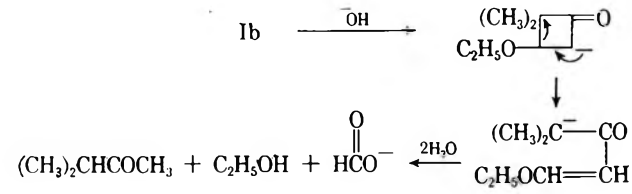
Dimethylketene adds readily to a variety of vinyl ethers to form 3-alkoxy-2,2-dimethylcyclobutanones. Higher dialkyl ketenes, which dimerize much more slowly than dimethylketene, can be forced into cycloaddition to the less reactive allyl ethers and vinyl esters.

The cycloaddition of diphenylketene[3] and dimethylketene[4] to vinyl ethers was first noted by Staudinger in 1920. A few years ago, Hurd and Kimbrough reexamined the cycloadduct of diphenylketene and ethyl vinyl ether, and corrected Staudinger's original structural assignment by demonstrating that the product was 3-ethoxy-2,2-diphenylcyclobutanone (Ia).[5] They also prepared and characterized the corresponding cycloadducts, IIa and IIb, of ketene and diphenylketene with dihydropyran. Here it was apparent that ketene added to the olefinic bond much less readily than diphenylketene, and in this respect the behavior of the two ketenes followed the relative reactivities in cycloadditions to cyclopentadiene.[3,6-8] On the other hand, Kimbrough found that diphenylketene failed to yield cycloadducts with higher alkyl vinyl ethers,[9] which is rather surprising in view of its well-known ease of addition to a variety of other (and presumably less nucleophilic) olefinic compounds.



Dimethylketene is rated as less active than diphenylketene in cycloaddition reactions.[10] For example, dimethylketene does not react with styrene,[4] while diphenylketene forms an adduct.[3,6a] The reaction of dimethylketene with ethyl vinyl ether at −20° required three or four days and was accompanied by some dimerization of the ketene. Neither the yield nor the structure of the product was determined.[4]

In the light of these observations, the ready addition of dialkyl ketenes to a variety of vinyl ethers was somewhat unexpected. The cycloadduct of dimethylketene and ethyl vinyl ether was obtained in 80% yield by adding the ketene to the ether at room temperature. Formulation of the product as 3-ethoxy-2,2-dimethylcyclobutanone (Ib) was compatible with infrared and n.m.r. spectra and with the alkaline degradation to 3-methyl-2-butanone. The mechanism of this degradation probably involves an opening of the ring, followed by a saponification and cleavage similar to that of hydroxymethylene ketone derivatives.[11]



Vinyl ethers with larger alkyl groups, which failed to yield adducts with diphenylketene,[9] reacted readily with dimethylketene to form alkoxy cyclobutanones in good yields. Inert substituents, such as chloro and phenoxy, on the alkyl group had no adverse effect on the reaction. In a vinyl ether containing an amino group, a vigorous acylation of the amine function occurred; the derivative then underwent normal cycloaddition with more dimethylketene. An attempt to use a vinyl ether containing a tertiary amino group gave only a polymer of dimethylketene, in keeping with the well-known catalytic action of trialkyl amines on dimethylketene.[12]

Ethyl propenyl ether formed an adduct with dimethylketene in good yield, but ethyl isobutenyl ether failed to react. The latter addition presumably failed because steric effects override the nucleophilic reactivity of the vinyl ether; the more nucleophilic enamines of analogous structure (isobutenyl amines) react readily with ketenes.[1] It is noteworthy that the vinyl ethers, unlike enamines, did not form 1:2 and 1:3 adducts with dimethylketene; furthermore, the cycloaddition product of ethyl propenyl ether and dimethylketene consisted of two isomers in amounts corresponding to the ratio of *cis–trans* isomers in the starting propenyl ether. These results, indicating a 1:1 stereospecific addition, are too fragmentary to afford any significant conclusions, but they suggest that the cycloaddition of ketenes to vinyl ethers is a

(1) Paper I in this series: R. H. Hasek and J. C. Martin, *J. Org. Chem.*, **28**, 1468 (1962).

(2) To whom inquiries should be sent.

(3) H. Staudinger and E. Suter, *Ber.*, **53**, 1092 (1920).

(4) H. Staudinger and P. J. Meyer, *Helv. Chim. Acta*, **7**, 19 (1924).

(5) C. D. Hurd and R. D. Kimbrough, *J. Am. Chem. Soc.*, **82**, 1373 (1960).

(6) (a) H. Staudinger and A. Rheiner, *Helv. Chim. Acta*, **7**, 8 (1924); (b) J. R. Lewis, G. R. Ramage, J. L. Simonsen, and W. G. Wainwright, *J. Chem. Soc.*, 1837 (1937).

(7) E. H. Farmer and M. O. Farooq, *ibid.*, 1925 (1938); L. I. Smith, C. L. Agre, R. M. Leekley, and W. W. Pritchard, *J. Am. Chem. Soc.*, **61**, 7 (1939); C. S. Marvel and M. I. Kohan, *J. Org. Chem.*, **16**, 741 (1951).

(8) B. T. Brooks and G. Wilbert, *J. Am. Chem. Soc.*, **63**, 870 (1941); A. T. Blomquist and J. Kwiatek, *ibid.*, **73**, 2098 (1951); J. D. Roberts and W. F. Gorham, *ibid.*, **74**, 2278 (1952); H. L. Dryden, Jr., and B. E. Burgert, *ibid.*, **77**, 5633 (1955).

(9) R. D. Kimbrough, Ph.D. thesis, Northwestern University, 1959.

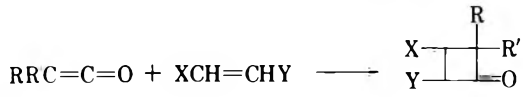
(10) J. D. Roberts and C. M. Sharts, "Organic Reactions," Coll. Vol. 12, R. Adams, Ed., John Wiley and Sons, Inc., New York, N. Y., 1962, p. 27.

(11) E. E. Royals and K. C. Brannock, *J. Am. Chem. Soc.*, **75**, 2050 (1953).

(12) H. Staudinger, F. Felix, P. Meyer, and H. Harder, *Helv. Chim. Acta*, **8**, 322 (1925).

TABLE I

CYCLOADDUCTS OF DIALKYL KETENES



R	R′	X	Y	Method[a]	Yield, %	B.p. °C.	B.p. mm.	$n^{20}D$	% C Calcd.	% C Found	% H Calcd.	% H Found
CH_3	CH_3	OC_2H_5	H	A	80	82–83	38	1.4270	67.6	67.8	9.9	10.0
CH_3	CH_3	OC_2H_5	CH_3	A	64	90–92	34		69.2	68.8	10.3	10.3
CH_3	CH_3	OC_4H_9	H	A	65	72–78	6.5	1.4323	70.6	70.0	10.6	10.6
CH_3	CH_3	$OCH_2CH(CH_3)_2$	H	A	54	70	6.9	1.4287	70.6	70.7	10.6	10.9
CH_3	CH_3	$OCH(C_2H_5)(C_4H_9)$	H	A	56	85	0.7	1.4419	74.3	74.2	11.5	11.6
CH_3	CH_3	OCH_2CH_2Cl	H	A	70	91.5–93.5	4.9	1.4578	54.7	54.6	7.5	7.5[b]
CH_3	CH_3	$OCH_2CH_2OC_6H_5$	H	A	67	118–119	0.5	1.5104	71.8	71.7	7.7	7.8
CH_3	CH_3	$OCH_2CH_2NHCOCH(CH_3)_2$	H	A	80	62–67	0.003–0.007	1.4666	63.5	63.9	9.3	9.3[c]
CH_3	CH_3	$OC_6H_4OCH_3$ (*p*)	H	A	46	134–138	3.5	1.5290	76.4	76.7	7.9	7.8
CH_3	CH_3	$SCH_2CH_2OCOCH_3$	H	A	41	119–124	1.5		55.6	55.5	7.4	7.4[d]
CH_3	CH_3	$-OCH_2CH_2CH_2-$		A	80	89–90	11	1.4632	70.1	70.4	9.2	9.1
CH_3	CH_3	$-OCH(OC_2H_5)CH_2CH_2-$		A	85	116[e]	3		66.6	66.5	9.2	9.2
CH_3	CH_3	OC_2H_5	OC_2H_5	A	20	90–92.5	9.7	1.4355	64.5	63.9	9.7	9.7
C_2H_5	n-C_4H_9	OC_2H_5	H	B	81	80	1.6	1.4443	72.8	72.8	11.1	11.3
C_2H_5	n-C_4H_9	$OCOCH_3$	H	C	30	97	0.5	1.4554	67.9	67.8	9.5	9.4
C_2H_5	n-C_4H_9	$CH_2OC_2H_5$	H	C	31	76	0.4	1.4497	73.5	73.0	11.4	11.4
C_2H_5	n-C_4H_9	$CH_2OC_6H_5$	H	C	15	133–134	0.4		78.4	78.3	9.3	9.4
C_2H_5	i-C_4H_9	$OCOCH_3$	H	C	31	64	0.6	1.4550	67.9	67.7	9.5	9.4
C_2H_5	i-C_4H_9	$-CH_2OCH_2-$		C	30	*f*			73.4	73.8	10.3	10.2
C_6H_5	C_6H_5	$OCOCH_3$	H	A	72	114–115.5[g]			77.1	77.1	5.7	5.8
C_6H_5	C_6H_5	$SCH_2CH_2OCOCH_3$	H	A	87	90–91[h]			70.6	70.7	5.9	6.0

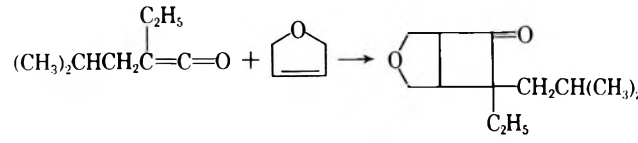
[a] A, reaction in inert solvent at room temp.; B, reactants heated at 100° (no solvent); C, reactants heated at 180° (autoclave). [b] % Cl: calcd., 19.6; found, 19.5. [c] % N: calcd., 6.2; found, 6.1. [d] % S: calcd., 14.8; found, 15.3. [e] Product solidified, m.p. 55° (from ethyl alcohol). [f] Purified by gas–liquid chromatography (see Experimental). [g] Melting point (from benzene–hexane). [h] Melting point (from ethyl alcohol).

more concerted process than the addition to enamines.[13]

Steric effects were also noted in the cycloaddition of dimethylketene to cyclic structures. Dihydropyran was very reactive and gave the bicyclic adduct IIc in excellent yield, but butyl 1-cyclohexen-1-yl ether failed to react.

Although polarity is an important factor in the reactivity of nucleophilic olefins with ketenes, the symmetrical vinyl ether, 1,2-diethoxyethylene, added to dimethylketene to give 3,4-diethoxy-2,2-dimethylcyclobutanone in 20% yield. A measure of the electron-donating effect of the alkoxy group was shown by the cycloaddition of *p*-methoxystyrene to dimethylketene; styrene itself does not react.

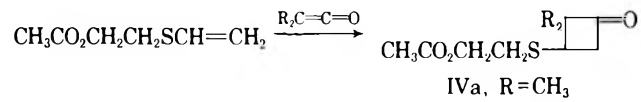
The nucleophilic character of the olefinic linkage is sharply reduced in allyl ethers, and the rapid dimerization of dimethylketene nullified efforts to obtain cycloadducts with such compounds. Higher dialkyl ketenes, due to their much lower rates of dimerization,[16] could be forced into cycloadditions with allyl ethers at elevated temperatures. Butylethylketene, heated with allyl ethyl ether at 180° for 8 hr. gave the adduct in 24% yield. Under similar conditions,



III

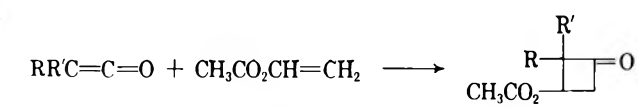
ethylisobutylketene and 2,5-dihydrofuran afforded the bicyclic adduct III in 32% yield.

Vinyl thioethers also added to disubstituted ketenes; 2-(vinylthio)ethyl acetate gave adducts IVa and IVb with dimethylketene and diphenylketene in 41 and 87% yields, respectively.



IVa, R = CH_3
b, R = C_6H_5

Vinyl acetate exhibited a relatively low reactivity, comparable to that of allyl ethers, in its cycloaddition to ketenes. Butylethylketene and ethylisobutylketene, heated with vinyl acetate at 180°, gave the acetoxycyclobutanones Va and Vb in 30% yields. Diphenylketene and vinyl acetate combined very slowly at room temperature to give the cycloadduct Vc in 72% yield.



Va, R = C_2H_5; R′ = C_4H_9
b, R = C_2H_5; R′ = $CH_2CH(CH_3)_2$
c, R = R′ = C_6H_5

(13) It is tempting to suggest a correlation with the question of one- and two-step Diels–Alder mechanisms[14]; however, 1,2-cycloadditions of strongly nucleophilic and electrophilic partners, while they may involve a similar mechanistic question, exhibit fundamental differences from Diels–Alder reactions (*e.g.*, pronounced solvent effects).[15]

(14) For a review, see J. A. Berson and A. Remanick, *J. Am. Chem. Soc.*, **83**, 4947 (1961); C. Walling and H. J. Schugar, *ibid.*, **85**, 607 (1963).

(15) C. A. Stewart, Jr., *ibid.*, **84**, 119 (1962).

(16) The rates of dimerization of dialkyl ketenes fall off rapidly with increase in size and branching of alkyl groups. At room temperature, approximate rate constants ($k \times 10^6$) are dimethyl-, 70; ethylmethyl-, 10; diethyl-, 0.2[17]; butylethyl-, 0.04; and ethylisobutyl-, 0.006.[18]

(17) H. Staudinger, H. Schneider, P. Schotz, and P. M. Strong, *Helv. Chim. Acta*, **6**, 219 (1923).

(18) Unpublished estimates from the authors' laboratory.

Table I is a summary of the data obtained from all the cycloadducts prepared from ketenes and unsaturated ethers during the course of this work.

Experimental

Dialkyl ketenes were prepared by pyrolysis of the corresponding anhydrides.[19] Diphenylketene was prepared by dehydrohalogenation of diphenylacetyl chloride. 1,2-Diethoxyethylene was prepared by the method of McElvain and Stammer[20]; benzyl vinyl ether, by vinylation of benzyl alcohol with acetylene at 150° using potassium hydroxide as a catalyst; allyl vinyl ether, by an exchange reaction between allyl alcohol and butyl vinyl ether[21]; and 2-(vinylthio)ethyl acetate, by acetylation of the alcohol obtained from Rohm and Haas Company. Allyl ethyl ether was obtained from Distillation Products Industries, 2,5-dihydrofuran from General Aniline and Film Corporation, *p*-methoxystyrene from Monomer-Polymer Laboratories, and the remainder of the unsaturated ethers from Union Carbide Chemicals Division of Union Carbide Corporation.

3-Ethoxy-2,2-dimethylcyclobutanone (Ib).—To 960 g. (13.3 moles) of ethyl vinyl ether, stirred at room temperature under a nitrogen atmosphere, 600 g. (8.6 moles) of dimethylketene was added over a period of 4 hr. The mixture was stirred at room temperature for several hours. Distillation through a 12-in. Vigreux column gave 315 g. (4.4 moles) of unchanged ethyl vinyl ether and 975 g. (80%) of 3-ethoxy-2,2-dimethylcyclobutanone, b.p. 82–83° (38 mm.).

The n.m.r. spectrum of Ib[22] contained a single peak at 1.12 (CH_3), a triplet at 1.2 and a quartet at 3.47 (OCH_2CH_3), a pair of doublets at 2.98 and 3.08 (CH_2), and a triplet at 3.82 p.p.m. (CH).

Hydrolysis of 3-Ethoxy-2,2-dimethylcyclobutanone (Ib).—A mixture of 96 g. (0.675 mole) of Ib and 150 ml. of 20% sodium hydroxide solution was refluxed with stirring for 10 hr. The organic layer was extracted with two 400-ml. portions of ether; the extracts were washed with water, dried over anhydrous magnesium sulfate, and distilled through a 10-in. packed column to give 43 g. (74%) of 3-methyl-2-butanone, b.p. 90–91°. The 2,4-dinitrophenylhydrazone of this material melted at 123–124°, lit.[23] m.p. 124.7.

3-(2-Ethylhexyloxy)-2,2-dimethylcyclobutanone.—Under a nitrogen atmosphere, 140 g. (2 moles) of dimethylketene was added to a stirred solution of 312 g. (2 moles) of 2-ethylhexyl vinyl ether in 1000 ml. of ether. The solution was stirred at room temperature for 6 hr. and then distilled through a 12-in. packed column to give 103 g. of recovered vinyl 2-ethylhexyl ether and 253 g. (57%) of 3-(2-ethylhexyloxy)-2,2-dimethylcyclobutanone, b.p. 85° (0.1 mm.).

8,8-Dimethyl-2-oxabicyclo[4.2.0]octan-7-one (IIc).—Approximately 2 moles of dimethylketene was passed into a solution of 252 g. (3 moles) of freshly distilled dihydropyran in 1000 ml. of ether over a period of 1 hr. The solution was stirred for several hours at room temperature and distilled through an 18-in. packed column to give 99.8 g. (1.18 moles) of recovered dihydropyran and 224.3 g. (73%) of 8,8-dimethyl-2-oxabicyclo[4.2.0]octan-7-one, b.p. 89–90° (11 mm.).

2-Butyl-3-(ethoxymethyl)-2-ethylcyclobutanone.—A mixture of 63 g. (0.5 mole) of butylethylketene and 65 g. (0.75 mole) of allyl ethyl ether was heated in an autoclave at 180° for 8 hr. The solution was distilled through a 12-in. packed column to give 43 g. of recovered allyl ethyl ether and 33 g. (31%) of 2-butyl-3-(ethoxymethyl)-2-ethylcyclobutanone, b.p. 76° (0.4 mm.).

3-(2-Acetoxyethylthio)-2,2-diphenylcyclobutanone (IVb).—Admixture of 24 g. (0.12 mole) of diphenylketene and 18 g. (0.12 mole) of 2-(vinylthio)ethyl acetate produced an exothermic reaction which appeared complete in a few hours. The viscous solution slowly crystallized over a period of several days. The yield of crude solid, m.p. 86–89°, was nearly quantitative. An analytical sample, prepared by recrystallization from ethyl alcohol, melted at 90–91°.

N-[2-(2,2-Dimethyl-3-oxocyclobutyloxy)ethyl]-2-methylpropionamide.—Under a nitrogen atmosphere, 136 g. (1.94 moles) of dimethylketene was added to a stirred solution of 84 g. (0.97 mole) of 2-(vinyloxy)ethylamine in 300 ml. of benzene. The reaction of the first mole of dimethylketene was very exothermic and extensive cooling was required. After the addition was complete, the reaction solution was stirred at room temperature for 5 hr., then distilled at 3 mm. to a base temperature of 150°. The residue was distilled in a molecular still to give 175 g. (80%) of N-[2-(2,2-dimethyl-3-oxocyclobutyloxy)ethyl]-2-methylpropionamide, b.p. 62–67° (3–7μ).

7-Ethyl-7-isobutyl-3-oxabicyclo[3.2.0]heptan-6-one (III).—A mixture of 63 g. (0.5 mole) of ethylisobutylketene and 70 g. (1.0 mole) of 2,5-dihydrofuran was heated in an autoclave at 180° for 8 hr. The resulting solution was separated into two fractions by distillation through a 12-in. packed column under reduced pressure. By gas–liquid chromatography (20% Carbowax 20M on Chromosorb P), the first fraction, 35 g., b.p. 69.5–71.5° (0.3 mm.), contained about 70% of III and 30% of 2,4-diethyl-2,4-diisobutyl-1,3-cyclobutanedione (the dimer of ethylisobutylketene); the second fraction, 17 g., b.p. 71.5–77.0° (0.3 mm.), contained 25% of III and 75% of dimer. A pure sample of III was isolated by a preparative-scale chromatography unit (same packing).

3-Oxo-2,2-diphenylcyclobutyl Acetate (Vc).—A mixture of 9.7 g. (0.05 mole) of diphenylketene and 4.3 g. (0.05 mole) of vinyl acetate was sealed in a flask under a nitrogen atmosphere. After several days, the mixture crystallized. The solid was rinsed with cold hexane to give 11.4 g. of crude 3-oxo-2,2-diphenylcyclobutyl acetate. An analytical sample, recrystallized from a mixture of benzene and hexane, melted at 114–115.5°.

Acknowledgment.—The authors thank V. Wilson Goodlett for interpretation of n.m.r. spectra and E. U. Elam and Mary B. Miller for preparation of some compounds.

(19) R. H. Hasek and E. U. Elam (to Eastman Kodak Company), Canadian Patent 618,772 (1961).

(20) S. M. McElvain and C. H. Stammer, *J. Am. Chem. Soc.*, **73**, 915 (1951).

(21) G. A. Weeks and W. J. Grant (to British Oxygen Co., Ltd.), British Patent 709,106 (1954).

(22) N.m.r. spectra were recorded on a Varian A-60 instrument at 60 Mc. Values reported are parts per million (p.p.m.) referred to tetramethylsilane as an internal standard.

(23) E. M. McMahon, J. N. Roper, Jr., W. P. Utermohlen, Jr., R. H. Hasek, R. C. Harris, and J. H. Brant, *J. Am. Chem. Soc.*, **70**, 2976 (1948).

Cycloaddition Reactions of Diphenylketene with Carbon–Nitrogen Double Bonds of Heterocycles

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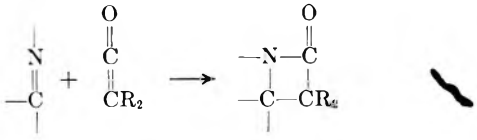
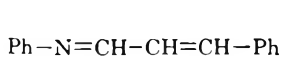
The cycloaddition of diphenylketene to certain oxazoles, thiazoles, and imidazoles has been studied. The reaction of two molecules of diphenylketene and one of the heterocycle produces a piperidinedione. These six-membered ring products are generally observed in the reaction of ketenes with carbon–nitrogen double bonds, except when both the carbon and the nitrogen of the double bond are attached to aromatic groups.

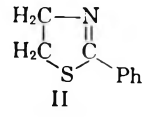
The special case of β-lactam formation from the cycloaddition of ketenes to carbon–nitrogen double bonds has been extensively investigated.[1,2] In most of



these cases, both the carbon and the nitrogen of the double bond are attached to aromatic groups; however, exceptions are known, such as the reaction of I[1] and II.[3]

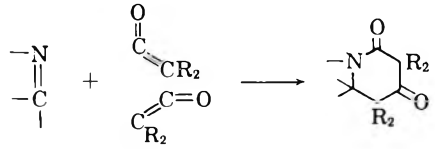


I

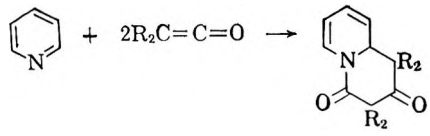


II

The cycloaddition reaction of two molecules of a ketene with a carbon–nitrogen double bond to form a six-membered ring, a piperidinedione, is more general.

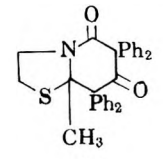


With the above exceptions, this reaction occurs unless both the carbon and the nitrogen of the double bond hold an aromatic group. The most common examples of piperidinedione formation are with open chain compounds containing carbon–nitrogen double bonds, Schiff bases from aliphatic amines, and/or aliphatic aldehydes or ketones.[3,4] Another example of this type of cycloaddition reaction is the reaction of two molecules of a ketene with pyridine or quinoline.[4,5] Here the carbon–nitrogen double bond is part of the aromatic system.

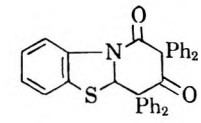


III

Cycloaddition reactions of ketenes with the carbon–nitrogen double bonds of other heterocyclic systems have not been studied extensively. Cycloaddition reactions of several thiazoles with ketenes were investigated in the work on penicillin.[3] In addition to the reaction of II with diphenylketene to form a β-lactam, both 2-methylthiazoline and benzothiazole were found to react with two molecules of diphenylketene to form IV and V, respectively. These reactions leading to IV and V were repeated and confirmed in the present study. Good yields were obtained even in the presence of excess 2-methylthiazoline or benzothiazole.



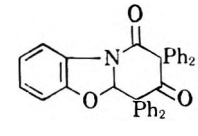
IV



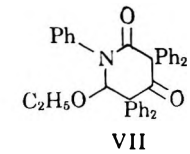
V

The present paper describes the addition of diphenylketene to benzoxazole, benzimidazole, *N*-methylbenzimidazole, and related compounds. In all the reactions studied, the products formed contained new six-membered rings, showing that the heterocyclic carbon–nitrogen double bond had added two molecules of diphenylketene. The structures were supported by analyses, infrared spectra, and analogy to known reactions.

Two molecules of diphenylketene were found to react with one of benzoxazole to produce the adduct VI in 88% yield. Compound VI was obtained in nearly as high a yield based on the diphenylketene when benzoxazole was in excess. Similar results were obtained in the reaction of diphenylketene with ethyl *N*-phenylformimidate (like the oxazoles, the oxygen of this compound is attached to the carbon–nitrogen double bond); the product VII was isolated in 60% yield.



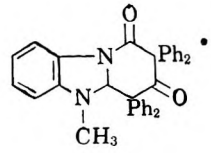
VI



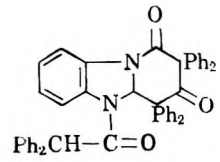
VII

Two molecules of diphenylketene reacted exothermically with *N*-methylbenzimidazole to give the adduct VIII. Benzimidazole reacted with three molecules of diphenylketene to produce IX. The reaction of benzimidazole with one molecule of diphenylketene gave the amide (X), but the yield was low (30%). The infrared spectrum showed that the crude reaction mixture contained unreacted benzimidazole, IX, and perhaps XI. The presence of IX and unchanged benzimid-

(1) H. Staudinger, *Ann.*, **356**, 51 (1970).
(2) J. C. Sheehan and E. J. Corey, *Org. Reactions*, **9**, 395 (1957).
(3) H. T. Clark, J. R. Johnson, and Sir R. Robinson, "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949, pp. 975–991.
(4) H. Staudinger, H. W. Klever, and P. Kober, *Ann.*, **374**, 1 (1910).
(5) H. Staudinger, *Ber.*, **40**, 1145 (1907); J. A. Berson and W. M. Jones, *J. Am. Chem. Soc.*, **78**, 1625 (1956).

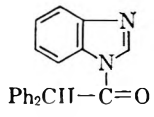


VIII

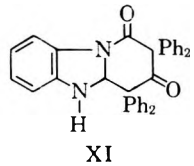


IX

azole indicates that the rate of the cycloaddition forming the six-membered ring is comparable to that of amide formation with benzimidazole, which is not the case with imidazole (see below). The amide (X) was converted into IX by treatment with two molecules of diphenylketene.

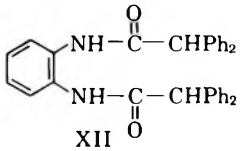


X

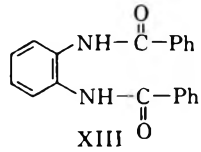


XI

The amide (X) was prepared also from benzimidazole and diphenylacetyl chloride, but the product was contaminated with appreciable amounts of XII. The identity of XII was established by comparison with the product of the reaction of excess diphenylacetyl chloride with *o*-phenylenediamine in pyridine. Acylation of benzimidazole with benzoyl chloride reveals a similar side reaction yielding XIII.[6]

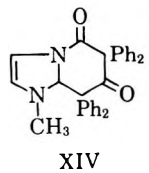


XII

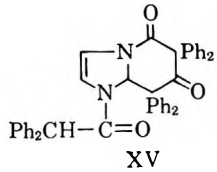


XIII

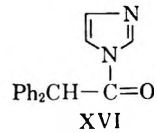
The reaction of diphenylketene with *N*-methylimidazole gave XIV. As expected, imidazole reacted with three molecules of diphenylketene to give XV, and, if only one mole of diphenylketene were used, the expected amide (XVI) was formed in good yield (71%). Here the infrared spectrum of the crude product was identical with that of the purified product, indicating that only one reaction had occurred, amide formation, and that the rate of amide formation was so fast that cycloaddition was not a competing reaction. The amide (XVI) was converted into XV by the addition of two molecules of diphenylketene.



XIV



XV

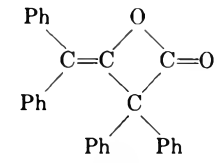


XVI

The amides (X and XVI) could not be synthesized by the action of dicyclohexylcarbodiimide on a tetrahydrofuran solution of the imidazole and diphenylacetic acid.

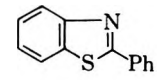
The *N*-(diphenylacetyl)imidazole (XVI) was an active acetylating agent.[7] It gave diphenylacetanilide with aniline at 100° and ethyl diphenylacetate with ethanol at 80°. In moist air it was hydrolyzed to the salt, imidazolium diphenylacetate, which was also obtained from imidazole and diphenylacetic acid.

The cycloaddition of ketenes to enamines is known to proceed readily.[8] In an attempt to obtain cycloaddition at both double bonds of the *N*-methylimidazole, 5 moles of diphenylketene was mixed with 1 mole of *N*-methylimidazole. An exothermic reaction occurred, but the desired cycloaddition at both double bonds of the *N*-methylimidazole was not obtained. In addition to the adduct XIV, another compound was isolated that was identified as 2,2,4,4-tetraphenyl-3-hydroxy-3-butenoic lactone (XVII), the β-lactone dimer of diphenylketene.[9,10] That no cycloaddition of diphenylketene occurs at the carbon–carbon double bond of *N*-methylimidazole is less surprising in view of the fact that no further addition has been reported to occur at the carbon–carbon double bonds in the adducts of a ketene and pyridine (III).

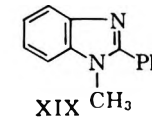


XVII

In 2-phenylbenzothiazole (XVIII) and 1-methyl-2-phenylbenzimidazole (XIX) both the carbon and nitrogen of the carbon–nitrogen double bond are attached to aromatic groups. If reaction occurred, such compounds would be expected to react with one molecule of diphenylketene to give a β-lactam. No products could be isolated from the reaction of either XVIII of XIX with diphenylketene, even when the substances were heated in a sealed tube at 100° for 5 days. The recovery of XVIII was 86%. The recovery of XIX was 63%, and here the diphenylketene was converted to XVII, isolated in 67% yield.



XVIII



XIX

Very little is known about the mechanism of the type of cycloaddition reaction forming the piperidinediones, but the high yield with an excess of the compound containing the carbon–nitrogen double bond is an indication that the reaction does not have the β-lactam as a precursor.

Experimental

All analyses were by Galbraith Laboratories, Inc., Knoxville, Tenn. Melting points are uncorrected. Infrared spectra were measured on a Perkin-Elmer Infracord.

Diphenylketene, b.p. 115–125° at 1 mm., was freshly distilled before use.[11]

***N*-Methylbenzimidazole** was prepared by a modification of the method of Fischer.[12] A sealed tube containing 9.4 ml. of methyl iodide and 17.7 g. of benzimidazole dissolved in 100 ml. of methanol was heated at 100° for an hour. After the cooled tube was opened, the solvent was evaporated and 75 ml. of chloroform was added to the residue. The insoluble material

(6) B. Oddo and F. Ingraffia, *Gazz. chim. ital.*, **62**, 1092 (1932); *Chem. Abstr.*, **27**, 2687 (1933).

(7) E. R. Stadtman and F. H. White, Jr., *J. Am. Chem. Soc.*, **75**, 2022 1953); T. Wieland and G. Schneider, *Ann.*, **580**, 159 (1953); H. A. Staab, *Chem. Ber.*, **89**, 1927 (1956).

(8) R. H. Hasek and J. C. Martin, *J. Org. Chem.*, **28**, 1468 (1963), and references given there.

(9) R. D. Kimbrough, Jr., *ibid.*, **29**, 1246 (1964).

(10) R. Anet, *Chem. Ind.* (London), 1313 (1961).

(11) L. I. Smith and H. H. Hoehn, *Org. Syn.*, **20**, 47 (1940).

(12) O. Fisher and H. Veiel, *Ber.*, **38**, 321 (1905).

was removed, the chloroform was evaporated, and the residue was distilled at 0.2–0.3 mm. A fraction of 8 ml., collected 108–123°, was redistilled to obtain a fraction boiling at 102–106° at 0.2 mm., which solidified in the receiver. After two recrystallizations from pentane, the yield was 2.1 g. (11%), m.p. 61–62° (lit.[12] m.p. 61°); infrared ($CHCl_3$): 3.00, 3.36, 4.00, 6.18, 6.69, 6.88, 7.07, 7.15, 7.53, 7.69, 8.25, 8.70, 9.51, 9.95, 11.24, and 11.56 μ.

Diphenylketene and Benzimidazole (1:1).—A tetrahydrofuran solution of 2.0 g. of diphenylketene and 1.2 g. of benzimidazole was kept under nitrogen at 25° overnight. The solvent was evaporated and the residual oil was treated with boiling pentane. The hot solution was filtered and crystals separated from the pentane on cooling. After another such recrystallization the yield of *N*-(diphenylacetyl)benzimidazole was 0.96 g. (30%), m.p. 72–73°; infrared ($CHCl_3$): 2.90, 3.32, 5.78, 6.22, 6.68, 6.89, 7.32, 7.66, 7.81, 8.69, 9.10, 10.26 and 11.28 μ.

Anal. Calcd. for $C_{21}H_{16}N_2O$: C, 80.8; H, 5.1; N, 9.0. Found: C, 80.7; H, 4.9; N, 9.4.

Diphenylacetyl Chloride and Benzimidazole.—When 1.0 g. of diphenylacetyl chloride[13] was added to a solution of 1.0 g. of benzimidazole in 10 ml. of dry tetrahydrofuran, the mixture warmed and a precipitate formed. The reaction mixture was kept overnight at 25°. The solid benzimidazole hydrochloride was separated and the filtrate was evaporated. The residual oil was boiled with 50 ml. of pentane and the pentane was decanted. The residue was about 0.1 g. of *N*,*N*′-*o*-phenylenebis(diphenylacetamide), m.p. 185–190°. Its melting point was not depressed by mixture with an authentic sample (below). The pentane solution was cooled in ice and the solid that formed was impure *N*-(diphenylacetyl)benzimidazole, 0.52 g., m.p. 55–65°. The cold pentane solution was evaporated, yielding 0.10 g. (8%) of product with m.p. and m.m.p. 70–72°.

N,*N*′-*o*-**Phenylenebis(diphenylacetamide)** (**XII**).—Diphenylacetyl chloride,[13] 1.0 g., was added to a solution of *o*-phenylenediamine in 10 ml. of benzene containing 5 ml. of pyridine. The mixture was heated on a steam bath for 20 min. and poured into 75 ml. of water. The benzene layer was separated, washed with 20 ml. of 5% sodium carbonate, dried ($MgSO_4$), filtered, and evaporated. The crystalline residue was dissolved in 10 ml. of benzene and 20 ml. of pentane was added. The solid was collected on a filter, yielding 0.47 g. (88.%) of product, m.p. 187–192°. Recrystallization from 15 ml. of ethanol yielded 0.33 g. (62%) of product, m.p. 192–193°; infrared ($CHCl_3$): 2.84, 2.96, 3.19, 5.96, 6.24, 6.70, 6.90, 7.70, 8.62, 9.29, and 9.73 μ.

Anal. Calcd. for $C_{34}H_{28}N_2O_2$: C, 82.2; H, 5.7; N, 5.6. Found: C, 82.2; H, 6.0; N, 5.3.

N-(**Diphenylacetyl**)**imidazole from Diphenylketene and Imidazole** (1:1).—To a solution of 1.36 g. of imidazole in 10 g. of dry tetrahydrofuran was added 3.88 g. of diphenylketene. The reaction mixture warmed and the yellow color of the diphenylketene disappeared instantly. Solvent was removed and the solid residue was recrystallized from 15 ml. of benzene. The yield was 4.1 g. (71%), m.p. 127–129. The melting point was not depressed on mixture with the product of diphenylacetyl chloride and imidazole.

N-(**Diphenylacetyl**)**imidazole from Imidazole and Diphenylacetyl Chloride.**—A mixture, 4.60 g. of diphenylacetyl chloride[13] and 1.36 g. of imidazole, was heated on the steam bath for an hour. A solution of the product in 50 ml. of chloroform was extracted with 50 ml. of 5% sodium bicarbonate and was dried ($MgSO_4$). The filtered chloroform solution was evaporated and the residue crystallized. The solid was recrystallized twice from 15 ml. of benzene. The yield was 3.3 g. (65%) of product, m.p. 127–129°; infrared ($CHCl_3$): 2.92, 3.29, 5.73, 6.22, 6.79, 7.28, 7.66, 9.03, 9.29, and 10.31 μ.

Anal. Calcd. for $C_{17}H_{14}N_2O$: C, 77.8; H, 5.4; N, 10.7. Found: C, 77.8; H, 5.1; N, 10.7.

N-(**Diphenylacetyl**)**imidazole and Ethanol.**—A solution of 1.0 g. of *N*-(diphenylacetyl)imidazole in 5 ml. of ethanol was refluxed for 15 min. To the cooled solution was added 5 ml. of water. After 10 hr. the ethyl diphenylacetate was collected, yielding 0.65 g. (71%) of product, m.p. and m.m.p. 56–58°, lit.[14] m.p. 58–59°.

N-(**Diphenylacetyl**)**imidazole and Aniline.**—A solution of 1.0 g. of *N*-(diphenylacetyl)imidazole in 2 ml. of aniline was heated on the steam bath for an hour. The brown reaction mixture was poured into 10 ml. of 5% hydrochloric acid. The precipitate of diphenylacetic anilide was 1.1 g. (100%), m.p. 174–178°, lit.[15] m.p. 180°. The melting point was not depressed by mixture with authentic diphenylacetic anilide.

Hydrolysis of *N*-(**Diphenylacetyl**)**imidazole to Give Imidazolium Diphenylacetate.**—A very finely powdered sample of 1.0 g. of *N*-(diphenylacetyl)imidazole was kept in the air for 2 days during warm humid weather. The melting point of this crude material was 125–135°. Recrystallization from benzene gave m.p. 137–139°. The yield of imidazolium diphenylacetate was 0.60 g. (56%). The melting point of this material was not depressed on mixture with authentic imidazolium diphenylacetate.

Imidazolium Diphenylacetate.—A solution of 0.68 g. of imidazole in 3 ml. of tetrahydrofuran was added to 2.12 g. of diphenylacetic acid. The solvent was evaporated, and the salt crystallized. The yield was 2.8 g. (100%) of product, m.p. 130–135°. Recrystallization from 10 ml. of benzene raised the melting point to 138–139°; infrared ($CHCl_3$): 3.31, 3.85, 5.12, 6.26, 6.39, 6.70, 6.90, and 7.29 μ.

Anal. Calcd. for $C_{17}H_{16}N_2O_2$: C, 72.9; H, 5.7; N, 10.0. Found: C, 72.7; H, 5.7; N, 10.0.

1-Methyl-2-phenylbenzimidazole.[16]—A solution containing 11.64 g. of 2-phenylbenzimidazole, 2.4 g. of sodium hydroxide, and 3.72 ml. of methyl iodide in 75 ml. of methanol was kept for 4 days at 25°. The solvent was evaporated, 75 ml. of chloroform was added, and the insoluble material (sodium iodide and 2-phenylbenzimidazole) was removed by filtration. The filtrate was chromatographed over 100 ml. of neutral alumina in a column with an inside diameter of 2.0 cm. The column was eluted with chloroform and 15-ml. fractions were taken. Fractions 5 and 6 each contained 2.5 g. of product, m.p. 92–95°. These fractions were combined and recrystallized from hexane. The yield of 1-methyl-2-phenylbenzimidazole was 4.25 g. (34%), m.p. 94–96°, lit.[17] m.p. 98°; infrared ($CHCl_3$): 2.94, 3.32, 3.94, 6.20, 6.85, 6.96, 7.25, 7.55, 7.83, 8.69, 8.89, 9.80, 9.95, and 12.22 μ.

Diphenylketene and 1-Methyl-2-phenylbenzimidazole.—A mixture of 0.60 g. of 1-methyl-2-phenylbenzimidazole and 0.60 g. of diphenylketene was sealed in a tube under nitrogen and was heated at 100° for 4 days. The contents of the tube were added to 15 ml. of ethanol, and the solid that formed was collected on a filter. This was XVII, the β-lactone dimer of diphenylketene,[9,10] 0.40 g. (67%), m.p. and m.m.p. 146–148°. The filtrate was evaporated and the residue was triturated with 10 ml. of hexane. The solid was collected on a filter, yielding 0.38 g. (63% recovery) of 1-methyl-2-phenylbenzimidazole, m.p. 85–89°.

Diphenylketene and 2-Phenylbenzothiazole.—A sealed tube containing 2.0 g. of diphenylketene and 2.1 g. of 2-phenylbenzothiazole under nitrogen was heated at 100° for 4 days. The reaction mixture was treated with pentane and 1.8 g. (86% recovery) of 2-phenylbenzothiazole was obtained with m.p. and m.m.p. 109–112°.

Cycloaddition Reactions of Diphenylketone.—A reaction, typical of those outlined in Table I, is described for the preparation of VI.

2,2,4,4-Tetraphenyl-1,2,3,4-tetrahydro-4a*H*-**pyrido[2,1-***b***]benzoxazole-1,3-dione** (**VI**).—A mixture of 2.0 g. of diphenylketene (0.010 mole) and 0.60 g. of benzoxazole (0.005 mole) was kept under nitrogen at 25° for a week, then was made to crystallize by treatment with 5 ml. of ethanol. The solid was rinsed with 5 ml. of ethanol to yield 2.3 g. (88%) of product, m.p. 207–209°. Recrystallization from a mixture of ethyl acetate and ethanol gave a product with m.p. 209–210°; infrared ($CHCl_3$): 3.21, 3.37, 5.60, 6.02, 6.24, 6.76, 6.91, 7.48, 7.93, 9.14, 9.97, 10.99, and 11.60 μ.

Anal. Calcd. for $C_{35}H_{25}NO_3$: C, 82.8; H, 4.9; N, 2.8. Found: C, 82.4; H, 5.2; N, 2.8.

6,6,8,8-Tetraphenyl-8a-methyl-2,3,5,6,7,8-hexahydro-8a*H*-**thiazolo[3,2-***a***]pyridine-1,3-dione** (**IV**).—The infrared spectrum in chloroform showed bands at 3.24, 5.65, 6.10, 6.70, 6.95, 7.66, 8.71, 9.41, 9.81, 10.04, and 10.35 μ.

2,2,4,4-Tetraphenyl-1,2,3,4-tetrahydro-4a*H*-**pyrido[2,1-***b***]benzothiazole-1,3-dione** (**V**).—The infrared spectrum in chloro-

(13) H. Staudinger, *Ber.*, **44**, 1619 (1919).

(14) R. S. Yost and C. R. Hauser, *J. Am. Chem. Soc.*, **69**, 2325 (1947).

(15) F. Klingemann, *Ann.*, **275**, 84 (1893).

(16) The only reference to this compound in Beilstein is O. Fischer, *Ber.*, **25**, 2842 (1892). Here the melting point is given as 170–171°. This has been corrected by R. Weidenhagen,[17] who gives the melting point as 98°.

(17) R. Weidenhagen and J. Train, *ibid.*, **75**, 1936 (1942).

TABLE I

CYCLOADDITION REACTIONS OF DIPHENYLKETENE[a]

Other reactant	Conditions	Solvent of crystallization	Product	Yield, %	M.p., °C.	Formula		Anal., % C	H	N
2-Methylthiazoline	No solvent 25° for 1 wk.	Ethyl acetate–ethanol	IV	73	167–167.5[b]	$C_{32}H_{25}NO_2S$	Calcd.	78.5	5.5	
							Found	78.6	5.5	
Benzothiazole	No solvent 25° for 1 day	Ethyl acetate–ethanol	V	86	163–164[c]	$C_{35}H_{25}NO_2S$	Calcd.	80.4	4.8	2.7
							Found	80.2	5.4	2.5
Benzoxazole	No solvent 25° for 1 wk.	Ethyl acetate–ethanol	VI	88	209–210	$C_{35}H_{25}NO_3$	Calcd.	82.8	4.9	2.8
							Found	82.4	5.2	2.8
Ethyl *N*-phenylformimidate[d]	No solvent 25° for 1 wk.	Ethanol	VII	60	163–164	$C_{37}H_{31}NO_3$	Calcd.	82.6	5.8	2.6
							Found	82.4	6.1	2.6
N-Methylbenzimidazole	In ether 25° for 1 day	Ethyl acetate	VIII	85	206–208	$C_{36}H_{28}N_2O_2$	Calcd.	83.0	5.4	5.4
							Found	82.7	5.4	5.2
Benzimidazole	No solvent 100° for 1 hr.	Triturated with ethyl acetate	IX	83	152–153	$C_{49}H_{36}N_2O_3$	Calcd.	84.0	5.1	4.0
							Found	83.9	5.2	4.1
N-(Diphenylacetyl)benzimidazole	No solvent 100° for 1 hr.	Triturated with ethyl acetate	IX	86	152–153					
N-Methylimidazole	No solvent 25° for 1 day	Ethanol	XIV	64	157–158	$C_{32}H_{26}N_2O_2$	Calcd.	81.7	5.6	5.9
							Found	81.9	5.9	5.8
Imidazole	No solvent 100° for 1 hr.	Triturated with benzene	XV	19	132 dec.	$C_{45}H_{34}N_2O_3$	Calcd.	83.1	5.2	4.3
							Found	83.2	5.1	4.2
N-(Diphenylacetyl)imidazole	In tetrahydrofuran, 25° for 1 day	Triturated with benzene	XV	56	132 dec.					

[a] All reactions were run under nitrogen. [b] Lit.[3] m.p. 160–161°. [c] Lit.[3] m.p. 163–164°. [d] R. M. Roberts and P. J. Vogt, *Org. Syn.*, **35**, 65 (1955).

form showed bands at 3.26, 5.66, 6.10, 6.26, 6.34, 6.71, 6.84, 7.27, 8.10, 8.39, 9.16, 9.45, 9.93, 10.21, 11.05 μ.

1,3,3,5,5-Pentaphenyl-6-ethoxypiperidine-2,4-dione (VII).—The infrared spectrum in chloroform showed bands at 3.27, 5.64, 6.13, 6.26, 6.69, 6.91, 7.10, 7.53, 7.77, 8.10, 8.91, 9.40, and 11.65 μ.

2,2,4,4-Tetraphenyl-5-methyl-1,2,3,4,4a,5-hexahydropyrido[1,2-*a*]benzimidazole-2,4-dione (VIII).—The infrared spectrum in chloroform showed bands at 3.02, 3.32, 3.39, 4.00, 5.70, 6.24, 6.69, 6.88, 7.20, 7.55, 7.80, 8.54, 8.91, and 9.43 μ.

2,2,4,4-Tetraphenyl-5-(diphenylacetyl)-1,2,3,4,4a,5-hexahydropyrido[1,2-*a*]benzimidazole-2,4-dione (IX).—The infrared spectrum in chloroform showed bands at 2.26, 5.66, 5.98, 6.29, 6.76, 6.94, 7.23, 7.53, 8.65, 8.78, 9.24, 9.85, 9.98, and 11.03 μ.

1-Methyl-6,6,8,8-tetraphenyl-1,5,6,7,8,8a-hexahydroimidazo[1,2-*a*]pyridine-5,7-dione (XIV).—The infrared spectrum in chloroform showed bands at 2.98, 3.35, 3.98, 5.73, 6.25, 6.70, 6.91, 7.82, 8.85, 9.29, 9.73, 9.99, 10.35, 10.92, and 11.40 μ.

1-(Diphenylacetyl)-6,6,8,8-tetraphenyl-1,5,6,7,8,8a-hexahydroimidazo[1,2-*a*]pyridine-5,7-dione (XV).—The infrared spectrum in chloroform showed bands at 2.95, 3.25, 5.64, 6.01, 6.25, 6.70, 6.91, 7.20, 8.87, and 9.26 μ.

Acknowledgment.—The author gratefully acknowledges the assistance of Mr. N. Burke, Mr. J. R. Carlile, and Mr. D. F. Hill.

Notes

Reactions of the β-Lactone Dimer of Diphenylketene and Derivatives of α,α,γ,γ-Tetraphenylacetoacetic Acid

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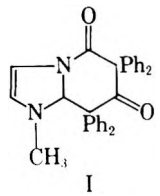
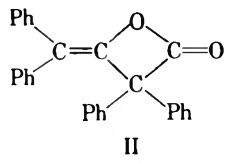
In an investigation of the cycloaddition of diphenylketene to carbon–nitrogen double bonds,[1] the reaction of diphenylketene and *N*-methylimidazole was studied. When 2 moles of diphenylketene was mixed with 1 mole of *N*-methylimidazole, adduct I was formed. In an attempt to obtain cycloaddition at both double bonds of the *N*-methylimidazole, 5 moles of diphenylketene was mixed with 1 mole of *N*-methylimidazole; however, the desired cycloaddition at both double bonds was not obtained. In addition to adduct I, another compound was isolated which was identified as 2,2,4,4-tetraphenyl-3-hydroxy-3-butenoic lactone, the β-lactone dimer of diphenylketene (II) which has been characterized by R. Anet.[2]

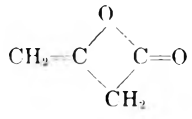


I

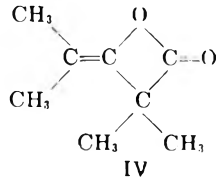


II

Before the identity of II had been established, it was found that ethanol was the solvent of choice for its recrystallization. That II should be stable in boiling ethanol is unexpected, since the β-lactone dimers of ketene[3] (III) and dimethylketene[4] (IV) react with ethanol to give ethyl acetoacetate and ethyl α,α,γ,γ-tetramethylacetoacetate, respectively.

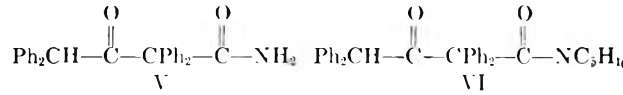


III



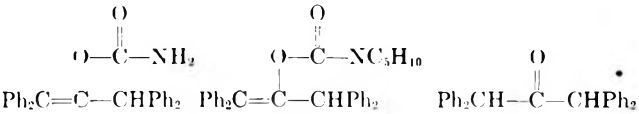
IV

Because of this unexpected behavior, the study of II was continued. One of the characteristic reactions of β-lactone dimers of ketenes, such as III or IV, is with ammonia or amines to produce the corresponding acetoacetamides. The reaction of II with an equimolar quantity of ammonia in absolute ethanol at 25° gave the expected amide V, and reaction of II with excess piperidine at 25° gave the expected piperidide VI. That these products were V and VI rather than the



V VI

isomeric carbamates, VII and VIII, is evident from the fact that they do not decolor permanganate. The infrared spectra are in agreement with the assigned structures. With excess ethanolic ammonia, both II and V are converted to *sym*-tetraphenylacetone (IX) and urea, but no reaction occurred when VI was treated with ammonia under these conditions.

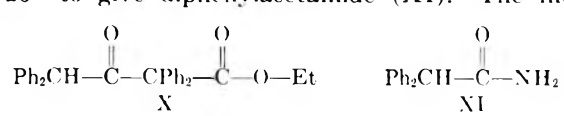


VII VIII IX

The reaction of an amide with ammonia to give urea under such mild conditions is unusual, although similar reactions under more forcing conditions are known. Acetoacetanilide reacts with aniline at 200° to give acetone and *sym*-diphenylurea,[5] and tetraalkylacetoacetamides react with amines to give the corresponding ketones and ureas at 150–175°.[6]

Several other reactions that are characteristic of the β-lactone dimer of ketene (III) and dimethylketene (IV) were studied with II. Both III[7] and IV[4] react readily with dry hydrogen chloride to give the corresponding acetoacetyl chloride. After II was treated with anhydrous hydrogen chloride in ether at 20°, the starting material was recovered almost quantitatively. Both III[3] and IV[4] react readily with aniline at 100° to give the corresponding acetoacetanilide. After II had been heated with aniline at 100°, no reaction product was obtained and the starting material was recovered (73%).

Ethyl α,α,γ,γ-tetraphenylacetoacetate[8] (X) was found to react with two molecules of ammonia in ethanol at 20° to give diphenylacetamide (XI). The inter-



X XI

mediate in this reaction cannot be the amide V, since V with excess ethanolic ammonia yields IX rather than XI. Hence, this reaction must proceed with attack of the ammonia on the keto carbonyl of X giving XI and ethyl diphenylacetate which is converted to XI by the second molecule of ammonia.

The difference in reactivity of the α,α,γ,γ-tetraphenylacetoacetic acid derivatives (V, VI, and X), toward ammonia presents interesting mechanistic possibilities which are to be investigated further.

(1) R. D. Kimbrough, Jr., *J. Org. Chem.*, **29**, 1242 (1964).

(2) R. Anet, *Chem. Ind.* (London), 1313 (1961).

(3) A. B. Boese, *Ind. Eng. Chem.*, **32**, 16 (1940); C. D. Hurd and C. A. Blanchard, *J. Am. Chem. Soc.*, **72**, 1461 (1950).

(4) R. H. Hasek, R. D. Clark, E. U. Elam, and J. C. Martin, *J. Org. Chem.*, **27**, 60 (1962); Technical Data Report X-129, Eastman Chemical Products, Inc., Kingsport, Tenn., 1961, p. 14.

(5) L. Knorr, *Ann.*, **236**, 76 (1886).

(6) E. U. Elam and R. H. Hasek, U. S. Patent 3,072,724 (1963).

(7) C. D. Hurd and C. D. Kelso, *J. Am. Chem. Soc.*, **62**, 1548 (1940).

(8) D. C. Dean, W. B. Dickinson, O. R. Quayle, and C. T. Lester, *ibid.* **72**, 1740 (1950).

Experimental

All analyses were by Galbraith Laboratories, Inc., Knoxville, Tenn. Melting points are uncorrected. Infrared spectra were measured on a Perkin-Elmer Infracord.

2,2,4,4-Tetraphenyl-3-hydroxy-3-butenoic Lactone (II).—Freshly distilled diphenylketene[9] (5.0 g.) was added to 0.43 g. of *N*-methylimidazole.[10] The mixture became hot and was stored at room temperature under nitrogen for a day. (The yield of II varied and the details of processing depend on this yield.) Benzene (15 ml.) was added to the reaction mixture and it was heated gently until all the solid dissolved. The solution was cooled and any solid that formed was filtered off. (This solid is the diphenylketene dimer, tetraphenyl-1,3-cyclobutandione.[11]) Petroleum hexane (20 ml.) was added to the benzene solution. (The solid that forms at this point is mostly the adduct I; however, it may contain appreciable amounts of II.) The solid was collected on a filter, and the filtrate was evaporated to dryness. The residue was primarily II. Since I is more soluble in ethanol than II, II was purified readily by recrystallization from ethanol. The yield of II, m.p. 146–148°, lit.[2] m.p. 148°, varied from 0.3 to 1.5 g. (The identity of the dimer can be established by a strong absorption at 5.4 μ in the infrared.) The observed infrared spectrum checks with that in the literature.[2]

Anal. Calcd. for $C_{28}H_{20}O_2$: C, 86.6; H, 5.2. Found: C, 86.4; H, 5.1.

Reaction of II with Ammonia.—A mixture of 50 ml. of absolute ethanol containing 2.58 mmoles of ammonia and 1.00 g. (2.58 mmoles) of II was kept stoppered at 25° for a week. The solvent was evaporated and the solid residue was recrystallized from ethanol. The yield of V was 0.79 g. (82%), m.p. 174–175°; infrared spectrum ($CHCl_3$): 2.78, 2.88, 3.23, 5.90, 5.94, 6.68, 6.89, 7.45, 9.27, and 9.98 μ.

Anal. Calcd. for $C_{28}H_{23}NO_2$: C, 82.9; H, 5.7; N, 3.4. Found: C, 82.8; H, 5.5; N, 3.3.

Reaction of II with Excess Ammonia.—A mixture of 50 ml. of absolute ethanol saturated with anhydrous ammonia at 0° and 0.50 g. of II was kept stoppered at 25° for 3 days. The volatile material was evaporated and the residue was boiled with 10 ml. of water. The aqueous solution was decanted and the water was evaporated. The yield of urea was 0.05 g. (67%), m.p. 124–131°, m.m.p. 126–133°. When heated in an oil bath at 150–180°, this substance formed biuret and gave off ammonia, identified by its odor and its effect on moist red litmus. The biuret was identified by the characteristic purple color it gave with a solution of cupric ions which was made basic.[12] The residue from which the water was decanted was recrystallized from ethanol to yield 0.35 g. (75%) of *sym*-tetraphenylacetone, m.p. 133–135°, lit.[8] m.p. 133–134°.

Anal. Calcd. for $C_{27}H_{22}O$: C, 89.5; H, 6.1. Found: C, 89.6; H, 6.4.

Reaction of V with Excess Ammonia.—The above procedure with 0.50 g. of V gave essentially identical results.

Reaction of II with Piperidine.—A solution of 0.50 g. of II in 5 ml. of piperidine was kept at 25° for 2 days. The white solid precipitate was filtered and washed with 2 ml. of ethanol. This ethanol and 8 ml. more were added to the filtrate and more crystals formed; the total yield of X was 0.45 g. (75%), m.p. 193–195°. After recrystallization from ethanol the melting point was 195–196°; infrared spectrum ($CHCl_3$): 5.79, 6.16, 6.69, 6.93, 8.01, 8.76, 9.41, and 9.78 μ.

Anal. Calcd. for $C_{33}H_{31}NO_2$: C, 83.7; H, 6.6; N, 3.0. Found: C, 83.5; H, 6.6; N, 2.9.

Reaction of X with Excess Ammonia.—A mixture of 20 ml. of absolute ethanol, saturated with anhydrous ammonia at 0°, and 50 mg. of X[8] was kept stoppered at 25° for 3 days. The volatile material was evaporated and the solid residue was triturated with 2 ml. of ethanol to yield 40 mg. (77%) of diphenylacetamide, m.p. 164–167°, lit.[13] m.p. 168°, m.m.p. 165–167°.

For comparison purposes, *N*-(diphenylacetyl)piperidine was made from diphenylacetyl chloride[14] and excess piperidine; the yield, recrystallized from aqueous ethanol, was 1.0 g. (83%), m.p. 117–118°; infrared spectrum ($CHCl_3$): 6.12, 6.71, 6.95, 7.89, 8.83, 9.30, 9.88, 10.51, and 11.73 μ.

Anal. Calcd. for $C_{19}H_{21}NO$: C, 81.7; H, 7.5; N, 5.0. Found: C, 81.3; H, 7.4; N, 5.0.

(9) L. I. Smith and H. H. Hoehn, *Org. Syn.*, **20**, 47 (1940).
(10) M. Hoering, *Helv. Chim. Acta*, **42**, 1845 (1959).
(11) H. Staudinger, *Ber.*, **44**, 530 (1911).
(12) L. Gattermann, H. Wieland, and T. Wieland, "Die Praxis des organischen Chemikers," Walter DeGruyter and Co., Berlin, 1959, p. 122.
(13) F. Klingemann, *Ann.*, **275**, 85 (1893).
(14) H. Staudinger, *Ber.*, **44**, 1619 (1911).

Lactone Formation in the Free-Radical Addition of Iodoperfluoroalkanes to Alkenoic Acids and Esters

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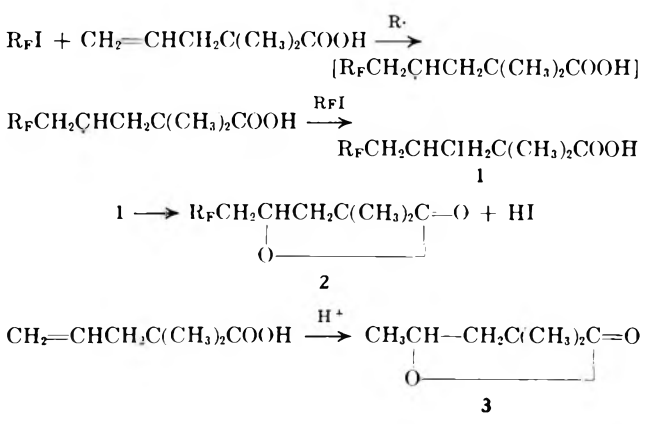
The tendency for acids with unsaturation in the γ- or δ-position to cyclize to lactones is well-known.[1,2] The primary adduct, $R_FCH_2CHI(CH_2)_3COOH$, was obtained[3] by free-radical-induced reaction of iodoperfluoroalkanes (R_FI) with 5-hexenoic acid or esters, using azonitrile initiator at 75°. By contrast, the products from thermally induced reaction of 5-hexenoic acid and R_FI at 175 or 200° included both the primary adduct and the derived δ-lactone. This has precedent in the thermal conversion at 150 to 180° of $CH_3CHBr(CH_2)_2COOC_2H_5$ to ethyl bromide and 4-hydroxypentanoic acid γ-lactone.[4] The formation of *γ-lactone* from $R_FCH{=}CH(CH_2)_3COOH$ (the expected dehydrohalogenation product)[3] or from the primary adduct would have required shifting of the double bond in our case.

In reaction of R_FI with 2,2-dimethyl-4-pentenoic acid, lactone formation was unusually facile, occurring even at 75° with the cleavage of hydrogen iodide. Soon after initiator was added to the 2,2-dimethyl-4-pentenoic acid–R_FI mixture, a reddish color of hydrogen iodide–iodine appeared; samples analyzed by gas–liquid chromatography (g.l.c.) showed both γ-lactones **3** and **2** were present. That γ-lactone rather than δ-



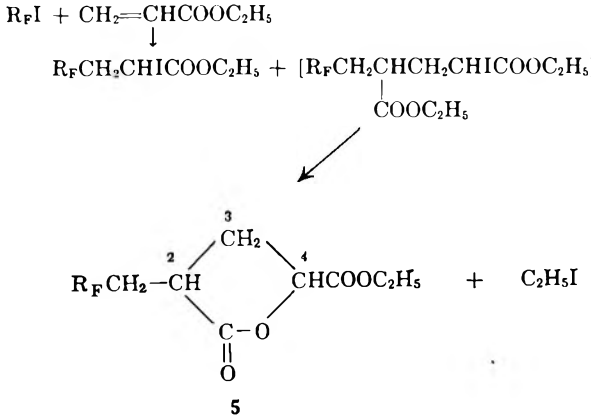
(1) See, for example, L. F. Fieser and Mary Fieser, "Organic Chemistry," 3rd Ed., D. C. Heath and Co., Boston, Mass., 1956, p. 324.
(2) M. F. Ansell and M. H. Palmer, *J. Chem. Soc.*, 2640 (1963).
(3) N. O. Brace, *J. Org. Chem.*, **27**, 4491 (1962).
(4) M. S. Kharasch, P. S. Skell, and P. Fisher, *J. Am. Chem. Soc.*, **70**, 1055 (1948).

lactone was obtained was to be expected from the results of Ansell and Palmer.[2]

Lactone **2** also was formed from reaction of ethyl 2,2-dimethyl-4-pentenoate and R_FI at 70°, with ethyl iodide being cleaved in this instance. An 83% yield of a mixture of $R_FCH_2CHICH_2C(CH_3)_2COOC_2H_5$ (**4**) (34%) and **2** (66%) was isolated by distillation; none of lactone **3** was isolated and g.l.c. showed only a very small amount of **3** was present in the reaction mixture.

This extraordinary cleavage of ethyl iodide was convincing evidence that ring closure is greatly facilitated by *gem*-dimethyl substitution. Brown and van Gulick[5] have suggested that geminate alkyl substitution affects the distribution of molecular conformations, favoring those coiled structures which have minimum nonbonded interactions. A reduction in the activation entropy for the process leading to ring-closed product results. These authors presented some calculations to show that, in spite of an unfavorable equilibrium, the entropy effect may suffice to give a measurable conversion to cyclic product.

A third instance of lactone formation in the free-radical addition of R_FI to unsaturated esters was discovered. 1-Iodoperfluoroheptane and ethyl acrylate at 200° in ethyl acetate solution gave primary adduct and a lactone **5** derived from the 2:1 telomer.[3,6]



5

The infrared spectrum of **5** (and the reaction product mixture) had carbonyl bands at 5.60 and 5.75 μ. The band at 5.60 is characteristic for γ-lactones and the band at 5.75 μ is typical for carboxylic esters (or δ-lactones).[7] An n.m.r. spectrum of **5** showed both the ethyl ester group and a —CH resonance of C-4 split into a doublet and shifted downfield, consistent with the structure anticipated.

Experimental

Source of Starting Materials.—The 1-iodoperfluoroalkanes, azobisisobutyronitrile (AIBN), 5-hexenoic acid, and ethyl acrylate used were those previously described.[3] 2-Heptanone peroxide ("Cadox MAK") was a product of Cadet Chemical Corporation, Burt, New York. 2,2-Dimethyl-4-pentenoic acid from Eastman Chemical Products, Inc., was redistilled, b.p. 82° (4.2 mm.), $n^{25}D$ 1.4318. Infrared spectrum was consistent with structure. Reaction[8] with thionyl chloride gave 2,2-dimethyl-4-pentenoyl chloride, b.p. 69° (50 mm.), $n^{25}D$ 1.3995. The infrared spectrum was consistent. Acid chloride (19.5 g., 0.13 mole) and pyridine (11.9 g., 0.15 mole) were added simultaneously from two dropping funnels to ethanol (9.2 g., 0.2 mole) at 26–40° (ice-bath cooling) while stirring during a 20-min. period. The funnels were rinsed with 10 ml. of diethyl ether, and the white slurry was extracted by shaking with 100 ml. of water. After drying with magnesium sulfate, **ethyl 2,2-dimethyl-4-pentenoate** was distilled in a 12-in. platinum spinning band column (column A), b.p. 78° (39 mm.), $n^{25}D$ 1.4272. An infrared spectrum showed CH_2=CH bands at 3.22, 6.10, and 10.05 μ, and a carbonyl stretching band at 5.75 μ.

Anal. Calcd. for $C_9H_{16}O$: C, 69.19; H, 10.3. Found: C, 69.0; H, 10.3.

Gas chromatography (g.l.c. analysis) was performed using a Perkin-Elmer vapor fractometer at 172°, with 15 p.s.i. of helium applied pressure. A 2-m. column packed with firebrick on which was absorbed 20% of a telomer oil of tetrafluoroethylene and propylene was used. Infrared spectra were obtained with a Perkin-Elmer Model 221 spectrophotometer with the assistance of Dr. R. K. Miller. N.m.r. spectra were taken, using a Varian Associates high-resolution spectrometer, by T. E. Beukelman.

2-[(2–8)-Pentadecafluorooctyl]-4-hydroxy-4-ethoxycarbonylpentanoic Acid γ-Lactone (**5**).—Ethyl acrylate (20.0 g., 0.2 mole), 1-iodoperfluoroheptane (100 g., 0.2 mole), and ethyl acetate (100 ml.) were heated at 200° for 6 hr. while shaking in a 400-ml. Hastelloy C lined steel shaker tube. Distillation in a 30-in. platinum spinning band column (column B) gave (1) a foreshot of ethyl iodide and ethyl acetate, $n^{25}D$ 1.4039, 2.1 g.; (2) ethyl acetate, b.p. 75°, $n^{25}D$ 1.3732, 100 g.; and (3) residual oil (106.2 g.). An infrared spectrum of cut 3 showed an intense C=O stretching band at 5.56 μ (γ-lactone[7]) and an ester band at 5.72 μ. Cut 3 also contained 1-iodoperfluoroheptane. The oil (106 g.), ethanol (100 ml.), and zinc (20–40 mesh, 10.0 g., 0.15 g.-atom) were stirred while hydrogen chloride was bubbled in. Exothermic reaction carried the temperature to reflux; after 4 hr. heating at 80°, solid perfluorotetradecane (23.8 g., 32%) had sublimed into the reflux condenser. The solid was recrystallized from 2-propanol, m.p. 99–101°, and from 1,1,2-trichloro-1,1,2-trifluoroethane, m.p. 102.5–104°.

Anal. Calcd. for $C_{14}F_{30}$: C, 22.78; F, 77.2. Found: C, C, 21.2; F, 75.6; H, <0.1.

After quenching in water, extraction into benzene, and drying, fractionation of the product in column B gave ethyl (4–10)-pentadecafluorodecanoate,[3] b.p. 98–99° (10 mm.), $n^{25}D$ 1.3291, 16.0 g. (17%); and lactone **5**, b.p. 126° (0.5 mm.), 24 g. (22%); leaving a residue (6.2 g.). An infrared spectrum of **5** showed two carbonyl bands at 5.57 and 5.72 μ of equal intensity in carbon tetrachloride or methanol solution. The γ-lactone was recrystallized from cyclohexane and from ethanol, m.p. 83–84.5°. An oil (10%) remained.

Anal. Calcd. for $C_{15}H_{10}F_{15}O_4$: C, 33.35; H, 2.04; F, 52.8; ester number, 208.5. Found: C, 33.4; H, 2.0; F, 52.5; ester number, 201.

An n.m.r. spectrum of **5** at 56.4 Mc. in deuteriochloroform solution gave resonances (tetramethylsilane, internal reference): at −1.30 p.p.m., a triplet (CH_3 of C_2H_5); at −4.25 p.p.m., a 4-line pattern (CH_2 of C_2H_5); at −4.84 and −5.01 p.p.m., a doublet of one-proton area; and broad undefined resonances of 5 protons from −1.70 to −2.75 p.p.m. The doublet may be ascribed to a proton on C-4.

(7–9)-Heptafluoro-5-hydroxynonanoic Acid δ-Lactone (**6**).—5-Hexenoic acid (50.0 g., 0.44 mole), 1-iodoperfluoropropane (100 g., 0.33 mole), di-*t*-butyl peroxide (1.0 g., 0.03 mole), and ethyl acetate (20 ml.) were heated at 140° for 5 hr. and at 175° for 5 hr., and the shaker tube was rinsed with 15 g. of ethyl acetate. Fractionation (column B) gave 1-iodoperfluoropropane (40 g., 40% recovery); ethyl iodide, b.p. 68–71°, $n^{25}D$ 1.448; ethyl acetate, b.p. 54–58° (100 mm.), $n^{25}D$ 1.3702, 47.0 g. (total); 4- and 5-hexenoic acid, b.p. 90–99° (10 mm.), $n^{25}D$ 1.4355–1.4332, 29.0 g. (52% recovery); and residual oil, 48.5 g. An infrared spectrum showed in the hexenoic acid cuts both CH_2=CH and CH_3CH=C–. The residual oil was reduced by

(5) R. F. Brown and N. M. van Gulick, *J. Org. Chem.*, **21**, 1046 (1956).
(6) R. N. Haszeldine, *J. Chem. Soc.*, 1199 (1953).
(7) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, p. 178.
(8) R. F. Brown and N. M. van Gulick, *J. Am. Chem. Soc.*, **77**, 1092 (1955).

zinc and acid as above, and the products were fractionated. Ethyl (7-9)-heptafluorononanoate, b.p. 89–94° (10.0 mm.), $n^{25}D$ 1.3757, 6.0 g. (16%); an intermediate cut (3.5 g.); (7-9)-heptafluoro-5-hydroxynonanoic acid δ-lactone (6), b.p. 125–127° (10 mm.), $n^{25}D$ 1.3772, 30.0 g. (60%); and a residue (5.1 g.) were obtained. The lactone 6 was solid, m.p. 44–45.5°, and had a carbonyl band at 5.75 μ in its infrared spectrum, identical with ester carbonyl band position. It was a δ-lactone, therefore. N.m.r. spectra were consistent with this structure; splitting of proton and F^{19} resonances of the R_FCH_2– grouping was seen. No vinyl unsaturation or ethyl ester group resonances appeared.

Anal. Calcd. for $C_9H_9F_7O_2$: C, 38.3; H, 3.21; F, 47.1; ester number, 198. Found: C, 38.6; H, 3.7; F, 46.6; ester number, 193.

5-Iodo-(7-10)-Nonafluorodecancic Acid.—1-Iodoperfluorobutane (19.0 g., 0.077 mole), 5-hexenoic acid (7.0 g., 0.06 mole), and AIBN (0.2 g., 0.0012 mole) were heated under nitrogen at 75° in an oil bath. Exothermic reaction carried the temperature to 90° in 4 min.; the flask was cooled to 70° and returned to the bath. After 6 hr., AIBN (0.1 g.) was added. After 11.5 hr., the reaction mixture contained very little 1-iodoperfluorobutane (g.l.c. analysis). An infrared spectrum showed no vinyl band at 6.00 μ, the carboxylic acid band at 5.80 μ, but no lactone bands at 5.60 or 5.75 μ. The liquid was light yellow in color. These results were consistent with those previously reported.[3]

(6-11)-Tridecafluoro-4-hydroxy-2,2-dimethylundecanoic Acid γ-Lactone (2).—1-Iodoperfluorohexane (36.0 g., 0.08 mole), 2,2-dimethyl-4-pentenoic acid (9.6 g., 0.075 mole), and AIBN (0.26 g., 0.0016 mole), while stirring under nitrogen, were heated to 85° in an oil bath. Exothermic reaction set in after a few minutes, and external heating was adjusted to keep the temperature at 80–85°. Solid precipitated and a dark color appeared. After 3 hr., a sample showed by g.l.c. analysis that reaction was incomplete, but that lactone 2 (21%) and a trace of 3 were present. 2-Heptanone peroxide (0.5 ml.) was added at 80°. The color of iodine initially faded, the temperature rose to 82°, then darkening occurred. After 7 hr., lactone 2 (25%), 3 (10%), and adduct 1 (5.4%) were present. After 10 hr., all of the 2,2-dimethyl-4-pentenoic acid was gone. Analysis showed 4% of inorganic iodine, a third of which was hydrogen iodide. The mixture was washed successively with sodium sulfite solution and water. Distillation in column A gave (1) 1-iodoperfluorohexane, b.p. 70° (160 mm.), $n^{25}D$ 1.3248, 12.4 g. (2.5 g. collected in cold trap, recovery of 42%); (2) lactone 3, b.p. 64° (5.5 mm.) to 58° (4.5 mm.), m.p. 48–51°, 6.6 g.; and (3) lactone 2, b.p. 90–94° (0.5 mm.), m.p. 77–79°, 6.9 g. (21%); and residue, 0.9 g. Lactone 2 was recrystallized from hexane, m.p. 82°. An infrared spectrum of 2 (Nujol mull or perfluorokerosene mull) showed a carbonyl band at 5.60 μ. An infrared spectrum of 3 (potassium bromide pellet) showed a carbonyl band at 5.65 μ and no vinyl band at 6.00 μ.

Anal. Calcd. for $C_7H_{12}O_2$: C, 65.6; H, 9.44. Found: C, 65.1; H, 9.3.

Anal. Calcd. for $C_{13}H_{11}F_{13}O_2$: C, 35.0; H, 2.49; F, 55.35. Found: C, 35.0; H, 2.6; F, 55.4.

Ethyl (6-11)-Tridecafluoro-4-Iodo-2,2-Dimethylundecanoate (4).—1-Iodoperfluorohexane (25.0 g., 0.06 mole), ethyl 2,2-dimethyl-4-pentenoate (7.5 g., 0.05 mole), and AIBN (0.20 g., 0.0012 mole) were heated at 66–67° for 18 hr. A sample analyzed by g.l.c. contained (approximate weight, %) n-$C_6F_{13}I$ (15.5%), $CH_2{=}CHCH_2C(CH_3)_2COOC_2H_5$ (4.6%), lactone 3 (0.74%), lactone 2 (28.2%), and 4 (44%). The solution remained colorless. When cooled, crystalline lactone 2 separated and the yield was 2.77 g., m.p. 79–81°, and after 7 days the oil became red in color. Distillation in column A gave (1) b.p. 36–40° (48 mm.), 1.6 g. (unchanged starting materials); and (2) b.p. 80–84° (0.35 mm.), 17.4 g., low melting solid mixture of 2 and 4. G.l.c. analysis showed lactone 2 (66%) and ester 4 (34%) in cut 2, and evidence of some decomposition of 4 (tailing of last peak). There was no residue, but a dark red liquid collected in the cold trap (3.1 g., mixture of n-$C_6F_{13}I$ and $CH_2{=}CHCH_2C(CH_3)_2COOC_2H_5$). An infrared spectrum of cut 2 showed strong carbonyl absorption bands at 5.60 and 5.75 μ, and no band at 6.00 μ, confirming the composition as 2 and ester 4. The total yield was 83%. In view of the instability of 4, no further attempt was made to separate it from 2.

Anal. Calcd. for $C_{16}H_{16}F_{13}IO_2$: I, 19.46. Found: I, 10.0.

Pyrolysis of Esters. XXV. Pyrolysis of Malonic Esters[1,2]

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Work in these laboratories[4–6] has shown that the pyrolysis of esters is an excellent synthetic tool, not only for the synthesis of olefins, but also for the preparation of acids, nitriles, and ketones. It was shown that the pyrolysis of ethyl esters was superior to hydrolysis in many cases for the synthesis of acids, particularly for water-soluble and sterically hindered acids.[4] It was further shown that the ketone cleavage of acetoacetic esters by pyrolysis had many advantages over the usual hydrolysis with dilute base for the preparation of ketones[5] and the pyrolysis of cyanoacetic esters gave extremely high yields of the corresponding nitriles.[6]

It appeared, therefore, that the pyrolysis of a malonic ester might be a very convenient one-step synthesis of the corresponding acetic ester. This one-step procedure presumably could replace the conventional three-step procedure of hydrolysis, acidification, and decarboxylation, followed by re-esterification of the resulting substituted acetic acid. Ethyl phenylmalonate (I) was chosen for the initial study because of its availability. In selecting the pyrolysis conditions it was obvious that quantitative conversion to the substituted acetic ester was not possible because a high temperature would result in secondary pyrolysis of the substituted acetate to the corresponding acetic acid. For these reasons, a temperature of 470° was chosen for the initial studies in this series. When the liquid ester I was dropped through the pyrolysis tube packed with glass helices, at the rate of 40 g. per hr., a 36% yield of ethyl phenylacetate (II) resulted, together with a 44% recovery of the starting malonic ester. The yield, based on unrecovered starting material was 64%.

In a similar manner, the pyrolysis of ethyl (1-methylbutyl)malonate (III) at 470° gave a 36% conversion to ethyl 3-methylcaproate (IV), plus a 57% recovery of starting material. In this case the yield, based on unrecovered starting material, was 84%. Levine and Marker[7] previously carried out the three-step hydrolysis, decarboxylation, and re-esterification to produce the ethyl 3-methylcaproate in an unreported yield.

Since the pyrolysis of the monosubstituted malonic esters appeared to be reasonably successful, an attempt was made to extend this to a series of disubstituted malonic esters. Thus, when ethyl α-ethyl-α-phenylmalonate (V) was pyrolyzed at 470°, a 25% yield of the ethyl α-phenylbutyrate (VI) was obtained. Since 33% of the starting malonate was recovered, the yield, based

(1) Previous paper in this series, *J. Org. Chem.*, **28**, 828 (1963).

(2) Presented in part before the Division of Organic Chemistry at the 126th National Meeting of the American Chemical Society, New York, N. Y., Sept., 1954.

(3) Office of Naval Research Fellow, 1950–1952; Union Carbide Fellow, 1952–1953; Du Pont Fellow, 1953–1954.

(4) W. J. Bailey and W. N. Turek, *J. Am. Oil Chemists' Soc.*, **33**, 317 (1956).

(5) W. J. Bailey and J. J. Daly, Jr., *J. Org. Chem.*, **22**, 1189 (1957).

(6) W. J. Bailey and J. J. Daly, Jr., *J. Am. Chem. Soc.*, **81**, 5397 (1959).

(7) P. A. Levine and R. E. Marker, *J. Biol. Chem.*, **91**, 87 (1931).

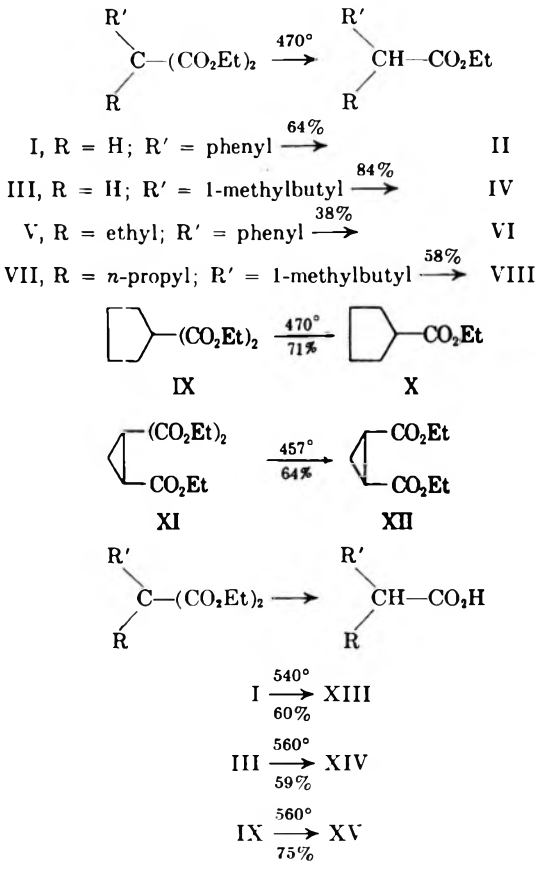
TABLE I
PYROLYSIS OF

Malonic ester	B.p. (mm.), °C.	n_D (°C.)	Amount, g.	Temp. of pyrolysis, °C.	Rate of addition, g./min.
Ethyl phenylmalonate (I)	158 (12)	1.4898 (25)	126	470	0.63
			50	540	0.52
Ethyl 1-methylbutylmalonate (III)	122–124 (15)	1.4262 (25)	125	470	0.50
			50	560	0.42
Ethyl α-ethyl-α-phenylmalonate (V)	168 (17)	1.4895 (26)	49	470	0.63
Ethyl α-(1-methylbutyl)-α-n-propylmalonate (VII)	146–149 (18)	1.4350 (25)	43	470	0.46
Ethyl cyclopentane-1,1-dicarboxylate (IX)[e]	128–131 (20)	1.4380 (26)	41.5	470	0.56
			89	560	0.49
Ethyl cyclopropane-1,1,2-tricarboxylate (XI)	139–141 (3.5)	1.4425 (26)	182.8	457	0.76

[a] See ref. 14. [b] M.p. 76–77°; R. Adams and A. M. Thal ("Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 437) report m.p. 76–76.5°. [c] See ref. 7. [d] *Anal.* Calcd. for $C_{12}H_{24}O$: C, 71.80; H, 11.97. Found: C, 71.39; H, 11.67. [e] Prepared in a 65% yield by the alkylation of malonic ester with 1,4-dichlorobutane by the method of Skinner, G. Limperos,

on unrecovered starting material, was 38%. Similarly, when ethyl α-(1-methylbutyl)-α-n-propylmalonate (VII) was pyrolyzed at 470°, a 32% yield of the ethyl 2-n-propyl-3-methylcaproate (VIII) was obtained, together with a 42% recovery of the starting material. The yield, based on unrecovered starting material, in this case was 58%. (See Scheme I.)

SCHEME I



Since the cyclopentane ring had shown marked stability during the pyrolysis of the cyanoacetic esters[6] to produce a very high yield of the 1-cyanocyclopentane, study of the pyrolysis of the malonic ester in this series was undertaken. The pyrolysis of ethyl cyclopentane-1,1-dicarboxylate (IX) at 470° resulted in a 42% conversion to ethyl cyclopentanecarboxylate (X). Since 41% of the starting malonic ester IX was recovered, the yield, based on unrecovered material, was 71%. This yield compares very favorably with the method of Whitmore, *et al.*,[8] who obtained the ethyl cyclopentanecarboxylate (X) in a 48% yield by the treatment of cyclopentylmagnesium bromide with diethyl carbonate. Whitmore and coworkers[8] stated that all methods reported in the literature for the preparation of the cyclic ester X showed little promise.

In another related problem, a quantity of ethyl cyclopropane-1,2-dicarboxylate (XII) was desired. One logical method of synthesis of this compound was from the ethyl cyclopropane-1,1,2-tricarboxylate (XI). Although it was possible to prepare ethyl cyclopropane-1,1,2-tricarboxylate (XI) in a 77% yield by the alkylation of malonic ester with ethyl dibromopropionate, it was not possible to hydrolyze and decarboxylate IX to any appreciable amount of the corresponding cyclopropane-1,2-dicarboxylic acid. Wassermann[9] reported the preparation of a 10% yield of the diacid, but we were not able even to duplicate this yield. It was possible to obtain reasonable yields of the cyclopropane-1,1,2-tricarboxylic acid, but all attempts to decarboxylate this acid failed. In contrast, the pyrolysis of the triester XI at 457° gave a 24% conversion to ethyl cyclopropane-1,2-dicarboxylate (XII) plus a 63% recovery of the starting triester. The yield of XII, based on unrecovered material, was 64%. An attempt was made to carry out this reaction on ethyl butylidenemalonate, but pyrolysis at 500° produced a complex mixture of products which had higher refractive indices than those of the expected products.

An attempt was made to extend the pyrolysis of the malonic esters to the preparation of the corresponding acetic acids. Thus, when ethyl phenylmalonate (I) was pyrolyzed at 540°, a 60% yield of phenylacetic acid (XIII) was obtained. Similarly, when ethyl 1-

(8) F. C. Whitmore, J. N. Cosby, W. S. Sloatman, and B. G. Clarke, *J. Am. Chem. Soc.*, **64**, 1801 (1942).
(9) A. Wassermann, *Helv. Chim. Acta*, **13**, 229 (1930).

MALONIC ESTERS

Product	Found B.p. (mm.), °C.	n_D (°C.)	Reported B.p. (mm.), °C.	n_D (°C.)	Yield, g., %	Recovered malonic ester, g.	Yield, based on unrecovered starting material, %
Ethyl phenylacetate (II)	107–110 (15)	1.4951 (25)	227 (760)	1.4953 (25)[a]	31.4, 36	55.1	64
Phenylacetic acid (XIII)	151–153 (20)	*b*	176–189 (50)		17.3, 60		
Ethyl 3-methylcaproate (IV)	68–69 (15)	1.4113 (25)	60 (10)	1.4102 (30)[c]	30.7, 36	71.4	84
3-Methylcaproic acid (XIV)	110–111 (17)	1.4214 (25)	113 (17)	1.4214 (25)[c]	16.7, 59		
Ethyl α-phenylbutyrate (VI)	120–121 (17)	1.4883 (26)	238.7 (760)	1.4879 (25)[a]	9.0, 25	16.0	38
Ethyl 2-propyl-3-methylcaproate (VII)[d]	107–109 (18)	1.4258 (25)			10.1, 32	18.2	58
Ethyl cyclopentanecarboxylate (X)	73–74 (21)	1.4314 (26)	89.3 (45)	1.4360 (20)[f]	11.3, 42	17.0	71
Cyclopentanecarboxylic acid (XV)	120–123 (24)	1.4514 (26)	215–216 (760)	1.4520 (20)[g]	35.2, 75		
Ethyl cyclopropane-1,2-dicarboxylate (XII)[h,i]	115–120 (13)	1.4390 (27)			31.6, 24	115.3	64

and R. Pettebone, *J. Am. Chem. Soc.*, **72**, 1649 (1950). [f] See ref. 8. [g] W. O. Ney, *J. Am. Chem. Soc.*, **65**, 774 (1943). [h] The structure was proved by hydrolysis to *trans*-cyclopropane-1,2-dicarboxylic acid, m.p. 172–175°; C. K. Ingold, *J. Chem. Soc.*, **119**, 316 (1921). [i] *Anal.* Calcd. for $C_9H_{14}O_4$: C, 58.06; H, 7.53. Found: C, 58.16; H, 7.41.

methylbutylmalonate (III) was pyrolyzed at 560°, a 59% yield of 3-methylcaproic acid (XIV) was obtained. With these yields this process will not compete successfully with the conventional hydrolysis and decarboxylation for the preparation of these simple acids. However, the pyrolysis of the malonic ester appears to be of some synthetic use in the cyclopentane series. Thus, when the ethyl cyclopentane-1,1-dicarboxylate (IX) was pyrolyzed at 560°, a 75% yield of cyclopentanecarboxylic acid (XV) was obtained. Haworth and Perkins[10] reported the synthesis of XV by the hydrolysis and decarboxylation of the cyclic diester IX but gave no yields. Talbot and Adams[11] synthesized cyclopentanecarboxylic acid (XV) in a 56% yield by the carbonation of cyclopentylmagnesium bromide.

It can be concluded, therefore, that the pyrolysis of substituted malonic esters is a fairly good synthetic tool for the preparation of the corresponding substituted acetic esters in many cases (see Table I). However, the pyrolysis of the malonic esters directly to the substituted acetic acids is useful only in certain specialized cases. Presumably, it would be of use for the preparation of water-soluble acids or sterically hindered acids.

Experimental[12]

Ethyl Phenylacetate (II).—Through a Vycor combustion tube, packed to a depth of 12 in. with 1/8-in. glass helices and externally heated at 470°, as previously described,[13] 126 g. (0.534 mole) of ethyl phenylmalonate (I), b.p. 158° (12 mm.), $n^{25}D$ 1.4898, was added dropwise over a period of 3.3 hr. Distillation of the pyrolysate through a 12-in., helix-packed column gave 31.4 g. (36%) of ethyl phenylacetate (II), b.p. 107–110° (15 mm.), $n^{25}D$ 1.4951 (lit.[14] b.p. 227°, $n^{25}D$ 1.4953), and 55.1 g. (44% recovery) of the starting ester I. The yield, based on unrecovered malonic ester I, was 64%.

Ethyl α-(1-Methylbutyl)-α-*n*-propylmalonate (VII).—A mixture of 270 g. (1 mole) of ethyl α-allyl-α-1-methylbutylmalonate (Benzol Products Co., Newark, N.J.), b.p. 145–148° (17 mm.), $n^{25}D$ 1.4430, lit.[15] b.p. 95° (1 mm.); 2 g. of 5% palladium on carbon catalyst; and 300 ml. of 95% ethanol was placed in a 1-l. Pyrex bottle and shaken with hydrogen at 1-atm. After the theoretical amount of hydrogen had been absorbed, the catalyst was removed by filtration and the alcohol was removed by distillation under reduced pressure. Fractionation of the residue through a 6-in., helix-packed column gave 260 g. (96%) of ethyl α-(1-methylbutyl)-α-*n*-propylmalonate (VII), b.p. 146–149° (18 mm.), $n^{25}D$ 1.4350.

Anal. Calcd. for $C_{15}H_{28}O_4$: C, 66.10; H, 10.30. Found: C, 65.87; H, 10.05.

Ethyl Cyclopropane-1,1,2-tricarboxylate (XI).—By a modification of the procedure of Conrad and Gutzeit[16] 140 g. (6.1 g.-atoms) of sodium was dissolved in 1700 ml. of absolute alcohol in a 5-l., three-necked flask, fitted with a stirrer, a condenser, and a dropping funnel. After 480 g. (3.0 moles) of ethyl malonate had been added dropwise to the hot solution, the solution was stirred for an additional 10 min. and then 780 g. (3.0 moles) of ethyl α,β-dibromopropionate was added dropwise over a period of 4.5 hr. After the mixture had been stirred overnight, the excess alcohol was removed by distillation under reduced pressure. Water was added to dissolve the sodium bromide and the organic layer, after being dried over magnesium sulfate, was distilled through an 8-in., helix-packed column to give 594 g. (77%) of ethyl cyclopropane-1,1,2-tricarboxylate (XI), b.p. 139–141° (3.5 mm.), $n^{26}D$ 1.4425, lit.[9] b.p. 276°, 124° (2 mm.).

Cyclopropane-1,2-dicarboxylic Anhydride.—While a mixture of 50 g. (0.194 mole) of ethyl cyclopropane-1,1,2-tricarboxylate (XI) and 200 ml. of 3 *N* hydrochloric acid was heated under reflux, ethyl alcohol was slowly removed through a 12-in., helix-packed column until the temperature of the distillation head rose to 100°. The carbon dioxide evolved during the reaction was qualitatively measured by absorption into a solution of calcium hydroxide. When the evolution of carbon dioxide had ceased, the hydrochloric acid and water were removed by distillation under reduced pressure and the residue was dried by a stream of air for a period of 12 hr. An ether solution of the residue was extracted with a small amount of cold sodium bicarbonate solution and then dried over magnesium sulfate. After the ether had been removed by distillation, the residue was fractionated through a 6-in., helix-packed column to yield three fractions: (A) b.p. 70–73° (2 mm.), (B) b.p. 103–107° (1.2 mm.), and (C) 163–170° (0.7 mm.). From fraction B was isolated 0.5 g. of *cis*-1,2-cyclopropanedicarboxylic acid, m.p. 139°, lit.[9] m.p. 139–140°. Fraction C, on treatment with ether, gave 1 g. of cyclopropane-1,2-dicarboxylic anhydride, m.p. 54–56°, lit.[16] m.p. 57°.

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Pyrolysis of Esters. XXVI. Synthesis of Half Acids by the Pyrolysis of Diesters

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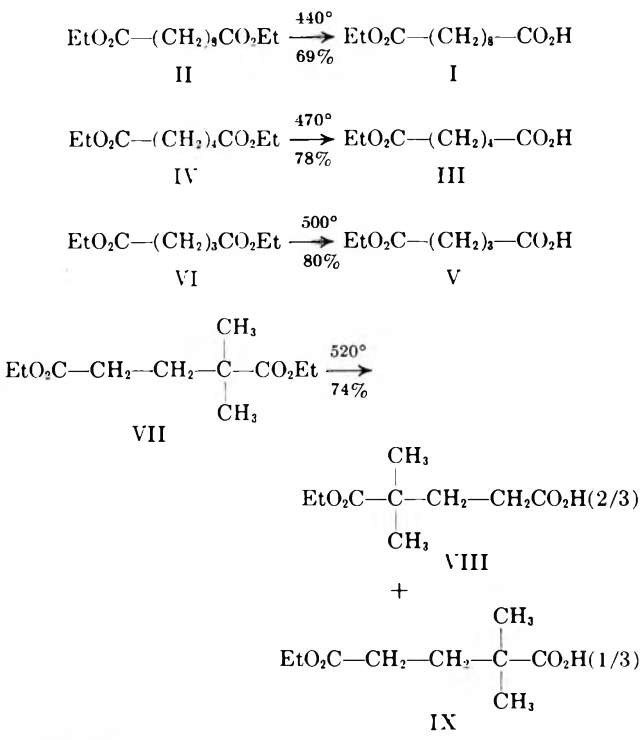
Since it was shown in these laboratories that the pyrolysis of esters was an excellent tool for the synthesis not only of olefins but also a variety of compounds derived from the acid portion, such as acids,[3,4] ketones,[5] nitriles,[6] and esters,[4] a search for other synthetic applications was undertaken. Because of the convenience of recycling unchanged starting material, it appeared that the pyrolysis of esters could be successfully applied to the preparation of half esters of dibasic acids. Three general methods for the synthesis of half esters have been used: the first involves the esterification of the dibasic acid under conditions mild enough to permit only one of the acid groups to be esterified; the second employs the partial saponification of a diester; and the third involves the disproportionation of a diester and a diacid. Applied to the preparation of ethyl hydrogen sebacate (I), the first method generally gives poor yields.[7] The second method, although very satisfactory where steric factors are important, gives low yields for the preparation from diethyl sebacate (II).[8] Fourneau and Sebetay[9] used the third method to prepare ethyl hydrogen sebacate (I) in a 54% yield by heating a mixture of diethyl sebacate (II) and sebacic acid at 280–300° for 5 hr. This procedure has the disadvantage that both the diester and diacid are required. Swan, Oehler, and Buswell[10] used a combination of the first and third methods to give, in the best available synthesis, a 60 to 65% yield of ethyl hydrogen sebacate (I). In this preparation sebacic acid (1 mole), diethyl sebacate (0.58 mole), ethanol (1.3 moles), dibutyl ether, and concentrated hydrochloric acid are heated for four hours in a complex procedure. The presence of the diethyl ester suppresses formation of additional diester and is recovered for use in a subsequent run. It seemed likely that pyrolysis of diethyl sebacate could be a simpler synthesis for the preparation of the half acid.



When diethyl sebacate (II) was added dropwise to a Vycor pyrolysis tube packed with Pyrex helices at 440°, a 28% conversion to ethyl hydrogen sebacate (I), a 7.7% conversion to sebacic acid, and a 59% recovery of starting material II were noted. The yield of half ester, based on unrecovered starting diester II, was, therefore, 69%. (The yield, based on both unrecovered diester and diacid, was 85%.) The temperature of pyrolysis was critical; at 430° a 21% conversion to ethyl hydrogen sebacate (I) or a 50% yield, based on unrecovered diester II, was realized, while at 450° a 34% conversion to half ester or a 50% yield, based on unrecovered diester II, was obtained. At lower temperatures less of the diester is pyrolyzed while at higher temperatures secondary pyrolysis of the ethyl hydrogen sebacate (I) to sebacic acid becomes more important.

When diethyl adipate (IV) was pyrolyzed at 470°, a 28% conversion to ethyl hydrogen adipate (III) was obtained, at the same time a 7.5% conversion to adipic acid plus a 64% recovery of starting material IV were realized. The yield of half ester III, based on unrecovered diester IV, was, therefore, 78%, while the yield, based on both unrecovered diester and diacid, was 99%. The 78% yield of ethyl hydrogen adipate (III) compares favorably with the 71 to 75% yield obtained by the method of Swan, Oehler, and Buswell.[10]

Pyrolysis of diethyl glutarate (VI) at 500° gave a 41% conversion to ethyl hydrogen glutarate (V) plus a 48.5% recovery of starting diester VI. The yield of half ester V, based on unrecovered diester VI, was 80%. Bachmann, Kushner, and Stevenson[11] reported a 90% yield of ethyl hydrogen glutarate (V) from glutaric anhydride for a small run with a short reaction time. In this laboratory, however, large runs with a necessarily longer reaction time gave only a 60% yield of half ester plus considerable quantities of diethyl glutarate and glutaric acid. Apparently ethyl hydrogen glutarate (V) is a strong enough acid to catalyze the disproportionation during the 10-hr. heating period. If the reaction mixture of glutaric anhydride and ethanol was allowed to stand several days at room temperature, a 78% yield of the half ester was obtained.

(1) Previous paper in this series, *J. Org. Chem.*, **29**, 1249 (1964).

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(3) W. J. Bailey and W. N. Turek, *J. Am. Oil Chemists' Soc.*, **33**, 317 (1956).

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(9) E. Fourneau and S. Sebetay, *Bull. soc. chim.*, [4]**43**, 859 (1928).

(10) S. Swan, R. Oehler, and R. Buswell, "Organic Syntheses," Coll. Vol. II John Wiley and Sons, Inc., New York, N. Y., 1943, p. 276.

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Since it appeared that the pyrolysis of diesters to half esters was a useful synthetic method, it was of interest to determine the influence of steric hindrance on the selectivity of the elimination reaction. Diethyl α,α-dimethylglutarate (VII), which has one hindered ester group and one unhindered group, was prepared in 55% yield by the oxidation of commercially available 2,2-dimethyl-4-cyanobutyraldehyde with a mixture of nitric and sulfuric acids, followed by esterification of the resulting diacid. A high selectivity was not expected, since it was shown previously[3] that ethyl 2,4,6-trimethylbenzoate pyrolyzed at 560° to give a 90% yield of the corresponding acid. Since the coordination number of the carbonyl carbon atom apparently is not increased beyond three during cleavage, the pyrolysis does not exhibit the great sensitivity to steric hindrance that do reactions involving addition to the carbonyl group. When the diethyl α,α-dimethylglutarate (VII) was saponified with 0.7 molar equivalent of potassium hydroxide, a 65% yield of 4-methyl-4-carbethoxypentanoic acid (VIII), which gave only a single peak on vapor phase chromatography, was obtained. However, when the diester was pyrolyzed at 520°, a 51% conversion to a mixture of half esters VIII and IX was obtained. Since 32% of starting ester VII also was recovered, the yield of half esters, based on unrecovered starting materials, was 74%. Vapor phase chromatography indicated that the mixture of half esters consisted of about two-thirds 4-methyl-4-carbethoxypentanoic acid (VIII) and one-third 2,2-dimethyl-4-carbethoxybutanoic acid (IX). It can be concluded that steric hindrance plays a small but definite role in the pyrolysis of esters.

Experimental[12]

Pyrolysis of Diethyl Sebacate (II).—Preliminary pyrolyses of diethyl sebacate (II) (Eastman Kodak Co., $n^{25}D$ 1.4333) at 475 and 450° with the apparatus described previously[13] indicated the formation of 140 and 77% of one molar equivalent of titratable hydrogen ion, respectively. These amounts were determined by solution of the pyrolysates in 250 ml. of alcohol, followed by titration of 25-ml. aliquots with standard sodium hydroxide, with phenolphthalein as the indicator.

At a nitrogen flow rate of 60 bubbles per min., 233 g. (0.903 mole) of diethyl sebacate (II) was added dropwise to the Vycor pyrolysis tube packed with 1/8-in. Pyrex helices and externally heated at 440° over a period of 11 hr. To avoid any charring, the pyrolysis tube was changed after approximately half the material had been added. The pyrolysate, 218.7 g., was fractionated under reduced pressure through a 10-in., helix-packed column to yield 59.1 g. (28%) of ethyl hydrogen sebacate (I), b.p. 152° (0.6 mm.), m.p. 35° [reported[14] b.p. 210° (18 mm.), m.p. 36°]; 137.5 g. (59% recovery) of diethyl sebacate (II); and 12.3 g. of sebacic acid, m.p. 135°. The yield of ethyl hydrogen sebacate (I), based on unrecovered diester II, was 69%.

Pyrolysis of Diethyl Adipate (IV).—Preliminary runs at 430 and 450° indicated that the extents of pyrolysis at these temperatures were 38.5 and 86.5%, respectively, of one molar equivalent of titratable hydrogen ion.

By the procedure described for diethyl sebacate (II), 96.5 g. (0.477 mole) of diethyl adipate (IV) (Eastman Kodak Co., $n^{25}D$ 1.4240) was pyrolyzed at 470° over a period of only 1 hr. Fractionation of the 89.9 g. of pyrolysate through a 10-in. Vigreux column under reduced pressure produced 23.6 g. (28%) of ethyl hydrogen adipate (III), b.p. 98° (0.03 mm.), m.p. 29° [reported[15] b.p. 180° (19 mm.), m.p. 29°]; and 61.5 g. (64% recovery) of diethyl adipate (IV). At the end of the distillation a considerable amount of solid adipic acid was observed in the column. In order to recover this, 100 ml. of ethanol was added to the distillation flask and refluxed into the column and distillation head until all the adipic acid was washed into the flask. Evaporation of the ethanol produced 5.2 g. (7.5%) of adipic acid. The yield of ethyl hydrogen adipate (III), based on unrecovered diester IV, was 78%.

Pyrolysis of Diethyl Glutarate (VI).[16]—Over a period of 3.5 hr., 224 g. (1.19 moles) of diethyl glutarate (VI) was pyrolyzed at 500°. Fractionation of the pyrolysate through a 12-in., helix-packed column gave 77.7 g. (41%) of ethyl hydrogen glutarate (V), b.p. 126–130° (3.2 mm.), $n^{26}D$ 1.4350 [reported[11] b.p. 159–165° (17 mm.)]; and 108.5 g. (48.5% recovery) of starting diester VI. The yield of V, based on unrecovered VI, was, therefore, 80%.

Diethyl α,α-Dimethylglutarate (VII).—By the method of Hoch and Karrer[17] 2,2-dimethyl-4-cyanobutyraldehyde[18] was oxidized with a mixture of nitric and sulfuric acids to form the dimethylglutaric acid, m.p. 82° (reported[17] m.p. 84–85°), in a 55% yield. To a 1-l. flask equipped with a 10-in. Vigreux column were added 173 g. (1.08 moles) of α,α-dimethylglutaric acid, 378 ml. (6.49 moles) of absolute alcohol, 195 ml. of toluene, and 0.94 ml. of concentrated sulfuric acid. The azeotrope was removed by distillation until the temperature of the vapors rose to 78°. The distillate then was dried over 150 g. of potassium carbonate and returned to the reaction flask. The distillation was continued until the temperature again rose to 78°. (The oil-bath temperature did not exceed 150°.) The residue was then fractionated through a 10-in., helix-packed column to give 194.9 g. (77%) of diethyl α,α-dimethylglutarate (VII), b.p. 128° (28 mm.), $n^{25}D$ 1.4250.

Anal. Calcd. for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 61.12; H, 9.37.

Vapor phase chromatography of VII on a commercial Tide column at 327° with helium flow of 0.25 ml. per sec.; sensitivity: 7, and detector current of 25 ma. gave a single peak with a retention time of 1.6 min.

Pyrolysis of Diethyl α,α-Dimethylglutarate (VII).—Pyrolysis of 5- to 10-g. quantities of diethyl α,α-dimethylglutarate (VII) by the procedure described above indicated that, at 450, 500, 520, and 550°, 13, 58, 98, and 147% of one molar equivalent of titratable hydrogen ion, respectively, were liberated.

At 520°, 42.7 g. (0.198 mole) of diethyl α,α-dimethylglutarate (VII) was pyrolyzed over a period of 2.5 hr. The pyrolysate (37.5 g.) was fractionated through a 2-ft., spiral-wire column to yield 18.8 g. (51%) of material, b.p. 98° (0.05 mm.), $n^{25}D$ 1.4406, assumed to be a mixture of 4-methyl-4-carbethoxypentanoic acid (VIII) and 2,2-dimethyl-4-carbethoxybutanoic acid (IX). In addition to the half esters, 13.5 g. (32% recovery) of starting material and 3.6 g. (11%) of α,α-dimethylglutaric acid were obtained. The yield of half esters, based on unrecovered starting material, was 74%.

Anal. Calcd. for $C_9H_{16}O_4$: C, 57.44; H, 8.57. Found: C, 57.40; H, 8.27.

Examination of crude pyrolysate before fractionation, under conditions identical with those described for 4-methyl-4-carbethoxypentanoic acid (VIII), revealed three peaks: (1) a large peak (1.6 min.) which corresponded to the diester starting material (VII); (2) a peak (2.5 min.) which was assumed to be the other possible half ester, 2,2-dimethyl-4-carbethoxybutanoic acid (IX); and (3) a peak identified by its retention time (4.6 min.) to be 4-methyl-4-carbethoxypentanoic acid (VIII). With the assumption that the total area under the second and third peaks represents only the two half esters, it can be said that, of the total amount of half esters formed by pyrolysis of diethyl α,α-dimethylglutarate, about two-thirds was 4-methyl-4-carbethoxypentanoic acid (VIII) and about one-third was 2,2-dimethyl-4-carbethoxybutanoic acid (IX).

4-Methyl-4-carbethoxypentanoic Acid (VIII).—To a 1-l., three-necked flask, equipped with a dropping funnel, a thermometer,

(12) The authors are grateful to Mrs. Kathryn Baylouny and Mrs. Jane Ratka for the microanalyses.

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(14) A. Grün and T. Wirth, *Ber.*, **55B**, 2206 (1922).

(15) N. A. Lange, "Handbook of Chemistry," Handbook Publisher, Inc., Sandusky, Ohio, 1944, p. 472; E. E. Blaise and A. Koehler, *Bull. soc. chim.*, [4]**7**, 218 (1910).

(16) The authors are grateful to Dr. John J. Daly, Jr., for this pyrolysis.

(17) D. Hoch and P. Karrer, *Helv. Chim. Acta*, **37**, 397 (1954).

(18) The authors are grateful to the Tennessee Eastman Co., Kingsport, Tenn., for a generous sample of this material.

and a stirrer, were added 24.1 g. (0.122 mole) of diethyl α,α-dimethylglutarate (VIII), 10 ml. of water, and 200 ml. of methyl alcohol. A solution of 4.5 g. (0.08 mole) of potassium hydroxide in 15 ml. of water was then added at a rate sufficient to keep the reaction mixture below 26° over a period of 6 hr. The mixture was then stirred at room temperature for an additional 10 hr. After the major portion of the methyl alcohol was removed by distillation under reduced pressure, 300 ml. of water was added and the residue was acidified to pH 4 by the dropwise addition of concentrated hydrochloric acid. The aqueous solution was then extracted with four 100-ml. portions of ether. After the ether extracts had been dried over anhydrous magnesium sulfate, the mixture was fractionated through a 2-ft. spiral-wire column to yield 13.7 g. (65%) of 4-methyl-4-carbethoxypentanoic acid (VIII), b.p. 100° (0.4 mm.), n^{25}D 1.4355.

Anal. Calcd. for $C_9H_{16}O_4$: C, 57.44; H, 8.57. Found: C, 57.36; H, 8.72.

Vapor phase chromatography under the exact conditions described above for diethyl α,α-dimethylglutarate (VII) gave only one peak with a retention time of 4.6 min.

Reduction of the Double Bond in Ethylidenemalonic Ester by Lithium Aluminum Hydride

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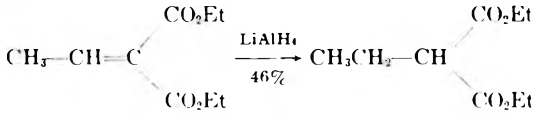
In an attempt to prepare a sample of 2-hydroxymethyl-2-buten-1-ol, ethylidenemalonic ester was treated with a large excess of lithium aluminum hydride. Surprisingly, the product was not the unsaturated diol but the saturated ester, ethyl ethylmalonate.



The reduction of the double bond in several unsaturated esters with lithium aluminum hydride has been previously reported in the literature. Ethyl *o*-hydroxycinnamate was reduced to *o*-(3-hydroxypropyl)-phenol[2] and methyl α-cyanocinnamate was reduced to 2-benzyl-3-amino-1-propanol[3] in a 30% yield. Cinnamaldehyde is also reduced to 3-phenylpropanol, but in this case it has been shown that the mechanism of the reduction involves the reduction of the carbonyl group to give a salt of cinnamyl alcohol which is subsequently reduced to the saturated alcohol.[4] In fact cinnamyl alcohols can be prepared in good yields by the reverse addition of the lithium aluminum hydride to various ethyl cinnamates.[5] A few other cases are reported in which a carbon–carbon double bond is reduced in preference to a highly reducible group in the same molecule. Gilsdorf and Nord[6] found that the reverse addition of the hydride to 1-phenyl-2-nitropropene at −40 to −50° gave a 56% yield of 1-phenyl-2-nitropropane. At higher temperature they isolated some benzylacetoxime. Since this work was completed LeMoal, Carrie, and Bargain[7] reported the reduction of α-cyano-β-phenylcinnamonitrile and the related cyanoacetic ester to the corresponding dihydro derivatives with several complex hydrides. Surprisingly they also reported that it was not possible to reduce the α-carbethoxy-β-phenylcinnamic ester to its dihydro derivatives with any of the hydrides used.

Since prolonged reflux during the reduction of unsaturated esters with lithium aluminum hydride resulted in lower yields[8] than with the saturated esters, ethylidenemalonic ester was reduced with a large excess (eight equivalents) of hydride for 1 hr. at 15° to give a 31% yield of ethyl ethylmalonate. Vapor phase chromatography showed that the material gave only one symmetrical peak and its infrared spectrum was identical with that for an authentic sample of ethyl ethylmalonate. When the reduction was carried out with a 10% excess of hydride, a 43% yield of ethylmalonic ester was obtained, together with a large amount of polymeric residue. With two equivalents of hydride a 46% yield of the ethylmalonate was obtained plus a somewhat smaller amount of polymeric residue.

Brown, Mead, and Subba Rao[9] showed that sodium borohydride plus lithium bromide in diglyme gave excellent yields of alcohols from esters. Its increased selectivity was illustrated by the reduction of ethyl cinnamate to cinnamyl alcohol in high yields. However, the reduction of ethyl ethylidenemalonate with an excess of this reagent gave a 30% yield of ethylmalonate plus a large amount of a high boiling residue. With an equivalent amount of this hydride, a 20% yield of the ethylmalonate resulted.

One can rationalize the results described by the assumption that the hydride ion preferentially adds in a 1,4 manner to the ethylidenemalonate to produce the stable enolate of ethylmalonic ester. The charge on the enolate retards further reduction to the saturated diol. With only a slight excess of hydride the low concentration of enolate favors the Michael addition to the starting unsaturated ester to produce the polymeric residue.

Experimental[10]

Reduction of Ethyl Ethylidenemalonate with Lithium Aluminum Hydride.—To a slurry of 2.36 g. (0.0625 mole) of lithium aluminum hydride in 100 ml. of dry ether was added a solution of 23.2 g. (0.125 mole) of ethyl ethylidenemalonate in 50 ml. of ether at a rate such as to keep the temperature of the reaction mixture below 15° while the flask was immersed in an ice bath. After the mixture had been stirred for an additional hour, it was poured into a mixture of ice and dilute hydrochloric acid. The aqueous layer was extracted with two 50-ml. portions of ether. After the combined ether layer and ether extracts were dried over anhydrous magnesium sulfate and the ether had been removed by distillation at atmospheric pressure, the residue was fractionated through a 10-in. Vigreux column to give 11.1 g. (46%) of ethyl ethylmalonate, b.p. 70° (4 mm.), n^{25}D 1.4172 [lit.[11] b.p. 94–96° (13 mm.), n^{20}D 1.4170].

Anal. Calcd. for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.81; H, 8.55.

V.p.c. of this ester at 205° on a silicone grease–Chromosorb column gave only one symmetrical peak; under the same condi-

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(3) A. Dornow, G. Messwarb, and H. Frey, *Ber.*, **83**, 445 (1950).

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(6) R. T. Gilsdorf and F. Nord, *J. Am. Chem. Soc.*, **74**, 1837 (1952).

(7) H. LeMoal, R. Carrie, and M. Bargain, *Compt. rend.*, **251**, 2541 (1960).

(8) W. J. Bailey and J. Economy, *J. Am. Chem. Soc.*, **77**, 1133 (1955).

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(10) The authors are grateful to Mrs. Kathryn Baylouny for the microanalysis.

(11) V. Wallingford, A. Homeyer, and D. Jones, *J. Am. Chem. Soc.*, **63**, 2056 (1941).

tion a synthetic mixture of authentic ethyl ethylmalonate and ethyl ethylidenemalonate were completely resolved.

Reduction of Ethyl Ethylidenemalonate with Sodium Borohydride and Lithium Bromide.—To a solution of 3.78 g. (0.10 mole) of sodium borohydride in 100 ml. of diglyme was added 8.7 g. (0.10 mole) of anhydrous lithium bromide (prepared by the addition of bromine to a slurry of lithium in ether, followed by the evaporation of the ether). After the mixture had been stirred for 30 min., 14.8 g. (0.08 mole) of ethyl ethylidenemalonate was added dropwise. Spontaneous heating was noted during the addition. After the mixture had been stirred for 1 hr. without external heating and 1.5 hr. on a steam bath, 24 g. (0.40 mole) of acetic acid was added to decompose the excess hydride and alkoxide complexes. The reaction mixture was then heated at 120° for 18 hr. with 24 g. (0.24 mole) of acetic anhydride. After the salts were removed by filtration, the filtrate was poured into 300 ml. of a 5% sodium carbonate solution. The oily layer was dried over anhydrous magnesium sulfate and fractionally distilled through a 6-in. Vigreux column to yield 4.5 g. (30%) of ethyl ethylmalonate, b.p. 62° (1.0 mm.), $n^{25}D$ 1.4165; and 9.0 g. of a higher boiling residue.

Intramolecular Participation of the Amide Group in Ester Hydrolysis[1]

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Numerous hydrolytic reactions are known to occur with intramolecular nucleophilic participation of an amide function.[2] Considerable evidence exists which suggests that, in suitable instances, the intramolecular participation of the amide group in ester hydrolysis results in very large rate increases over the uncatalyzed reaction.[2a,b] Particularly striking is the observation of Bernhard, *et al.*, that properly constituted β-benzyl esters of aspartyl peptides are cleaved, with amide participation, more than one-millionfold more rapidly than similar substrates not possessing a neighboring amide function.[2a] Results of this type have led several authors to suggest that amide groups present in protein or substrate molecules may be directly involved in the catalytic process of some enzymatic reactions. This suggestion is particularly appealing in light of the usual exchange reactions observed by Katchalski, *et al.*,[3] and by Fruton, *et al.*,[4] in the course of pepsin-catalyzed cleavage of peptide substrates. These reactions may be rationalized in terms of the intermediate formation of imides resulting from the attack of an amide group of a substrate molecule on the carboxyl group of a second substrate molecule.

We have examined the kinetics of amide group participation in ester hydrolysis employing substrates derived from salicylamide and phthalamic acid. These substrates were chosen to provide a basis for quantitative comparison of the catalytic efficiency of the amide group with other nucleophilic catalysts, previously studied in similar systems, for ester hydrolysis. While these studies were in progress, Shafer and Morawetz reported similar results on amide group participation in ester and amide hydrolysis in substrates derived from phthalamic acid.[2b]

The first-order rate constants for imide formation from O-acetylsalicylamide and methyl phthalamate increase linearly with hydroxide ion concentration in the pH range 6.2 to 8.8. The calculated second-order rate constants for these reactions are 1.2×10^6 and 1.8×10^5 M^{-1} min.$^{-1}$, respectively, at 25° and ionic strength 0.50. The latter value is in excellent agreement with the figure of 1.86×10^5 M^{-1} min.$^{-1}$ obtained by Shafer and Morawetz for this reaction at 25.9° and ionic strength 0.12.[2b] That imide formation was, in fact, the reaction being followed was established from the identity of the ultraviolet spectra and rate of hydrolysis of the initial reaction products with the corresponding properties of authentic samples of the imides. These results, together with those of Shafer and Morawetz,[2b] demonstrate that, for systems of these types in neutral or basic aqueous solutions, the amide group is several orders of magnitude more effective as an intramolecular nucleophilic reagent toward ester or amide linkages than either the imidazolyl[5] or the carboxylate[6] functions. The neighboring formyl group is similar to the neighboring amide group in terms of nucleophilic reactivity toward methyl esters.[7] On the other hand, the intermediate product (imide) obtained from amide group participation is somewhat more resistant to hydrolysis, completing the catalytic process, than corresponding intermediates for reactions involving the nucleophilic reagents indicated above.[2b]

Imide formation from O-acetylsalicylamide was found not to be detectably subject to general acid–base catalysis by 1.0 *M* N-methylmorpholine at pH 7.5.

Imide formation from O-acetylsalicylamide was not subject to detectable acid catalysis in hydrochloric acid solutions ranging in concentration from 1 to 5 *M*.

The reaction of acetamide with *p*-nitrophenyl acetate, an intermolecular analog for imide formation from O-acetylsalicylamide, was studied at 25° and pH 10.2. Under these conditions, the rate of *p*-nitrophenolate release was not detectably increased over the background hydrolysis rate, $k_{obsd} = 0.047$ min.$^{-1}$, by the presence of 2 *M* acetamide. Assuming that a 10% increase in this first-order rate constant might have been overlooked, this data indicates that the intramolecular reaction is at least 60,000 times more rapid than the intermolecular reaction in the presence of 1 *M* acetamide.[8] This is a minimum value since *p*-nitrophenyl acetate is almost certainly more reactive toward nucleophilic reagents than O-acetylsalicylamide. The observation of Shafer and Morawetz[2b] that the reactivity of amides in systems of this type is largely independent

(1) Contribution No. 1191 of the Department of Chemistry, Indiana University. Supported by Grant No. GB 431 from the National Science Foundation.

(2) (a) S. A. Bernhard, A. Berger, J. H. Carter, E. Katchalski, M. Sela, and Y. Shalitin, *J. Am. Chem. Soc.*, **84**, 2421 (1962). (b) J. A. Shafer and H. Morawetz, *J. Org. Chem.*, **28**, 1899 (1963); (c) L. Benoiton and H. N. Rydon, *J. Chem. Soc.*, 3328 (1960); (d) P. E. Zimmering, E. W. Westhead, Jr., and H. Morawetz, *Biochim. Biophys. Acta*, **25**, 376 (1957); (e) E. Sondheimer and R. W. Holley, *J. Am. Chem. Soc.* **76**, 2467 (1954); (f) A. R. Battersby and J. C. Robinson, *J. Chem. Soc.*, 259 (1955); (g) M. Brenner, *J. Cellular Comp. Physiol.*, **54**, 221 (1959).

(3) H. Neumann, Y. Levin, A. Berger, and E. Katchalski, *Biochem. J.*, **73**, 33 (1959).

(4) J. S. Fruton, S. Fujii, and M. H. Knappenberger, *Proc. Natl. Acad. Sci. U. S.*, **47**, 759 (1961).

(5) (a) G. Schmir and T. C. Bruice, *J. Am. Chem. Soc.*, **80**, 1173 (1958); (b) U. K. Pandit and T. C. Bruice, *ibid.*, **82**, 3386 (1960).

(6) (a) E. R. Garrett, *ibid.*, **79**, 3401 (1957); (b) M. L. Bender, F. Chloupek, and M. C. Neveu, *ibid.*, **80**, 5384 (1958); (c) M. L. Bender, Y. Chow, and F. Chloupek, *ibid.*, **80**, 5380 (1958).

(7) M. L. Bender and M. Silver, *ibid.*, **84**, 4589 (1962).

(8) For a discussion of similar comparisons in related systems, see M. L. Bender, *Chem. Rev.*, **60**, 53 (1960).

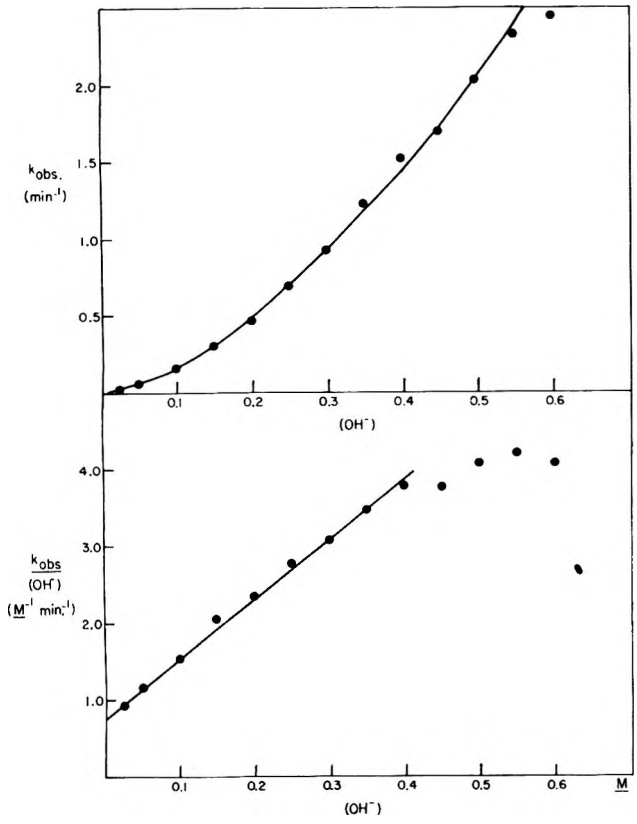


Fig. 1.—Upper half: First-order rate constants for the hydrolysis of N-acetylsalicylamide plotted against hydroxide ion concentration. The curve is a calculated line based on eq. 1 (see text). Lower half: Second-order rate constants $[k_{obs}/(OH)^-]$ for the hydrolysis of N-acetylsalicylamide plotted against hydroxide ion concentration. Reactions were followed at 258 mμ at 25° and ionic strength 0.50.

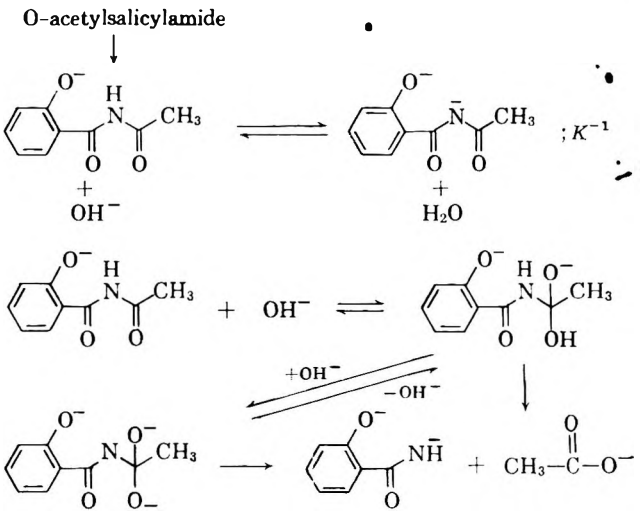
of the acid dissociation constant of the amide suggests that acetamide is a suitable model for the amide group of O-acetylsalicylamide.

The first-order rate constants for the hydrolysis of N-acetylsalicylamide, the initial product of the intramolecular amide reaction with O-acetylsalicylamide, exhibit a very interesting dependence on hydroxide ion concentration. First-order rate constants for this reaction are shown as a function of hydroxide ion concentration in the top half of Fig. 1. A plot of $k_{obs}/(OH^-)$ against (OH^-) is linear from 0.025 to 0.40 M hydroxide ion concentration (Fig. 1, lower half). At higher hydroxide ion concentrations, the second-order rate constants are less than predicted from the behavior in less alkaline solutions. Although, on the basis of the present data, a definitive explanation for these results cannot be given, the data is consistent with the reasonable mechanism shown in Scheme I.

A spectrophotometric titration of N-acetylsalicylamide at 25° and ionic strength 0.50 yielded a pK_a of 6.8 for the first dissociation constant of this substrate, so that the substrate is essentially completely converted to the monoanion under the conditions of these experiments. A spectral analysis of the reaction products from the hydrolysis of N-acetylsalicylamide indicated that at least 95% of the reaction yielded salicylamide as product.[9] The rate expression for the mechanism indicated above is shown in eq. 1 following.

$$k_{obsd}\ (\text{min.}^{-1}) = \frac{K}{(OH^-) + K}\,[k_1\,(OH^-) + k_2\,(OH^-)^2] \quad (1)$$

SCHEME I



k_1 and k_2 were calculated from the intercept and slope, respectively, of the plot shown in the lower half of Fig. 1 under conditions in which this plot is linear. K = (monoanion) (OH^-)/(dianion) was chosen as 3.70 M^{-1} to give the best fit of the experimental data to eq. 1. The line drawn in the upper half of Fig. 1 is a calculated line based on eq. 1 with k_1 = 0.75 M^{-1} min.$^{-1}$ and k_2 = 7.76 M^{-2} min.$^{-1}$. Several additional reactions exhibit a term in the rate law proportional to the second power of hydroxide ion concentration which may also be interpreted in terms of pre-equilibrium hydroxide ion addition.[10]

On the other hand, the hydrolysis of related imides, such as phthalimide or succinimide, does not exhibit a second-order reaction in hydroxide ion.[11] However, the undissociated species of these substrates are much more reactive toward hydroxide ion than is the monoanion of N-acetylsalicylamide. The second-order rate constants for the attack of hydroxide ion on phthalimide[11a] and succinimide[11b] at 25° are approximately 700 and 200 M^{-1} min.$^{-1}$, respectively, compared with a corresponding value of 0.75 M^{-1} min.$^{-1}$ for the N-acetylsalicylamide monoanion. Thus, a second-order hydroxide ion term having a rate constant considerably larger than that observed for the present reaction would not have been detected for these substrates. The relatively large ratio of the rate constants for the second-order compared to the first-order term in hydroxide ion concentration for the present reaction may be rationalized in terms of the suggested mechanism, since the expulsion of the amide as the dianion should require considerably more driving force than in cases in which the amide departs as a monoanion.

Experimental

Materials.—O-Acetylsalicylamide was prepared according to the method of McConnan and Titherely.[12] Methyl phthalamate

(9) A similar result has been obtained for the hydroxaminolysis of acetyl benzoic anhydride [T. Wieland and D. Stimming, *Ann.*, **579**, 97 (1953)].

(10) (a) R. G. Pearson and E. A. Mayerle, *J. Am. Chem. Soc.*, **73**, 926 (1951); (b) S. S. Biechler and R. W. Taft, Jr., *ibid.*, **79**, 4927 (1957); (c) M. Zanger, C. A. VanderWerf, and W. E. McEwen, *ibid.*, **81**, 3806 (1959); (d) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 350.

(11) (a) J. T. Edward and K. A. Terry, *J. Chem. Soc.*, 3527 (1957), and references therein; (b) J. Tirouflet and E. L. Trouil, *Compt. rend.*, **241**, 1053 (1955).

(12) J. McConnan and J. A. Titherely, *J. Chem. Soc.*, **89**, 1318 (1906).

was prepared as follows. Methyl hydrogen phthalate[13] (18 g.) was converted to the acyl chloride with thionyl chloride.[13] The acyl chloride was dissolved in 100 ml. of anhydrous ether and dry ammonia was bubbled through the solution for 1 hr. at 0°. The white precipitate was recovered by filtration and dissolved in 50 ml. of chloroform. After discarding the insoluble material, the chloroform was removed by evaporation under reduced pressure. The resulting residue was recrystallized from ether to yield methyl phthalamate, m.p. 102–104°, lit.[11] m.p. 98–99°.

Anal. Calcd.: C, 59.88; H, 5.06; N, 7.90. Found: C, 60.33; H, 5.06; N, 7.82.

Infrared analysis ($CHCl_3$) revealed strong bands at 1680 and 1700 cm.$^{-1}$; n.m.r. spectrum (Varian A 60, deuterioacetone, tetramethylsilane as internal standard) revealed a complex multiplet centered at 7.05, a broad band near 6.6, and a sharp singlet at 3.3 p.p.m. (approximate integrated intensities are in the ratio 4:2:3, respectively).[13] Other materials were obtained commercially and recrystallized or redistilled before use. Distilled water was employed throughout.

Kinetic measurements were carried out spectrophotometrically with a Zeiss PMQ II spectrophotometer equipped with a thermostatted cell carriage as previously described.[14] All reactions were carried out at 25° in aqueous solution at ionic strength 0.5 (adjusted with potassium chloride). Dilute phosphate, borate, or carbonate buffers were employed in appropriate pH regions. For the studies of imide formation from methyl phthalamate, infinite time readings were determined artificially by immediately neutralizing strongly basic solutions of this substrate with hydrochloric acid. This procedure was necessary since the hydrolysis of the imide product was sufficiently rapid to introduce appreciable errors into the observed infinite time readings.[2b] Measurements of pH were obtained with the glass electrode and a Radiometer PHM 4c pH meter.

(13) We are indebted to Mr. D. P. Cords for recording the n.m.r. spectrum.
(14) W. P. Jencks, *J. Am. Chem. Soc.*, **81**, 475 (1959).

The Acetylation of Biferrocenyl[1,2]

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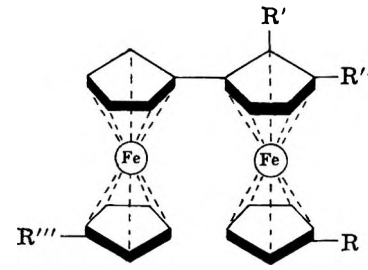
The development of suitable synthetic procedures for biferrocenyl (I)[3–5] has enabled a general study concerning various ring-substitution reactions of this metallocene to be undertaken. The ability of biferrocenyl to undergo acylation and metalation reactions, as well as the isomerism of substituted biferrocenyls, has been discussed in previous communications.[1,6,7] In this paper, details concerning the acetylation of biferrocenyl and the configuration of various acetylated biferrocenyls are presented.

Three positional isomers are possible for a monoacetylated biferrocenyl: (1) isomer II, in which the acetyl group is attached to a cyclopentadienyl ring opposite the two rings joining the two ferrocenyl nuclei; (2) isomer III, in which the acetyl group is located at a position α to a bridging carbon atom; (3) isomer IV, in which the acetyl group is similarly β disposed.



I, R, R′, R″, R‴ = H
II, R = CO–CH_3; R′, R″, R‴ = H
III, R′ = CO–CH_3; R, R″, R‴ = H
IV, R″ = CO–CH_3; R, R′, R‴ = H
V, R, R‴ = CO–CH_3; R′, R″ = H

Treatment of biferrocenyl with equimolar amounts of acetyl chloride and aluminum chloride in methylene chloride solution produced a mixture of products which could be separated by chromatography on alumina. The major product from the reaction, isolated in 14% yield, was a monoacetylbiferrocenyl of m.p. 143°. This product is assigned as acetylbiferrocenyl II on the basis of its proton nuclear magnetic resonance spectrum (Fig. 1).[8] A resonance peak at τ 7.85 representing three protons is noted in the region where the proton peak of an acetyl group attached to ferrocene is known to occur.[2] A singlet representing five protons is present at τ 6.03. The chemical shift of this peak is similar to chemical shifts of peaks representing protons of unsubstituted cyclopentadienyl rings in ferrocene (τ 5.86)[2] and biferrocenyl (τ 6.02).[9] A triplet due to two protons is noted somewhat upfield (τ 5.42) from the triplet representing the α protons in acetylferrocene (τ 5.23).[2] It is known, however, that the two directly bonded ferrocene nuclei in biferrocenyl exert a mutual shielding effect on all protons present.[9] The differential shift ($\Delta\tau$) of the triplet representing the α protons in acetylbiferrocenyl II compared to the unsubstituted ring protons in biferrocenyl is τ 0.60. This value is in good agreement with a $\Delta\tau$ value of τ 0.63 for the corresponding α protons of acetylferrocene compared to ferrocene.[2] Complex absorption in the region centered around *ca.* τ 5.71 accounts for the remaining ten protons in acetylbiferrocenyl II.

A second isomeric acetylbiferrocenyl of melting point 158–159° was isolated in *ca.* 1% yield from the reaction products. The proton n.m.r. spectrum of this product exhibited a singlet at τ 7.59 attributable to three acetyl protons, an apparent singlet at τ 5.98 attributable to ten protons on unsubstituted cyclopentadienyl rings, and complex absorption between τ 5.0 and 5.9 due to seven additional ring protons. Using an expanded (50 c.p.s.) scale, the resonance peak at τ 5.98 was further resolved into two peaks of approximately equal

(1) Presented in part at the 138th National Meeting of the American Chemical Society, New York, N. Y., Sept. 11, 1960; see Abstracts of Papers, p. 54P.
(2) Part IX of a series "Organometallic π-Complexes."
(3) M. D. Rausch, *ibid.*, **26**, 1802 (1961).
(4) E. G. Perevalova and O. A. Nesmeyanova, *Doklady Akad. Nauk SSSR*, **132**, 1093 (1960).
(5) M. D. Rausch, *Inorg. Chem.*, **1**, 414 (1962).
(6) M. D. Rausch, *J. Am. Chem. Soc.*, **82**, 2080 (1960).
(7) Electrophilic aromatic substitution reactions of biferrocenyl since have been described by other investigators: S. I. Goldberg, J. S. Crowell, and R. L. Matteson, XIX International Congress of Pure and Applied Chemistry, London, England, July 10, 1963; see Abstracts A, p. 184.
(8) Acetylbiferrocenyl II also has been synthesized recently by means of an unambiguous route, *viz.*, mixed Ullmann-type coupling of bromoferrocene and 1-bromo-1′-acetylferrocene [S. I. Goldberg and R. L. Matteson, *J. Org. Chem.*, **29**, 323 (1964)]. These investigators have likewise shown that Ullmann-type coupling of the latter derivative gives rise to diacetylbiferrocenyl V. The proton n.m.r. spectra of acetylbiferrocenyl II and diacetylbiferrocenyl V produced in this manner are identical with the spectra of the corresponding products isolated in the present study.
(9) Analogous results concerning the proton n.m.r. spectrum of biferrocenyl in chloroform solution have been reported previously: S. I. Goldberg, D. W. Mayo, and J. A. Alford, *J. Org. Chem.*, **28**, 1708 (1963).

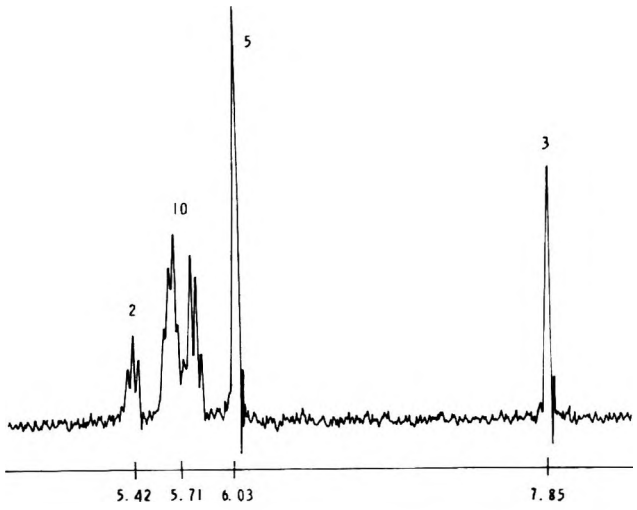
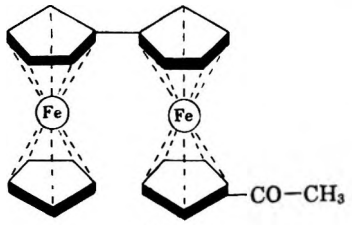


Fig. 1.—Proton n.m.r. spectrum of acetylbiferrocenyl II.



II

intensity at τ 5.97 and 5.99. Either acetylbiferrocenyl III or acetylbiferrocenyl IV is consistent with such a spectrum, and further elucidation of the structure of this product is in progress. In acetylation reactions involving a variety of other substituted ferrocenes, the 1,2 isomer was eluted from alumina before the 1,1′ and the 1,3 isomers.[10-12] Further, Rosenblum[13] has shown that the 2-position of aryl-substituted ferrocenes is preferentially attacked by electrophilic reagents. On this basis, the product is tentatively assigned as acetylbiferrocenyl III.

In addition to an appreciable amount of recovered biferrocenyl, a very small amount of acetylferrocene was isolated and characterized by means of its melting point and proton n.m.r. spectrum. Since highly purified biferrocenyl was used as starting material, it is conceivable that acetylferrocene resulted from partial decomposition of biferrocenyl or an acetylated intermediate during the course of the reaction.

The reaction of biferrocenyl with an appreciable molar excess of both acetyl chloride and aluminum chloride produced a variety of acetylated biferrocenyls. The major product of the reaction, isolated in 40% yield, was a diacetylbiferrocenyl of m.p. 191–192°. Although fourteen isomeric diacetylbiferrocenyls are theoretically possible, the product can be assigned as diacetylbiferrocenyl V on the basis of its proton n.m.r. spectrum (Fig. 2).[8] A singlet representing six acetyl protons is found at τ 7.84. A low-field triplet representing four protons occurs at τ 5.43 and is assigned to the four equivalent protons which are α to the two acetyl groups. Absorption due to twelve ring protons occurs as a complex multiplet centered at *ca.* τ 5.67. It is significant that no resonance peak is noted near τ 6.0, where singlets representing unsubstituted cyclopentadienyl ring protons in acetylbiferrocenyls are known to occur. In addition to diacetylbiferrocenyl V, a second isomeric diacetylbiferrocenyl of m.p. 147–147.5° as well as other acetylated biferrocenyls were noted. A detailed investigation of these isomeric products is in progress and will be reported later.

The infrared spectra of acetylbiferrocenyl II and diacetylbiferrocenyl V exhibited strong carbonyl stretching frequencies at 6.0 and absorptions at *ca.* 9.0 μ characteristic of acetylferrocenes.[14] Acetylbiferrocenyl II also exhibited an absorption shoulder at 9.05 and an absorption band at 10.0 μ, in accordance with the presence of an unsubstituted cyclopentadienyl ring.[14]

The recovery of appreciable amounts of biferrocenyl from these and related acylation reactions and the rather low conversions to acylated biferrocenyls are striking in contrast to the facile acylation of ferrocene itself. It is of further interest that a ferrocenyl group appears to deactivate the cyclopentadienyl ring to which it is attached, and preferential acetylation occurs in the unsubstituted ring. A similar deactivating influence of the phenyl group in acetylation reactions of phenylferrocenes previously has been observed.[13,15,16]

Experimental

General.—Biferrocenyl was prepared according to published procedures[3-5] and was repeatedly recrystallized from *n*-heptane before use. Acetyl chloride and anhydrous aluminum chloride were of reagent grade purity and were taken from freshly opened bottles. Methylene chloride was dried over calcium hydride before use. Elemental analyses and molecular weight determinations were performed by the Schwarzkopf Microanalytical Laboratory, Woodside N. Y., and by the analytical section of this laboratory. Melting points are uncorrected. Nuclear magnetic resonance spectra were determined on a Varian Model A-60 spectrometer. Sample concentrations were *ca.* 5 to 10% (w./v.) in deuteriochloroform except for biferrocenyl; the latter was examined as a saturated solution in this solvent. Infrared spectra were obtained on a Beckman Model IR-4 spectrophotometer by means of potassium bromide pellets. Chromatography was performed on columns wrapped with aluminum foil to protect the compounds from light.

Monoacetylation of Biferrocenyl.—A mixture of acetyl chloride (4.93 mmoles, 0.35 ml.) and anhydrous aluminum chloride (6.0 mmoles, 0.80 g.) in 40 ml. of methylene chloride was prepared under nitrogen. The solution of acetylating agent was transferred under nitrogen to a dropping funnel, a glass wool filter being used to separate the undissolved aluminum chloride. The acetylating agent was added dropwise with stirring and under nitrogen to a solution of biferrocenyl (4.93 mmoles, 1.822 g.) in 200 ml. of methylene chloride. The violet-colored reaction mixture was stirred at room temperature for 2 hr. and then hydrolyzed with de-oxygenated water. The organic phase was separated and the methylene chloride washings of the aqueous phase were added to it. The organic solution was washed several times with water and then dried over anhydrous sodium sulfate. The mixture was filtered and the solvent was removed by means of a rotary evaporator at reduced pressure.

The residue was extracted repeatedly with ethyl ether and the extracts were chromatographed on a 3 cm. × 60 cm. column of

(10) K. L. Rinehart, Jr., K. L. Motz, and S. Moon, *J. Am. Chem. Soc.*, **79**, 2749 (1957).

(11) M. Rosenblum, W. G. Howells, A. K. Banerjee, and C. Bennett, *ibid.*, **84**, 2726 (1962).

(12) D. W. Hall and J. H. Richards, *J. Org. Chem.*, **28**, 1549 (1963).

(13) M. Rosenblum and W. G. Howells, *J. Am. Chem. Soc.*, **84**, 1167 (1962).

(14) M. Rosenblum, *Chem. Ind.* (London), 953 (1958).

(15) M. Rosenblum, *J. Am. Chem. Soc.*, **81**, 4530 (1959).

(16) A. N. Nesmeyanov, E. G. Perevalova, S. P. Gubin, T. V. Nikitina, A. A. Ponomarenko, and L. S. Shilovtseva, *Doklady Akad. Nauk SSSR*, **139**, 888 (1961).

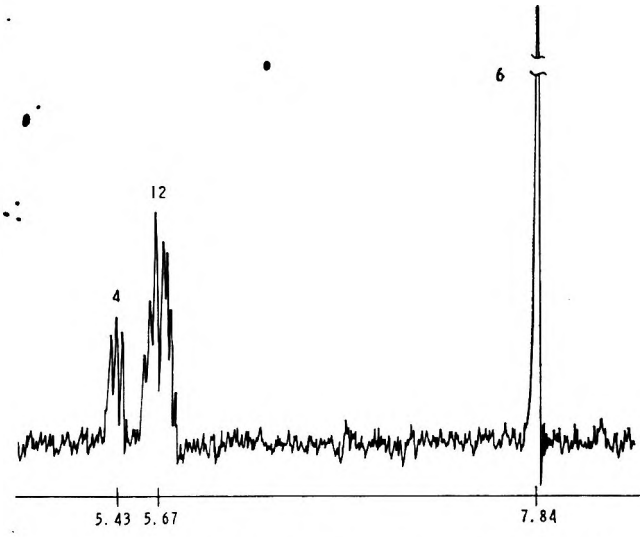
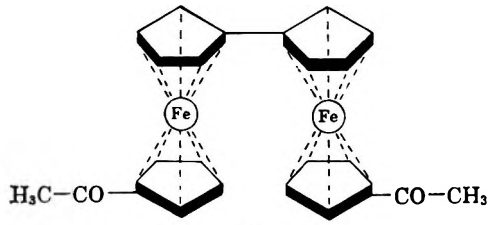


Fig. 2.—Proton n.m.r. spectrum of diacetylbiferrocenyl V.



V

Merck alumina. Elution with ether rapidly removed a broad yellow band from which 1.13 g. of an orange solid was obtained. Recrystallization of the solid produced 0.95 g. of biferrocenyl, m.p. 237–239° (nitrogen). The n.m.r. spectrum of this product exhibited a triplet at τ 5.65 due to four protons, a triplet at 5.83 due to four protons, and a singlet at 6.02 due to ten protons.[9] The n.m.r. and infrared spectra of biferrocenyl obtained from this reaction were identical with the corresponding spectra of an authentic sample. Continued elution with ether removed a faint yellow band; the latter yielded 8 mg. of red crystals, m.p. 83–85°. A mixture melting point determination of this product with acetylferrocene (m.p. 85–86°)[17] was undepressed, and the n.m.r. spectrum of the product was identical with the n.m.r. spectrum of acetylferrocene. Elution with ether next removed a faint red band. There was obtained 23 mg. of an orange solid, m.p. 153–158°. Recrystallization of the solid from *n*-heptane produced 15 mg. (1%) of acetylbiferrocenyl III, m.p. 158–159°.

Anal. Calcd. for $C_{22}H_{20}Fe_2O$: C, 64.12; H, 4.89; mol. wt., 412. Found: C, 63.96; H, 5.11; mol. wt., 417.

Elution of the final band produced 290 mg. (14%) of acetylbiferrocenyl II in the form of red crystals, m.p. 140–141°. Recrystallization of the product raised the melting point to 143°.

Anal. Calcd. for $C_{22}H_{20}Fe_2O$: C, 64.12; H, 4.89; Fe, 27.10; mol. wt., 412. Found: C, 64.04; H, 4.89; Fe, 27.34; mol. wt., 417.

Diacetylation of Biferrocenyl.—A solution of biferrocenyl (1.0 mmole, 0.370 g.) in 30 ml. of methylene chloride was added dropwise with stirring and under nitrogen to a solution of acetyl chloride (3.0 mmoles, 0.22 ml.) and anhydrous aluminum chloride (3.0 mmoles, 0.40 g.) in 20 ml. of the same solvent. Following the addition, the reaction mixture was refluxed for 1 hr. and then hydrolyzed with de-oxygenated water. The phases were separated and the aqueous phase was extracted with methylene chloride. The combined organic phases were washed several times with water and dried over anhydrous sodium sulfate. The mixture was filtered and concentrated to dryness.

The residue was dissolved in *ca.* 15 ml. of methylene chloride–benzene (1:1) and the solution was chromatographed on a 1.5 cm. × 50 cm. column of Merck alumina. Elution with benzene removed a yellow band. Recrystallization of the resulting product from *n*-heptane produced 60 mg. of biferrocenyl, m.p. 237–239° (nitrogen). Further elution removed a salmon-colored band. The product from this band was recrystallized from *n*-heptane to yield 15 mg. of crude acetylbiferrocenyl II, m.p. 137–139°. The infrared spectrum of this product was identical with the spectrum of acetylbiferrocenyl II obtained from the monoacetylation of biferrocenyl. A broad red band was next eluted with methylene chloride. Recrystallization of the resulting product from a mixture of benzene and *n*-hexane produced 180 mg. (40%) of diacetylbiferrocenyl V in the form of deep red crystals, m.p. 191–192°.

Anal. Calcd. for $C_{24}H_{22}Fe_2O_2$: C, 63.48; H, 4.88; Fe, 24.60; mol. wt., 454. Found: C, 63.85; H, 4.98; Fe, 24.20; mol. wt., 454.

A narrow red band was next eluted with 5% methanol in chloroform. The product was rechromatographed in benzene solution and a red band was eluted with mixtures of benzene and chloroform. The resulting product was recrystallized from methanol to yield 20 mg. of red crystals, m.p. 147–147.5°.

Anal. Calcd. for $C_{24}H_{22}Fe_2O_2$: C, 63.48; H, 4.88; Fe, 24.60. Found: C, 63.32; H, 5.10; Fe, 24.68.

(17) P. J. Graham, R. V. Lindsey, G. W. Parshall, M. L. Peterson, and G. M. Whitman, *J. Am. Chem. Soc.*, **79**, 3416 (1957).

Preparation of Methyl L-Arabinothiapyranoside and Disulfide Derivatives of 5-Mercapto-L-arabinose[1]

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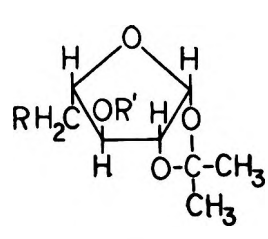
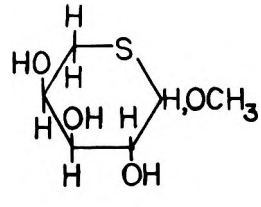
In the preparation of analogs of natural sugars wherein sulfur replaces the normal ring oxygen, the analog of the common plant sugar, L-arabinose, is now made. As in several previous preparations[2-5] of thia sugars, sulfur is introduced by nucleophilic displacement of the tosyloxy group with the thiobenzylate anion. The starting compound is 1,2-*O*-isopropylidene-5-*O*-tosyl-L-arabinofuranose[6] (I) which is converted to



I R = OTs, R' = H
II R = SCH$_2$Ø, R' = H
III R = SH, R' = H
IV R = SAc, R' = Ac



V

II with the thiobenzylate ion. Reduction with sodium in liquid ammmonia gives 5-deoxy-1,2-*O*-isopropylidene-5-mercapto-L-arabinofuranose (III). Methanolysis produces an anomeric mixture of methyl

(1) Journal Paper No. 2206 of the Purdue Agricultural Experiment Station, Lafayette, Ind. Presented in part at the 145th National Meeting of the American Chemical Society, New York, N. Y., Sept., 1963.

(2) R. L. Whistler, M. S. Feather, and D. L. Ingles, *J. Am. Chem. Soc.*, **84**, 122 (1962).

(3) R. L. Whistler and D. L. Ingles, *J. Org. Chem.*, **27**, 3896 (1962).

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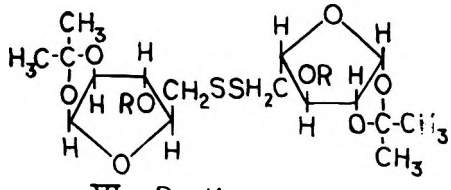
(5) V. S. R. Rao, J. F. Foster, and R. L. Whistler, *ibid.*, **28**, 1730 (1963).

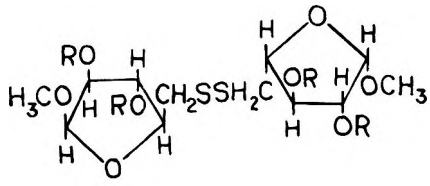
(6) P. A. Levene and J. Compton, *J. Biol. Chem.*, **116**, 189 (1936).

L-arabinothiapyranosides, in low yield with formation of a large amount of sugar disulfide (VIII). Similar results are obtained even under essentially oxygen-free conditions. Methanolysis of the thioacetate (IV) gives 27% of V and 70% of disulfide (VIII). Periodate oxidation of V produced the expected amount of formic acid. The disulfide of III is easily prepared by bubbling air through a hot ethanol solution of III. The crystalline disulfide (VI) can be converted, by acetylation in pyridine, to bis(3-*O*-acetyl-5-deoxy-1,2-*O*-isopropylidene-L-arabinofuranose) 5,5′-disulfide (VII), or by methanolysis to the crystalline bis(methyl 5-deoxy-β-L-arabinofuranoside) 5,5′-disulfide (VIII). The very high specific optical rotation of VIII is suggestive that



VI R = H

VII R = Ac



VIII R = H

IX R = Ac

this disulfide is in the β-L-configuration. Methanolysis of VIII in 2% hydrochloric acid in absolute methanol showed a decrease in the specific optical rotation from +404 to +194 in 36 hr. Acetylation of VIII in pyridine gives a crystalline acetate (IX).

Experimental

5-Deoxy-1,2-*O*-isopropylidene-5-thiobenzyl-L-arabinofuranose (II).—1,2-*O*-Isopropylidene-5-*O*-tosyl-L-arabinofuranose (I, 12 g.) reacted with 12 g. of the sodium salt of benzyl mercaptan in a manner described previously,[3] except that the chloroform extracts were washed with water until neutral. After drying with sodium sulfate, the chloroform was distilled under reduced pressure. The dry product, II, was taken up in 25 ml. of chloroform, 75 ml. of petroleum ether (b.p. 66–68°) was added, and the mixture was cooled to 4° until crystallization was complete. The yield was 8.2 g. (80%), m.p. 72°, $[\alpha]^{25}D$ +29.57° (*c* 1.40, chloroform).

Anal. Calcd. for $C_{15}H_{20}O_4S$: C, 60.81; H, 6.76; S, 10.81. Found: C, 61.04; H, 6.65; S, 10.71.

5-Deoxy-1,2-*O*-isopropylidene-5-mercapto-L-arabinofuranose (III).—Compound II (10 g.) was converted to III in the manner previously described except that the product was worked up under a dry, oxygen-free nitrogen atmosphere. Titration of the product with 0.1 *N* iodine solution[7] showed that 85% of the thiol groups were free. The compound gave an immediate color at 25° with both sodium nitroprusside (SNP)[8,9] and 2,3,5-triphenyl-2*H*-tetrazolium chloride (TTC).[10]

Anal. Calcd. for $C_8H_{14}O_4S$: S, 15.53. Found: S, 15.37.

3-*O*-Acetyl-5-deoxy-1,2-*O*-isopropylidene-4-thioacetyl-L-arabinofuranose (IV).—Sirupy III (5 g.) was dissolved in 40 ml. of dry pyridine and the solution was cooled to 0°. To this was added 30 ml. of acetic anhydride with shaking. The mixture was allowed to stand at 25° overnight, under nitrogen, and then was poured into 600 ml. of ice and water. In a short time the thick sirup which separated crystallized and was removed by filtration. It was recrystallized from ethanol to give 5.65 g. (81%), m.p. 85°, $[\alpha]^{25}D$ −13.67° (*c* 1.39, chloroform). The thioacetyl derivative gave an immediate color with TTC and showed characteristic absorption for thioacetate in the ultraviolet region of 230–240 mμ.[11]

Anal. Calcd. for $C_{12}H_{18}O_6S$: C, 49.70; H, 6.20; S, 11.05. Found: C, 49.91; H, 5.89; S, 11.19.

Methyl L-arabinothiapyranoside (V).—Compound IV (3 g.) was dissolved in 100 ml. of 1% methanolic hydrogen chloride and allowed to stand at 25° for 24 hr. At the end of this time, silver carbonate was added until the solution was neutral. After filtration and concentration, the solution was applied to Whatman No. 3 MM filter paper and irrigated with 1-butanol–ethanol–water (40:11:19 v./v.). Three compounds were isolated: starting material (IV), a disulfide (VIII), and methyl L-arabinothiapyranoside (V). The product V did not crystallize and had $[\alpha]^{25}D$ +21.84° (*c* 0.87, water).

Anal. Calcd. for $C_6H_{12}O_4S$: S, 17.77; OCH_3, 17.22; Rast mol. wt., 180. Found: S, 17.92; OCH_3, 16.96; Rast mol. wt., 169.

Periodate oxidation showed 4 moles of periodate consumed, 1.7 moles of total acids produced, and 1 mole of formic acid produced per mole of V. These results indicate the presence of a pyranoside. The excess periodate consumed was probably due to the oxidation of sulfur to a sulfone or sulfoxide.[12]

Bis(5-deoxy-1,2-*O*-isopropylidene-L-arabinofuranose) 5,5′-Disulfide (VI).—A solution of 1 g. of III in 25 ml. of hot ethanol was oxygenated by bubbling air through it for 3 hr. The solution was concentrated to a sirup which crystallized. Titration of this compound with 0.1 *N* iodine solution showed no thiol activity. Reaction with TTC and SNP gave no color test until after reduction of the disulfide bond with lithium aluminum hydride[13] in diethyl ether. The compound had m.p. 160°, $[\alpha]^{25}D$ −23.53° (*c* 1.02, chloroform).

Anal. Calcd. for $C_{16}H_{26}O_8S_2$: C, 46.81; H, 6.38; S, 15.62; Rast mol. wt., 410. Found: C, 46.55; H, 6.43; S, 15.48; Rast mol. wt., 419.

Bis(3-*O*-acetyl-5-deoxy-1,2-*O*-isopropylidene-L-arabinofuranose) 5,5′-Disulfide (VII).—A solution of 2 g. of VI in 20 ml. of dry pyridine was cooled to 0°. To this was added 15 ml. of acetic anhydride, and the solution was kept at 25° overnight and then poured into 500 ml. of ice and water. The compound was extracted with two 100-ml. portions of chloroform, and the combined extracts were washed with a saturated sodium bicarbonate solution, dilute copper sulfate solution, and finally with water. The chloroform was dried over sodium sulfate and concentrated to a thick sirup which crystallized. Recrystallization from ethanol gave VII, m.p. 108°, $[\alpha]^{25}D$ +12.15° (*c* 1.81, chloroform). The compound developed no color with TTC and SNP until after reduction with lithium aluminum hydride in diethyl ether.

Anal. Calcd. for $C_{20}H_{30}O_{10}S_2$: S, 12.96; Rast mol. wt., 494. Found: S, 13.21; Rast mol. wt., 498.

Bis(methyl 5-deoxy-L-arabinofuranoside) 5,5′-Disulfide (VIII).—A solution of 1 g. of VI and 50 ml. of 1% methanolic hydrogen chloride was refluxed for 1 hr. The solution was passed through a column of Amberlite IR-45 (OH^-) resin to remove acids, and the effluent was concentrated under reduced pressure to dryness. The product was crystallized in ethanol to m.p. 184°, $[\alpha]^{25}D$ +403.5° (*c* 1.33, water). Reaction with TTC and SNP gave no color test until after reduction with lithium aluminum hydride in diethyl ether.

Anal. Calcd. for $C_{12}H_{22}O_8S_2$: C, 40.23; H, 6.19; S, 17.89; OCH_3, 17.32; Rast mol. wt., 358. Found: C, 40.57; H, 6.28; S, 17.81; OCH_3 17.28; Rast mol. wt., 349.

Bis(methyl 2,3-di-*O*-acetyl-5-deoxy-L-arabinofuranose) 5,5′-Disulfide (IX).—A solution of 2 g. of VIII was acetylated and

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(13) R. C. Arnold, A. P. Lien, and R. M. Alm, *J. Am. Chem. Soc.*, **72**, 731 (1950).

worked up as described for VII. Recrystallization from ethanol gave product of m.p. 115°, $[\alpha]^{25}D$ +319.8° (*c* 1.26, chloroform). Reaction with TTC and SNP gave no color until after reduction with lithium aluminum hydride in diethyl ether.

Anal. Calcd for $C_{20}H_{30}O_{12}S_2$: S, 12.17; Rast mol. wt., 526. Found: S, 11.87; Rast mol. wt., 517.

Acknowledgment.—The authors gratefully acknowledge grants from the U. S. Department of Health, Education and Welfare and from the Corn Industries Research Foundation which helped support this work.

Reactions of Calcium with Organonitrogen Compounds and Aromatic Hydrocarbons[1]

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Received December 16, 1963

In a recent note[3] we described the reaction by which calcium in liquid ammonia and pyridine and methylpyridines form highly reactive compounds. We have also conducted exploratory investigations of reactions between ammonia solutions of calcium and other organonitrogen compounds, making similar observations. Following the suggestion that these reactions may involve electron addition to the aromatic rings by the calcium–ammonia system, we extended this investigation to aromatic hydrocarbons and observed similar reactions. Evaporation of the excess ammonia led to isolation of insoluble solid products that were mostly highly colored, easily hydrolyzed, and highly reactive with air. These products have not been well-characterized, but we wish to report them here in the hope of interesting others in studying them further.

Empirical compositions of the products together with color and general order of reactivity are given in Table I for the nitrogen compounds and in Table II for the hydrocarbons. Some evidence of reaction was also noted with ethylenediamine and piperidine, but not with benzene or tetrahydrofuran.

Experimental

Reagents.—Calcium metal was about 98% pure electrolytic lump from Fisher Scientific Co. Spectrographic analysis showed the major impurities to be magnesium and strontium, with minor amounts of manganese, aluminum, and copper and only a trace of iron. It was granulated in an inert atmosphere immediately before use. Ammonia was commercial liquefied anhydrous dried over solid potassium hydroxide. Ethylenediamine, 98–100%, was obtained from Matheson Coleman and Bell, stored over solid potassium hydroxide, and refluxed over barium oxide prior to distillation for use. Benzene from Fisher Scientific Co. and tetrahydrofuran from Matheson Coleman and Bell were dried over sodium wire before use. Acridine and 3-methylisoquinoline, both from Eastman, were recrystallized from ether, as were pyrene and 2,6-diaminopyridine from Reilly Tar and Chemical Corp. Indene, Eastman practical, was redistilled (b.p. 181°, lit. 182.4°). Diphenylethylene was a student preparation, boiling at 114° (1 mm.), as was tetraphenylethylene, m.p. 227–228°, lit. 227°. Freshly opened samples were used of phenanthrene and diphenyl from Matheson Coleman and Bell, purified naphthalene from Fisher Scientific Co., 1,10-phenanthroline and 2,2′-dipyridylamine from Aldrich Chemical Co., and Eastman triphenylmethane and 2,2′-dipyridine. Other reagents used as obtained from the suppliers were 2-aminopyridine from Matheson Co., m.p. 58–60°, chrysene and fluoranthene (95% minimum) from Reilly Tar and Chemical Corp., Eastman 2-amino-5-methylpyridine, anthracene, fluorene (98%), triphenylamine, and Paragon Testing Laboratories diphenylamine. Other chemicals used were standard laboratory reagents.

TABLE I

CALCIUM ORGANONITROGEN COMPOSITIONS AND PROPERTIES

Reagent (R)	Empirical formula[a]	Color	Air reactivity[b]
Quinoline	$CaRA_{1.54}$	Red-brown	L
	$CaRA$	Black	L
	$CaR_{1.46}$	Black	L
	$CaR_2A_{0.52}$	Black	L
3-Methylisoquinoline	$CaRA_{1.88}$	Orange-brown	H
Phenanthridine	$CaRA_{1.78}$	Orange-brown	M
Acridine	$CaRA_{1.69}$	Tan	M
2,2′-Dipyridine	$Ca_2RA_{1.29}$	Violet-black	M
1,10-Phenanthroline	$CaRA_{0.74}$	Purple	M
2-Aminopyridine	$CaRA_{0.88}$	White	H
	CaR_2	White	L
2-Amino-5-methylpyridine	$CaRA_{0.72}$	White	M
2,2′-Dipyridylamine	$CaRA_{0.73}$	Yellow	H
	$CaR_2A_{0.23}$	Light green	L
Diphenylamine	$CaRA_{2.13}$	Light green	H
	$CaR_2A_{0.83}$	Tan	M
Triphenylamine	$CaRA_{1.44}$	Tan	L

[a] A = NH_3. [b] H = high reactivity, incandescence, sometimes throwing off sparks; M = medium reactivity, immediate color change with evolution of heat and smoke, sometimes setting fire to paper in contact with it; L = low reactivity, only slightly exothermic with air or water.

TABLE II

CALCIUM HYDROCARBON COMPOSITIONS AND PROPERTIES

Reagent (R)	Empirical formula[a]	Color	Air reactivity[b]
Diphenyl	$CaRA_{1.48}$	Orange-brown	L
Naphthalene	$CaRA_{2.07}$	Light red	H
	$CaRA_{1.62}$	Light red	H
Anthracene	$CaRA_{1.49}$	Light green	H
Phenanthrene	$CaRA_{1.84}$	Tan	L
Chrysene	$CaRA_{1.81}$	Violet	M
Pyrene	$CaRA_{2.04}$	Red-violet	M
Fluoranthene	$CaRA_{1.70}$	Orange-green	L
Diphenylethylene	$CaRA_{2.06}$	Green	L
Tetraphenylethylene	$CaRA_{1.44}$	Light red	L

[a] A = NH_3. [b] See footnote *b*, Table I.

Apparatus and General Procedure.—These were identical with those described in detail in our earlier note.[3] Briefly the nitrogen compound or hydrocarbon was added to the calcium-ammonia solution at about −70°, excess ammonia was evaporated at its boiling point, and after long evacuation of the residue at room temperature, its composition was estimated by weight difference

Quinoline–Calcium, 1:1.—Two experiments were run with similar results. Formation of a red-brown solid was observed after evaporation of the ammonia and evacuation, 39 hr. at 27° for one product and 22 hr. at 31° for the other. The compositions were $Ca(Q)(NH_3)_{1.52}$ and $Ca(Q)(NH_3)_{1.43}$ The first product did not react very obviously with air except to change to a yellowish tan. It reacted with water forming a yellow solid that dissolved in dilute hydrochloric acid. Analysis of this solution showed 48.9% of the original quinoline to be present.

(1) Taken from the dissertation submitted to the University of Iowa by A. R. Utke in partial fulfillment of the requirements for a Ph.D. degree, 1963.

(2) To whom communications should be addressed; during the academic year 1963–1964, Department of Chemistry, Arizona State University, Tempe, Ariz.

(3) A. R. Utke and R. T. Sanderson, *J. Org. Chem.*, **28**, 3582 (1963).

The second product was heated at 100° *in vacuo* for 15 hr., which left a black solid of composition, $Ca(Q)_{0.99}(NH_3)_{0.82}$. Evacuation for 2 hr. at 150° removed only a little of the ammonia to yield $Ca(Q)_{0.99}(NH_3)_{0.73}$. A sample of this in air turned to an oily orange solid after 30 min. Hydrolysis by the ether–alcohol–water method produced orange products not further examined.

Quinoline–Calcium, 2:1.—Addition of the quinoline produced a precipitate which after evaporation of the ammonia and evacuation at 50° for 41 hr. was violet-black, of composition, $Ca(Q)_{1.99}(NH_3)_{0.52}$. On standing in air, this material changed in about 10 min. to an oily brown solid, which did not appear to undergo further change over another 5-hr. period. With water, the violet-black product became warm and turned yellow.

Quinoline–Calcium, 3:1.—Addition of the quinoline caused the mixture to turn green and then red-orange. Evaporation of the ammonia left a viscous red solution containing some red solid. This was subjected to evacuation at 60° for 140 hr., leaving a black solid. Assuming all the excess weight over that of calcium to be quinoline, the composition was $Ca(Q)_{1.46}$. By weight gain, the calcium content was 17.5%; by actual analysis of the black solid, it was 17.2% (theory for $Ca_2(Q)_3$, 17.9%). Exposed to air for 1 hr., this material changed completely to an oily orange solid and, after 24 hr. in the air, this solid was extracted with 250 ml. of ether, forming a yellow solution and leaving some orange insoluble matter. Evaporation of the ether filtrate left a very viscous orange-yellow oil.

3-Methylisoquinoline–Calcium, 1:1.—This amine is not very soluble in liquid ammonia. Its addition caused formation at once of a golden yellow precipitate. Evaporation of the ammonia left a yellow solid which became orange-brown after 6 hr. evacuation at 27°. Its composition was $Ca(Q)(NH_3)_{1.88}$. In air, it smoked, became incandescent, and turned light tan. With water, heat was evolved and the solid turned tan.

Phenanthridine–Calcium, 1:1.—This amine is colorless and insoluble in liquid ammonia. Five minutes after its addition, the blue calcium–ammonia color suddenly disappeared and an orange precipitate formed. Evaporation of the ammonia left an orange-brown solid, unchanged in color after 8-hr. evacuation at 28°. Its composition was then $Ca(phen)(NH_3)_{1.78}$. In air, it became very hot, smoked, and turned dark brown. In water it evolved heat and turned yellow but did not dissolve.

Acridine–Calcium, 1:1.—The acridine used was pale yellow even though recrystallized from ether and insoluble in ammonia. After about 15 min. of stirring the acridine with the calcium–ammonia solution, a pale green precipitate appeared Evaporation of the ammonia left an almost white solid which became light tan after evacuation for 18 hr. at 31°. This material, of composition $Ca(acr)(NH_3)_{1.69}$, became warm in air, smoking slightly, and turned first dark brown and then yellow-brown. With water a little heat was evolved, and the substance turned yellow.

2,2′-Dipyridine–Calcium, 1:2.—Dipyridine is colorless and insoluble in liquid ammonia. About 10 min. after its addition, a very dark violet color developed; no solid could be seen. Evaporation of the ammonia left a dark red-violet solid that turned dark violet-black when evacuated at 26° for 11 hr. The composition was $Ca_2(bipy)(NH_3)_{1.29}$. In air it became hot, smoked, and during about 5 min. turned pale yellow. In water it evolved heat and turned yellow-green.

1,10-Phenanthroline–Calcium, 1:1.—Phenanthroline is colorless and insoluble in liquid ammonia. It was added in two equal, separate portions. The first portion showed no reaction after 15 min. of stirring. Following addition of the second portion, a dark violet-red color developed. Evaporation of the ammonia left a purple solid which did not change appearance after evacuation at 31° for 11 hr. Its composition was then $Ca(phen)(NH_3)_{0.74}$. In air it became warm and smoked but required 15 min. to change color completely to yellow. In water it also turned bright yellow, with some heat evolved.

2-Aminopyridine–Calcium, 1:1.—Addition of this compound to the calcium–ammonia solution caused prompt appearance of a green precipitate. The color lightened as the ammonia was evaporated, becoming white. No more than a trace of hydrogen was evolved. After 6 hr. of evacuation at 28°, the composition was $Ca(AP)(NH_3)_{0.88}$. In air, this substance smoked and became incandescent, turning brown. With water, it formed a fluffy white precipitate and only a trace of hydrogen.

2-Aminopyridine–Calcium, 2:1.—The aminopyridine was added in two equal portions. Addition of the first caused appearance at once of a green suspension which soon became white. The second portion was then added, with no further visible change. Evaporation of the ammonia below 0° left a grayish white solid. This was extracted with 100 ml. of diethyl ether in which 2-aminopyridine is very soluble. Only a trace of solid was present in the evaporated extract. The insoluble solid was then dried in a stream of helium and analyzed. It seemed unreactive in air but reacted vigorously in water, forming a white precipitate and yellow solution. Calcium was determined as the oxalate: 18.1, 18.6%; theory for $Ca(AP)_2$, 17.7% Ca.

In a second experiment, the aminopyridine was added all at once, producing a white precipitate and removing the blue color of the ammonia solution. After evaporation of the ammonia and evacuation for 6 hr. at 28°, the composition was $Ca(AP)(NH_3)_{0.07}$. Analysis by ignition gave Ca 16.9, 17.0%, compared to 17.5% from the weights of reagents and 17.7% theory. This substance was hygroscopic, after 72 hr. in air being half-liquefied, but otherwise it seemed unreactive.

2-Amino-5-methylpyridine–Calcium, 1:1.—Addition of the pyridine derivative caused the blue ammonia solution to change to green, and a green precipitate appeared. Evaporation of the ammonia left a white solid which after evacuation for 15 hr. at 23° had the composition, $Ca(A)(NH_3)_{0.72}$. This became hot in air and smoked, turning dark brown. With water, heat was evolved, and a tan yellow solution with fluffy white precipitate was formed.

2-Amino-5-methylpyridine–Calcium, 2:1.—Addition of this compound caused immediate formation of a white precipitate. Evaporation of the ammonia and evacuation 14 hr. at 23° left a white solid of composition $Ca(A)_2(NH_3)_{0.31}$. No change in air was visible, but a sample gained 38% in weight after 24 hr. Only a color change from white to tan was observed with water. Analysis by ignition gave Ca 16.3, 16.8%, compared to 15.3% based on the original weights of reagents. Extraction with 100 ml. of ether separated only 4.9% of the original amine, identified by m.p. 62°, lit. m.p. 63°.

2,6-Diaminopyridine–Calcium, 1:2.—Initial addition of half the pyridine compound caused no visible change. Addition of the second half produced a dark gray precipitate. Cooling of the solution below the boiling point of ammonia permitted the observation of evolution of small gas bubbles—presumably hydrogen—which continued for an hour. Evaporation of the ammonia, followed by drying in a stream of nitrogen, left a ring of pink crystals halfway up the flask walls, and an olive green powder at the bottom. The pink crystals were removed and analyzed separately. They turned slightly brownish in air and seemed only slightly soluble in water, with no visible reaction. Calcium was determined as the oxalate: 6.1, 6.3%; theory for $Ca(C_5H_7N_3)_6$, 5.8%. The olive green solid turned brown in air in 10 min. In water it was largely soluble. Calcium was determined as the oxalate: 20.2, 21.1%.

2,2′-Dipyridylamine–Calcium, 1:1.—Addition of this substance caused the solution to turn dark green at once, and then an orange-yellow precipitate formed. Evaporation of the ammonia left a greenish orange solid which turned yellow after evacuation at 26° for 11 hr. Composition was $Ca(D)(NH_3)_{0.73}$. In air, the solid grew hot and smoked, with someparts becoming incandescent and turned a blackish brown. In water the color changed at once to yellow-green, and a strange odor was observed.

2,2′-Dipyridylamine–Calcium, 2:1.—Initial observations were the same as in the preceding experiment, but removal of the ammonia left a pale green solid which retained its color after 12 hr. evacuation at 26°. The composition was then $Ca(D)_2(NH_3)_{0.33}$. The solid turned white in air during 45 min. and gained 13% in weight in 24 hr. No reaction with water was visible except immediate loss of color. Analysis by ignition gave 11.3, 11.2% Ca; theory for the above-indicated composition, 10.3% Ca. Extraction of the bulk of the product with 100 ml. of ether separated a yellow, oily semisolid having the odor of dipyridylamine. The amount was 17% of the weight of the original amine. Water added to this oil caused it to crystallize. After air drying, this yellow-orange solid melted over a range of 55–70°, in contrast with the original amine, m.p. 88°.

Diphenylamine–Calcium, 1:1.—After about 30 min. following the addition of this amine, a clear blue-green solution was formed which suddenly changed to a clear yellow solution containing a tan precipitate. Evaporation of the ammonia left a pale green solid. After 3-hr. evacuation at 25°, this color was unchanged,

and the composition was $Ca(D)(NH_3)_{2.13}$. In air this substance became dark green at once, then smoked, glowed red-hot, and turned black. In water it turned pink with some heat being evolved.

Diphenylamine–Calcium, 2:1.—A bright yellow-green precipitate appeared within 10 min. of the addition of the amine. The ammonia was evaporated, leaving a green solid which quickly turned light brown *in vacuo*. After 25 hr. evacuation at 25°, the tan residue had the composition, $Ca(D)_2(NH_3)_{0.83}$. In air, it promptly turned dark green and black, with evolution of smoke and heat. In water, some heat was evolved and the substance turned pink.

Triphenylamine–Calcium, 1:1.—This amine is colorless and insoluble in liquid ammonia. When it was added to the calcium solution, a clear green color slowly developed over 30 min., and then suddenly the solution became clouded with an orange precipitate. Evaporation of the ammonia left a bright orange solid which lightened perceptibly during the first few minutes of evacuation. After 5-hr. evacuation at 31°, the solid was light tan, of composition $Ca(T)(NH_3)_{1.44}$. In either air or water it turned brown but evolved little heat. Extraction of the bulk of the product with 100 ml. of ether separated a colorless, crystalline substance melting at 112° and containing no calcium, in amount corresponding to 94% of the initial triphenylamine (m.p. 126.5°).

Ethylenediamine–Calcium, 1:1.—No visible reaction occurred when the diamine was added to the calcium–ammonia solution, but evaporation of the ammonia left a deep royal blue solid, which *in vacuo* turned gray at once. After 19 hr. evacuation at 27°, the residual solid seemed to be a mixture of gray and yellow-green particles, represented by $Ca(NH_3)_{2.47}$ or $Ca(en)_{0.07}$ assuming either all ammonia or all ethylenediamine was attached to the calcium. The substance smoked in air, becoming incandescent in places, and turned dark brown. With water there was some effervescence and formation of a white solid.

Ethylenediamine–Calcium, 6:1.—Again no visible reaction occurred, but evaporation of the ammonia left a deep royal blue solid which turned gray during 2 hr. *in vacuo*. After 19 hr. at 27°, evacuation left white or gray particles similar to the preceding product in behavior toward air and water. The composition corresponded to $Ca(NH_3)_{3.07}$ or $Ca(en)_{0.87}$.

Piperidine.—Several experiments were run in which piperidine, in quantity ranging from equimolar to large excess, was added to calcium–ammonia solutions. In none did any visible reaction occur. Evaporation of the ammonia and excess piperidine, followed by evacuation to nearly constant weight, led in each experiment to isolation of a blue-gray solid containing from 18 to 36% calcium. Since calcium hexamine is unstable *in vacuo*, whereas these products were stable, it seems probable that they contained at least some piperidine, since a mixture of calcium metal and calcium amide would contain more than 55% calcium. In air these products became incandescent, smoking and throwing off sparks. They were also highly reactive with water.

Tetrahydrofuran.—Addition of tetrahydrofuran to a calcium–ammonia solution produced no observable change even when 2 moles per mole of calcium had been added. Evaporation of the ammonia and vacuum evaporation of the tetrahydrofuran left a gray powder presumed to be metallic calcium, with perhaps some calcium amide, since approximately complete recovery of the furan was obtained.

Benzene.—For each mole of calcium in ammonia solution, 1, 2, and then 3 moles of benzene added had no visible effect. Evaporation of the ammonia left a violet-gray slurry, from which the color quickly disappeared as the solid was dried *in vacuo*. This solid, a grayish white, had the composition $Ca(NH_3)_{1.86}$ or $Ca(NH_2)_2$ but was not further investigated since no stable benzene derivative seemed indicated.

Diphenyl–Calcium, 1:1.—After addition of the diphenyl, no visible change occurred for 15 min. The mixture was then cooled to −80° and an orange precipitate suddenly appeared. Evaporation of the ammonia left an orange-red solid which became orange-brown after 12 hr. *in vacuo* at 22°, having the composition $Ca(D)(NH_3)_{1.48}$. In air this became only slightly warm and turned pale pink. It evolved some heat in reaction with water, forming a white solid.

Naphthalene–Calcium, 1:1.—No immediate reaction was observed when the naphthalene, which is insoluble in liquid ammonia, was added. Dry tetrahydrofuran (2 ml.) was then added, whereupon the blue of the ammonia solution disappeared at once, and an orange solid precipitated which rapidly became bright green. Evaporation of the ammonia left a violet-red solid, which on further evacuation faded to a very pale pink after 3 hr. at 28°. The formula after 5 min. was $Ca(N)(NH_3)_{2.07}$; compositions after continued evacuation were not determined accurately because of volatilization of naphthalene as well as ammonia.

In another experiment, no tetrahydrofuran was added. After about 30 min. at temperatures near −34°, the mixture was cooled to −80° which appeared to initiate reaction. Evaporation of the ammonia left a violet-red solid which faded perceptibly in 5 min. of evacuation and became light red after 11 hr. at 22°. The composition was uncertain since the product weight indicated the loss of naphthalene. In air, the solid smoked and became incandescent in spots, turning dark brown. Water turned the solid white, and the odor of naphthalene was detected.

Anthracene–Calcium, 1:1.—Anthracene is insoluble in liquid ammonia and caused no visible change for 5 min., when an orange-green precipitate suddenly appeared. Evaporation of the ammonia and evacuation for 11 hr. at 28° left a light green solid of composition $Ca(A)(NH_3)_{1.49}$. In air this smoked, became incandescent, and turned tan. With water, a little heat was evolved and an insoluble tan solid remained.

Phenanthrene–Calcium, 1:1.—Phenanthrene is insoluble in liquid ammonia, but its addition caused the ammonia solution to turn green promptly, and in about 3 min. it changed again, a red precipitate appearing. Evaporation of the ammonia left an orange-red solid which was light tan after 7 hr. evacuation at 22° and of composition $Ca(Ph)(NA_3)_{1.84}$. This became pale pink in air without other visible reaction. With water it became warm and an insoluble solid remained.

Chrysene–Calcium, 1:1.—Almost at once, with the addition of this ammonia-insoluble compound, a purple-violet color began forming, and a purple precipitate appeared in about 5 min. Evaporation of the ammonia left a purple solid which changed to a violet powder after evacuation for 6 hr. at 22°. The composition was $Ca(Ch)(NH_3)_{1.81}$. In air this became slightly warm and turned greenish brown. The only visible change in water was to a yellow color.

Pyrene–Calcium, 1:1.—About 15 min. after addition of this compound no visible change had occurred. The mixture was then cooled to −80° and a bright red precipitate suddenly appeared. Evaporation of the ammonia left a bright red solid. This, after 7-hr. evacuation at 25°, became a bright violet-red powder, of composition, $Ca(Py)(NH_3)_{2.04}$. In air this substance at once evolved heat and smoke and turned yellow-green. Water turned it the same color.

Fluoranthene–Calcium, 1:1.—A few minutes after this ammonia insoluble hydrocarbon was added, a bright red precipitate suddenly appeared. After the ammonia was evaporated, the solid turned orange. Evacuation at 27° for 3 hr. left a greenish orange solid of composition, $Ca(Fl)(NH_3)_{1.70}$. This only became slightly warm in air, turning brown, and was largely insoluble in water.

Diphenylethylene–Calcium, 1:1.—This hydrocarbon, which is ammonia insoluble, was added with stirring. Slowly, over about 1-hr., the blue color changed to dark green, and then a bright orange precipitate suddenly formed. Evaporation of the ammonia left a moist blue-green solid which remained sludge-like even after 12 hr. *in vacuo* at 25°. The composition was $Ca(Dip)(NH_3)_{2.06}$. In air, this material quickly turned black; in water it turned white. No other reaction was observed.

Tetraphenylethylene–Calcium, 1:1.—After about 1 hr. following the addition of this hydrocarbon, the blue of the calcium–ammonia solution suddenly changed to a dark violet purple. No precipitate could be seen. Evaporation of the ammonia left a violet purple powder which changed *in vacuo* to light red. After 3-hr. evacuation at 25° the composition was $Ca(T)(NH_3)_{1.44}$. In air the solid warmed slightly and turned white; the reaction with water was similar.

Triphenylmethane–Calcium, 1:1.—An hour after addition of this ammonia insoluble compound, a bright red precipitate suddenly formed. Evaporation of the ammonia left a bright red solid that paled rapidly when evacuated. After 5 hr. at 27° a pink solid of composition $Ca(Tr)(NH_3)_{2.03}$ remained. This became white in air but seemed otherwise unreactive. The only change observed with water was to a brown color. Extraction of the product with 100 ml. of ether separated a colorless solid containing no calcium and amounting to 96% of the weight of the original triphenylmethane, melting at 82° (triphenylmethane, m.p. 92.5°).

Triphenylmethane–Calcium, 2:1.—Similar observations to those above. Evaporation of the ammonia and evacuation for 5 hr. at 27° left a pale pink solid of composition $Ca(Tr)_2(NH_3)_{1.74}$. This would correspond to 7.2% Ca. Analysis by ignition gave 5.8% Ca. Extracted by 100 ml. of ether was a colorless crystalline solid amounting to 91% of the weight of initial triphenylmethane, melting at 88°.

Indene–Calcium, 1:1.—About 20 min. after addition of the indene, the blue calcium–ammonia color suddenly disappeared and a tan precipitate appeared. (This experiment was terminated by accident and not repeated.)

Fluorene–Calcium, 1:1.—During 30 min. of stirring, the mixture gradually turned dark green, and then a dark red precipitate suddenly appeared. This change appeared to be promoted by cooling. Evaporation of the liquid ammonia left a bright red solid which became orange-yellow in 5 min. of evacuation and was bright yellow after 16 hr. *in vacuo* at 24°. Its composition was $Ca(Fl)(NH_3)_{1.46}$. In air, the solid became hot and smoked, turning dark brown. Water turned it tan without other visible change. An oily yellow-orange semi-solid was removed by extraction with 100 ml. of ether, in amount corresponding to 16% of the original fluorene. Fluorene melts at 116° in contrast to 70° for complete melting of the orange material. This material contained no calcium.

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Diphenylamino Derivatives of Carbon, Silicon, Germanium, and Phosphorus

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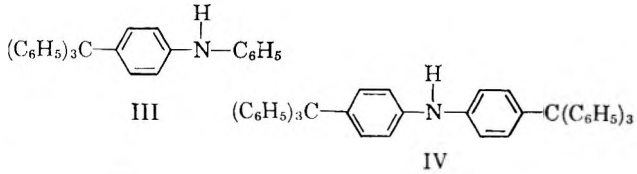
Wieland has reported the preparation[1a] of N-trityldiphenylamine (I), m.p. 172° dec., and the thermal rearrangement[1b] of I to *p*-trityldiphenylamine (III), m.p. 242°. In a more recent paper, Chugunov[2] formulated the product resulting from the lithium condensation of trityl chloride and diphenylamine in refluxing toluene as I, but gave a melting point of 249–250°. In the same paper, Chugunov reports the preparation of N-triphenylsilyldiphenylamine (II) and gives a melting point of 224–225°.

$(C_6H_5)_3CN(C_6H_5)_2$ I $(C_6H_5)_3SiN(C_6H_5)_2$ II

We have confirmed that the lower melting product reported by Wieland is indeed I and find that the trityl derivative obtained by Chugunov is the isomer, *p*-trityldiphenylamine (III). Compound III and *p,p'*-ditrityldiphenylamine (IV) have been prepared by Craig[3] *via* the acid-catalyzed tritylation of diphenylamine by triphenylcarbinol. Compounds I and III may be clearly distinguished by their infrared absorption spectra. Compound III exhibits absorption bands at 3300 and 840 cm.$^{-1}$ which have been assigned[4] to the N–H stretching frequency and to the out-of-plane C–H deformation for *para*-substituted aromatic compounds, respectively. The spectrum of I does not exhibit an N–H band nor those bands characteristic of disubstituted aromatic compounds.



III

IV

When Chugunov's procedure for the preparation of N-triphenylsilyldiphenylamine (II) was repeated, a silylamine melting at 163° was obtained in poor yield. The melting point given by Chugunov (224–225°) for II is nearly identical with the melting point of hexaphenyldisiloxane (226°). Hexaphenyldisiloxane is often found as a by-product in organometallic reactions of triphenylhalosilanes.

We now report an improved general synthesis procedure for the preparation of N-substituted diphenylamines of the general type, $(C_6H_5)_{n-1}M^nN(C_6H_5)_2$.

$$(C_6H_5)_2NH + C_4H_9Li \longrightarrow (C_6H_5)_2NLi + C_4H_{10}$$

or

$$(C_6H_5)_2NH + NaH \longrightarrow (C_6H_5)_2NHa + H_2$$

$$(C_6H_5)_2NLi(Na) + (C_6H_5)_{n-1}M^nCl \longrightarrow (C_6H_5)_2NM^n(C_6H_5)_{n-1}$$

M = C, Si, Ge, P

By this procedure, a 70% yield of N-trityldiphenylamine (I) was obtained along with 3% of isomer III. Similarly, a product which we propose to be N-triphenylsilyldiphenylamine (II), m.p. 162–163°, was obtained in 68% yield. N-Triphenylgermanyldiphenylamine, m.p. 153.5–155°, and N-diphenylaminodiphenylphosphine,[5] m.p. 131–132.5°, were also prepared by this route. Attempts to isolate the N-diphenylaminotriphenyltin were unsuccessful. Bis(triphenyltin) oxide which may have resulted from hydrolysis of the expected product[6] was found in the reaction mixture.

Experimental[7]

N-Lithiodiphenylamine.—A solution of 16.0 g. (0.01 mole) of diphenylamine in 70 ml. of anhydrous ether was added to an ice-cooled solution of 0.01 mole of butyllithium in 50 ml. of ether. The reaction was stirred for several hours until Color Test I[8] was negative, indicating the absence of butyllithium.

Preparation of N-Substituted Diphenylamine.—The preparation of **N-trityldiphenylamine** (I) from N-lithiodiphenylamine and from N-sodiodiphenylamine are described as examples of the procedures used.

Method A.—A solution of 0.10 mole of N-lithiodiphenylamine was added dropwise at room temperature to a stirred solution of 27.9 g. (0.10 mole) of trityl chloride in 75 ml. of THF. The reaction was mildly exothermic and became red-brown. The reaction was held at 35° for 1.5 hr. and was subsequently filtered. THF was replaced by benzene and 1.25 g. (3.2%) of *p*-trityldiphenylamine identical with III precipitated from solution. From the benzene solution, 28.8 g. (70%) of I was isolated. Two recrystallizations from ethyl acetate gave pure I, m.p. 175–177° dec.

Anal. Calcd. for $C_{31}H_{25}N$: C, 90.47; H, 6.12; N, 3.40. Found: C, 90.15; H, 6.09; N, 3.56.

(1) (a) H. Wieland, *Ann.*, **381**, 200 (1911); (b) H. Wieland, B. Dolgow, and T. J. Albert, *Ber.*, **52**, 893 (1919).

(2) V. S. Chugunov, *J. Gen. Chem. USSR*, **20**, 2765 (1956).

(3) D. Craig, *J. Am. Chem. Soc.*, **71**, 2250 (1949).

(4) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958.

(5) H. H. Sisler and N. L. Smith, *J. Org. Chem.*, **26**, 611 (1961).

(6) Organotin nitrogen compounds have been reported to be easily hydrolyzed [*cf.* K. Sisido and S. Kozima, *ibid.*, **27**, 4051 (1962); E. W. Abel, D. Brady, and B. R. Lerwill, *Chem. Ind.* (London), 1333 (1962)].

(7) All melting points are uncorrected. All reactions were performed under an atmosphere of dry, oxygen-free nitrogen. Tetrahydrofuran (THF) was distilled from CaH_2 prior to use.

(8) H. Gilman and F. Schulz, *J. Am. Chem. Soc.*, **47**, 2002 (1925).

Upon concentration of the benzene solution, 4.4 g. (17%) of triphenylcarbinol was also isolated.

Method B.—A solution of 5.57 g. (0.02 mole) of trityl chloride and 3.38 g. (0.02 mole) of diphenylamine in 30 ml. of THF was added to a slurry of 0.48 g. (0.02 mole) of a 52% dispersion of sodium hydride in mineral oil with stirring at room temperature. After the addition was complete, the reaction was refluxed for 4 hr. and a red-brown color slowly developed. The reaction mixture was allowed to stand overnight, 100 ml. of benzene then was added, and the reaction mixture was filtered. THF was driven off and replaced by hot petroleum ether (b.p. 30–60°). Upon cooling, 5.42 g. (66.2%) of crude I, m.p. 170–172° dec., precipitated from solution.

N-Triphenylsilyldiphenylamine (II). Method A.—The addition of triphenylchlorosilane to an equivalent amount of N-lithiodiphenylamine gave II in 68% yield, m.p. 162–163° after recrystallization from ethyl acetate.

Anal. Calcd. for $C_{30}H_{25}NSi$: C, 84.26; H, 5.89; N, 3.27; Si, 6.56; mol. wt., 427.6. Found: C, 84.23; H, 5.89; N, 3.20; Si, 6.7; mol. wt., 431.

From the reaction mixture, 5.2% of hexaphenyldisiloxane was isolated also, m.p. 225–226°, lit.[9] m.p. 226°. Identification was based on mixture melting point and comparison of its infrared spectrum with that of an authentic sample.

Method B.—The addition of triphenylchlorosilane and diphenylamine to an equivalent amount of sodium hydride gave II in 56% yield and 11% of hexaphenyldisiloxane.

Hydrolysis of N-Triphenylsilyldiphenylamine (II).—A solution of 1.0 g. (0.00234 mole) of II in 30 ml. of 95% ethanol and 2 ml. of concentrated hydrochloric acid was refluxed for 80 min. The hot solution was poured into water and the aqueous layer was extracted with ether. The ether layer was dried, evaporated to dryness, and the residue was recrystallized from petroleum ether (b.p. 60–90°) to give 0.49 g. (77.2%) of triphenylsilanol identified by mixture melting point and comparison of its infrared spectrum with that of an authentic sample.

N-Diphenylaminodiphenylphosphine (V). Method A.—The addition of N-lithiodiphenylamine to an equivalent amount of diphenylchlorophosphine gave 58% of V, m.p. 131–132.5 after recrystallization from ethyl acetate, lit.[5] m.p. 130–132°.

Anal. Calcd. for $C_{24}H_{20}NP$: C, 81.56; H, 5.70; N, 3.96; P, 8.77. Found: C, 80.13; H, 5.74; N, 4.10; P, 8.98.

Method B.—A solution of 5.07 g. (0.030 mole) of diphenylamine in 35 ml. of THF was added dropwise with stirring to 0.036 mole of sodium hydride (52% dispersion in mineral oil). The reaction mixture was refluxed for 2 hr. A solution of 6.62 g. (0.030 mole) of diphenylchlorophosphine in 30 ml. of THF was added dropwise to the hot reaction mixture. The resulting mixture was refluxed for 2 hr., cooled, filtered, and the filtrate was concentrated under reduced pressure. The residue was recrystallized from ethyl acetate to give 7.46 g. (70.3%) of V.

N-Triphenylgermanyldiphenylamine (VI). Method A.—The addition of triphenylchlorogermane to an equivalent amount of N-lithiodiphenylamine gave 23% of crude VI, m.p. 130–153°. Two recrystallizations from petroleum ether (b.p. 60–90°) gave VI, m.p. 153.5–155°.

Anal. Calcd. for $C_{30}H_{25}GeN$: C, 76.32; H, 5.34; N, 2.97. Found: C, 76.59, 76.75; H, 5.31, 5.29; N, 2.66, 2.60.

Method B.—A solution of 3.38 g. (0.020 mole) of diphenylamine in 30 ml. of THF was added to 0.020 mole of sodium hydride (48% dispersion in mineral oil) with stirring. The reaction mixture was refluxed for 0.5 hr., cooled, and to it a mixture of 6.78 g. (0.020 mole) of triphenylchlorogermane in 40 ml. of THF was added. The reaction mixture was refluxed for 2 hr. and filtered hot. The filtrate was concentrated and extracted with a small amount of petroleum ether (b.p. 60–90°) to remove unchanged diphenylamine. The residue was extracted with ethanol, and the alcohol soluble material was recrystallized several times from petroleum ether (b.p. 60–90°) to give VI in 25.2% yield.

***p*-Trityldiphenylamine (III) and *p,p'*-Ditrityldiphenylamine (IV).**—The procedure used was essentially that of Craig.[3] A solution containing 2.79 g. (0.0174 mole) of diphenylamine, 4.84 g. (0.0174 mole) of tritylchloride, 10 ml. of concentrated hydrochloric acid in 100 ml. of glacial acetic acid was refluxed for 3 hr. The cooled reaction mixture was diluted with water and 10 ml. of diethyl ether was added. The mixture was filtered and the precipitate was extracted with benzene to give 2.4 g. (33.5%) of III, m.p. 248–255°, lit.[3] m.p. 245–248°.

Anal. Calcd. for $C_{31}H_{25}N$: C, 90.47; H, 6.12; N, 3.40. Found: C, 90.64; H, 5.92; N, 3.35.

The benzene insoluble material was washed with carbon tetrachloride and afforded 3.3 g. (61.5%) of IV, m.p. 350–356°, lit. m.p. 350–351°.

Anal. Calcd. for $C_{50}H_{39}N$: C, 91.84; H, 6.01; N, 2.14. Found: C, 91.00; H, 5.92; N, 2.18.

The procedure of Chuganov[1] was repeated. A mixture of 14.0 g. (0.050 mole) of trityl chloride, 9.0 g. (0.056 mole) of diphenylamine, and 1.4 g. (0.203 g.-atom) of freshly cut lithium wire in 50 ml. of toluene was refluxed with stirring under nitrogen for 22 hr. From the reaction mixture, the following products were isolated: 0.50 g. (5.8%) of diphenylamine; 8.6 g. (41.5%) of III, mixture melting point showed no depression and infrared spectrum was superimposable with that of III described above; and 1.74 g. (13.9%) of triphenylcarbinol identified by mixture melting point and comparison of its infrared spectrum with that of an authentic sample.

(9) W. H. Daudt and J. F. Hyde, *J. Am. Chem. Soc.*, **74**, 386 (1952).

Base-Metal Sulfides as Reductive Alkylation Catalysts

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Base-metal sulfides[1] have been investigated as catalysts for the preparation of secondary amines by the reductive alkylation[2] of primary amines with ketones in the presence of hydrogen. It was hoped to minimize

$$RNH_2 + O{=}C< + H_2 \xrightarrow{\text{cat.}} RNH{-}CH< + H_2O$$

the nuclear hydrogenation of aromatic rings, an important and undesirable side reaction in nickel[3] and in platinum-metal-[4,5] catalyzed reductive alkylations of aryl amines.

The sulfides of rhenium, iron, cobalt, nickel, molybdenum, tungsten, and nickel–tungsten showed activity in the reductive alkylation of primary amines, or their nitro precursors, with aliphatic ketones. Good results were obtained with both alkyl and aryl amines.

The desired absence of nuclear hydrogenation with aryl amines was realized. In addition, there was little or no cleavage of carbon–nitrogen bonds such as caused by platinum-metal catalysts.[4-6] Such cleavage probably involves the hydrogenolysis of an unsaturated amine formed during an intermediate stage of nuclear hydrogenation.[7] That an allylic amine is the active intermediate is suggested by the hydrogenolysis

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(2) W. S. Emerson, "Organic Reactions," Coll. Vol. 4, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 174.

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(4) Naugatuck Chemical Development Dept., U. S. Rubber Co., Naugatuck, Conn., unpublished work, 1958.

(5) C. E. Moore, H. L. Larson, and S. Meinstein, U. S. Patent 3,074,908 (Jan. 22, 1963).

(6) S. Ward, S. A. Lamb, and M. A. E. Hodgson, British Patent 712,100 (July 21, 1954); S. Ward and S. A. Lamb, British Patent 716,239 (Sept. 29, 1954).

(7) M. Freifelder and G. R. Stone, *J. Org. Chem.*, **27**, 3568 (1962).

TABLE I

REDUCTIVE ALKYLATIONS[a]

Catalyst		Amine or nitro compd.		Ketone		Temp.,	Pressure,	Time,	
Compd.	Wt., g.	Compd.	moles	Compd.	moles	°C.	p.s.i.g.	hr.	Products, mole % yield
Re sulfide	2.5	Aniline	0.75	Acetone	2.25	140	1200–1400	4.4	N-Isopropylaniline, 90%[b, c]
Mo sulfide	10.0	Aniline	0.75	Acetone	2.25	185	1400–1600	3.5	N-Isopropylaniline, 91%[b]; aniline, 4%[b, d]
Ni–W sulfide	10.0	Aniline	0.75	Acetone	2.25	185	1400–1600	2.8	N-Isopropylaniline, 90%[b, c]; aniline, 8%[b, c]
Mo sulfide	20.0	N-Phenyl-*p*-phenylenediamine	0.80	Acetone	4.5	180–190	500–700	5.5	N-Isopropyl-N′-phenyl-*p*-phenylenediamine, 100%[f]
Ni sulfide	[g]	N-Phenyl-*p*-phenylenediamine	0.50	Acetone	2.18	210	1000–1800	6.3	N-Isopropyl-N′-phenyl-*p*-phenylenediamine, 77%[h]; N-phenyl-*p*-phenylenediamine, 19%[i, j]
W sulfide	16.0	N-Phenyl-*p*-phenylenediamine	0.75	Methyl ethyl ketone	3.0	245	1900–2550	2.5	N-Phenyl-N′-*sec*-butyl-*p*-phenylenediamine, 86%[b]; N-phenyl-*p*-phenylenediamine, 7%[i, k]
Fe sulfide	10.0[l]	Nitrobenzene	0.20	Acetone	2.72	180	1600–1800	3.6	N-Isopropylaniline, 12%[b]; aniline, 48%[b]; nitrobenzene, 30%[b]
Co sulfide	11.5[l]	*p*-Nitroaniline	0.30	Methyl ethyl ketone	1.80	110–150 180	1200–1400	0.1 6	N,N′-Di-*sec*-butyl-*p*-phenylenediamine, 94%[b]
Mo sulfide	10.0	Cyclohexylamine	0.50	Cyclohexanone[m]	0.50	190	1150–1700	5	Dicyclohexylamine, 88%[b]
Ni sulfide[n]	15.0	Cyclohexylamine	1.0	Cyclohexanone	1.90	180	1400–1700	14	Dicyclohexylamine, 95.5%[o]

[a] Each experiment was run in a 600-ml. Magne-Dash autoclave or a 1-l. stirred autoclave with a turbine impeller. [b] Determined by gas–liquid chromatographic analysis (g.l.c.). [c] Hydrogen absorption was *ca.* 280% of theory; g.l.c. analysis of the distillate showed that most of the excess acetone had been reduced to isopropyl alcohol. [d] No isopropyl alcohol, cyclohexylamine, or N-isopropylcyclohexylamine (determined by g.l.c.); negligible isopropylamine and diisopropylamine (determined by titration of distillate for base). [e] Weight % of topped residue product. [f] Topped residue product, m.p. 67–77.5° (mostly 70.5–77.5°); pure compound, m.p. 79.5–80°. The distillate was shown by titration for base to contain little or no aliphatic amines, and by g.l.c. to contain little or no isopropyl alcohol. [g] Prepared *in situ* from *ca.* 10 g. (on dry basis) of Raney nickel and 0.64 g. of sulfur. [h] Identified and analyzed by infrared. [i] Identified by infrared and analyzed by colorimetric determination of reaction product with salicylaldehyde in glacial acetic acid. [j] Distillate shown by titration for base to contain *ca.* 2 mole % yield of aliphatic amines, and by g.l.c. to contain *ca.* 10 mole % yield (based on acetone) of isopropyl alcohol. [k] Distillate shown by titration for base to contain *ca.* 1 mole % yield of aliphatic amines, and by g.l.c. to contain *ca.* 13.5 mole % yield (based on methyl ethyl ketone) of *sec*-butyl alcohol. [l] Weight given on dry basis. [m] Xylene (150 ml.) added as solvent. [n] Girdler T-920. [o] Isolated and identified by infrared as the hydrochloride. Chlorine analysis of 15.5% (theory is 16.3%) indicates 95% purity and actual yield of 91 mole %.

of benzyl amines[8] and the salts of allylic and propargylic amines.[9]

The use of rhenium sulfide resulted in hydrogenation of excess ketone to the corresponding alcohol. Little or no ketone reduction, a major disadvantage of copper chromite catalysts,[10] was observed with the other sulfides except under rather severe reaction conditions with nickel sulfide and with tungsten sulfide.

Rhenium sulfide appears to be the most active, and iron sulfide and tungsten sulfide the least active of the catalysts tested. However, variations both in reaction conditions and methods of catalyst preparation preclude all but gross qualitative comparisons.

Base-metal sulfides often will be the catalysts of choice for reductive alkylations because of their extreme resistance to poisoning[1] and their ability to minimize nuclear hydrogenation, carbon–nitrogen cleavage, and, in most cases, ketone reduction.

Experimental

Rhenium heptasulfide was prepared as described in the literature.[1] Cobalt polysulfide was prepared as described in the literature[11] and used as an isopropyl alcohol paste containing 13.5 wt. % solids. Iron sulfide was prepared by the addition of a solution of 40.4 g. (0.10 mole) of ferric nitrate, $Fe(NO_3)_3 \cdot 9H_2O$, in 200 ml. of water to a solution of 24.0 g. (0.10 mole) of sodium sulfide, $Na_2S \cdot 9H_2O$, and 6.4 g. (0.20 mole) of sulfur in 200 ml. of water at *ca.* 40°. The black precipitate was filtered and washed several times with water and then twice with isopropyl alcohol. The iron sulfide was used as an isopropyl alcohol paste containing 42% solids. It was observed to turn rust brown on exposure to air.

A powdered tungsten disulfide (Sylvania TTC-657) was obtained from Sylvania Electric Products, Inc. Powdered 20% molybdenum sulfide on alumina (Girdler T-318) was obtained from the Chemetron Corp. Nickel–tungsten sulfide on alumina (6% Ni, 19% W, Harshaw Ni-4405E) was obtained from the Harshaw Chemical Co. as 1/8-in. extrusions and was powdered before use. Nickel sulfide on activated Montmorillonite clay suspended in hardened cottonseed oil and containing 15% Ni (Girdler T-920) was obtained from the Chemetron Corp. A second nickel sulfide catalyst was prepared *in situ* from about 10 g. (on a dry basis) of Raney nickel and 0.64 g. of sulfur.

The results are summarized in Table I. A detailed description of one experiment is given to illustrate the experimental procedure.

To a 1-l. stainless steel autoclave fitted with a turbine agitator were added 147 g. (0.80 mole) of N-phenyl-*p*-phenylenediamine, 261 g. (4.5 moles) of acetone, and 20.0 g. of 20% molybdenum sulfide-on-alumina catalyst (Girdler T-318). The autoclave was sealed and purged first with nitrogen and then with hydrogen; hydrogen was added to a pressure of 500 p.s.i.g. The reaction

(8) W. H. Hartung and R. Simonoff, "Organic Reactions," Coll. Vol. 7, John Wiley and Sons, Inc., New York, N. Y., 1953, p. 263.

(9) R. Epsztein, M. Olomucki, and I. Marszak, *Bull. soc. chim. France*, 779 (1952).

(10) F. S. Dovell and H. Greenfield, *Ind. Eng. Chem. Prod. Res. Develop.*, **1**, 179 (1962).

(11) M. S. Farlow, M. Hunt, C. M. Langkammerer, W. A. Lazier, W. J. Peppel, and F. K. Signaigo, *J. Am. Chem. Soc.*, **70**, 1392 (1948).

mixture was heated with agitation for 5.5 hr. at 180–190° and 500–700 p.s.i.g. There was little or no hydrogen absorption in the last 0.5 hr. The autoclave was cooled and depressurized and its contents were filtered to remove the catalyst. The filtrate was concentrated under reduced pressure until the pot temperature reached 185° at 22 mm. The residue product consisted of 182 g. (quantitative yield) of N-isopropyl-N′-phenyl-*p*-phenylenediamine, m.p. 67–77.5° (mostly 70.5–77.5°), identified by its infrared spectrum. The distillate was shown by titration to contain little or no aliphatic amines, indicating the absence of carbon–nitrogen cleavage, and was shown by gas–liquid chromatographic analysis to contain little or no isopropyl alcohol, indicating the lack of ketone reduction.

Organotin Chemistry. IV.[1] Reduction of Hexaorganoditins with Lithium Aluminum Hydride

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Noltes and van der Kerk[2] have reported the reductive cleavage of the tetrabutyldichloroditin (I), re-

$$(C_4H_9)_2SnSn(C_4H_9)_2$$
$$\quad\;|\quad|$$
$$\quad Cl\;Cl$$
$$\quad\;I$$

ported by Johnson and Fritz,[3] to yield dibutyltin dihydride. Subsequently, I has been reformulated as bistetrabutyldichlorotin oxide (II).[4]

$$(CH_4H_9)_2Sn—O—Sn—(CH_4H_9)_2$$
$$\quad\;|\qquad\quad|$$
$$\quad Cl\qquad Cl$$
$$\quad\;II$$

Therefore, the work of Noltes and van der Kerk must be taken as evidence for reduction of the tin–oxygen bond. This hypothesis was further strengthened by the work of Considine and Ventura[5] who reduced bistributyltin oxide with lithium aluminum hydride and obtained good yields of tributylin hydride.

It, therefore, seemed appropriate to determine whether the Sn–Sn bond was, in fact, cleaved by lithium aluminum hydride.

The cleavage of ditins with reagents such as lithium in tetrahydrofuran is well-known. Both hexabutylditin and hexaphenylditin have been reduced with the above reagent to yield the corresponding triorganotin hydride.[6]

Hexabutylditin was treated with a large excess of lithium aluminum hydride in various solvents at different temperatures for different time periods. The results are shown in Table I. The reaction is complex. It appears to be an equilibrium reaction at lower temperatures giving, as the major cleavage product, tributyltin hydride. Presumably, the first step in the reaction is cleavage of the ditin by hydride ion (or its equivalent) as indicated below.

TABLE I

REACTION OF HEXABUTYLDITIN WITH LITHIUM ALUMINUM HYDRIDE

Solvent	Temp., °C.	Time, hr.	Products after work-up (%)
Ether	35	18	Recovered ditin (90), Bu_3SnH (4)
Tetrahydrofuran	64	18	Recovered ditin (73), Bu_3SnH (18)
Tetrahydrofuran	64	168	Recovered ditin (71), Bu_3SnH (19)
Dioxane	100	3	Recovered ditin (85), Bu_3SnH (10)
Dioxane	100	6.5	Recovered ditin (80), Bu_3SnH (10) (remainder tar)
Dioxane	100	21	Recovered ditin (26), Bu_3SnH (5), Bu_2SnO (33), Sn metal (5) (remainder tarry products)
Diglyme	135	2.5	Recovered ditin (20), Bu_3SnH (19), Bu_2SnO (22), Sn metal (17) (remainder tar)

$$(C_4H_9)_3SnSn(C_4H_9)_3 \overset{H^-}{\rightleftharpoons} (C_4H_9)_3SnH + (C_4H_9)_3Sn^-$$

The anion is neutralized by a cation such as Li^+ or its equivalent to form tributyltin lithium or its equivalent. Hydrolysis of this compound would give additional amounts of tributyltin hydride as well as regenerating starting material. The reverse reaction involved in the equilibrium, the regeneration of starting hexabutylditin, could be the attack of the tributyltin anion on tributyltin hydride. Gilman[7] has demonstrated in the phenyltin series the reaction of phenyllithium with triphenyltin hydride to give tetraphenyltin and lithium hydride.

Tributyltin lithium was prepared by the procedure of Gilman and Rosenberg[8] from stannous chloride and butyllithium. The reagent was hydrolyzed with ammonium chloride solution to yield 38% tributyltin hydride and 55% dibutyltin oxide. Coates[9] was unable to detect any tributyltin hydride among the hydrolysis products of tributyltin lithium prepared by the above method, while Tamborski[10] reported a 54% yield of tributyltin hydride and a 29% yield of hexabutylditin from hydrolysis of tributyltin lithium prepared from tributyltin chloride and lithium in tetrahydrofuran. It, therefore, appears that the hydrolysis products of tributyltin lithium vary, depending on the method of preparation as well as on the reaction solvent.

An equilibrium reaction is also indicated by the data in Table I which show that both 18- and 168-hr. reflux in tetrahydrofuran gave identical yields (20%) of tributyltin hydride. In a subsequent experiment, 20 mole % of tributyltin hydride was added to hexabutylditin, and the mixture reacted with lithium aluminum hydride. Instead of the expected 40% yield of tributyltin hydride, there was only obtained a 27% total yield showing that the equilibrium had been displaced to the left by the inclusion in the reaction of one of the products.

(1) Paper III: W. J. Considine and J. J. Ventura, *J. Org. Chem.*, **28**, 221 (1963).

(2) J. Noltes and G. van der Kerk, "Functionally Substituted Organotin Compounds," Tin Research Institute, Greenford, England, 1958, p. 43.

(3) O. Johnson and H. Fritz, *J. Org. Chem.*, **19**, 74 (1954).

(4) A. Gibbons, A. Sawyer, and A. Ross, *ibid.*, **26**, 2304 (1961).

(5) W. J. Considine and J. J. Ventura, *Chem. Ind.* (London), 1683 (1962)

(6) C. Tamborski, F. E. Ford, W. L. Lehn, G. J. Moore, and E. J. Soloski, *J. Org. Chem.*, **27**, 619 (1962).

(7) H. Gilman and H. Melvin, *J. Am. Chem. Soc.*, **71**, 4050 (1949).

(8) H. Gilman and S. Rosenberg, *ibid.*, **75**, 2507 (1953).

(9) G. Coates, "Organometallic Compounds," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1960, p. 193.

(10) C. Tamborski, F. Ford, and E. Soloski, *J. Org. Chem.*, **28**, 237 (1963).

As the temperature was raised, the reaction became even more complex and more profound cleavage products were formed so that, at 135° (in refluxing diglyme), the ultimate cleavage product, tin metal, was formed. The higher temperatures may promote the disproportionation of the intermediate tributyltin lithium.[11]

$$Bu_3SnLi \longrightarrow Bu_2Sn + BuLi$$

Air oxidation of the dibutyltin during work-up would lead to the product actually found, dibutyltin oxide, but the origin of the tin metal is obscure.

The reaction of hexaphenylditin with excess lithium aluminum hydride is also complex. As shown in Table II, at lower temperatures, the product isolated is diphenyltin oxide while, at elevated temperatures, tin metal is the product. No triphenyltin hydride could be detected in either reaction. It is difficult to explain the cleavage products as arising from the disproportionation of the intermediate triphenyltin lithium, since Tamborski[12] has indicated that the above intermediate is stable in refluxing tetrahydrofuran for 24 hr. No degradation of hexaphenylditin was noted in an experiment when the ditin was refluxed in tetrahydrofuran for 21 hr.; 98% of the ditin was recovered unchanged.

TABLE II
REACTION OF HEXAPHENYLDITIN WITH LITHIUM ALUMINUM HYDRIDE

Solvent	Temp., °C.	Time, hr.	Products (%)
Ether	35	18	Diphenyltin oxide (85), hexaphenylditin (5) (remainder tar)
Tetrahydrofuran	64	21	Tin metal (75) (residue unidentified tar containing 10% tin by analysis)

A preliminary experiment showed that tetraphenyltin is also cleaved by lithium aluminum hydride. The reaction was run at 0° for 6.5 hr. in tetrahydrofuran. Approximately 87% of starting material was recovered, but a trace of diphenyltin oxide was also found, and the presence of benzene was detected in the solvent distillate by vapor phase chromatography.

Experimental

Reaction of Hexabutylditin with Lithium Aluminum Hydride.—All of the reactions reported in Table I were run by the typical procedure shown below. In a typical run, 91 g. (0.157 mole) of hexabutylditin which had been freshly distilled (b.p. 180–200° at 1 mm.) was dissolved in 100 ml. of dry tetrahydrofuran and added dropwise under nitrogen to a slurry of 8.0 g. (0.84 equiv.) of lithium aluminum hydride in 400 ml. of tetrahydrofuran. The mixture warmed slightly and turned dark green after 1 hr. It was then refluxed and stirred for 18 hr. The mixture was then hydrolyzed with sodium potassium tartrate according to the procedure of van der Kerk,[13] but an incomplete separation occurred. The aqueous layer was, therefore, extracted with three 200-ml. portions of ether; the ethereal layer was combined with tetrahydrofuran layer formed on hydrolysis. The extracts were dried over exsiccated magnesium sulfate, and the mixed solvents were distilled through a 25-cm. Vigreux column. The still residue was then distilled through a small 10-cm. Vigreux column and there was obtained 17.0 g. (0.0585 mole, 18.5% yield) of tributyltin hydride, b.p. 75–85° (0.025 mm.), $n^{30}D$ 1.4682, lit.[14] $n^{22}D$ 1.4720; and 70.0 g. (0.121 mole, 77% recovery) of hexabutylditin, b.p. 156–160° (0.025 mm.), $n^{25}D$ 1.5100, lit.[14] $n^{25}D$ 1.5090.

The infrared spectrum of the tributyltin hydride was superimposible upon the spectrum of an authentic sample of tributyltin hydride prepared by reduction of bis(tributyltin oxide) with lithium aluminum hydride.

Preparation and Hydrolysis of Tributyltin Lithium.—Tributyltin lithium was prepared by the method of Gilman and Rosenberg[8] using 25.6 g. (0.135 mole) of stannous chloride and 173 g. of a 15% solution of *n*-butyllithium in hexane (0.405 mole of *n*-butyllithium). The mixture was hydrolyzed for 15 min. after preparation with saturated ammonium chloride solution, and then was worked up in the usual manner to yield 15 g. (0.052 mole) of tributyltin hydride, b.p. 123° (1.5 mm.), infrared spectrum and vapor phase chromatogram identical with an authentic sample; and 18.5 g. (0.075 mole) of di-*n*-butyltin oxide.

Anal. Calcd. for $(C_4H_9)_2SnO$: Sn, 47.8. Found: Sn, 47.65.

Reaction of Hexaphenylditin with Lithium Aluminum Hydride.—This reaction was carried out in a fashion similar to that described above. In a typical run, 90 g. (0.128 mole) of recrystallized hexaphenylditin [m.p. 230–231° (uncor.)] was mixed under nitrogen with a slurry of 15.0 g. (1.6 equiv.) of lithium aluminum hydride in 400 ml. of dry tetrahydrofuran. The initial dark green color turned dark brown on refluxing for 21 hr. The mixture was worked up as with hexabutylditin to yield 22.7 g. (0.191 mole, 74.3% yield) of metallic tin in the form of small spheres.

Anal. Calcd.: Sn, 100.0. Found: Sn, 99.0 (emission spectrograph shows all Sn lines).

There was also isolated 20 g. of an unidentified dark red-brown material from evaporation of the mixed solvents, probably polymeric diphenyltin. This material, on standing in air, slowly decolorized and formed a white powder which was probably impure diphenyltin oxide.

Anal. Calcd. for $(C_6H_5)_2SnO$: Sn, 41.2. Found: Sn, 41.0.

Considerable quantities of benzene were identified in the mixed solvent distillate by vapor phase chromatography, thus indicating phenyl–tin cleavage.

Reaction of Hexaphenylditin with Tetrahydrofuran.—Fifty grams (0.714 mole) of hexaphenylditin (m.p. 233–234°) was refluxed under nitrogen with 200 ml. of tetrahydrofuran for 21 hr. The ditin dissolved in the hot solution and reprecipitated when the solution was cooled. The filtrate was evaporated to 30 ml. and cooled; additional material precipitated. Both crops of crystals had m.p. 232–234°, and a mixture melting point with the starting material of 232–234°, thus confirming the identity of the recovered material as substantially pure starting material. The yield of recovered material was 49.1 g. (98%, substantially quantitative).

Reaction of Tetraphenyltin with Lithium Aluminum Hydride.—Seventy-five grams (0.15 mole) of tetraphenyltin was treated with 15 g. (0.394 mole) of lithium aluminum hydride in 400 ml. of tetrahydrofuran at 0° for 6.5 hr. under nitrogen. After work-up in the usual manner there was recovered 65.5 g. (87.4% recovery) of tetraphenyltin, m.p. and m.m.p. (with starting material) 222–224°.

A trace of diphenyltin oxide was also found as a precipitate in the mixed solvent–water layers after hydrolysis, and the presence of benzene was detected in the tetrahydrofuran layer by vapor phase chromatography.

(11) See ref. 9.

(12) C. Tamborski, F. Ford, and E. Soloski, *J. Org. Chem.*, **28**, 181 (1963).

(13) See ref. 2, p. 93.

(14) C. Tamborski, F. Ford, and E. Soloski, *J. Org. Chem.*, **28**, 237 (1963).

Dicarbenes. Some Isolable Bisdiazoalkanes

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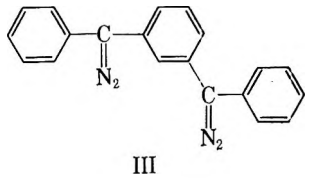
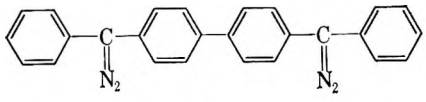
In connection with a study of species containing two divalent carbon atoms we have reported[1] the prepara-

(1) R. W. Murray and A. M. Trozzolo, *J. Org. Chem.*, **26**, 3109 (1961).

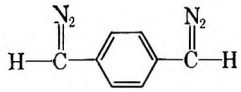
tion of 1,4-bis(α-diazobenzyl)benzene (I). Use of the low temperature glass technique[2,3] has permitted the assignment of a triplet ground state to a number of divalent carbon species.[4] More recently[5] this technique was used to demonstrate that the photolysis of I produces *p*-phenylenebis(phenylmethylene) (II), a dicarbene derivative possessing a triplet ground state. Since the examination of other dicarbenes promises to be of considerable importance, the synthesis of some additional dicarbene precursors including one in which the divalent carbon atoms are *meta* to one another was undertaken. The bisdiazo compounds, 1,3-bis(α-diazobenzyl)benzene (III) and 4,4′-bis(α-diazobenzyl)biphenyl (IV), were prepared by the manganese dioxide oxidation of the appropriate dihydrazone. Similarly, mercuric oxide oxidation of the dihydrazone of terephthalaldehyde led to 1,4-bis(α-diazomethyl)benzene (V).



III

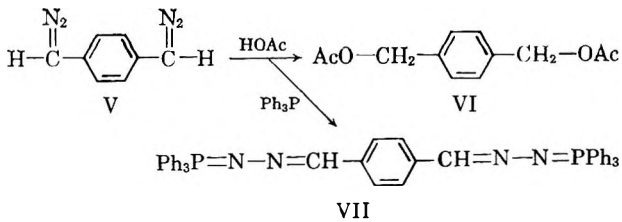


IV



V

Structural differences influence the stability of the bisdiazo compounds. Compounds III and IV are red solids which decompose at their melting points. A satisfactory elementary analysis can be obtained on III while IV appears to decompose slowly at room temperature. Compound V, a reddish orange solid, is rather unstable at room temperature. The infrared spectra of these substances all have the characteristic diazo band at 4.7–4.9 μ. The reaction of V with acetic acid leads to the known diacetate, α,α'-*p*-xylenediol diacetate (VI). Staudinger and Meyer[6] have shown that phosphazines, from the reaction of diazo compounds with phosphines, can be useful derivatives for the diazo compounds. In this work, this reaction has been extended to the bisdiazo compounds. Thus V can be converted to a crystalline bisphosphazine (VII), a material which is somewhat sensitive to moisture and oxidation. The bisphosphazines can be analyzed to



V VI VII

(2) W. A. Yager, E. Wasserman, and R. M. R. Cramer, *J. Chem. Phys.*, **37**, 1148 (1962).

(3) J. H. van der Waals and M. S. DeGroot, *Mol. Phys.*, **2**, 233 (1959); **3**, 191 (1960).

(4) R. W. Murray, A. M. Trozzolo, E. Wasserman, and W. A. Yager, *J. Am. Chem. Soc.*, **84**, 3213 (1962); A. M. Trozzolo, R. W. Murray, and E. Wasserman, *ibid.*, **84**, 4990 (1962).

(5) A. M. Trozzolo, R. W. Murray, G. Smolinsky, W. A. Yager, and E. Wasserman, *ibid.*, **85**, 2526 (1963).

(6) H. Staudinger and S. Meyer, *Helv. Chim. Acta*, **2**, 619 (1919).

demonstrate the presence of the 2 moles of nitrogen in the less stable bisdiazo compounds.

The crystals of all of the bisdiazo compounds described are strongly dichroic. There was a variation in the selective absorption of light depending upon the direction of polarization. Thus, when viewed with polarized light, some of the crystals appeared to be red while others were colorless. A study of this interesting phenomenon and an application to possible crystal structure assignments has been described elsewhere.[7]

Experimental[8]

1,3-Dibenzoylbenzene was prepared by the procedure given[9] for 1,4-dibenzoylbenzene using 38 g. (0.29 mole) of aluminum chloride, 30 g. (0.15 mole) of isophthaloyl chloride, and 250 ml. of dry benzene. The crude product was recrystallized from 95% ethanol to give white crystals (31.6 g., 74.8%), m.p. 104–105°, lit.[9] m.p. 99–101°.

1,3-Dibenzoylbenzene Dihydrazone.—A solution of 30 g. (0.105 mole) of 1,3-dibenzoylbenzene in 150 ml. of absolute ethanol was heated under reflux for 15 hr. with 202 g. of 95% hydrazine (192 g. hydrazine, 6.0 moles). Water was added to the cloud point and the solution was stored in the refrigerator. The yellow, sticky crystals which formed were collected and recrystallized from 95% ethanol to give white crystals (4.71 g., 14.3%), m.p. 157–160°; infrared spectrum: 6.25, 6.14, and 2.95 μ.

Anal. Calcd. for $C_{20}H_{18}N_4$: C, 76.4; H, 5.8; N, 17.8. Found: C, 76.4; H, 5.9; N, 17.6.

1,3-Bis(α-diazobenzyl)benzene (III).—An erlenmeyer flask was charged with 0.251 g. (0.80 mmole) of 1,3-dibenzoylbenzene dihydrazone, 2 g. of sodium sulfate, 0.702 g. (8.0 mmoles) of manganese dioxide, 125 ml. of anhydrous ether, and 0.5 ml. of a saturated solution of potassium hydroxide in ethanol. Addition of the potassium hydroxide catalyst caused an instantaneous formation of the red color of the bisdiazo compound. The reaction mixture, which was protected from light by an aluminum foil wrapper, was stirred vigorously for 4 hr. and filtered; the ether was evaporated to give a quantitative yield of red crystals. The analytical sample was prepared by recrystallization from cyclohexane, m.p. 125–126° dec.

Anal. Calcd. for $C_{20}H_{14}N_4$: C, 77.4; H, 4.6; N, 18.0. Found: C, 77.8; H, 4.8; N, 17.8.

Terephthalaldehyde Dihydrazone.—A solution of 13.4 g. (100 mmoles) of terephthalaldehyde, 300 ml. of absolute ethanol, and 135.2 g. of 95% hydrazine (128.2 g. hydrazine, 4.0 moles) was prepared and allowed to stand at room temperature for 11 days. The solution then was concentrated, water was added to the cloud point, and the solution was refrigerated. The white solid which formed was filtered off and had m.p. 165°,[10] lit.[11] m.p. 165°. The yield was 13.4 g. (83.2%).

1,4-Bis(α-diazomethyl)benzene (V).—An erlenmeyer flask was charged with 0.324 g. (2 mmoles) of terephthalaldehyde dihydrazone, 125 ml. of benzene, 2 g. of sodium sulfate, 2.16 g. (10 mmoles) of yellow mercuric oxide, and 0.5 ml. of ethanol saturated with potassium hydroxide. The reaction mixture was stirred vigorously for 100 min. at which time all of the dihydrazone had reacted as determined by the infrared spectrum. The benzene was evaporated to give a sticky red solid which decomposed slowly at room temperature. The red solid had a strong diazo band in the infrared (4.76 μ) and had $\lambda_{max}^{benzene}$ 318 and 500 mμ.

α,α'-*p*-Xylenediol Diacetate (VI).—A benzene solution of 1,4-bis(α-diazomethyl)benzene (from 0.648 g., 4 mmoles of di-

(7) R. W. Murray and A. M. Trozzolo, Proceedings of the 1961 International Symposium on Microchemical Techniques, Interscience Publishers, Inc., New York, N. Y., 1962, p. 233.

(8) Infrared spectra were determined by means of a Perkin-Elmer Infracord infrared spectrophotometer. Melting points were taken by the Köfler method and are uncorrected; ultraviolet spectra were obtained on a Beckman DK-2 spectrophotometer.

(9) E. Ador, *Ber.*, **13**, 320 (1880).

(10) This melting point value is observed only when the melting point is taken very rapidly. A yellow, high melting solid is formed when the dihydrazone is heated.

(11) R. Adams, J. E. Bullock, and W. C. Wilson, *J. Am. Chem. Soc.*, **45**, 526 (1923).

hydrazone) was added, with stirring, to a solution of 2 ml. of glacial acetic acid in 5 ml. of benzene. The red color of the bisdiazo compound was discharged instantaneously. The reaction mixture was extracted twice with aqueous sodium bicarbonate and the aqueous layers were backwashed with ether. The ether–benzene solution was dried (magnesium sulfate) and evaporated to give a yellow oil which solidified upon standing in the refrigerator. This solid was recrystallized from pentane to give white crystals with an infrared band at 5.70 μ and m.p. 45–49°, lit.[12] m.p. 47°. The yield was 0.10 g. (11.4%).

1,4-Bis(α-diazomethyl)benzene Bisphosphazine (VII).—A solution of 1,4-bis(α-diazomethyl)benzene (prepared from 0.958 g., 5.9 mmoles of dihydrazone) in 125 ml. of benzene was added, over a period of 5 hr., to a solution of 3.04 g. (11.5 mmoles) of triphenylphosphine in 50 ml. of benzene. The system was under a nitrogen atmosphere and the reaction solution was magnetically stirred. The bisphosphazine, which precipitated as a yellow solid, was filtered off and washed with dry ether. A nitrogen atmosphere was maintained over the filter funnel to prevent moisture from decomposing the bisphosphazine. The solid was recrystallized from ether–chloroform and dried *in vacuo*: it had m.p. 192–195° dec. The yield was 1.20 g. (30%).

Anal. Calcd. for $C_{44}N_{36}N_4P_2$: C, 77.5; H, 5.3; N, 8.22. Found: C, 77.7; H, 5.4; N, 7.82.

4,4′-Dibenzoylbiphenyl.—To a stirred slurry of 79.8 g. (0.6 mole) of aluminum chloride in 150 ml. of carbon disulfide, heated to gentle reflux, was added dropwise a solution of 69.2 ml. (84.6 g., 0.6 mole) of benzoyl chloride in 50 ml. of carbon disulfide. A solution of 20 g. (0.13 mole) of biphenyl in 60 ml. of carbon disulfide then was added to the stirred mixture over a period of 6 hr. The dark-colored reaction mixture then was poured into ice-cold concentrated hydrochloric acid. The reaction mixture was extracted with methylene chloride. The extracts were washed with dilute aqueous sodium hydroxide, dried (magnesium sulfate), and evaporated to give a white solid. This solid was recrystallized from ethanol to give pearl-white plates, m.p. 214–216°, lit.[13] m.p. 216°. The yield was 2.34 g. (4.96%). The major product of the reaction mixture was monobenzoyl biphenyl.

4,4′-Dibenzoylbiphenyl Dihydrazone.—A solution of 1.94 g. (5.38 mmoles) of 4,4′-dibenzoylbiphenyl, 125 ml. of absolute ethanol, and 33.7 g. of 95% hydrazine (32.0 g., 1.0 mole hydrazine) was refluxed under argon for 24 hr. The solution was concentrated on the rotary evaporator and stored in the refrigerator. The tan-colored solid which formed was filtered off and recrystallized from benzene–cyclohexane. The white crystals formed had m.p. 200–203° (taken rapidly).

Anal. Calcd. for $C_{26}H_{22}N_4$: C, 80.0; H, 5.7; N, 14.4. Found: C, 80.4; H, 5.9; N, 14.0.

4,4′-Bis(α-diazobenzyl)biphenyl (IV).—An erlenmeyer flask was charged with 0.39 g. (1 mmole) of 4,4′-dibenzoylbiphenyl dihydrazone, 100 ml. of anhydrous ether, 5 g. of sodium sulfate, 0.86 g. (10 mmoles) of manganese dioxide, and 0.5 ml. of ethanol saturated with potassium hydroxide. The reaction mixture was stirred vigorously for 70 min. The reaction mixture was filtered and the ether was evaporated to give a sticky red solid, which when triturated with methylene chloride gave red crystals, m.p. 132–134° dec. The crystals were dichroic and had a strong infrared band at 4.81 μ.

(12) E. Grimaux, *Ann.*, **155**, 342 (1870).

(13) W. Schlenk and M. Brauns, *Ber.*, **48**, 716 (1915).

Reactions of Indoles with Benzyne

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The postulation of benzyne has led to numerous investigations designed to prove the existence of this short-lived intermediate and to establish factors which affect is generation from precursors such as monohalobenzenes, *o*-dihalobenzenes, diphenyliodonium salts, *o*-benzenediazonium carboxylate, 1,2,3-benzothiadiazole 1,1-dioxide, di-*o*-iodophenylmercury, and *o*-chlorobenzophenone.[1] However, less attention has been given to the exploration of benzyne chemistry from the point of view of arylation reactions on carbon, which might be of synthetic interest. Thus, the only reports are on the arylation of carbanions derived from compounds with acidic hydrogen,[2] particularly in cyclization reactions,[3] the addition to olefins,[4] acetylenes,[5] and reactive dienes,[6] and the benzyne arylation of enamines.[7] This paper describes a partially successful attempt to extend this aspect of benzyne chemistry.

Indoles, like enamines, present a bidentate system to electrophiles, which may be attacked on nitrogen or on carbon at the 3-position. When benzyne (I) was generated from bromobenzene with sodium amide in liquid ammonia in the presence of the sodium salt of indole (IIa), N-phenylindole (III, 5%) and 3-phenylindole (IV, 15%) were formed, together with aniline, diphenylamine, and triphenylamine. Under the same conditions, benzyne formation in the presence of N-methylindole (V) did not lead to any N-methyl-3-phenylindole (VI) but only to the aryl amines derived from reaction of benzyne with the solvent.

The reaction products were identified by thin layer and vapor phase chromatographic comparison with authentic samples. Isolation of 3-phenylindole (IV), triphenylamine, and aniline (as picrate) was accomplished by preparative column chromatography.

Benzyne arylation of the indole sodium salt on nitrogen and predominantly on carbon may be contrasted with the corresponding methylation which leads only to nitrogen alkylation under the same conditions.

When the indole lithium salt (IIb) was treated with benzyne (I), generated from *o*-bromofluorobenzene and magnesium in tetrahydrofuran, N-phenylindole (III, 0.5%), 3-phenylindole (IV, 1%), and 2,3-phenylenedihydroindole (VII, 8%) were formed. N-Methylindole (V) and benzyne, generated under the same conditions, produced N-methyl-3-phenylindole (VI, 4%).

In the absence of a proton source, nucleophilic attack of the phenyl anion on the indolenine system of the intermediate VIII leads to the more stable anilide anion, corresponding to 2,3-phenylenedihydroindole (VII), which is then protonated on work-up. With the N-methyl immonium salt IX, abstraction of a more acidic proton and generation of 3-phenylindole (VI) is preferred over cyclization to a dihydroindole.

(1) For reviews, see G. Wittig, *Angew. Chem.*, **69**, 245 (1957); G. Wittig, *ibid.*, **74**, 479 (1962); R. Huisgen and J. Sauer, *ibid.*, **72**, 91 (1960); E. F. Jenny, M. C. Caserio, and J. D. Roberts, *Experientia*, **14**, 349 (1958); J. F. Bunnet, *Quart. Rev.* (London), **12**, 1 (1958); H. Heany, *Chem. Rev.*, **62**, 2 (1962); J. F. Bunnet and B. F. Hrutfiord, *J. Org. Chem.*, **27**, 4152 (1962); R. S. Berry, G. N. Spokes, and M. Stiles, *J. Am. Chem. Soc.*, **84**, 3570 (1962); and E. LeGoff, *ibid.*, **84**, 3786 (1962).

(2) F. W. Bergstrom and R. Agostinho, *ibid.*, **67**, 2152 (1945); W. W. Leake and R. Levine, *ibid.*, **81**, 1169, 1627 (1959); P. H. Dirstine and F. W. Bergstrom, *J. Org. Chem.*, **11**, 55 (1946); F. Scardiglia and J. D. Roberts, *Tetrahedron*, **3**, 197 (1958).

(3) J. F. Bunnett and B. F. Hrutfiord, *J. Am. Chem. Soc.*, **83**, 1691 (1961); J. F. Bunnett and J. A. Skorcz, *J. Org. Chem.*, **27**, 3836 (1962); J. F. Bunnett, *ibid.*, **28**, 1 (1963).

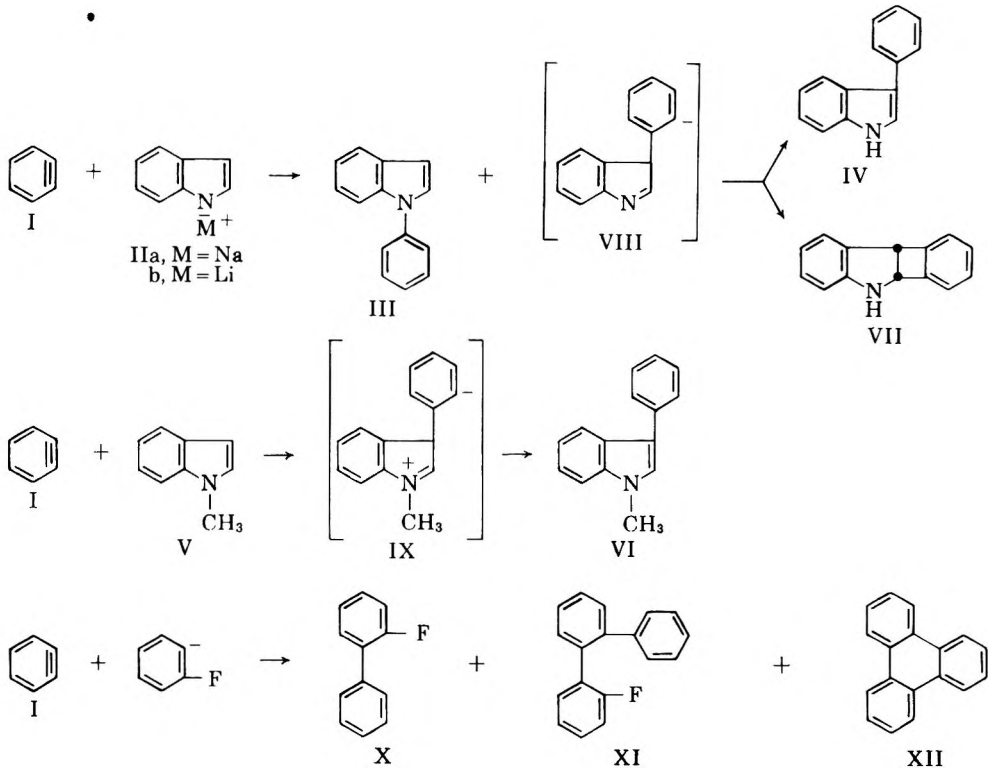
(4) H. E. Simmons, *J. Am. Chem. Soc.*, **82**, 1657 (1961).

(5) M. Stiles, U. Burckhardt, and A. Haag, *J. Org. Chem.*, **27**, 4715 (1962).

(6) G. Wittig and E. Knauss, *Ber.*, **91**, 895 (1958); G. Wittig, E. Knauss, and K. Niethammer, *Ann.*, **630**, 10 (1960).

(7) M. E. Kuehne, *J. Am. Chem. Soc.* **84**, 837 (1962).

SCHEME I

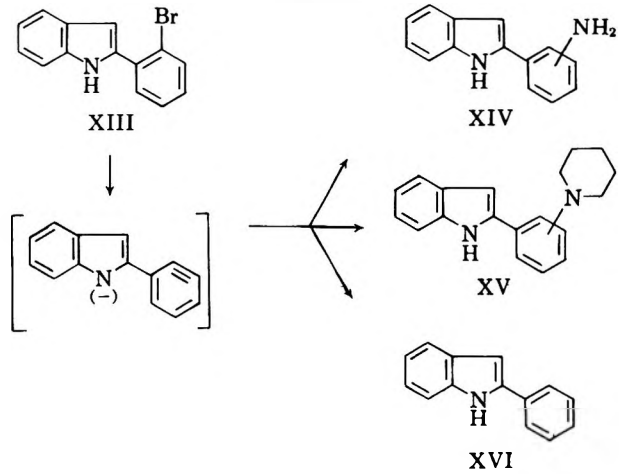


2,3-Phenylenedihydroindole (VII), isolated by column chromatography, showed ultraviolet absorption consistent with an *o*-alkyl N-alkylaniline and a mass spectrum with main peaks at 193 and 165 *m/e* corresponding to the molecular ion and loss of CH_2N, perhaps due to formation of a fluorene fragment. Large peaks were not found for the masses of benzyne or indole.

The only other well-defined products of these reactions were 2-fluorobiphenyl (X), 2-fluoro-2′-phenylbiphenyl (XI), and triphenylene (XII), derived from benzyne and the *o*-fluorophenyl anion. In addition, unstable amorphous materials were formed which could be shown to consist of several components by thin layer chromatography. Pyrolysis of these materials regenerated indole and N-methylindole, respectively.

For a possible synthesis of 1,2- and 2,3-phenyleneindoles, 2-(2′-bromophenyl)indole (XIII) was prepared by a Fischer indole synthesis and treated with strong bases. From the reaction with sodium amide, only a 2-aminophenylindole (XIV) was isolated as major product. When piperidyllithium was used, a 2-piperidinophenylindole (XV) and 2-phenylindole (XVI) were obtained. A reaction with *n*-butyllithium yielded mostly 2-phenylindole. The observed dehalogenation may be analogous to the formation of benzene and N-ethylethyleneimine from fluorobenzene and lithium diethylamide, which proceeds by a benzyne reduction.[8]

SCHEME II



Experimental

An Aerograph Model A-90-P instrument was used in all vapor phase chromatographic experiments. In each case a 20-ft. column was used with a flow rate of 56 ml./min. at a pressure of 21 lb. of helium and other experimental conditions as indicated. All R_f values and colors in thin layer chromatographic experiments and all vapor phase chromatographic retention times which are described for specified compounds were compared with duplicate values obtained with authentic samples. All isolated compounds were compared by infrared spectra and, when solid, by mixture melting points with authentic samples.

Reactions of Indole and N-Methylindole with Benzyne in Liquid Ammonia. Formation of N-Phenylindole (III), 3-Phenylindole (IV), Aniline, Diphenylamine, and Triphenylamine.—A solution of sodium amide was prepared by adding 1.99 g. (0.085 g.-atom) of sodium over 30 min. to a stirred solution of 0.2 g. of ferric chloride in 200 ml. of liquid ammonia. After 1 hr. 2.78 g. (0.025 mole) of indole in 10 ml. of dry ether and then 4.80 g. (0.030 mole) of bromobenzene were added to the decolorized solution. After 30 min., the reaction was quenched by addition of 5.2 g. (0.10 mole) of ammonium chloride, the ammonia was evaporated, 50 ml. of water was added, and the mixture was extracted with ether. Washing with water, drying over magnesium sulfate, and concentration gave 5.00 g. of oil.

Vapor phase chromatogram of 6.9 mg. of the oil on a Dow 11 column (temperatures: column 252°, collector 263°, detector 295°, injector 267°) showed the following retention times: aniline, 1.1 min.; indole, 2.7 min.; diphenylamine, 6.4 min.; N-phenylindole, 10.4 min.; triphenylamine, 17.1 min.; and 3-phenylindole, 20.5 min. A quantitative estimate calculated from areas and compared to authentic samples was 260 mg. of N-

(8) G. Wittig, H. J. Schmidt, and H. Renner, *Ber.*, **95**, 2377 (1962).

phenylindole[9] (5% yield) and 750 mg. of 3-phenylindole[10] (15% yield).

Thin layer chromatogram on Merck Alumina G with cyclohexane–benzene (1:1) showed the following R_f values and colors with sulfuric acid spray: 3-phenylindole, 0.09–0.14, yellow; indole, 0.14–0.27, red; diphenylamine, 0.45–0.55, blue; and N-phenylindole, 0.77–0.89, violet-red.

Chromatography of 4.93 g. of the oil on 30 g. of alumina (Woelm neutral II) gave the following amounts of products: 3.8 g. of oil (100 ml. of pentane), 0.2 g. of oil (100 ml. of 5:1 pentane–benzene), 0.52 g. of product with m.p. 75–78° (200 ml. of benzene), and 0.30 g. of product with m.p. 50–60° (200 ml. of methylene chloride). Recrystallization of the last two fractions gave a pure sample of 3-phenylindole identified by m.p. and m.m.p. 86–87°. Distillation of the first two eluates gave 0.40 g. of product, b.p. 110–130° (20 mm.), which was converted to aniline picrate, m.p. and m.m.p. 186–187° dec. (lit.[11] 181° dec.), which was recrystallized from ether–petroleum ether b.p. 30–60°) to give 2.45 g. of product with b.p. 130–170° (20 mm.), 0.6 g. of product with b.p. 170–210° (20 mm.), and 0.20 g. of residue. From the second fraction, 1.0 g. of indole and 0.20 g. of triphenylamine, m.p. 128–129°, could be crystallized from ether and petroleum ether.

Under the same conditions N-methylindole, prepared from indole in liquid ammonia with sodium amide and methyl iodide,[12] gave no detectable amount of N-methyl-3-phenylindole[13] (vapor phase chromatogram under above conditions requires a retention time of 20.7 min.; thin layer chromatography, alumina G, 1:1 benzene–cyclohexane, requires R_f 0.6–0.7). Only aniline, 1.1 min.; N-methylindole, 2.6 min.; diphenylamine, 6.5 min.; and triphenylamine, 18.4 min., could be detected by vapor phase chromatography. By thin layer chromatography, diphenylamine, R_f 0.6–0.7, could be detected under the above conditions.

Reaction of Indolyllithium with Benzyne. Formation of N-Phenylindole (III), 3-Phenylindole (IV), 2,3-Phenylenedihydroindole (VII), 2-Fluorobiphenyl (X), 2-Fluoro-2′-phenylbiphenyl (XI), and Triphenylene (XII).—To a solution of phenyllithium, prepared under a helium atmosphere from 0.55 g. (0.080 g.-atom) of lithium and 6.32 g. (0.040 mole) of bromobenzene in 30 ml. of anhydrous ether was added 3.51 g. (0.030 mole) of indole in 10 ml. of dry ether. After stirring for 1 hr. the solution was added under helium dropwise, over 1 hr., to a warmed and stirred mixture of 0.732 g. (0.030 g.-atom) of magnesium and 5.25 g. (0.030 mole) of *o*-bromofluorobenzene in 30 ml. of tetrahydrofuran, shortly after reaction of the metal and dihalobenzene had started. After an additional hour the solvents were removed *in vacuo*, 50 ml. of 5% aqueous hydrochloric acid was added, and the mixture was extracted with ether to give 5.83 g. of oil. Only traces of material were obtained from the acid solution on addition of excess sodium carbonate.

Analytical vapor phase chromatogram on a Dow 11 column (temperatures: column 255°, collector 267°, detector 297°, injector 274°) showed the following retention times: indole, 2.6 min.; 2-fluorobiphenyl, 3.3 min.; N-phenylindole (0.5% yield), 10.6 min.; 2-fluoro-2′-phenylbiphenyl (less than 4% yield), 11.5 min.; 2,3 phenylenedihydroindole (8% yield), 12.2 min.; 3-phenylindole (1% yield), 21.7 min; and triphenylene, 55 min.

The reaction was repeated with triple amounts and 14.4 g. of oily product was obtained. Solution in 50 ml. of benzene and the dropwise addition to 150 ml. of pentane gave a yellow precipitate which was filtered, redissolved in 10 ml. of benzene, and reprecipitated by addition to 50 ml. of pentane to give 0.60 g. of powder, m.p. 173–210° Chromatography of the powder on 20 g. of Woelm neutral II alumina gave a material, m.p. 166–168°, eluted with benzene and 8:2 benzene–dichloromethane, which by thin layer chromatography in benzene on alumina or silica gel showed several components but no indole. However, by vapor phase chromatography indole was produced as the main component by pyrolysis at 242°. The material was reactive with air, giving a new substance, m.p. 200–210°. The original benzene–pentane-soluble material was chromatographed on 85 g. of Woelm neutral II alumina, giving these eluates: 4 g. (200 ml. of pentane), 4 g. (300 ml. of cyclohexane), and 3 g. (200 ml. of benzene). From the third fraction 0.50 g. of 2,3-phenylenedihydroindole was obtained, m.p. 251–252° when recrystallized from ethanol. Ultraviolet absorption was at λ_{max}^{MeOH} 250 mμ (log ε 3.1) and 290 (2.8) and mass spectral peaks were at 193 and 165 *m/e*.

Anal. Calcd. for $C_{14}H_{11}N$: C, 87.03; H, 5.74; N, 7.29. Found: C, 86.75; H, 5.55; N, 7.19.

Treatment of the second fraction with petroleum ether gave 2.0 g. of recovered indole. Rechromatography of the combined mother liquors of the second fraction and the first fraction on 30 g. of Woelm basic I alumina gave 0.8 g. of indole, eluted with pentane and cyclohexane, and 0.3 g. of 2-fluorobiphenyl, m.p. 62–64°, eluted with pentane. A sample recrystallized from pentane showed m.p. 70–71°, undepressed by an authentic sample, and the same infrared spectrum as an authentic sample.[14]

Combination of the remaining eluate fractions and distillation gave 1.4 g. of material with b.p. to 145° (20 mm.) and 2.5 g. of residue, which was fractionated by thin layer chromatography on Merck Alumina G with petroleum ether. The most rapidly moving fraction of 0.60 g. was subjected to successive preparative vapor phase chromatography (Dow 11 column; temperatures: column 252°, collector 263°, detector 295°, injector 267°) to give 0.10 g. of crude, then 0.050 g. of pure, 2-fluoro-2′-phenylbiphenyl, distilled at 135–140°, bath (3 mm.). The ultraviolet absorption was at λ_{max}^{hexane} 230 mμ (log ε 3.1). The mass spectrum showed peaks at 248 and 228 *m/e* for molecular peak and fragment after loss of HF.

Anal. Calcd. for $C_{18}H_{13}F$: C, 87.07; H, 5.27. Found: C, 87.19; H, 5.18.

From the second thin layer chromatographic fraction, 0.050 g. of triphenylene,[15] m.p. and m.m.p. 192–194°, was obtained.

Reaction of N-Methylindole with Benzyne. Formation of N-Methyl-3-phenylindole (VI), 2-Fluorobiphenyl (X), 2-Fluoro-2-phenylbiphenyl (XI), and Triphenylene (XII).—A solution of 3.87 g. (0.030 mole) of N-methylindole in 20 ml. of tetrahydrofuran was added dropwise, with stirring over 1 hr., to a reacting mixture of 0.80 g. (0.033 g.-atom) of magnesium and 5.78 g. (0.030 mole) of *o*-bromofluorobenzene, heated in 70 ml. of tetrahydrofuran under an atmosphere of helium. After an additional hour the solvent was removed *in vacuo*; 2 ml. of water, 20 ml. of acetone, 150 ml. of dichloromethane, and, after 30 min., anhydrous magnesium sulfate were added. Filtration and concentration gave 6.33 g. of oil.

A vapor phase chromatogram of 7.0 mg. on a Dow 11 column (temperatures: column 252°, collector 263°, detector 295°, injector 272°) showed the following retention times: N-methylindole, 2.6 min.; 2-fluorobiphenyl, 3.3 min.; 2-fluoro-2′-phenylbiphenyl, 11.2 min.; N-methyl-3-phenylindole (3.3% yield), 20.7 min.; and triphenylene, 54.2 min.

Solution of the product in 10 ml. of benzene and addition to 200 ml. of petroleum ether gave 180 mg. of precipitate, m.p. 100–120°, which was purified to 130 mg., m.p. 140–145°, by three reprecipitations. This material showed several compounds on thin layer chromatography but no N-methylindole. Pyrolytic distillation at 140° (20 mm.) gave an oil showing ten components by vapor phase chromatography, the most abundant being N-methylindole. Concentration of the benzene–petroleum ether solution yielded 0.15 g. of triphenylene, recrystallized from ethanol, m.p. and m.m.p. 191–192°. Chromatography of the remaining oil on Merck Alumina G gave 5.0 g. of cyclohexane eluate from which 0.20 g. of 2-fluorobiphenyl, m.p. 70°, could be isolated in early fractions. Removal of material to b.p. 145° (20 mm.) left 2.5 g. of oil residue which was chromatographed on 50 g. of Woelm neutral II alumina. Fractions eluted with 1:1 petroleum ether–cyclohexane and cyclohexane gave 1.3 g. of oil enriched in 2-fluoro-2′-phenylbiphenyl. Repeated preparative vapor phase chromatography gave 0.10 g. of this product, distilled at 140–145°, bath (3 mm.).

2-(2′-Bromophenyl)indole (XIII).—A mixture of 3.98 g. (0.020 mole) of *o*-bromoacetophenone and 2.16 g. (0.020 mole) of phenylhydrazine was heated at 50° for 3 hr. The crude phenyl-

(9) E. Fischer and O. Hess *Ber.*, **17**, 559 (1884).

(10) F. Henle, *ibid.*, **38**, 1352 (1905).

(11) O. Silberrad and G. Rotter, *J. Chem. Soc.*, **89**, 167 (1906).

(12) W. J. Hickinbottom, "Reactions of Organic Compounds," Richard Clay and Co., Ltd., London, 1957, p. 409.

(13) W. H. Ince [*Ann.*, **253**, 35 (1889)] reports m.p. 64–65°, picrate m.p. 90°.

(14) G. Schiemann and W. Roselius, *Ber.*, **62**, 1809 (1929).

(15) G. Wittig and E. Benz, *ibid.*, **91**, 882 (1958).

hydrazone (no infrared carbonyl absorption) was heated in 30 g. of polyphosphoric acid at 100° for 3 hr. and at 170° for 3 min. Dilution with 150 ml. of water, addition of excess ammonia, and extraction with ether gave 4.0 g. of an oil from which 1.0 g. of the crude indole compound (XIII), m.p. 60–64°, was obtained by crystallization from ether–petroleum ether. A pure sample had m.p. 76–77°.

Anal. Calcd. for $C_{14}H_{10}BrN$: C, 61.86; H, 3.71; N, 5.15. Found: C, 61.85; H, 3.71; N, 5.19.

Alternatively, 3.0 g. of crude phenylhydrazone was heated for 5 min. at 170° with 20 g. of powdered zinc chloride and 40 g. of sand. Addition of 10 ml. of concentrated hydrochloric acid, extraction with ether, concentration, and chromatography on 25 g. of Woelm neutral I alumina in benzene gave 1.5 g. of crude product, m.p. 68–70°.

2-(3′-Bromophenyl)indole (XVII).—A solution of 8.2 g. (0.020 mole) of *m*-bromoacetophenone and 4.5 g. (0.020 mole) of phenylhydrazine in 5 ml. of ethanol deposited 10.4 g. of phenylhydrazone, m.p. 100–101° after recrystallization from ethanol. This compound decomposed to a black tar on standing in air for 3 days. A solution of 10.0 g. of the phenylhydrazone in 100 g. of polyphosphoric acid was heated at 80–90° for 2 hr. and at 135° for 5 min. Dilution with water, filtration, and crystallization from ethanol gave 7.0 g. of XVII, m.p. 152–154°, recrystallized to m.p. 157–158°.

Anal. Calcd. for $C_{14}H_{10}BrN$: C, 61.80; H, 3.71; N, 5.15. Found: C, 61.95; H, 3.83; N, 5.06.

Reaction of 2-(2′-Bromophenyl)indole (XIII) with Sodium Amide.—Within 10 min. a solution of 0.65 g. (2.4 mole) 2-(2′-bromophenyl)indole in 10 ml. of dry ether was added dropwise to a stirred solution of sodium amide, prepared from 0.30 g. (0.012 g.-atom) of sodium in 150 ml. of liquid ammonia. After 20 min., 0.80 g. (0.015 mole) of ammonium chloride was added, the ammonia was evaporated, the residue was dissolved in methylene chloride, and the solution was washed with 5% aqueous hydrochloric acid and evaporated.

Preparative thin layer chromatography of 0.4 g. of residual oil on Merck alumina G with 1:1 benzene–cyclohexane gave 0.150 g. of recovered starting material, 0.10 g. of an aminophenylindole (XIV) (m.p. 165–167°, recrystallized from dichloromethane and cyclohexane), and 120 mg. of dark oils in three fractions. Mass spectrum of the crystalline compound showed *m/e* 208 for the molecular peak.

Anal. Calcd. for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81; N, 13.47. Found: C, 80.62; H, 6.04; N, 13.27.

Reaction of 2-(2′-Bromophenyl)indole (XIII) with Piperidyllithium.—A solution of piperidyllithium, made by adding 2.7 ml. of a 13% solution of *n*-butyllithium in cyclohexane to 0.35 ml. of piperidine in 20 ml. of dry ether, was added to 0.54 g. of 2-(2′-bromophenyl)indole in 30 ml. of ether under nitrogen. After stirring for 18 hr., 1 ml. of water was added, the solvent was removed *in vacuo*, the residue was dissolved in dichloromethane, and the filtered solution was evaporated to 0.80 g. of oil. Successive preparative thin layer chromatography on Merck alumina G with 7:3 and 1:2 benzene–cyclohexane gave 0.25 g. of 2-phenylindole, m.p. and m.m.p. 176–178°, and 0.09 g. of a 2-piperidinophenylindole (XV), m.p. 86–87°; ultraviolet absorption showed $\lambda_{max}^{methanol}$ 230 mμ (log ε 4.52), 320 (4.20).

Anal. Calcd. for $C_{19}H_{10}N_2$: C, 82.00; H, 7.30; N, 10.14. Found: C, 82.40; H, 7.50; N, 9.95.

Reaction of 2-(2′-Bromophenyl)indole with *n*-Butyllithium.—To a stirred solution of 0.85 g. (0.0031 mole) of 2-(2-bromophenyl)-indole in 50 ml. of dry tetrahydrofuran was added, under nitrogen, 20 ml. of ether containing 3.6 ml. of 14% butyllithium in cyclohexane. After refluxing for 18 hr., 1 ml. of water was added, the solvent was removed *in vacuo*, the residue was extracted with acetone, and the concentrate (0.75 g.) was subjected to preparative thin layer chromatography on Merck alumina G with 1:1 benzene–cyclohexane to give 0.43 g. of 2-phenylindole, m.p. and m.m.p. 175–178°, and several small oily fractions.

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The Oxidation of Phenylhydrazides to Carboxylic Acids with Manganese Dioxide. II. By-products[1]

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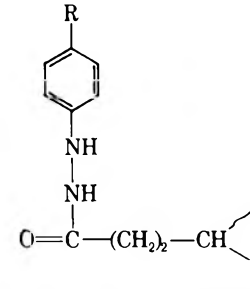
In a recent publication,[2] the smooth oxidation of phenylhydrazides to carboxylic acids with manganese dioxide was reported. The reaction is carried out in aqueous acetic acid at room temperature and is completed within 30 min. The γ-phenylhydrazide and the γ-(*p*-tolylhydrazide) of N-carbobenzoxy-L-glutamic acid (Ia and Ib, respectively), and dipeptides thereof, were found to undergo this reaction in good yield[3a] leaving protecting carbobenzoxy and ester groups intact and without racemization. These results prompted the suggestion that the phenylhydrazide group might well be used as a protective group in peptide chemistry.[2]



Ia, R = H; Z = $PhCH_2OCO$
b, R = CH_3; Z = $PhCH_2OCO$

In the present paper we report some investigations which have resulted in the discovery of essentially all of the products of the reaction and, consequently, have shed light on the mechanism.[3] All experiments were carried out on Ia under the conditions described in the preceding paper.[2]

Careful measurement of the nitrogen, which is rapidly evolved during the course of the reaction, showed that the nitrogen of the phenylhydrazide group is totally eliminated as elementary nitrogen within 30 min. Thus, obvious limitations are placed on the type of mechanism in operation.[3b]

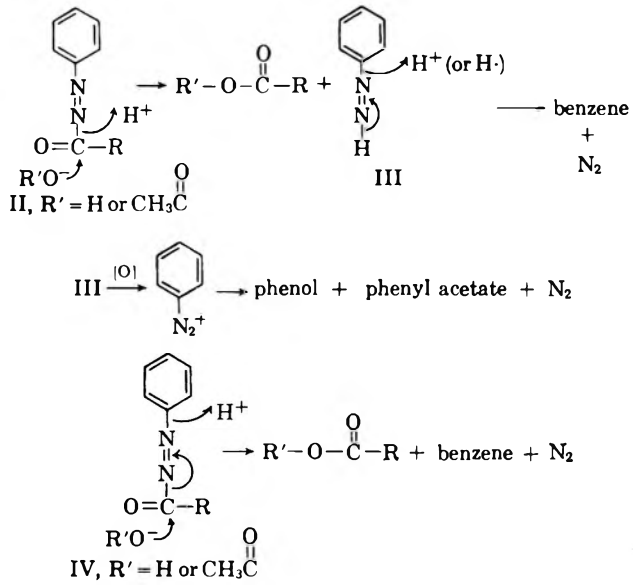
In order to determine the fate of the aromatic ring of the phenylhydrazide group, we resorted to analysis of reaction mixtures by gas chromatography. The following three aromatic products were detected in the yields indicated: benzene (30%), phenol (27%), and phenyl acetate (41%). It has already been demonstrated that the N-carbobenzoxy group survives intact the conditions of the reaction[2,3a] and, moreover, none of these products could be detected by gas chromatography when N-carbobenzoxyglycine was submitted to the reaction conditions. Therefore, the aromatic products and the nitrogen have their origin in the

(1) For the preceding paper, see ref. 2.
(2) R. B. Kelly, *J. Org. Chem.*, **28**, 453 (1963).
(3) (a) Yields of 80–90% of crystalline acids have been obtained (ref. 2); (b) see ref. 6d.

phenylhydrazide group and not in the N-carbobenzoxy group.

The presence of benzenediazonium ion in the reaction mixture is indicated by the appearance of dyes, due to coupling, when the reaction mixture is added to alkaline solutions of various phenols.[4] However, when benzenediazonium ion was substituted for phenylhydrazide and the reaction carried out as usual, both phenol and phenyl acetate were found in the reaction mixture by gas chromatography, *but no benzene could be detected.* Thus, under the conditions of the reaction, benzenediazonium ion cannot be a precursor of benzene, but it is a likely intermediate in the formation of phenol and phenyl acetate.

The mechanism of the reaction cannot be firmly established from the data presented above. However, the following sequence, that accounts for all the results, is suggested: (a) a preliminary oxidation of the hydrazide to the azo compound II; (b) solvolysis of II to a carboxylic acid or its mixed anhydride[5] (see II) and phenyldiimide[6] (III); (c) oxidation of some of III, by abstraction of a hydride ion, to benzenediazonium ion and decomposition of the ion to nitrogen, phenol, and phenyl acetate by interaction with hydroxyl ion and acetate ion; (d) decomposition of the remainder of III, by net transfer of hydrogen either as a proton or a hydrogen atom,[6b,c] to benzene and nitrogen (see III). Another possibility, which would account for only the carboxylic acid, benzene, and nitrogen, is the direct elimination of nitrogen from the azo compound by interaction with the solvent (see IV).[6d]



Experimental

For gas chromatography, an F and M Model 720 apparatus was used fitted with a 72 × 0.25 in. stainless steel column. The column was packed with 10% Carbowax 20M on Gas Chrom Z (80–100 mesh). The helium flow rate was 50 cc./min., the injection port temperature was 300°, and the detector temperature was 230°.

TABLE I

GAS CHROMATOGRAPHY DATA

Compound	Concn. in reaction mixture, mmole/ml.	Peak area (arbitrary units) Benzene	Phenol	Phenyl acetate
Benzene[a]	0.0113	1.82		
	0.0225	3.60		
		3.40		
Phenol[a]	0.0106		0.63	
	0.0212		1.22	
Phenyl acetate[a]	0.0079			1.61
				1.64
	0.0158			2.96
				2.99
Ia (14.70 mg.)[b]	0.0396	1.90	0.60	3.15
		1.82	0.70	3.06

[a] Calibration experiment. [b] Actual analytical experiment.

TABLE II

YIELDS OF AROMATIC PRODUCTS

Product	Yield,[a] mmole	Yield, %
Benzene	0.0121	30.0
	0.0116	
Phenol	0.0104	27.5
	0.0114	
Phenyl acetate	0.0163	40.7
	0.0159	

[a] From 0.0396 mmole of Ia.

Determination of Evolved Nitrogen.[6d]—The reaction was carried out in a small cell (capacity *ca.* 5 ml.) fitted near the top with a connection to the Dumas apparatus. The cell was also fitted with an inlet tube by which carbon dioxide gas was bubbled through the reaction mixture and a neck sealed with a syringe cap. A mixture of 4.040 mg. of Ia and 8.00 mg. of activated manganese dioxide[7] was sealed in the cell by means of the syringe cap, and the apparatus was swept for several minutes with a slow stream of carbon dioxide gas. The reaction was then started by injecting 1 ml. of a mixture of acetic acid and water (65% acetic acid) through the cap into the cell from a hypodermic syringe. Agitation of the reaction mixture was achieved by the bubbling action of the carrier gas which was passed through the train of the Dumas apparatus; the evolved nitrogen was measured by the usual Dumas technique. The reaction was allowed to continue until the evolution of nitrogen had ceased (30 min.). To determine the correction necessary for nitrogen absorbed onto the manganese dioxide a blank experiment (omitting Ia) was carried out as above. The following results were obtained: calcd. for phenylhydrazide nitrogen of Ia, 7.54%; found (corrected), 7.45% (98.8%).

Benzene, Detection and Yield.—A mixture of 14.70 mg. (0.0396 mmole) of Ia and 31.47 mg. of activated manganese dioxide[7] was sealed in a 2-ml. volumetric flask by means of a syringe cap. A mixture (1 ml.) of acetic acid and water (65% acetic acid) and 0.5 ml. of toluene were injected through the cap into the flask from a hypodermic syringe. Pressure was releaved through the hypodermic syringe. The reaction was allowed to proceed at room temperature for 40 min. with agitation. The contents of the flask were then thoroughly mixed and allowed to settle into two layers; 6 μl. of the top layer was removed with a microsyringe and injected into the gas chromatography apparatus. The initial column temperature was 80°, and it was programmed to increase at the rate of 5°/min. A peak, subsequently shown to be due to benzene, appeared at a retention time of 0.59 min. (relative to toluene). Benzene was identified as the compound responsible for this peak by the fact that, when benzene

(4) In the case of each phenol, the color corresponded to that obtained by addition of a solution of benzenediazonium chloride to an alkaline solution of the phenol in question. Addition of the reaction mixture to a "blank" alkaline solution resulted in a faint pink coloration readily distinguishable from the more intense colors produced in the presence of phenols.

(5) In experiments where the carboxylic acid was isolated (ref. 2), the conditions of work-up would result in hydrolysis of any anhydride present.

(6) *Cf.* (a) H. A. Itano and E. A. Robinson, *J. Am. Chem. Soc.*, **83**, 3339 (1961), and references there cited; (b) D. J. Cram and J. S. Bradshaw, *ibid.*, **85**, 1108 (1963); (c) A. Nickon and A. Sinz, *ibid.*, **82**, 753 (1960). (d) NOTE ADDED IN PROOF—The infrared spectrum of the gas collected directly from the reaction indicated the absence of oxides of nitrogen.

(7) 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).

was added to an aliquot of the reaction mixture before chromatography, the peak was enhanced without the appearance of an inflection or an additional peak, and, furthermore, when benzene was substituted for Ia and the experiment carried out as above, a peak with the same retention time resulted.

The yield of benzene was determined from the area of the peak by reference to a calibration curve constructed as follows. Appropriate, known amounts of benzene were substituted for Ia in reaction mixtures, chromatography was carried out as above, and the areas of the peaks due to benzene were plotted against the concentration of benzene in the mixture. Pertinent data are summarized in Table I; the yield of benzene is given in Table II.

Phenol and Phenyl Acetate, Detection and Yield.—The procedures used for the detection of these products and the determination of their yields were the same as those used for benzene with the exception that the column was kept at a constant temperature of 175°. Under these conditions the retention time for phenol was 5.55 min. and, for phenol acetate, it was 1.96 min. (both relative to toluene). Because of the slow rate of extraction of these products into toluene, due probably to adsorption onto solids in the reaction mixture, the yields were determined 5 hr. after the start of the reaction. Pertinent data are given in Table I and the yields in Table II.

Substitution of Benzenediazonium Ion for Ia.—A solution of 0.0396 mmole of aniline in 0.65 ml. of cold glacial acetic acid was treated with 0.35 ml. of cold, aqueous 0.11 *M* sodium nitrite solution and 31.47 mg. of activated manganese dioxide.[7] The mixture was agitated in a stoppered flask at room temperature for 40 min. It was then analyzed for aromatic products by gas chromatography as described above. Both phenol and phenyl acetate were found, but no benzene could be detected.

Valence Tautomerism of Vinyl-Substituted Three-Membered Heterocycles. I. Conversion of 1,2-Divinylethylene Oxide to 4,5-Dihydrooxepine

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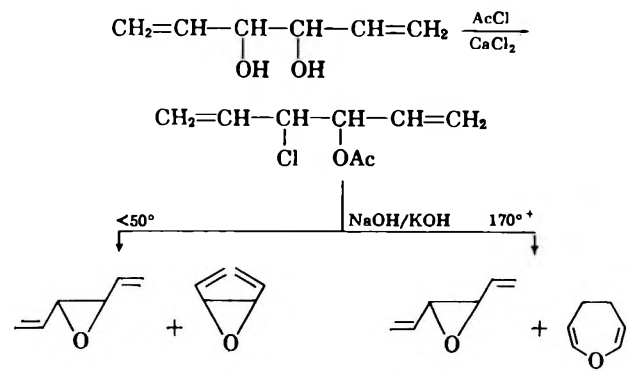
In recent years there has been considerable interest in the valence tautomerism of strained ring systems.[1-5] Until the work of Braun,[6] ring expansion of strained heterocyclic rings by a mechanism analogous to alicyclic systems had not been demonstrated. During the preparation of 1,2-divinylethylene oxide by the pyrolysis of *sym*-divinylethylene carbonate, Braun isolated its valence tautomer, 4,5-dihydrooxepine. Temperature requirements of cyclic carbonate pyrolysis precluded the isolation of *cis*- or *trans*-1,2-divinylethylene oxide free of 4,5-dihydrooxepine. We wish to report a convenient synthesis of *cis*- and *trans*-1,2-divinylethylene oxide together with the thermal requirements for conversion of each isomer to 4,5-dihydrooxepine.

The preparation of *cis–trans*-1,2-divinylethylene oxide and *trans*-1,2-divinylethylene oxide–4,5-dihydrooxepine was realized by the procedure shown.



In the absence of solvent, 1,5-hexadiene-3,4-diol was converted to 3-chloro-4-acetoxy-1,5-hexadiene in yields of 40–50%. Infrared spectra of the chloro ester exhibited C–Cl (12.7 μ), acetate (5.78, 8.15 μ), and terminal olefin absorption (6.1, 10.12, 10.7 μ)

Both high and low temperatures were used to accomplish ring formation from the chloro ester. The isomer distribution and ring size is a function of the ring closure temperature. At 170°+, only *trans*-1,2-divinylethylene oxide and 4,5-dihydrooxepine were formed in a ratio of 2:1. However, if the temperature was maintained at less than 50°, the *cis* and *trans* oxides were isolated in a ratio of 1:2. Under the latter conditions, only trace amounts (1–2%) of 4,5-dihydrooxepine were formed.

Neither the *trans*-1,2-divinylethylene oxide–4,5-dihydrooxepine nor *cis–trans*-1,2-divinylethylene oxide mixtures could be fractionated by distillation through a 75-plate concentric tube column. Pure *trans* and *cis–trans* oxides and 4,5-dihydrooxepine, for structural determination and thermal isomerization studies, were obtained by preparative g.c. separation.

Braun was unable to establish definitely the structure of the 1,2-divinylethylene oxide he isolated. Since we were able to isolate the *cis* and *trans* epoxide, structural assignment could be made on the basis of infrared and n.m.r. The infrared spectra of *trans*-1,2-divinylethylene oxide exhibits intense absorption at 11.51 μ.[7] In the *cis–trans* mixture, the presence of the *cis* isomer is indicated by a band at 12.1 μ and a decrease in intensity of the 11.51-μ absorption. 1,2-Divinylethylene oxide, *cis* and *trans*, give τ values of 6.85 and 7.15, respectively, for the methine protons. The chemical shifts[8] for the *cis* and *trans*-2-butene oxides exhibit this pattern; *i.e.*, the *cis* protons have a smaller τ value than the *trans* protons. The spin–spin splitting pattern of the oxide ring protons[8] also distinguishes between the *cis* and *trans* isomers.

Unequivocal evidence for the origin of 4,5-dihydrooxepine during high temperature 1,2-divinylethylene oxide preparation was obtained by the thermal isomerization of *trans*- and *cis–trans*-1,2-divinylethylene oxide. The *trans* oxide of 93% purity was heated in a sealed tube for 17 hr. at 230°. The composition after this heating period was 48.3% *trans*-1,2-divinylethylene oxide and 42.9% 4,5-dihydrooxepine. Under identical conditions, the 4,5-dihydrooxepine was recovered unchanged. However, a *cis–trans*-1,2-divinylethylene

(1) T. Nozoe, "Progress in Organic Chemistry, Vol. 5, J. W. Cook and W. Carruthers, Butterworth, Inc., Washington, D. C., 1961, pp. 132-165.
(2) W. E. Parham, *et al.*, *J. Am. Chem. Soc.*, **82**, 4085 (1960).
(3)(a) E. Vogel, Abstracts, 141st National Meeting of the American Society, Washington, D. C., April, 1962, p. 20; (b) E. Vogel, *Angew. Chem. Intern. Ed. Engl.*, **1**, 53 (1962).
(4) A. Cope, *et al.*, *J. Am. Chem. Soc.*, **74**, 4867 (1952).
(5) W. E. Doering and M. J. Goldstein, *Tetrahedron*, **5**, 53 (1959).
(6) R. A. Braun, *J. Org. Chem.*, **28**, 1383 (1963).
(7) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, New York, N. Y., 1959, pp. 118-119.
(8) M. H. Gianni, E. L. Stogryn, and C. M. Orlando, Jr., *J. Phys. Chem.*, **67**, 1385 (1963).

oxide mixture (64.4% *trans*, 27.8% *cis*, and 7.8% 4,5-dihydrooxepine) heated on a steam bath overnight resulted in the disappearance of *cis*-1,2-divinylethylene oxide. The composition after the heating period was 61.8% *trans* oxide and 38.2% 4,5-dihydrooxepine.

The thermal requirements for ring expansion of 1,2-divinylethylene oxide and 1,2-divinylcyclopropane[3] are apparently analogous. In both cases, ring expansion of the *cis* isomer requires about 200° less than the corresponding *trans* isomer. Extension of valence tautomerism to other small ring heterocycles is currently under investigation in our laboratories.

Experimental

3-Chloro-4-acetoxy-1,5-hexadiene.—The procedure used for the preparation of 3-chloro-4-acetoxy-1,5-hexadiene was an adaptation of Searles[9] technique for preparation of chloro esters from 1,3-diols.

Acetyl chloride, 190 g. (2.44 moles), was added to a stirred suspension of 41.6 g. (0.38 mole) of calcium chloride and 228 g. (2.0 moles) of 1,5-hexadiene-3,4-diol over a period of 45 min. During the addition, the temperature was maintained below 10°. The reaction mixture then was stirred for 40 hr. at room temperature and then 1 hr. at 50°. The dark brown viscous product was poured into ice, neutralized with cold aqueous sodium bicarbonate extracted with ether, and dried over anhydrous potassium carbonate. After filtration and removal of ether, there remained 269 g. of crude chloro ester.

The crude chloro ester was distilled through a spinning band column to give a water-white, sweet-smelling liquid, b.p. 88–93° (19 mm.).

Anal. Calcd. for $C_8H_{11}ClO_2$: C, 55.17; H, 6.32; Cl, 20.11. Found: C, 54.53; H, 6.26; Cl, 20.00.

1,2-Divinylethylene Oxide. High Temperature Ring Closure.—Crude 3-chloro-4-acetoxy-1,5-hexadiene, 257 g., was slowly added to a reactor containing 362 g. (9.05 moles) of sodium hydroxide 362 g. (6.46 moles) of potassium hydroxide, and 36.2 g. (2.01 moles) of water at 170°. The addition of the chloro ester caused a rapid rise in temperature. During the addition, the pressure in the reactor was decreased so that an overhead temperature of 90–100° was maintained. If the pressure were too low, the overhead temperature dropped and the caustic foamed up into the distillation head causing it to plug. Approximately 80 ml. of product–water mixture was collected in a receiver cooled to −78°. Separation of the crude product from water, drying over anhydrous magnesium sulfate, and atmospheric distillation yielded 40 g. of *trans*-1,2-divinylethylene oxide–4,5-dihydrooxepine mixture, b.p. 105–113° (760 mm.), in a ratio of 2:1.

The composition of this mixture was determined on a Perkin-Elmer g.c. 2-m. column (Dow-Corning silicone oil no. 200 on firebrick) at 75°. The relative retention times of *trans*-1,2-divinylethylene oxide to benzene was 1.83 and 2.81 for 4,5-dihydrooxepine. Separation of the epoxide–oxepine mixture was not effective by distillation through a 75-plate concentric tube column. Pure *trans*-1,2-divinylethylene oxide and 4,5-dihydrooxepine for structural determination and subsequent reactions were obtained with an Autochrome preparatory g.c. unit. A Carbowax–Chromosorb column operated at 175° was utilized.

trans-1,2-Divinylethylene oxide (93% pure by g.c.) gave the following physical constants: b.p. 108° (760 mm.)[10]; $n^{25}D$ 1.4470; d^{20}_4 0.870; infrared maxima (neat) 3.35 (m), 6.10 (m), 7.03 (m), 10.17 (s), 10.82 (vs), 11.38 (s), 11.50 (vs), and 14.79 (s)μ. 4,5-Dihydrooxepine (93% pure by g.c.) had b.p. 113° (760 mm.)[10]; $n^{25}D$ 1.4735; d^{20}_4 0.978; infrared maxima (neat) 3.45 (m), 6.05 (s), 6.10 (s), 7.46 (m), 7.70 (vs), 8.99 (vs), and 13.35 (s) μ.

Anal. Calcd. for C_6H_8O (*trans* epoxide): C, 75.01; H, 8.33. Found: C, 74.68; H, 8.46.

Low Temperature Ring Closure.—The apparatus and quantities used in this procedure were identical with that used in the high temperature ring closure except that 700 ml. of ethylene glycol was used in addition to the caustic and water. The reactor temperature was maintained at 40–50° and the pressure at 10–15 mm. during the addition of the chloro ester. In this way, 241 g. of crude chloro ester yielded 109 ml. of *cis–trans* 1,2-divinylethylene oxide in ratio of 1:2 (composition determined by g.c.). This product showed only trace quantities (1–2%) of 4,5-dihydrooxepine. Distillation of the *cis–trans* mixture through a 75-plate concentric tube column at 45 mm. failed to separate the isomeric oxides. The *cis–trans* epoxide mixture (ratio 1:2) gave the following physical constants: b.p. 107° (760 mm.)[10]; $n^{25}D$ 1.4520; d^{20}_4 0.899; infrared maxima (neat) 3.35 (m), 6.10 (m), 7.03 (m), 10.17 (s), 10.82 (vs), 11.50 (s), 12.10 (w), and 14.79 (s) μ.

Anal. Calcd. for C_6H_8O: C, 75.01; H, 8.33. Found: C, 74.88; H, 8.03.

Acknowledgment.—This research was supported by the Advanced Research Projects Agency, Propellant Chemistry Office, and was monitored by Army Ordnance under Contract No. DA-30-069-ORD-2487.

(9) S. Searles, K. A. Pollart, and F. Block, *J. Am. Chem. Soc.*, **79**, 952 (1957).

(10) Determined by the inverted capillary tube technique.

cis–trans Isomerism of Exocyclic α,β-Unsaturated Indanones and Tetralones

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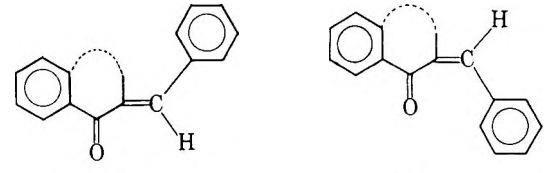
Exocyclic α,β-unsaturated ketones have a fixed *syn–cis* conformation of the C=C with respect to the C=O. Assignments of the *cis* and *trans* isomers of three such compounds by proton magnetic resonance spectroscopy are reported.



trans *cis*

The deshielding effect resulting from the diamagnetic anisotropy of the carbonyl group leads to the vinyl proton in the *trans* isomer (with the proton *cis* to the carbonyl group) giving a signal at a greater chemical shift than in the *cis* isomer.

2-Benzal derivatives of 4,4-dimethyl-1-tetralone,[2] 1-indanone,[2] and 3,3-dimethyl-1-indanone,[3] as prepared by condensation with benzaldehyde in the presence of base, were isolated as sharp melting solids having the *trans* arrangement of phenyl and carbonyl groups (see Table I).

In methanol these *trans* isomers were largely converted by ultraviolet irradiation into the corresponding *cis* isomers. Chromatography of the crude irradiation products gave pure specimens of each of these *cis* iso-

(1) To whom communications concerning this paper should be addressed.

(2) A. Hassner and N. H. Cromwell, *J. Am. Chem. Soc.*, **80**, 893 (1958).

(3) B. D. Pearson, R. P. Ayer, and N. H. Cromwell, *J. Org. Chem.*, **27**, 3038 (1962).

TABLE I

PROPERTIES OF *cis* AND *trans* ISOMERS OF EXOCYCLIC α,β-UNSATURATED TETRALONES AND INDANONES

	2-Benzal-4,4-dimethyl-1-tetralone		2-Benzal-1-indanone		2-Benzal-3,3-dimethyl-1-indanone	
	trans	*cis*	*trans*	*cis*	*trans*	*cis*
M.p., °C.	110	Oil	109–111	95–96	80–82	Oil
Ultraviolet equilibration,[a] %	10	90	22	78	32	68
Chemical equilibration,[b] %	100	0	100	0	56	44
Chemical shifts in p.m.r. spectrum (τ)						
$=CH$ (1)[c]	2.29	3.37	?[d]	3.11	2.35	3.20
$-CH_2$[e] (2)[c]	7.10	7.27	6.07	6.17		
$-CH_3$ (6)[c]	8.72	8.58			8.50	8.45
β to $>C=O$[f] (1)[c]	1.97	1.97	?	1.90	2.20	?
Mol. wt.[g]	(262) 258		(220)	219	(248)	251

[a] Irradiation of *trans* isomer in methanol. [b] Of either *trans* or *cis* isomer in acetonitrile. [c] Number of protons by integration. [d] Signal masked by aromatic peaks but $\tau < 2.7$. [e] Doublet, split by vinyl proton; $J_{ax} = 2$ c.p.s. [f] Doublet; $J_{ab} = 7$ c.p.s. [g] Determined by thermistor method [J. J. Neumayer, *Anal. Chim. Acta*, 20, 519 (1959)] using chloroform as solvent; values in parentheses are theoretical values.

mers. The *cis* isomers were of lower melting point, consistent with a *trans* to *cis* conversion.[4]

It can be seen from Table II that the ultraviolet spectral data, frequently found useful for assigning *cis* and *trans* isomers,[4] are of little assistance in assigning the isomers of these exocyclic α,β-unsaturated ketones. The infrared spectral data also present a confusing picture, but it is noteworthy that a peak assigned as due to C=C in the spectra of the *trans* isomers is absent in the spectra of the *cis* isomers.

TABLE II

ULTRAVIOLET AND INFRARED SPECTRA OF *cis* AND *trans* ISOMERS OF EXOCYCLIC α,β-UNSATURATED TETRALONES AND INDANONES

Compound	Ultraviolet spectra[a] λ_{max}, mμ	$\epsilon \times 10^{-3}$	Infrared spectra[b] (cm.$^{-1}$/absorption of 10 mg. per ml. of soln.)	
trans-2-Benzal-4,4-dimethyl-1-tetralone[c]	307	16.5	$\nu_{C=O}$	1673/94
	227	11.4	$\nu_{C=C}$	1610/90
			ν_{Ar}	1605/90
cis-2-Benzal-4,4-dimethyl-1-tetralone	311	11.3	$\nu_{C=O}$	1676/82
	269	9.3	ν_{Ar}	1602/54
	234	9.7		
trans-2-Benzal-1-indanone[d]	320	28.0	$\nu_{C=O}$	1706/100
	227	10.0	$\nu_{C=C}$	1640/85
			ν_{Ar}	1615/76
cis-2-Benzal-1-indanone	316	21.0	$\nu_{C=O}$	1700/75
	228	9.4	ν_{Ar}	1619/71
trans-2-Benzal-3,3-dimethyl-1-indanone[d]	310	17.5	$\nu_{C=O}$	1705/98
	275 (sh)	11.5	$\nu_{C=C}$	1627/80
	224	7.8	ν_{Ar}	1612/85
cis-2-Benzal-3,3-dimethyl-1-indanone	322	17.8	$\nu_{C=O}$	1695/96
	280 (sh)	7.1	ν_{Ar}	1615/89
	230	7.8		

[a] In methanol. [b] In carbon tetrachloride. [c] See ref. 2. [d] See ref. 3.

The melting points and the p.m.r. spectra of the products show that equilibration of 2-benzal-4,4-dimethyl-1-tetralone and 2-benzal-1-indanone in acetonitrile by means of hydrogen bromide or piperidine[5] leads to the pure *trans* isomer, irrespective of whether one starts with the *trans* or *cis* isomer.

(4) For an excellent discussion of the physical properties of geometrical isomers of olefins, see E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, Chapter 12, Section 12-3.

(5) See ref. 4, p. 344, for a discussion of the mechanism of these acid and secondary amine promoted interconversions.

Equilibration of 2-benzal-3,3-dimethyl-1-indanone gave a product which was shown by analysis of its p.m.r. spectrum to consist of about 56% *trans* isomer and 44% *cis* isomer (see Table III).

TABLE III

cis–trans ISOMER RATIOS AFTER TREATMENT OF AN ACETONITRILE SOLUTION OF *cis*- OR *trans*-2-BENZAL-3,3-DIMETHYL-1-INDANONE WITH VARIOUS ADDITIVES

Olefin	[Olefin]	Additive	[Additive]	Time, hr.	Temp., °C.	% *cis*
trans	0.025	None		72	105	0
trans	0.049	NEt_4Br	0.20	43	90	0
trans	0.048	$C_5H_{11}N$	0.20	9	25	16
trans	0.017	$C_5H_{11}N$	0.10	168	25	42
trans	0.048	$C_5H_{11}N$	0.20	2	90	43
trans	0.049	$C_5H_{11}N$	0.20	43	90	44
trans	0.053	$C_5H_{11}N$	0.10	48	105	46
trans	0.048	HBr	0.16	23	25	38
trans	0.043	HBr	0.16	21	90	44
cis	0.049	$C_5H_{11}N$	0.17	44	25	45
cis	0.020	$C_5H_{11}N$	0.17	1.5	90	44
cis	0.037	$C_5H_{11}N$	0.17	43	90	41
cis	0.030	HBr	0.16	23	25	44

The ultraviolet spectrum of the *trans*-2-benzal-3,3-dimethyl-1-indanone has previously been found to indicate steric hindrance between a hydrogen atom attached to the aromatic nucleus of the 2-benzal substituent and a 3-position methyl group.[3] The presence of a considerable proportion of *cis* isomer on equilibration of this exocyclic α,β-unsaturated indanone is almost certainly related to this presence of steric hindrance in the *trans* isomer.

For *trans*-2-benzal-3,3-dimethyl-1-indanone the relationship between the peak at τ 2.35 and the vinyl proton was confirmed by preparing *trans*-2-(α-deuteriobenzal)-3,3-dimethyl-1-indanone by condensing 3,3-dimethyl-1-indanone with deuteriobenzaldehyde. The spectra were identical except that the signal at τ 2.35 was absent.

For the *cis* and *trans* isomers of both 2-benzal-4,4-dimethyl-1-tetralone and 2-benzal-1-indanone, a long-range coupling between the vinyl proton and the methylene protons is observed. The methylene protons appear as a doublet ($J \sim 2$ c.p.s.) and the vinyl proton as a somewhat ill-defined triplet. Deuterium substitution for the vinyl proton in *trans*-2-benzal-1-indanone

resulted in a sharp singlet for the methylene protons, consistent with the proposed coupling.[6]

Experimental[7]

Preparation of the *cis* Isomers.—Solutions containing about 1 g. of *trans* isomer in 100 ml. of methanol were irradiated, in a Pyrex flask, for 1–2 days by means of a B-100A Blakray source (Ultra-Violet Products, Inc.). Evaporation gave a product whose p.m.r. spectrum was analyzed to give the *cis–trans* isomer ratios for equilibration in the presence of the ultraviolet irradiation; this data is presented in Table I.

The product was chromatographed on Alcoa F-20 alumina using as eluent 1% benzene in petroleum ether (b.p. 60–70°). In this way samples were obtained whose p.m.r. spectra indicated pure *cis* isomers. Only the *cis*-2-benzal-1-indanone was a solid, m.p. 93–96°. The two oils obtained had the correct molecular weights (Table I) and one of them, *cis*-2-benzal-4,4-dimethyl-1-tetralone, was analyzed.

Anal. Calcd. for $C_{19}H_{18}O$: C, 86.98; H, 6.91. Found: C, 87.03; H, 6.84.

Spectral characteristics for the *cis* isomers are recorded in the first two tables.

Irradiation of 2-benzal-4,4-dimethyl-1-tetralone in carbon tetrachloride led to 80% *cis* isomer and irradiation of 2-benzal-3,3-dimethyl-1-indanone in acetonitrile to 74% *cis* isomer in the equilibrium mixtures.

Equilibration of the *cis* and *trans* Isomers.—Small quantities of either the pure *cis* or pure *trans* isomer were dissolved in acetonitrile together with 0.1 to 0.2 *M* amounts of hydrogen bromide or piperidine. Eventually, the solutions were evaporated to dryness and the *cis–trans* ratio in the product was determined by analysis of its p.m.r. spectrum. When equilibrations were carried out at elevated temperatures, sealed bulbs were used.

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(7) Infrared spectra were measured with a Perkin-Elmer Model 21 double beam recording instrument employing 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 containing a trace of tetramethylsilane (τ 10.00) as internal reference.

Radical Efficiency from 2,2′-Azobis(2-methylpropionitrile)

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The decomposition of 2,2′-azobis(2-methylpropionitrile) (ABN) has been studied by many workers,[2] and it has been shown that the production of cyanopropyl radicals is appreciably inefficient. Ziegler[3] reported that ABN decomposition in the presence of air does not produce a pressure change since the nitrogen evolved is exactly compensated by simultaneous oxygen uptake by cyanopropyl radicals. Talât-Erben[4] isolated 2-cyano-2-propyl hydroperoxide (stable to 120°) from ABN decomposition in xylene under oxygen.

It was of interest to study ABN decomposition in chlorobenzene under oxygen under conditions similar to those used in autoxidation studies with ABN initiation. A definite oxygen uptake is found, which we assume is due to the following reactions.

$$\text{ABN} \longrightarrow N_2 + 2e\text{R}\cdot + (1 - e)\ \text{R-R (in solvent cage)}$$

$$2e\text{R}\cdot + O_2 \longrightarrow 2e\text{RO}_2\cdot$$

$$2e\text{RO}_2\cdot \longrightarrow \text{products; no } O_2 \text{ evolution}$$

$R_{O_2}/R_{N_2} = 2e$, where e = efficiency of radical production from ABN, R = cyanopropyl radicals, R-R = tetramethylsuccinonitrile (or other nonoxygen consuming products), and R = rate of reaction.

The data in Table I show that R_{O_2}/R_{N_2} is 1.17 at 60–65° and, therefore, e = 0.59 which compares favorably with the value reported by Hammond[5] (0.57–0.60). This result favors the assumed reactions and formation of 2-cyano-2-propyl hydroperoxide which is stable *under our* experimental conditions. A repeat of the oxidation inhibition method, using cumene oxidation in chlorobenzene, inhibited by 2,6-di-*t*-butyl-4-methylphenol, as used by Hammond,[5] gave e = 0.60 at 60°

TABLE I

ABN DECOMPOSITION IN CHLOROBENZENE[a]

Wt. of ABN, g.	Temp., °C.	$R_{O_2} \times 10^{3}$[b]	R_{N_2}	R_{O_2}/R_{N_2}
0.5987	60.0	0.162	0.942	1.17
0.7030	60.0	0.215	1.10	1.20
0.6508	65.0	0.289	1.78	1.16
0.7519	65.0	0.302	2.06	1.15
			Av.	1.17

[a] Total pressure, 1 atm. of oxygen; chlorobenzene partial pressure, 63 mm. at 60.0° and 79.5 mm. at 65.0°. Each run was made for 100 min. in 10 ml. of chlorobenzene, and the rate was taken for the linear portion which was approximately over the 20–90 min. interval. [b] All rates are ml. (STP) × sec.$^{-1}$; R'_{O_2} is the observed rate of oxygen consumption; R_{O_2} is the true rate of oxygen consumption and equals $R'_{O_2} + R_{N_2}$ where R_{N_2} is the measured rate of nitrogen evolution under nitrogen.

Experimental

ABN was Eastman Organic Chemicals, No. 6400, and chlorobenzene was No. 10 from the same source. Reaction cells were 50-ml. erlenmeyer flasks connected by 0.25-in. neoprene to a constant temperature gas buret using mercury. The reaction flasks were shaken in an oil bath controlled to 0.05° and temperatures were read on an N.B.S. certified mercury-glass thermometer. By variation of shaking rates, it was shown that the reaction was not diffusion controlled. Straight lines were computed from the data using a least-squares method on an IBM Model 1620 computer. R_{N_2} from ABN in chlorobenzene, under nitrogen at 50–65°, gave values in good agreement with the literature and an activation energy of 30.1 kcal.

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