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Cyclopropylpyridines. Interaction with Acid and Hydrogen. The Synthesis of Cyclopropane "Ring-Opened" Analogs[1]

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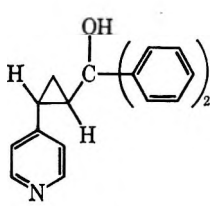
Under acid conditions, the cyclopropane ring of *trans*-2-(4-pyridyl)-α,α-diphenylcyclopropanemethanol (I) cleaves to a relatively minor extent to give derivatives of 4-(4-pyridyl)-1,1-diphenyl-1-buten-4-ol accompanied by substantial amounts of recovered I. The relative resistance of I to acid is contrasted to the lability of analogs in which the pyridine ring has been reduced and of others in which the cyclopropane ring has been replaced by a saturated ethylene chain and is interpreted in terms of electronic interaction between the pyridinium and cyclopropane rings. The course of the reaction is suggestive of a concerted process. Catalytic hydrogenation of the methobromide salt of I gives the corresponding piperidine derivative without hydrogenolysis of the cyclopropane ring. Sodium borohydride reduction affords the related Δ^3-piperideine. Catalytic hydrogenation of the methobromide salts of other substituted cyclopropylpyridines is associated with concomitant hydrogenolysis of the cyclopropyl group giving straight propylene chain derivatives. Analogs of I in which the pyridine ring is replaced by a dimethylaminopropyl group and in which the cyclopropane ring is replaced by acetylenic and by *cis*- and *trans*-olefinic linkages have also been prepared. A useful synthesis of 4-ethynylpyridine has been devised.

The interesting pharmacological actions of *trans*-2-(4-pyridyl)-α,α-diphenylcyclopropanemethanol (I) on the central nervous system[1,3] encouraged us to study the chemical properties of the pyridine–cyclopropane interacting system in greater detail. The preceding paper[1] advanced physical evidence [ultraviolet (uv), pK_a] in support of electronic interaction, particularly in the charged pyridinium cation. The present work considers implications of the behavior of I and certain of its



I

relatives when treated with acid and when subjected to conditions of catalytic hydrogenation. The effects of replacing the pyridine and cyclopropane rings with other moieties have also been investigated.

The effect of acid on cyclopropylcarbinols has been studied extensively following the classic paper of Roberts and Mazur;[4] the outcome depends on the structure of the reactants and on the reaction conditions. Treatment with strong acid usually effects cleavage of the cyclopropane ring smoothly in the cold,[4,5] although the action of acetic anhydride on appropriately substituted cyclopropylcarbinols can result in predominate formation of simple dehydration products accompanying products of ring cleavage.[6] The course of solvolytic reactions proceeding *via* cyclopropylcarbonium ions has been reviewed recently;[7,8] under kinetically controlled conditions unrearranged cyclopropyl, ring-expanded cyclobutyl[4,9] and ring cleavage products are generated in proportions apparently determined by the relative stabilities of the respective carbonium-ion canonical forms.[4,7,8,10]

Compound I proved to be comparatively resistant to acid treatment. When heated at 90–100° for 6 hr in 1 *N* sulfuric acid solution, 36% of I was recovered unchanged accompanied by 27% (based on recovered I) of the ring-cleaved product, 4-(4-pyridyl)-1,1-diphenyl-1-buten-4-ol (IIa) (eq 1), isolated as the hydrochloride salt. The structure of IIa was confirmed by its in-

(1) The preceding paper in this series: A. P. Gray and H. Kraus, *J. Org. Chem.*, **31**, 399 (1966).

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(3) L. Miller, M. Napoli, and T. B. O'Dell, *Arch. Intern. Pharmacodyn.*, **166**, 313 (1967).

(4) J. D. Roberts and R. H. Mazur, *J. Amer. Chem. Soc.*, **73**, 2509 (1951), and succeeding papers.

(5) See, *inter alia*, S. Julia, M. Julia, and L. Brasseur, *Bull. Soc. Chim. Fr.*, 1634 (1962); M. Hanack and H. Eggensperger, *Ann.*, **663**, 31 (1963); *Chem. Ber.*, **96**, 1259 (1963).

(6) *E.g.*, see S. Sarel, E. Breuer, Sh. Ertag, and R. Salamon, *Israel J. Chem.*, **1**, 451 (1963); S. K. Begidov, T. V. Domareva, and I. A. D'yakonov, *Zh. Obshch. Khim.*, **33**, 3426 (1963) [*Chem. Abstr.*, **60**, 5345 (1964)].

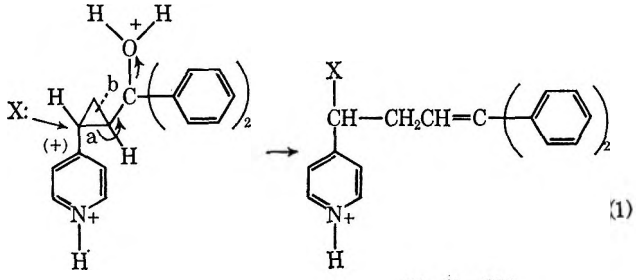
(7) M. Hanack and H. J. Schneider, *Angew. Chem. Intern. Ed. Engl.*, **6**, 666 (1967); see especially pp 671, 672.

(8) Also see R. Breslow in "Molecular Rearrangements," Vol. I, P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, pp 259–273.

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

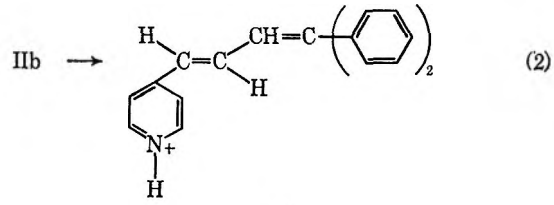
(10) *Cf.* P. von R. Schleyer and G. W. Van Dine, *J. Amer. Chem. Soc.*, **88**, 2321 (1966), and references cited therein.

frared (ir), nuclear magnetic resonance (nmr) (one double-bond proton absorbing as a triplet), and uv (Table I, diphenylethylene absorption, essentially unchanged in acid) spectra. In the course of the preparation of kilogram quantities of I hydrochloride required for clinical trials, ice-cold tetrahydrofuran–ether solutions of I were treated with cold, aqueous hydrochloric acid to precipitate the hydrochloride salt in good yield. When, however, combined mother liquors from several such runs were worked up, a small amount of the chloro analog of IIa (IIb) was obtained in the form of its hydrochloride salt, again showing diphenylethylene absorption in the ultraviolet (Table I). Heating IIb as the base to a bath temperature of 185° caused dehydrohalogenation and formation of the yellow hydrochloride salt of the butadiene derivative (III) (eq 2), structure



(1)

IIa, X = OH
b, X = Cl



(2)

III

confirmed by its ir, nmr, and uv (Table I, 1,1,4-triarylbutadiene, absorption, shifted in acid) spectra. The coupling constant of the multiplet ascribable to the acyclic double-bond protons in the nmr spectrum of III (J = 15 cps) suggests a *trans* configuration for the double bond adjacent to the pyridine ring.

The fact that bond a is cleaved rather than bond b and the direction of bond migration are of interest. Although the observed result could be rationalized in terms of thermodynamic rather than kinetic control, the course of the reaction is in accord with the idea of a concerted process, as shown in eq 1, without involvement of a carbonium-ion intermediate. Carbonium-ion formation from I with an already protonated pyridine ring, particularly if the electron-withdrawing effect is transmitted through the cyclopropyl group,[1] should be a rather high energy process and this is reflected in the relative stability of I under acid conditions. Certainly the carbon α to the pyridinium ring would be expected to bear very little of the positive charge in any generated carbonium ion and, consequently, II would not be an obvious product of a carbonium-ion reaction. On the other hand, the rate of a concerted displacement at the α carbon would be enhanced by the electronic interaction of the positively charge pyridine ring with an approaching nucleophile. In this connection it is worth noting that, although phenyl substitution on the carbinyl carbon markedly enhances the rate of a solvolytic process,[11] attachment of phenyl at the 2 position of the cyclopropane ring has little influence on rate.[12] Of course, the influence of a phenyl substituent on carbonium-ion stability may be somewhat equivocal[8] and certainly less clear than that of a pyridinium substituent.

TABLE I

ULTRAVIOLET ABSORPTION MAXIMA[a]

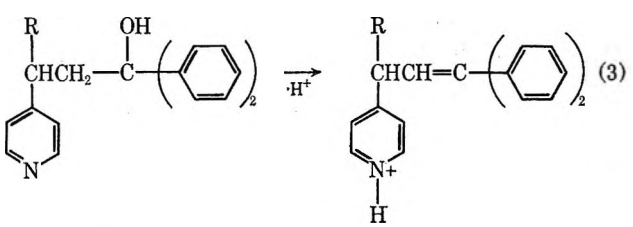
Compound	λ_{max} (log ϵ), mμ Base[b]	Acid[c]
I[d]	258 (3.44)	257 (4.21)
IIa	254 (4.14)	253 (4.21)
IIb	254 (4.17)	254 (4.18)
III	247 (4.22)	256 (4.19)
	340 (4.52)	384 (4.52)
IVa	255.5 (3.40)	252 (3.75)
IVb	257 (3.36)	...
Va	253 (4.24)	251 (4.27)
Vb	256 (4.21)	251 (4.23)
VIa	258.5 (2.70)	258 (2.69)[e]
VIb	258 (2.85)	258 (2.85)[f]
IX	252 (4.18)	251 (4.15)
XI	258.5 (2.62)	252 (4.28)[g]
XII	227 (4.22)	262 (4.04)
	260 (s) (3.78)	
XIII	253.5 (3.20)	253 (3.18)
XIV	248 (4.16)	273 (4.30)
XVa	253.5 (4.32)	281 (4.33)
XVb	245 (s) (4.00)	267 (4.00)
XVIa	257.5 (3.38)	254.5 (3.83)
XVIb	257.5 (3.40)	255 (3.79)
1,1-Diphenylethylene	250 (4.04)[h]	
1,1,3-Triphenylbutadiene	252 (4.20)[i]	
1,1,4-Triphenylbutadiene	240 (4.2)[j]	
	268 (3.7)	
	336 (4.6)	
1,1-Diphenylbutadiene	287 (4.37)[k]	
4-Vinylpyridine	242.5 (4.12)[l]	

[a] Spectra were determined with a Bausch and Lomb spectronic 505 recording spectrophotometer; absorption peaks were checked with a Beckman Model DU spectrophotometer. [b] Medium, 0.1 N sodium hydroxide in aqueous ethanol. [c] Medium, 0.1 N hydrochloric acid in aqueous ethanol. [d] See ref 1. [e] λ_{max} 251 mμ (log ϵ 4.07) after the acid solution had been allowed to stand for several hours. The neutralized solution showed λ_{max} 252 mμ (log ϵ 4.07). [f] Absorption when spectrum was determined immediately; after the solution had stood for 45 min at room temperature, λ_{max} 252 mμ (log ϵ 3.30). [g] Immediate reading; after the solution had been allowed to stand for 1 hr at room temperature, λ_{max} 252 mμ (log ϵ 4.81). [h] "Organic Electronic Spectral Data," Vol. I, M. J. Kamlet, Ed., Interscience Publishers, Inc., New York, N. Y., 1960, p 557; solvent ethanol. [i] "Organic Electronic Spectral Data", Vol. III, O. H. Wheeler and L. A. Kaplan, Ed., 1966, p 860; solvent acetonitrile. [j] "Organic Electronic Spectral Data," Vol. II, H. E. Ungnade, Ed., 1960, p 687; solvent ethanol. [k] T. Holm, *Acta Chem. Scand.*, 17, 2437 (1963); solvent cyclohexane. [l] Reference *h*, p 138; solvent ethanol.

The lability to acid of the formally "ring-opened" analogs of I, 3-(4-pyridyl)-1,1-diphenyl-1-propanol (IVa) and especially 3-(4-pyridyl)-1,1-diphenyl-1-butanol (IVb), synthesized by the methods indicated in the Experimental Section, may be contrasted to that of I. The hydrochloride salt of I could be prepared without difficulty under various conditions in protic or aprotic solvents. Although the hydrochloride salt of IVa could readily be prepared by treatment of an ice-cold benzene–chloroform solution of the base

(11) R. A. Sneen and A. C. Baron, *J. Amer. Chem. Soc.*, **83**, 614 (1961).
(12) R. A. Sneen, K. M. Lewandowski, I. A. I. Taha, and B. R. Smith, *ibid.*, **83**, 4843 (1961).

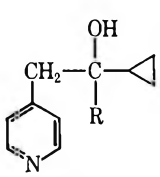
with ethereal hydrogen chloride and recrystallization of the precipitated salt from ethanol, treatment of an ice-cold methanol solution of the base with ethereal hydrogen chloride afforded isolated yields of 65% of IVa hydrochloride and 12% of the salt of the dehydrated product, 3-(4-pyridyl)-1,1-diphenyl-1-propene (Va). On the other hand IVb was so sensitive to acid that its hydrochloride salt could not be obtained under any conditions tried. Treatment of an ice-cold chloroform solution of IVb with ethereal hydrogen chloride yielded 75% of the corresponding dehydrated product (Vb) as the sole isolated product. Not too much can be made of these observations, particularly since acid treatment of IVa and IVb involves simple dehydration with loss of a proton (eq 3), whereas that of I effects rearrangement with breaking of a carbon–carbon bond. The special instability of IVb, moreover, must reflect steric crowding by the methyl substituent which, though apparently slight, is enough to throw the balance over to the side of dehydration. Nevertheless, it is tempting to think about the possibility that the site of carbonium-ion formation in IVa and IVb may be more effectively insulated from the charged pyridinium ring. (Clearer support for this hypothesis is gained from a comparison with derivatives in which the pyridine ring has been reduced, *vide infra*.)



IVa, R = H
b, R = CH_3

Va
b

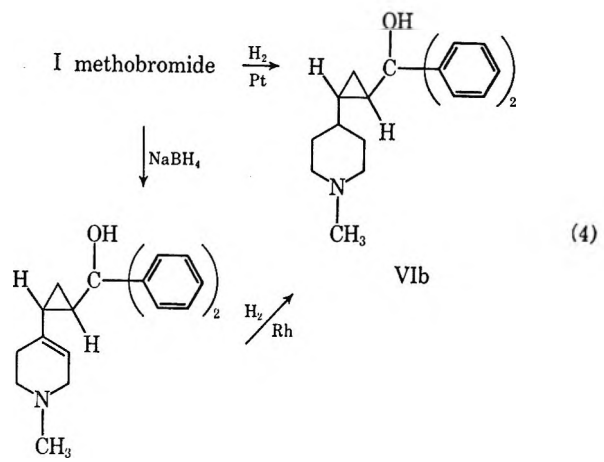
Although perhaps not directly pertinent to this discussion, it is of interest that α,α-dicyclopropyl-4-pyridineethanol (XVIa) and α-cyclopropyl-α-phenyl-4-pyridineethanol (XVIb), in which the carbinol carbon is closer to the pyridine ring, were not unusually unstable to acid.



XVIa, R = cyclopropyl
b, R = phenyl

Platinum-catalyzed hydrogenolysis of monoalkyl-substituted cyclopropanes, possibly proceeding *in part via* hydrogenation of a ring-opened intermediate,[13] occurs under mild conditions at room temperature and leads predominantly to branched-chain derivatives (hydrogenolysis of the unsubstituted, unhindered, carbon–carbon bond) accompanied by minor amounts of straight-chain products.[13,14] Ease of palladium-catalyzed hydrogenolysis of phenyl-substituted cyclopropanes decreases in the following order: *trans*-1,2-diphenyl- > phenyl- > *cis*-1,2-diphenyl- > 1,1-diphenyleyclopropane (the last was not hydrogenolyzed under the reaction conditions).[15] Phenylcyclopropanes are cleaved at the more substituted carbon–carbon bond and generally are hydrogenolyzed more readily than alkylcyclopropanes. The results have been explained in terms of conjugative effects.[15,16]

In view of these data it is of interest that Adams platinum-catalyzed hydrogenation of the methobromide salt of I[1] led smoothly, and without any appreciable cleavage of the cyclopropane ring, to a reasonably good yield (61%) of the N-methylpiperidine derivative, VIb. The same product was readily obtained by sodium borohydride reduction of the methobromide salt to yield *trans*-2-[4-(1-methyl-Δ^3-piperideinyl)]-α,α-diphenylcyclopropanemethanol (VIa, the structure of which was confirmed by its ir and nmr spectra, the latter showing the retention of the cyclopropane ring attached protons) followed by rhodium-catalyzed hydrogenation of VIa (eq 4). In contrast, hydrogenation

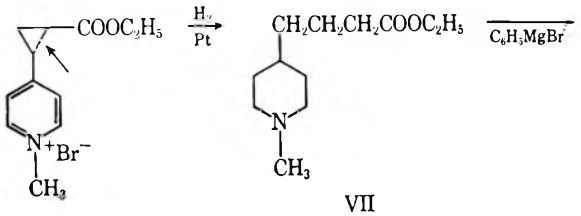


VIb

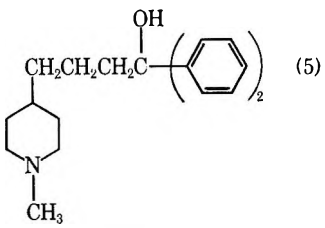
VIa

of the crude (predominantly *trans* but mixed with some of the *cis* isomer) methobromide salt of 4-(2-carbethoxycyclopropyl)pyridine[1] over Adams platinum oxide gave the cyclopropane ring cleaved, unbranched, ethyl γ-(1-methyl-4-piperidine)butyrate (VII) as the only isolable product. Treatment of VII with 2 equiv of phenylmagnesium bromide produced the diphenylcarbinol VIII (eq 5), the structure of which was confirmed by its ir and nmr spectra. A combination of decreased cyclopropane ring bond strength owing to opposing conjugative effects and decreased steric hindrance can serve to explain this observed hydrogenolysis. On the other hand, it is difficult to rationalize, on the basis of our earlier results and those reported in the literature,[16] our finding that the methobromide salt of 2-(4-pyridyl)-1,1-diphenycyclopropane (XII), prepared by reaction of 4-vinylpyridine with diphenyldiazomethane (see the Experimental Section for comments on this synthesis), was hydrogenolyzed over platinum oxide to give 3-(1-methyl-4-piperidyl)-1,1-diphenylpropane (XIII) as the only isolated product (eq 6), the structure of which was confirmed by spectral data. It is worth noting, however, that in both instances hydrogenolysis involves the most substituted

(13) M. Yu. Lukina, *Russ. Chem. Rev.*, **31**, 419 (1962); see pp 427, 428.
(14) See J. Newham and R. L. Burwell, Jr., *J. Phys. Chem.*, **66**, 1431 (1962), and references cited therein.
(15) B. A. Kazanskii, M. Yu. Lukina, and I. L. Safonova, *Dokl. Akad. Nauk SSSR*, **130**, 322 (1960) [*Chem. Abstr.*, **54**, 10953 (1960)].
(16) See ref 13, pp 435, 436.

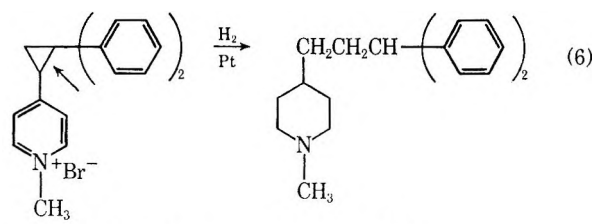


VII



(5)

VIII



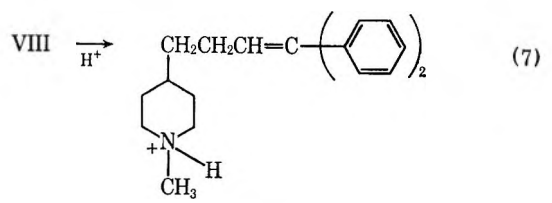
(6)

XII methobromide XIII

carbon–carbon bond. The difference in behavior of the methobromide salts of I and XII may possibly be ascribed to steric interaction in the salt of XII, which slows hydrogenation of the pyridinium group enough to allow hydrogenolysis to precede reduction. When hydrogenation of the pyridinium ring occurs first (as does happen with the salt of I) the cyclopropyl group is left unconjugated and therefore presumably more resistant to hydrogenolytic cleavage.[16a]

It is particularly useful to contrast the acid lability of VIa and VIb to that of I inasmuch as the partial or complete saturation of the pyridine ring in VIa and VIb eliminates orbital overlap between the π electrons of the pyridinium ring and the cyclopropane ring electrons as a possible cause of resistance to carbonium-ion formation. In support of this concept, VIa and VIb were found to be much more sensitive to acid than I. VIa could be titrated with acetous–perchloric acid and could be converted into a reasonably stable hydrochloride salt. However, whereas the ultraviolet absorption spectrum of I in 0.1 *N* hydrochloric acid showed no change after storage of the solution for up to 1 week at room temperature and the spectral shift in going from basic to acid solution was completely reversible,[1] the spectrum of VIa in 0.1 *N* hydrochloric acid changed quite rapidly from that of a simple benzene derivative to one reminiscent of a diphenylethylene in a matter of hours and this change was irreversible (Table I, see footnote *e*). The saturated compound VIb was especially sensitive to acid. Compound VIb could not be titrated with acetous–perchloric acid, giving evidence of decomposition during the titration, and could not be converted into a hydrochloride salt; the ultraviolet absorption spectrum of VIb in 0.1 *N* hydrochloric acid started undergoing irreversible change immediately on dissolution of the compound (Table I, see footnote *f*).[17]

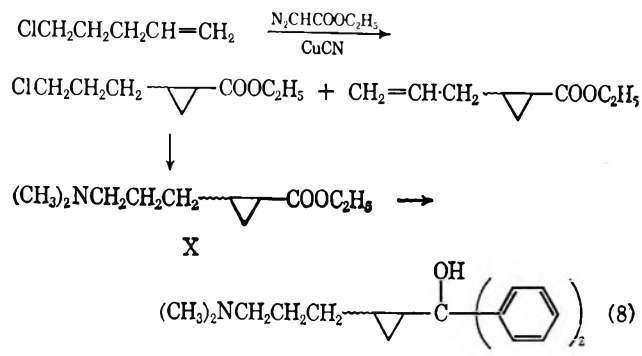
It should be noted that the cyclopropane ring opened compound VIII also proved to be significantly more labile to acid than its approximate (one methylene group less) pyridine counterpart IVa. Compound VIII could be titrated with acetous–perchloric acid and its hydrochloride salt could be prepared by careful treatment of a cold chloroform solution of the base with ethereal hydrogen chloride. Use of a slight excess of hydrogen chloride under the same conditions effected essentially quantitative dehydration of the material to give the hydrochloride salt of 4-(1-methyl-4-piperidyl)-1,1-diphenyl-1-butene (IX) (eq 7).



(7)

IX

In order to ascertain the effect of replacing the pyridine ring of I by a dimethylaminopropyl group, 5-chloro-1-pentene was heated with ethyl diazoacetate in the presence of cuprous cyanide to give ethyl 2-(3-chloropropyl)cyclopropanecarboxylate in low yield and accompanied by its dehydrohalogenated derivative. Treatment of the chloro compound with dimethylamine afforded ethyl 2-(3-dimethylaminopropyl)cyclopropanecarboxylate (X) which reacted with phenylmagnesium bromide to yield the desired 2-(3-dimethylaminopropyl)-α,α-diphenylcyclopropanemethanol (XI, configuration not established) (eq 8). It was intriguing

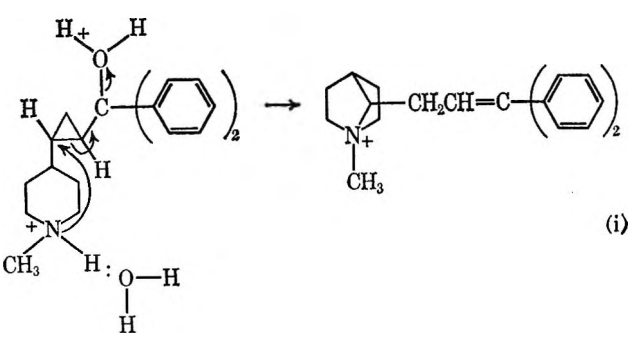


(8)

XI

(16a) NOTE ADDED IN PROOF.—A recent communication, W. J. Irwin and F. J. McQuillin, *Tetrahedron Lett.*, 2195 (1968), provides additional supportive evidence in regard to the influence of electrophilic conjugation on the direction and rate of hydrogenolysis of the cyclopropyl group, compares platinum *vs.* palladium as hydrogenolytic catalysts, and offers a plausible rationale for the observed results.

(17) Unfortunately, since the products of acid treatments of VIa and VIb were not isolated, nothing definitive can be said about their structures. The special lability of VIb, however, entices one into speculating about the possible involvement of the basic nitrogen (in equilibrium with the protonated form) in the process, *e.g.* eq i.



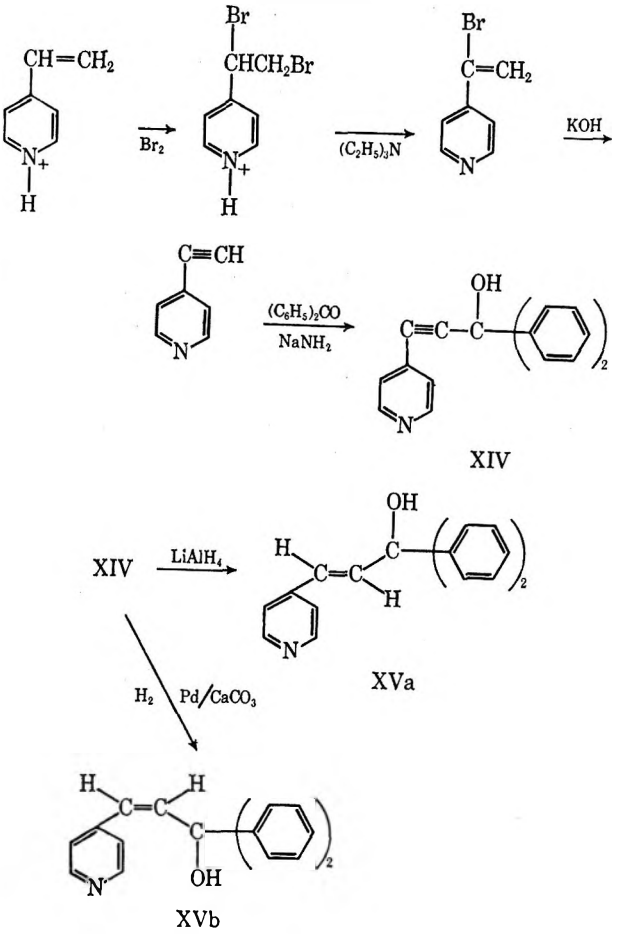
(i)

to find that XI, with its basic nitrogen the same number of carbon atoms away from the cyclopropyl group, was at least as sensitive to acid as VIb and behaved toward acid in strictly comparable fashion, although the extremely high extinction coefficient at 252 mμ developed by a solution of XI in 0.1 *N* hydrochloric acid after 1 hr at room temperature is not readily explicable (Table I, see footnote *g*).[17]

Analogs of I in which unsaturated groups replaced the cyclopropane ring were prepared from 4-ethynylpyridine since reactions of ethyl 4-pyridylacrylate with phenylmagnesium bromide or with phenyllithium afforded complex mixtures of 1,2- and 1,4-addition products.[18] To accomplish this end, a synthesis was developed which provided 4-ethynylpyridine in up to 29% yield from 4-vinylpyridine hydrochloride, a considerably better yield than had previously been realized (see pertinent references cited in the Experimental Section). The key was simply a two-step dehydrohalogenation of 4-vinylpyridine dibromide involving initial treatment of the dibromide with triethylamine under mild conditions followed by harsh treatment of the monobromo product with fused potassium hydroxide, care being taken to ensure minimum contact time of the product with alkali. Reaction of the sodium salt of 4-ethynylpyridine with benzophenone afforded α,α-diphenyl-γ-(4-pyridine)propynol (XIV) in good yield. Lithium aluminum hydride reduction of XIV yielded *trans*-α,α-diphenyl-γ-(4-pyridine)propenol (XVa) (Scheme I); the expected[19] *trans* configuration was supported by the nmr spectrum of the product which showed a coupling constant of $J = 16$ cps for the protons attached to the double bond. The *cis* isomer XVb was prepared by catalytic hydrogenation of XIV over Lindlar's catalyst. Neither XVa or XVb showed any special acid lability.

Of the compounds reported, only VIa produced central effects in animals comparable with those of I,[1,3] but activity in this instance was associated with a significant peripheral anticholinergic action.

SCHEME I



Experimental Section[20]

Effect of Acid on *trans*-2-(4-Pyridyl)-α,α-diphenylcyclopropanemethanol (I). A. 4-(4-Pyridyl)-1,1-diphenyl-1-buten-4-ol Hydrochloride (IIa).—A solution of 24.0 g (0.08 mol) of I[1] in a mixture of 500 ml of 1 *N* aqueous sulfuric acid and 50 ml of ethanol was heated on a steam bath for 6 hr. The cooled solution was made alkaline with aqueous ammonia and the precipitate was dissolved in benzene. The benzene solution was shaken with 3% aqueous hydrochloric acid and the precipitated hydrochloride salt was collected. Addition of dilute sodium hydroxide to a methanol solution of the only slightly water-soluble salt gave a precipitate which was taken into chloroform. Drying and removal of the chloroform and recrystallization from benzene–hexane afforded 8.7 g (36%) of recovered I, mp 168–169°; the mixture melting point was undepressed.

Making the aqueous hydrochloric acid filtrate basic with sodium carbonate, extracting the alkaline mixture with chloroform and drying, and removal of the organic solvent left a residue in the form of a yellow oil. An ice-cold ether solution of the oil was treated with ethereal hydrogen chloride to give a precipitate which was recrystallized from ethanol–ether and then from isopropyl alcohol to yield 4.0 g (17%) of the hydrochloric salt of IIa: mp 216–217° (the melting point of a mixture with the hydrochloride salt of I was markedly depressed); ir, ν_{max} (KBr), 3320 (OH), 1633 and 1605 (pyridinium); nmr ((DMSO-d_6), multiplet centered at δ 7.27 (phenyl protons), triplet at 6.23 (single double-bond proton).

Anal. Calcd for $C_{21}H_{20}ClNO$: C, 74.65; H, 5.97; Cl, 10.50. Found: C, 75.21; H, 5.99; ionic Cl, 10.48.

B. 4-Chloro-4-(4-pyridyl)-1,1-diphenyl-1-butene Hydrochloride (IIb).—In the course of work-up of larger scale runs of the Grignard reaction used for the preparation of I,[1] concentrated, ice-cold tetrahydrofuran–ether solutions of I were treated with cold 5% aqueous hydrochloric acid to precipitate the I hydrochloride. Low melting, mother liquor fractions obtained from recrystallizations of the hydrochloride salt were pooled and dissolved in methanol and the methanol solution was made alkaline with aqueous sodium hydroxide. The resultant precipitate was taken into chloroform and the chloroform solution was dried and concentrated to give a residue which was extracted with cold hexane (the material insoluble in the hexane proved to be I, mp 169–170° after recrystallization). Concentration of the hexane solution left a residual oil which was dissolved in ether. Treatment of the ether solution with ethereal hydrogen chloride gave a yellow precipitate which was recrystallized from mixtures of isopropyl alcohol, ether, and hexane to give IIb hydrochloride as colorless crystals: mp 129–132°; ir, ν_{max} (KBr), OH stretching absorption absent, 1637 and 1592 (pyridinium).

Anal. Calcd for $C_{21}H_{19}Cl_2N$: C, 70.79; H, 5.37; Cl, 19.90; ionic Cl, 9.95. Found: C, 70.35; H, 5.81; Cl, 19.53; ionic Cl, 9.72.

C. 4-(4-Pyridyl)-1,1-diphenyl-1,3-butadiene Hydrochloride (III).—Heating of 14 g of crude IIb (oil) under vacuum at a bath temperature of 185° caused rapid gas evolution and the

(18) Unpublished work from this laboratory.

(19) See J. D. Chanley and H. Sobotka, *J. Amer. Chem. Soc.*, **71**, 4140 (1949); W. Oroshnik, G. Karmas, and A. D. Mebane, *ibid.*, **74**, 3807 (1952); E. B. Bates, E. R. H. Jones, and M. C. Whiting, *J. Chem. Soc.*, 1854 (1954).

(20) Microanalyses were performed by the Galbraith Laboratories, Knoxville, Tenn. Melting points are corrected. "Basic nitrogens" were determined by titration with acetous–perchloric acid, ionic halogens by potentiometric titration. Infrared spectra were determined with a Beckman Model IR-5 spectrophotometer; peak positions are given in reciprocal centimeters (cm^{-1}). Nuclear magnetic resonance spectra were determined with a Varian Model A-60; pertinent chemical shifts are expressed in parts per million (ppm) downfield from tetramethylsilane and coupling constants in cycles per second (cps).

formation of a yellow solid. Recrystallization of the solid from isopropyl alcohol afforded 4.4 g of the hydrochloride salt of III as yellow crystals: mp 229–230°; ir, ν_{max} (KBr), OH band absent, 1640 and 1593 (pyridinium); nmr ($CDCl_3$), singlet at δ 7.39 (phenyl protons), multiplet centered at 6.94 (J = 15 cps, double-bond protons).

Anal. Calcd for $C_{21}H_{18}ClN$: C, 78.86; H, 5.67; Cl, 11.09. Found: C, 78.55; H, 5.74; ionic Cl, 11.00.

3-(4-Pyridyl)-1,1-diphenyl-1-propanol (IVa).—To a stirred solution of approximately 0.3 mol of phenylmagnesium bromide in 300 ml of ether, cooled in an ice bath, was added 12 g of crude methyl β-(4-pyridine)propionate[21] in 125 ml of dry ether. A vigorous reaction ensued. After the addition was complete, the reaction mixture was allowed to stand for 16 hr in the refrigerator and then poured with rapid stirring on a slurry of ice and 33 g of ammonium chloride. The ether layer was separated and the aqueous mixture was extracted with benzene. The combined benzene–ether solution was concentrated almost to dryness and diluted with hexane to precipitate a solid which was recrystallized from benzene to yield 6.4 g (30%) of IVa, mp 159–160°.

Anal. Calcd for $C_{20}H_{19}NO$: N, 4.83. Found: basic N, 4.76.

The **hydrochloride salt**, prepared by treatment of an ice-cold benzene–chloroform solution of IVa with ethereal hydrogen chloride and recrystallized from ethanol, showed mp 182–183° (gas evolution); ir, ν_{max} (KBr) 3340 (OH), 1630 and 1590 (pyridinium).

Anal. Calcd for $C_{20}H_{20}ClNO$: C, 73.70; H, 6.18; Cl, 10.88. Found: C, 73.89; H, 6.16; ionic Cl, 10.83.

3-(4-Pyridyl)-1,1-diphenyl-1-propene Hydrochloride (Va).—To an ice-cold solution of 396 g of IVa in 6 l. of methanol was added, slowly with stirring, 300 ml of ethereal hydrogen chloride. After the mixture was stirred for about 45 min at ice-bath temperature, it was diluted with ether to precipitate a combined total of 288 g (65%) of the hydrochloride salt of IVa, mp 179–180°. Concentration of the mother liquor to dryness, crystallization of the residual oil from ethanol, and recrystallization from isopropyl alcohol afforded 45.7 g (12%) of the hydrochloride salt of Va in the form of colorless crystals: mp 158–159.5°; ir, ν_{max} (KBr), OH band absent, 1628 and 1593 (pyridinium).

Anal. Calcd for $C_{20}H_{18}ClN$: C, 78.04; H, 5.89; Cl, 11.52. Found: C, 78.11; H, 5.84; ionic Cl, 11.56.

3-(4-Pyridyl)-1,1-diphenyl-1-butanol (IVb).—A slurry of 9.0 g (0.23 mol) of powdered sodium amide and 25.0 g (0.23 mol) of 4-ethylpyridine (Eastman) in approximately 350 ml of liquid ammonia was stirred for 30 min and then a mixture of 45.3 g (0.23 mol) of diphenylethylene oxide[22] in 150 ml of tetrahydrofuran was added in portions over a 30-min period. Stirring was continued and the evaporating ammonia was gradually replaced by tetrahydrofuran. After all of the ammonia had evaporated, the reaction mixture was heated at reflux for 5 hr. A small amount of isopropyl alcohol was added to the cooled reaction mixture, followed by the dropwise addition of 350 ml of water. The tetrahydrofuran layer was separated and the water layer was extracted with ether. The combined organic layers were extracted with 5% aqueous hydrochloric acid. The acid extract was made alkaline to precipitate a red oil which was taken into ether. Drying and removal of the ether left a residue which was washed with hexane and recrystallized from isopropyl alcohol to yield 34.9 g (50%) of IVb as colorless crystals: mp 141–142°; ir, ν_{max} (KBr), broad OH stretching absorption, 1600 (pyridine).

Anal. Calcd for $C_{21}H_{21}NO$: C, 83.14; H, 6.98; N, 4.62. Found: C, 83.29; H, 6.96; basic N, 4.52.

3-(4-Pyridyl)-1,1-diphenyl-1-butene Hydrochloride (Vb).—An ice-cold chloroform solution of 15.0 g of IVb was treated with ethereal hydrogen chloride and the acidified solution was diluted with more ether to precipitate an oil, which crystallized from a mixture of ethyl acetate, isopropyl alcohol, and ether, and was recrystallized from isopropyl alcohol–ether to give 11.8 g (75%) of Vb as colorless crystals, mp 162–164°. No other material could be isolated from mother liquors. After one additional recrystallization from isopropyl alcohol–ether, the material had mp 165–167°; ir, ν_{max} (KBr), OH band absent, 1625 and 1600 (pyridinium).

Anal. Calcd for $C_{21}H_{20}ClN$: C, 78.38; H, 6.26; Cl, 11.02. Found: C, 78.50; H, 6.57; ionic Cl, 10.97.

3-(4-Pyridyl)-1,1-diphenyl-1-propanol (IVa).—A solution of 290 g (3.1 mol) of 4-picoline in 500 ml of dry tetrahydrofuran was added, dropwise with stirring over a 45-min period, to a slurry of 125 g (3.2 mol) of powdered sodium amide in approximately 5 l. of liquid ammonia. After being stirred for an additional 2 hr, the reaction mixture was treated, dropwise over a 2.5-hr period, with a solution of 362 g (1.55 mol) of 2-chloro-1,1-diphenylethanol.[22] Stirring was continued, tetrahydrofuran was added to replace the evaporating ammonia, and finally the reaction mixture was heated at reflux for 2.5 hr. A small amount of isopropyl alcohol followed by 1500 ml of water was added to the cooled reaction mixture. The tetrahydrofuran layer was separated and the water layer was washed with ether. The combined tetrahydrofuran–ether layers were washed with water, dried, and evaporated to dryness. Crystallization of the residue gave 308 g (69%) of IVa, mp 157–159°, identical with the material obtained from methyl β-pyridinepropionate.

***trans*-2-[4-(1-Methyl-Δ^3-piperideinyl)]-α,α-diphenylcyclopropanemethanol (VIa).**—To a stirred solution of 32.6 g (0.082 mol) of the methobromide salt of I[1] in 150 ml of methanol was added 25 g (0.66 mol) of sodium borohydride dissolved in 150 ml of methanol at a rate sufficient to maintain gentle reflux. After the addition was complete, the solution was heated at reflux for 2 hr and concentrated, and the solid residue was taken up in water and exhaustively extracted with ether. Drying and removal of the ether and crystallization of the residue from benzene–hexane gave 22.6 g (86%) of VIa: mp 154–156°; mp 156–158° after further recrystallization.

Anal. Calcd for $C_{22}H_{25}NO$: N, 4.39. Found: basic N, 4.31.

The **hydrochloride salt of VIa**, prepared in ice-cold chloroform–ether and recrystallized from isopropyl alcohol–hexane, showed mp 188–189° (gas evolution); ir, ν_{max} (KBr), 3330 (OH), 1667 (double bond), 1597 (phenyl); pK'_a (80% Methyl Cellosolve) 7.83; nmr (DMSO-d_6), multiplet centered at δ 7.37 (phenyl protons), multiplet centered at 5.40 (single piperideine double-bond proton), singlet at 2.73 (N–CH_3 protons), complex multiplet at below 1.0 (cyclopropane protons).

Anal. Calcd for $C_{22}H_{26}ClNO$: C, 74.24; H, 7.36; Cl, 9.96; neut equiv, 355.9. Found: C, 74.05; H, 7.55; ionic Cl, 9.76; neut equiv, 361.

***trans*-2-(1-Methyl-4-piperidyl)-α,α-diphenylcyclopropanemethanol (VIb).** A.—Acetic acid was added dropwise to a suspension of 8 g (0.025 mol) of VIa in *ca.* 200 ml of ethanol until all of the material had dissolved. The solution was shaken with 2 g of 5% rhodium on carbon at 50 psi of hydrogen and room temperature in an Adams–Parr apparatus. The calculated amount of hydrogen was taken up in 10 min. Dilute, aqueous sodium hydroxide was added to the filtered solution to precipitate a solid which was recrystallized from heptane to yield 5.7 g (71%) of VIb: mp 155–156°; mp 158–159.5° after further recrystallization from heptane; ir, ν_{max} ($CHCl_3$), 3610 (OH), 1600 (phenyl); unstable in acid; titration with acetous–perchloric acid anomalous; hydrochloride salt could not be prepared.

Anal. Calcd for $C_{22}H_{27}NO$: C, 82.20; H, 8.47; N, 4.36. Found: C, 82.13; H, 8.55; N, 4.41.

B.—A solution of 16.0 g (0.04 mol) of the methobromide salt of I[1] in 200 ml of ethanol was shaken with 0.5 g of platinum oxide at room temperature under 50-psi hydrogen pressure in an Adams–Parr apparatus. The calculated amount of hydrogen was taken up in 1 hr. The filtered solution was concentrated to one-half its volume, dilute aqueous ammonia was added, and the resultant precipitate was dissolved in ether. Drying and removal of the ether and recrystallization of the solid residue from benzene–hexane afforded 7.8 g (61%) of VIb, identical with the product obtained by method A above.

Ethyl γ-(1-Methyl-4-piperidine)butyrate (VII).—A solution of 73.0 g (0.25 mol) of the crude methobromide salt of 4-(2-carbethoxycyclopropyl)pyridine[1] in 200 ml of 50% aqueous ethanol was hydrogenated over 1 g of platinum oxide at 50 psi and room temperature. Hydrogen uptake was complete in 4 hr. The filtered solution was concentrated, diluted with water and made alkaline with sodium carbonate. The oil that separated was dissolved in ether. Drying and removal of the ether and distillation of the residual oil yielded 41.0 g (78%) of VII: bp 116–118° (4.5 mm); $n^{22}D$ 1.4600; ir, ν_{max} (CCl_4) 1733 (ester carbonyl). This was probably a mixture of isomers in view of difficulties encountered in isolating pure derivatives from it.

Anal. Calcd for $C_{12}H_{23}NO_2$: N, 6.57. Found: basic N, 6.49.

The **hydrochloride salt of VII** showed mp 105–106° after recrystallization from ethyl acetate; repeated crystallization from ethyl acetate raised the melting point to 146–148°; the ir spectrum showed a band at ν_{max} ($CHCl_3$) 1721 (ester carbonyl).

(21) A. R. Katritzky, *J. Chem. Soc.*, 2581 (1955).

(22) H. E. Zaugg and R. J. Michaels, *J. Amer. Chem. Soc.*, **80**, 2770 (1958).

Anal. Calcd for $C_{12}H_{24}ClNO_2$: C, 57.70; H, 9.68; Cl, 14.20. Found: C, 57.64; H, 9.28; ionic Cl, 14.23.

4-(1-Methyl-4-piperidyl)-1,1-diphenyl-1-butanol (VIII).—To the Grignard reagent prepared from 37.7 g (0.24 mol) of bromobenzene and 7.2 g (0.3 g-atom) of magnesium in 250 ml of tetrahydrofuran was added, dropwise with stirring at ice-bath temperature, a solution of 21.1 g (0.01 mol) of crude VII in 200 ml of tetrahydrofuran. After addition was complete the reaction mixture was stirred at room temperature for 3 hr, a 20% solution of ammonium chloride was added, and the reaction mixture was extracted with ether. The ether solution was extracted with dilute hydrochloric acid, the acid solution was made basic, and the oil precipitate was extracted with ether. No characterizable product could be isolated from the oil residue obtained from the ether solution. A white solid which remained undissolved during the ether extraction was recrystallized from heptane to give 6.5 g (20%) of VIII as colorless crystals: mp 184–185°; ir, ν_{max} (KBr), broad absorption in OH stretching region, 1597 (phenyl); nmr (DMSO-d_6), multiplet centered at δ 7.33 (phenyl protons), 2.64 (N-CH_3 protons), C-CH_3 peak absent.

Anal. Calcd for $C_{22}H_{29}NO$: C, 81.69; H, 9.04; N, 4.33. Found: C, 81.89; H, 9.21; basic N, 4.28.

Ethereal hydrogen chloride was added dropwise to a chloroform solution of 3.0 g of VIII, cooled in an ice bath, to the point at which the solution proved acid to moist pH paper. Dilution of the solution with hexane afforded a precipitate which was recrystallized from isopropyl alcohol to give 2.0 g of the **hydrochloride salt** of VIII as colorless crystals, mp 203–204° (gas evolution).

Anal. Calcd for $C_{22}H_{30}ClNO$: Cl, 9.85. Found: Cl, 9.94; ionic Cl, 9.80.

4-(1-Methyl-4-piperidyl)-1,1-diphenyl-1-butene Hydrochloride (IX).—Dropwise addition of a slight excess of ethereal hydrogen chloride to an ice-cold chloroform solution of 3.0 g of VIII and dilution with ether gave a precipitate which was recrystallized from isopropyl alcohol–ether to yield 2.3 g of the **hydrochloride salt of IX** as colorless crystals: mp 210–211°, mixture melting ponit with the hydrochloride salt of VIII markedly depressed; ir, ν_{max} (KBr), OH band absent, 1595 (phenyl).

Anal. Calcd for $C_{22}H_{28}ClN$: C, 77.27; H, 8.25; Cl, 10.37. Found: C, 77.30; H, 7.82; Cl, 10.71.

Ethyl 2-(3-Dimethylaminopropyl)cyclopropanecarboxylate (X).

A.—A solution of approximately 1 mol of ethyl diazoacetate[1] in 775 ml of xylene was added, dropwise with stirring, to a mixture of 100 g (0.95 mol) of 5-chloro-1-pentene and 3.6 g of cuprous cyanide in 250 ml of xylene heated on a steam bath. The addition took 2 hr, during which a total of 27.2 l. of nitrogen was evolved. After being heated for 1 hr more, the mixture was allowed to cool and filtered and the filtrate was concentrated at atmospheric pressure to remove xylene and starting material. The residual oil was vacuum distilled and redistilled through a 28-in. Nester–Faust spinning-band column to give 33.4 g (18%) of impure ethyl 2-(3-chloropropyl)cyclopropanecarboxylate, bp 121–123° (16 mm), $n^{25}D$ 1.4566. A forerun, boiling range 80–110° (16 mm), $n^{25}D$ 1.435–1.440, was found to be low in chlorine and apparently was largely ethyl 2-(2-propenyl)cyclopropanecarboxylate: ir, ν_{max} ($CHCl_3$) 1725 (ester carbonyl), 1643 (double bond). A high boiling residue was not further characterized.

B.—A solution of 33.2 g (0.17 mol) of crude ethyl 2-(3-chloropropyl)cyclopropanecarboxylate and 40.1 g (0.88 mol) of anhydrous dimethylamine in 200 ml of benzene was heated with shaking at 65–70° for 50 hr in a stoppered Parr pressure bottle. A total of 12.1 g (88%) of crude dimethylamine hydrochloride was filtered from the cooled reaction mixture. The filtrate was extracted with cold 5% hydrochloric acid solution; the aqueous extract was made basic with potassium carbonate and extracted with ether. Drying and removal of the ether followed by distillation of the residual yellow oil afforded 24.8 g (72%) of X: bp 118–119° (13 mm); $n^{25}D$ 1.4451; ir, ν_{max} ($CHCl_3$) 1715 (ester carbonyl); nmr ($CDCl_3$), quartet centered at δ 4.15 (ethoxy CH_2), triplet at 1.27 (ethoxy CH_3), singlet at 2.90 [N-$(CH_3)_2$], complex multiplet centered at about 1.0 (cyclopropane protons).

Anal. Calcd for $C_{11}H_{21}NO_2$: N, 7.03. Found: basic N, 7.08.

The **cyclohexanesulfamate salt of X**, prepared in ether–isopropyl alcohol and recrystallized from ethyl acetate, showed mp 94–95°.

Anal. Calcd for $C_{17}H_{34}N_2O_5S$: C, 53.94; H, 9.05; S, 8.47. Found: C, 54.32; H, 9.13; Schöniger S, 8.52.

2-(3-Dimethylaminopropyl)-α,α-diphenylcyclopropanemethanol (XI).—To an ice-cold slurry of the Grignard reagent prepared from 55 g (0.35 mol) of bromobenzene and 8.9 g (0.36 g-atom) of magnesium turnings in 225 ml of dry tetrahydrofuran was added, dropwise with stirring, a solution of 18.0 g (0.09 mol) of X in 50 ml of tetrahydrofuran. After the addition was complete, the reaction mixture was allowed to warm to room temperature and stirring was continued for 2 hr. The reaction mixture was poured into 300 ml of saturated ammonium chloride solution and extracted with ether. The ether extract was dried and evaporated to a thick oil residue that solidified on standing. This was dissolved in ice-cold, dilute aqueous hydrochloric acid. The aqueous solution was washed with ether, made basic, and extracted with ether. Drying and removal of the ether left an oily solid which was crystallized from acetone and recrystallized from pentane to give 6.8 g (22%) of colorless crystals of XI: mp 90–92°; ir, ν_{max} ($CHCl_3$) 3300 (OH), 1600 (phenyl); nmr ($CDCl_3$), multiplet centered at δ 7.33 (phenyl protons), singlet at 2.11 [N-$(CH_3)_2$], complex multiplet at below 1.0 (cyclopropane protons); unstable to acid; titration with acetous perchloric acid anomalous; acid addition salt could not be prepared.

Anal. Calcd for $C_{21}H_{27}NO$: C, 81.50; H, 8.80; N, 4.53. Found: C, 81.47; H, 8.88; N, 4.71.

2-(4-Pyridyl)-1,1-diphenylcyclopropane Hydrochloride (XII).—A solution of 25.2 g (0.13 mol) of crude diphenyldiazomethane[23] and 14.7 g (0.14 mol) of 4-vinylpyridine in 150 ml of tetrahydrofuran was slowly warmed[24] to reflux and heated at reflux for 11 hr during which period nitrogen was slowly evolved. The cooled, dark solution was diluted with hexane and filtered from a small amount of precipitate; the filtrate was concentrated under vacuum to a small volume and diluted with ether. Extraction of the ether solution with 5% aqueous hydrochloric acid caused formation of a precipitate which was recrystallized from isopropyl alcohol to yield 29.4 g (73%) of the hydrochloride salt of XII in the form of colorless crystals: mp 237° dec; ir, ν_{max} ($CHCl_3$) 1633 and 1605 (pyridinium).

Anal. Calcd for $C_{20}H_{18}ClN$: C, 78.04; H, 5.89; Cl, 11.52. Found: C, 77.71; H, 5.77; ionic Cl, 11.51.

The **methobromide salt of XII**, prepared by treating an acetonitrile solution of the base (oil) with methyl bromide and recrystallized from isopropyl alcohol–ether, showed mp 226° dec.

Anal. Calcd for $C_{21}H_{20}BrN$: C, 68.85; H, 5.50; Br, 21.82. Found: C, 68.84; H, 5.56; ionic Br, 21.75.

3-(1-Methyl-4-piperidyl)-1,1-diphenylpropane Hydrochloride (XIII).—A solution of 16.1 g (0.044 mol) of the methobromide salt of XII in 250 ml of 90% ethanol was shaken with 0.5 g of platinum oxide in an Adams–Parr apparatus under a hydrogen pressure of 50 psi. The calculated amount of hydrogen was absorbed in 1.5 hr. The filtered solution was concentrated to a smaller volume, diluted with water, made alkaline, and extracted with ether. Drying and removal of the ether left an oil which could not be crystallized. A dry ether solution of the oil was treated with ethereal hydrogen chloride and the precipitate recrystallized twice from isopropyl alcohol–ether–hexane and then from ethyl acetate–ether to give 4.3 g (30%) of the hydrochloride salt of XIII: mp 173–174° (further recrystallization from ethyl acetate–ether raised the melting point to 177–178°); ir, ν_{max} ($CHCl_3$) 1600 (phenyl); nmr ($CDCl_3$), singlet at δ 7.27 (phenyl protons), triplet centered at 3.84 (diphenylmethyl CH), singlet at 2.73 (N-CH_3).

Anal. Calcd for $C_{21}H_{28}ClN$: C, 76.45; H, 8.55; Cl, 10.75. Found: C, 76.63; H, 8.53; ionic Cl, 10.73.

4-Ethynylpyridine.[25,26]—A solution of 116 g (0.82 mol) of 4-

(23) D. A. Shirley, "Preparation of Organic Intermediates," John Wiley and Sons, Inc., New York, N. Y., 1951, p 134.

(24) The same product was obtained when the reactants were allowed to stand at room temperature in ether solution for 3 days. When, however, diphenyldiazomethane was added to excess 4-vinylpyridine heated at 130° in the presence of copper powder, very little nitrogen was evolved and a product, which was not entirely freed from impurities but which probably was a 2-pyrazoline derivative, was isolated. This material was stable to heating at above 200°; decomposition and nitrogen evolution took place at higher temperatures but without formation of a characterizable product. It seems likely that in the presence of a large excess of 4-vinylpyridine base at the higher temperature rearrangement of the presumably initially formed 1-pyrazoline to a more stable 2-pyrazoline superseded loss of nitrogen.

(25) Procedure patterned after that used by D. Leaver, W. K. Gibson, and J. D. R. Vass [*J. Chem. Soc.*, 6053 (1963)] for preparation of 2-ethynylpyridine in 30% yield. Conditions had to be modified in order to obtain a comparable yield of the 4 isomer.

(26) U. Haug and H. Fürst [*Chem. Ber.*, **93**, 593 (1960)] report mp 94.5–95° for 4-ethynylpyridine prepared by another method in 3.9% yield.

vinylpyridine hydrochloride (mp 240–243°, prepared from freshly distilled 4-vinylpyridine) in 550 ml of chloroform was treated, dropwise with stirring and cooling in an ice bath, with 262 g (1.62 mol) of bromine. After all of the bromine had been added, the reaction mixture was stirred for 1 hr at ice-bath temperature and then for 1 hr at room temperature. The reaction mixture was diluted with ether and the precipitated orange oil was washed with ether and treated with 500 ml of acetone to yield 209 g of the crude salt of **4-vinylpyridine dibromide**, mp 148–150°.

A 60.2-g portion of the crude salt was treated with aqueous sodium carbonate and the resulting base was taken into ether. The yellow ether solution was dried over magnesium sulfate, concentrated to a volume of 350 ml, and treated with a solution of 22.2 g (0.22 mol) of triethylamine in 100 ml of tetrahydrofuran. The reaction mixture was stirred at room temperature for 2 hr and at reflux for 1.5 hr, 21 g of precipitated triethylamine hydrobromide was filtered off, and the filtrate was concentrated at reduced pressure to 39 g of an amber oil, presumed to be crude 4-pyridyl-1-bromoethylene.

To an intimate mixture of 56 g (1 mol) of powdered potassium hydroxide and 50 g of paraffin (mp ~56°), magnetically stirred and heated in an oil bath at 160° under a reduced pressure of 200 mm, 36 g of the crude 4-pyridyl-1-bromoethylene was added in small portions through a dropping funnel. The pressure was held at 200 mm for 1–2 min after the addition of each portion and then slowly reduced to 4 mm as the product distilled out of the reaction mixture and was collected in a recovery flask in the form of colorless crystals. This process was repeated until all of the material had been added. Recrystallization of the distilled material from pentane afforded 5.0 g of **4-ethynylpyridine**, mp 95–97°.[26] The mother liquor was concentrated and the residue was again subjected to treatment with potassium hydroxide–paraffin to provide an additional 1.6 g of **4-ethynylpyridine**, mp 95–98°, for a total of 6.6 g, representing an over-all yield from 4-vinylpyridine hydrochloride of 29%.

α,α-Diphenyl-γ-(4-pyridine)propynol (XIV).—To a stirred slurry of 7.8 g (0.2 mol) of sodamide in 300 ml of liquid ammonia was added 19.0 g (0.185 mol) of 4-ethynylpyridine followed by 33.7 g (0.185 mol) of benzophenone in 100 ml of dry ether. The evaporating ammonia was replaced by a total of 800 ml of ether and the reaction mixture was allowed to warm to room temperature. After a small amount of isopropyl alcohol had been added, the reaction mixture was shaken with 2.5% aqueous hydrochloric acid to give a white precipitate which was suspended in dilute sodium carbonate solution and exhaustively extracted with a mixture of chloroform and ether. Drying and evaporation to dryness of the organic extract and recrystallization of the residue from benzene–pentane yielded 40.0 g (76%) of XIV as colorless plates, mp 187–188°.

Anal. Calcd for $C_{20}H_{15}NO$: N, 4.91. Found: basic N, 4.89.

The **methanesulfonate salt of XIV** formed colorless needles from a mixture of isopropyl alcohol, ether, and hexane: mp 164–165°; ir, ν_{max} (KBr) 3280 (broad OH band), 2235 (triple bond), 1638 and 1602 (pyridinium).

Anal. Calcd for $C_{21}H_{19}NO_4S$: C, 66.12; H, 5.02; S, 8.41. Found: C, 66.75; H, 5.03; Schöniger S, 8.39.

***trans*-α,α-Diphenyl-γ-(4-pyridine)propenol (XVa).**—A slurry of 1.48 g (0.039 mol) of lithium aluminum hydride in 250 ml of dry ether was added in small portions to a stirred mixture of 12.5 g (0.044 mol) of XIV in 200 ml of ether. After completion of the addition, the resulting orange reaction mixture was heated at reflux for 3 hr, allowed to cool to room temperature, and treated with 10 ml of ethyl acetate followed by 50 ml of water. The precipitated aluminum hydroxide was filtered off, the water layer was separated from the filtrate, and the ether layer was diluted with chloroform and dried over magnesium sulfate. Evaporation of the ether–chloroform solution to a smaller volume caused precipitation of XVa as a white solid: 5.3 g (42%); mp 178–179°, mp 178.5–180° after recrystallization from benzene–hexane. A mixture melting point with XIV showed a slight but definite depression.

Anal. Calcd for $C_{20}H_{17}NO$: N, 4.87. Found: basic N, 4.80.

The **methanesulfonate salt of XVa** formed fine, colorless needles from isopropyl alcohol–ether: mp 178° (gas evolution); ir, ν_{max} (KBr) 3310 (broad OH band), 1632 and 1604 (pyridinium); nmr (D_2O), singlet at δ 7.48 (phenyl protons), 7.08 and 6.83 (double-bond protons, J_{trans} = 16 cps).

Anal. Calcd for $C_{21}H_{21}NO_4S$: C, 65.77; H, 5.52; S, 8.36. Found: C, 65.96; H, 5.60; Schöniger S, 8.55.

***cis*-α,α-Diphenyl-γ-(4-pyridine)propenol (XVb).**—A solution of 15.4 g (0.054 mol) of XIV and 1.4 g of quinoline in 300 ml of methanol was hydrogenated over 1.4 g of freshly prepared palladium–calcium carbonate (Lindlar's catalyst)[27] at room temperature and atmospheric pressure.[28] The calculated volume of hydrogen was absorbed in 1 hr. Concentration of the filtered solution to dryness under vacuum and recrystallization of the solid residue from benzene–heptane and from benzene–pentane yielded 7.0 g (49%) of XVb, mp 141–143°. Further recrystallization gave colorless needles: mp 147–149°, melting point depressed on admixture with IVa; ir, ν_{max} (KBr) 3150 (broad OH band), 1642 (double bond), 1600 (pyridine).

Anal. Calcd for $C_{20}H_{17}NO$: N, 4.87. Found: basic N, 4.89.

It may be noted that a crystalline methanesulfonate but not a crystalline hydrochloride salt was obtainable from XVa; the reverse was true of XVb. The **hydrochloride salt of XVb**, recrystallized from ethanol–ether, showed mp 168–168.5°; ir, ν_{max} (KBr) 3350 (OH), 1630 and 1603 (pyridinium); nmr (DMSO-d_6), multiplet centered at δ 7.40 (phenyl protons), singlet at 6.93 (double-bond protons).

Anal. Calcd for $C_{20}H_{18}ClNO$: C, 74.18; H, 5.60; Cl, 10.95. Found: C, 74.06; H, 5.54; ionic Cl, 10.97.

α,α-Dicyclopropyl-4-pyridineethanol (XVIa).—To a stirred slurry of 12.3 g (0.31 mol) of sodium amide in 400 ml of liquid ammonia was added 28.4 g (0.3 mol) of 4-picoline followed by the dropwise addition of a solution of 33.4 g (0.3 mol) of dicyclopropyl ketone (Aldrich) in 150 ml of dry ether. The evaporating ammonia was replaced by an additional 500 ml of ether. The resultant reaction mixture was stirred for 1 hr at room temperature and poured on cracked ice, the ether layer was separated, and the aqueous phase was extracted with fresh ether. The combined, dried ether solution was concentrated to dryness under vacuum and the residual oil was distilled to yield 20.4 g (34%) of XVIa as a colorless oil, bp 135–141° (0.2 mm), which crystallized on standing, mp 51–53°.

Anal. Calcd for $C_{13}H_{17}NO$: N, 6.89. Found: basic N, 6.88.

The **hydrochloride salt of XVIa**, prepared by careful treatment of a cold ether solution of the base with ethereal hydrogen chloride and recrystallized from acetonitrile, formed large colorless needles: mp 140–141°; ir, ν_{max} (KBr) 3340 (OH), 1630 and 1592 (pyridinium).

Anal. Calcd for $C_{13}H_{18}ClNO$: C, 65.10; H, 7.56; Cl, 14.78. Found: C, 65.33; H, 7.65; Cl, 14.79.

α-Cyclopropyl-α-phenyl-4-pyridineethanol (XVIb).—A similar reaction of 4-picoline with cyclopropyl phenyl ketone (Aldrich) and recrystallization of the crude, distilled product [boiling range 90–185° (0.1 mm)] from acetone–pentane yielded 7.95 g (19.5%) of XVIb, mp 98–99°.

Anal. Calcd for $C_{16}H_{17}NO$: N, 5.85. Found: basic N, 5.80.

The **hydrochloride salt of XVIb**, recrystallized from isopropyl alcohol, showed mp 189.5–190° (gas evolution); ir, ν_{max} (KBr) 3340 (OH), 1628 and 1600 (pyridinium).

Anal. Calcd for $C_{16}H_{18}ClNO$: C, 69.68; H, 6.58; Cl, 12.86. Found: C, 69.20; H, 6.60; ionic Cl, 12.96.

Registry No.—I, 6529-62-0; IIa, 16898-00-3; IIa hydrochloride, 16898-01-4; IIb, 16898-02-5; IIb hydrochloride, 16898-03-6; III, 16898-20-7; III hydrochloride, 16898-04-7; IVa, 16898-05-8; IVa hydrochloride, 16898-06-9; IVb, 16898-07-0; Va, 16898-08-1; Va hydrochloride, 16898-09-2; Vb, 16898-10-5; Vb hydrochloride, 16898-11-6; VIa, 16898-12-7; VIa hydrochloride, 16898-13-8; VIb, 16898-14-9; VII, 16898-15-0; VII hydrochloride, 16898-16-1; VIII, 16898-17-2; VIII hydrochloride, 16898-21-8; IX, 16898-22-9; IX hydrochloride, 16898-18-3; X, 16898-19-4; X cyclohexanesulfamate, 16898-23-0; XI, 16897-65-7; XII, 16897-73-7; XII hydrochloride, 16915-91-6; XII methobromide, 16897-66-8; XIII, 16897-67-9; XIII hydrochloride, 16897-68-0; XIV, 16897-53-3; XIV methanesulfonate,

(27) H. Lindlar, *Helv. Chim. Acta*, **35**, 446 (1952). When palladium on charcoal was used, the saturated compound (IVa), identified by comparison with authentic material, was obtained.

(28) The hydrogenation could also be carried out in an Adams–Parr apparatus at 40 psi.

16897-54-4; XVa, 16897-55-5; XVa methanesulfonate, 16915-95-0; XVb, 16897-69-1; XVb hydrochloride, 16897-70-4; XVIa, 16897-71-5; XVIa hydrochloride, 16897-74-8; XVIb, 16897-75-9; XVIb hydrochloride, 16897-76-0; 4-ethynylpyridine, 2510-22-7.

Acknowledgments.—We thank Mr. D. F. Cortright and his associates for analytical data and for ir and uv spectral determinations and Dr. E. B. Whipple and associates for providing and aiding in the interpretation of nmr data.

The Reaction of Amino Heterocycles with Reactive Esters. I. 2-Aminopyridines

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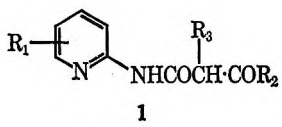
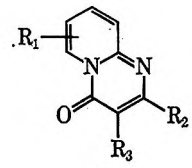
Received October 3, 1968

Very good yields of 4H-pyrido[1,2-*a*]pyrimidin-4-ones have been obtained in a one-stage synthesis by the condensation of 2-aminopyridines with β-keto esters or ethyl ethoxymethylenemalonate, and the corresponding 2,4-diones with diethyl malonate, in the presence of polyphosphoric acid (PPA). It is suggested that the cyclization of 2-acylacetamidopyridines with PPA to give pyrido[1,2-*a*]pyrimidin-4-ones involves the formation of N-(2-pyridyl)-β-(2′-pyridylamino)crotonamides since the latter on treatment with PPA give the same products.

It has recently been shown by Staskun and Israelstam[1] and Mallams and Israelstam[2] that hydroxyquinolines can be synthesized in one stage in good yields by heating arylamines with β-keto esters in the presence of PPA. This method avoids the necessity of following the two-stage method of Conrad and Limpach.[3-6] In an analogous way, we have now shown that pyrido[1,2-*a*]pyrimidin-4-ones can also easily be obtained in a one-stage process by condensing 2-aminopyridines with β-keto esters in the presence of PPA. The yields are much higher (in many cases 80% or more) than those obtained by other methods using a two-stage procedure involving the intermediate 2-acylacetamidopyridine (**1**) and its subsequent cyclization to the pyrido[1,2-*a*]pyrimidin-4-one (**2**).



1



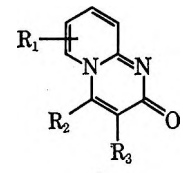
2

Optimum yields were obtained by heating 1 mol of the 2-aminopyridine with 1.5 mol of β-keto ester at 100° for about 1 hr together with a four- to sixfold quantity of PPA. Kato, *et al.*,[7] have obtained a 28% yield of 2-methyl-4H-pyrido[1,2-*a*]pyrimidin-4-one by treating 2-aminopyridine with diketene.

Table I gives some of the pyrido[1,2-*a*]pyrimidin-4-ones prepared, many of which are water soluble and pharmacologically active. 5-Nitro-2-aminopyridine failed to react.

Alkaline hydrolysis of these compounds yielded the 2-aminopyridines from which they were derived. This according to Lappin[8] proves that they were pyrido-[1,2-*a*]pyrimidines and not 1,8-naphthyridines. Furthermore, oxidation yielded 4-hydroxypyrimidines.

Although some workers[9-14] considered that the base obtained from 2-aminopyridine and ethyl acetoacetate was 4-methyl-2H-pyrido[1,2-*a*]pyrimidin-2-one (**3**, $R_1 = R_3 = H$; $R_2 = CH_3$), Antaki and Petrow[15]



3

showed that the product was in fact the 2-methyl-4-keto isomer **2** ($R_1 = R_3 = H$; $R_2 = CH_3$) by virtue of its alternate synthesis from 2-bromopyridine and ethyl β-aminocrotonate.

The 4-keto structure was confirmed by Adams and Pachter[16] who converted 3-bromo-2-phenyl-4H-pyrido-[1,2-*a*]pyrimidin-4-one into 2-phenylimidazo[1,2-*a*]-pyridine.

However, further evidence has now been adduced not only in support of the 4-keto structure, but also of a possible mechanism for the reaction. Kucherov[13,14] has shown that, when N-(5-chloro-2-pyridyl)-β-(5′-chloro-2′-pyridylamino)crotonamide (**4**, $R_1 = R_4 =$ 5-Cl) is treated with sulfuric acid, a 7-chloropyrido-[1,2-*a*]pyrimidinone was formed, which he incorrectly regarded as the 2-keto isomer.

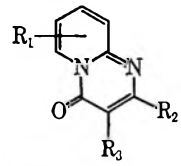
It was therefore decided to investigate the products obtained by cyclization of unsymmetrical crotonamides (**4**) since the nature of these products would provide evidence both of the structure of the pyrimidinone and of a possible mechanism.

The conversion of the crotonamide into the pyrimidinone probably occurs in two stages: first, hydrolytic fission could occur at either bonds a or b with

(1) B. Staskun and S. S. Israelstam, *J. Org. Chem.*, **26**, 3191 (1961).
(2) A. K. Mallams and S. S. Israelstam, *ibid.*, **29**, 3548 (1964).
(3) M. Conrad and L. Limpach, *Chem. Ber.*, **20**, 944 (1887).
(4) M. Conrad and L. Limpach, *ibid.*, **21**, 523 (1888).
(5) M. Conrad and L. Limpach, *ibid.*, **21**, 1649 (1888).
(6) M. Conrad and L. Limpach, *ibid.*, **24**, 2990 (1891).
(7) T. Kato, H. Yamanaka, T. Mitsuma, and M. Aizumi, *Chem. Pharm. Bull.*, **12** (8), 910 (1964).
(8) G. R. Lappin, *J. Amer. Chem. Soc.*, **70**, 3348 (1948).
(9) C. R. Hauser and M. J. Weiss, *J. Org. Chem.*, **14**, 453 (1949).
(10) F. Palazzo and A. Tamburini, *Atti Accad. Lincei*, **20** I, 37 (1911); *Chem. Abstr.*, **6**, 1586 (1911).
(11) Crippa and Scevola, *Gazz. Chim. Ital.*, **67**, 327 (1937); *Chem. Abstr.*, **32**, 166 (1938).
(12) S. N. Khitrik, *J. Gen. Chem. USSR*, **9**, 1109 (1939); *Chem. Abstr.* **33**, 8615 (1939).
(13) V. H. Kucherov, *J. Gen. Chem. USSR*, **20**, 1890 (1950); *Chem. Abstr.*, **45**, 2951 (1951).
(14) V. H. Kucherov, *J. Gen. Chem. USSR*, **21**, 1145 (1951); *Chem. Abstr.*, **46**, 5043 (1952).
(15) H. Antaki and V. Petrow, *J. Chem. Soc.*, 551 (1951).
(16) R. Adams and I. Pachter, *J. Amer. Chem. Soc.*, **74**, 5491 (1952).

TABLE I

4H-PYRIDO[1,2-*a*]PYRIMIDIN-4-ONES

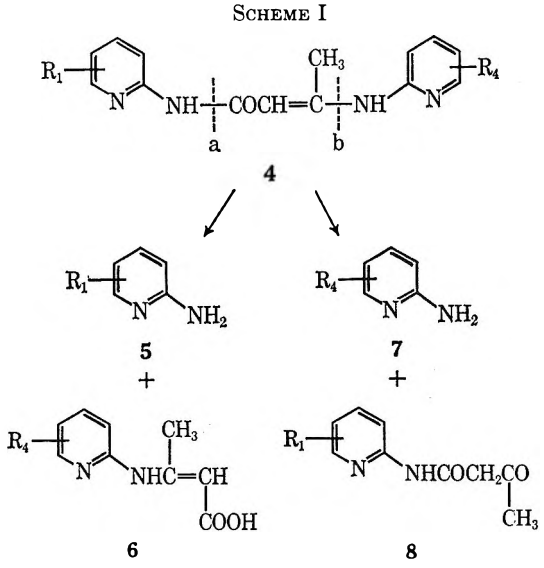


Substituent			Registry	Yield,	Mp,	Lit. yield,[a]	Lit. mp,		Anal, % Calcd			Found		
R_1	R_2	R_3	no.	%	°C	%	°C	Formula	C	H	N	C	H	N
H	CH_3	H		96	123	NR	123–124[b]							
9-CH_3	CH_3	H		74	131–132	NR	130[c]							
6-CH_3	CH_3	H	16867-28-0	69	105	NR	NR	$C_{10}H_{10}N_2O$	68.98	5.75		68.99	5.91	
7-Cl	CH_3	H		98	169–170	22[d]	165–166[d]							
7,9-di-Br	CH_3	H	16878-10-7	86	167	NR	NR	$C_9H_6Br_2N_2O$	33.96	1.89		34.07	2.00	
H	CH_3	CH_3	16867-29-1	86	120–121	NR	NR	$C_{10}H_{10}N_2O$	68.98	5.75		68.91	5.68	
7-CH_3	CH_3	CH_3	16878-11-8	80	129–130	NR	NR	$C_{11}H_{12}N_2O$			14.89			14.80
7-Br	CH_3	C_6H_5	16867-30-4	82	138–139	NR	NR	$C_{11}H_{11}BrN_2O$	49.44	4.12		49.40	4.06	
H	CH_3	C_2H_5	16867-31-5	76	92–93	NR	NR	$C_{11}H_{12}N_2O$			14.89			14.90
6,8-di-CH_3	CH_3	C_2H_5	16867-32-6	88	128–129	NR	NR	$C_{13}H_{16}N_2O$	72.21	7.41		72.46	7.62	
H	CH_3	Cl	16867-33-7	51	186–187	NR	NR	$C_9H_7ClN_2O$	55.53	3.59		55.80	3.68	
7-Cl	C_6H_5	H	16867-34-8	54	170–171	NR	NR	$C_{14}H_9ClN_2O$			10.91			10.98
H	CH_2Cl	H	16867-35-9	44	169–170	NR	NR	$C_9H_7ClN_2O$	55.53	3.59		55.58	3.65	

[a] NR = not reported. [b] Reference 15. [c] Reference 7. [d] Reference 13.

the formation of either the aminopyridine (**5**) and the β-pyridylaminocrotonic acid (**6**) or the aminopyridine (**7**) and the 2-acetoacetamidopyridine (**8**) (Scheme I).

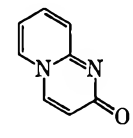
SCHEME I



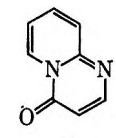
The second stage would be the cyclization of either **6** to give the pyrimidin-4-one (**2**, $R_2 = CH_3$; $R_3 = H$) or of **8** which would be expected to give the pyrimidin-2-one (**3**, $R_2 = CH_3$; $R_3 = H$). It was found that the 2-aminopyridine formed was in fact **5** and that the pyrido[1,2-*a*]pyrimidinone formed contained the group R_4, and hence it may be concluded that the pyrimidinone is the 4-keto isomer **2** ($R_1 = R_4$; $R_2 = CH_3$; $R_3 = H$).

A number of symmetrical and unsymmetrical or "mixed" crotonamides were prepared. Symmetrical crotonamides were obtained by the interaction of 2-aminopyridines and the 2-acetoacetamidopyridine obtained from it and unsymmetrical crotonamides from 2-aminopyridines and a 2-acetoacetamidopyridine derived from a different 2-aminopyridine according to Khitrik[12] and Kucherov.[14] Attempts to prepare crotonamides from 6-methyl-2-aminopyridines led to the formation of symmetrical di(6-methyl-2-pyridyl)-ureas. It is interesting to note that, when 5-chloro-2-aminopyridine was heated with 4-methyl-2-acetoacetamidopyridine (**2**, $R_1 = 4\text{-}CH_3$; $R_2 = CH_3$; $R_3 = H$), only the symmetrical crotonamide, N-(5-chloro-2-pyridyl)-β-(5′-chloro-2′-pyridylamino)crotonamide (**4**, $R_1 = R_4 = 5\text{-}Cl$) was isolated. The conversion of the crotonamides (Table II) into the pyrido[1,2-*a*]-pyrimidin-4-ones was effected by heating them with PPA.

The ultraviolet spectra of a number of pyrido[1,2-*a*]-pyrimidin-4-ones obtained by the one-stage synthesis were determined and compared with those of **9** and **10**, obtained by Adams and Pachter.[16] The 4H-pyrido-[1,2-*a*]pyrimidin-4-ones show a characteristic two-band spectrum, one with maximum at about 350 mμ being ascribed[17,18] to the N-substituted pyridone-2-imine chromophore. The second band with maximum at about 245 mμ has been attributed[19] to the —C=C—C=O chromophore of the pyrimidine moiety. The ultraviolet absorption spectra of the pyrido[1,2-*a*]-pyrimidinones prepared were found to be very similar to that of 4H-pyrido[1,2-*a*]pyrimidin-4-one (**10**).



9



10

The 4H-pyrido[1,2-*a*]pyrimidin-4-ones obtained in the one-stage synthesis were also obtained by the cyclization of alkyl β-pyridylaminocrotonates (**11**) and

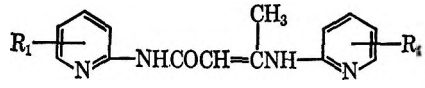
(17) H. Antaki, *ibid.*, **80**, 3066 (1958).

(18) L. C. Anderson and N. V. Seeger, *J. Amer. Chem. Soc.*, **71**, 340 (1949).

(19) H. Antaki, *J. Org. Chem.*, **27**, 1371 (1962).

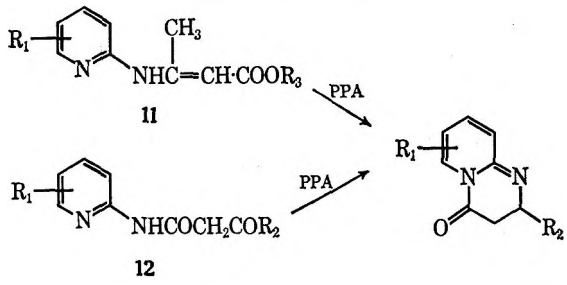
TABLE II

N-(2-PYRIDYL)-β-(2′-PYRIDYLAMINO)CROTONAMIDES



Substituents		Registry	Yield,			Anal, %			
						Calcd		Found	
R_1	R_4	no.	%	Mp, °C	Formula	C	H	C	H
4-CH_3	4-CH_3	16878-12-9	35	152–153	$C_{16}H_{18}N_4O$	68.10	6.38	68.08	6.49
5-CH_3	5-CH_3	16867-36-0	48	171–173	$C_{16}H_{18}N_4O$	68.10	6.38	68.29	6.65
H	5-Cl	16867-37-1	36	194–195	$C_{14}H_{13}ClN_4O$	58.20	4.51	58.11	4.58
H	4-CH_3	16867-38-2	41	127–128	$C_{15}H_{16}N_4O$	67.17	5.97	66.94	6.05
H	5-CH_3	16867-39-3	36	162–163	$C_{15}H_{16}N_4O$	67.17	5.97	67.29	6.00
H	5-Br	16867-40-6	32	184–185	$C_{14}H_{13}BrN_4O$	50.46	3.90	50.42	3.99
5-CH_3	5-Cl	16867-41-7	36	198–199	$C_{15}H_{15}ClN_4O$	59.55	4.96	59.66	5.02

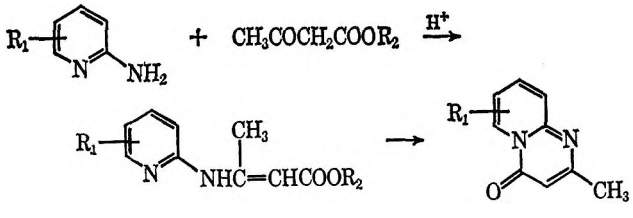
2-acylacetamidopyridines (**12**) in the presence of PPA. This method was shorter and offered better yields than the sulfuric acid method used by other workers.[12–14]



When preparing the acylacetamidopyridines it was found that the reaction between 6-methyl- and 4,6-dimethyl-2-aminopyridines and the α-methyl- and α-ethylacetoacetates did not yield any of the expected α-alkyl-2-acetoacetamidopyridines. As in the case of the preparation of the crotonamides mentioned above, dipyridylureas were formed instead, together with the corresponding methyl alkyl ketone. This is similar to the observation of Mallams and Israelstam[2] who obtained diarylureas by the interaction of certain arylamines and α-alkyl acetoacetates, instead of α-alkylacetoacetanilides.

It should be noted that Allen, *et al.*,[20] considered the compound obtained by the condensation of 3-methyl-2-aminopyridine and diketene to be 3-methyl-2-acetoacetamidopyridine (**12**, R_1 = 3-CH_3; R_2 = CH_3); we have shown that in fact this compound is 2,9-dimethyl-4H-pyrido[1,2-*a*]pyrimidin-4-one (**2**, R_1 = 9-CH_3; R_2 = CH_3; R_3 = H).

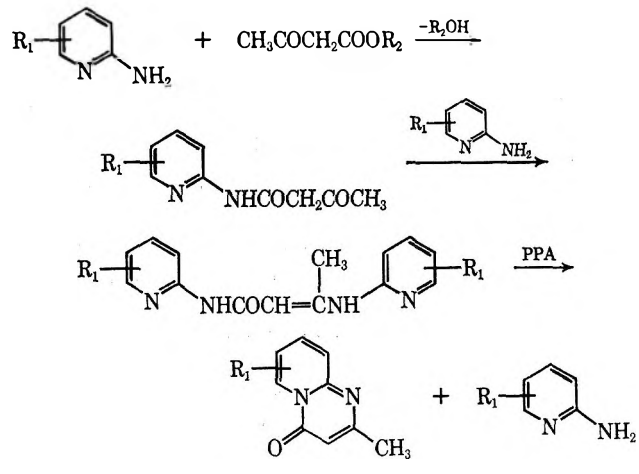
Since the crotonates have been shown to undergo cyclization to pyrimidin-4-ones when heated in PPA, it may be assumed that the mechanism of the direct synthesis in cases where the 2-aminopyridine is known to give a crotonate, is straightforward.



R_1 = 3-CH_3, 5-Cl, 5-Br, 3,5-diBr; R_2 = CH_3, C_2H_5

On the other hand, the mechanism for the formation of those pyrimidin-4-ones derived from 2-aminopyridines, which form 2-acylacetamidopyridines, is more complicated. It is suggested that in such cases a crotonamide is formed as an intermediate although no crotonamide was isolated in these reactions. However, Galasko and Israelstam[21] have isolated a crotonamide in the cyclization of 2-acetoacetamidothiazoles to thiazolo[3,2-*a*]pyrimidin-5-ones on heating with PPA. The mechanism shown in Scheme II is therefore proposed for the direct synthesis of 4H-pyrido[1,2-*a*]pyrimidin-4-ones from such 2-aminopyridines.

SCHEME II



R_1 = H, 4-CH_3, 5-CH_3, 6-CH_3, 5-Cl, 5-Br

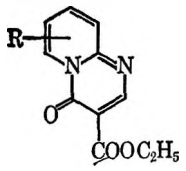
It is important to note that the yields of the pyrido-[1,2-*a*]pyrimidin-4-ones obtained by the cyclization of 2-acylacetamidopyridines in the presence of PPA were generally less than 50%, whereas by cyclization of the alkyl β-(aminopyridyl)crotonates with the same reagent were almost quantitative. The lower yield in the former cyclization may be ascribed to the fact that only one-half of the aminopyridine used goes to form the pyridopyrimidin-4-one so that 2 mol of the aminopyridine are required to produce 1 mol of the pyridopyrimidin-4-one. In fact it was shown that, when an equimolecular quantity of 2-aminopyridine was added to the 2-acetoacetamidopyridine in the presence of PPA, the yield of 2-methyl-4H-pyrido[1,2-*a*]pyrimidin-4-one was raised from 56 to 81%.

(20) C. Allen, J. Van Allan, and C. Wilson, *J. Amer. Chem. Soc.*, **66**, 1805 (1944).

(21) G. Galasko and S. S. Israelstam, private communication.

TABLE III

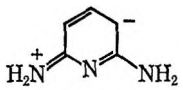
3-CARBETHOXY-4H-PYRIDO[1,2-a]PYRIMIDIN-4-ONES



Substituent R	Registry no.	Yield, %	Mp, °C	Lit. mp, °C	Formula	Anal, % Calcd C	Calcd H	Found C	Found H
9-CH_3[a]	16878-14-1	79	144–145	NR	$C_{12}H_{12}N_2O_3$	62.07	5.17	62.02	5.30
6-CH_3	16867-53-1	86	148–149	NR	$C_{12}H_{12}N_2O_3$	62.07	5.17	62.30	5.15
6,8-di-CH_3	16867-54-2	78	148–149	NR	$C_{13}H_{14}N_2O_3$	63.41	5.69	63.52	5.80
7-Cl	16867-55-3	76	147–148	132–133[b]	$C_{11}H_9ClN_2O_3$	52.28	3.56	52.21	3.60
7-Br	16867-56-4	81	155–156	134–135[b]	$C_{11}H_9BrN_2O_3$	44.44	3.03	44.65	3.41

[a] Obtained from ethyl (3-methyl-2-pyridylamino)methylenemalonate, mp 68–69°. *Anal.* Calcd for $C_{14}H_{18}O_4N_2$: C, 60.43; H, 6.47. Found: C, 60.47; H, 6.70. [b] Reference 8.

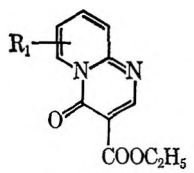
Although the various aminopyridines discussed above yielded pyrido[1,2-*a*]pyrimidin-4-ones when allowed to react with β-keto esters in the presence of PPA, it is interesting that in the case of 2,6-diaminopyridine the product obtained was 7-amino-2-hydroxy-1,8-naphthyridine. This is in accordance with the work of others.[8,22–24] It appears that the resonance structure (**13**) of 2,6-diaminopyridine makes the most important



13

contribution to the molecule, and, together with the steric effect of the 6-amino group, position 3 is more likely to be attacked than the ring nitrogen.

A similar investigation was carried out to study the reaction between 2-aminopyridines and ethyl ethoxymethylenemalonate (EMME) in the presence of PPA. A direct synthesis of 3-carbethoxy-4H-pyrido[1,2-*a*]-pyrimidin-4-ones (**14**) was thereby accomplished, the same compounds being obtained by the cyclization of the 2-pyridylaminomethylenemalonates (**15**) with PPA.



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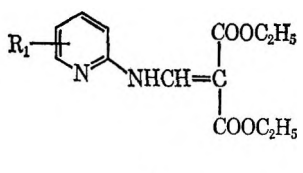

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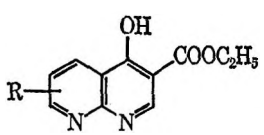
The malonates were made by using the method of Lappin,[8] who cyclized the malonates by boiling them in diphenyl ether and obtained either the pyrimidin-4-one (**14**) or the 3-carbethoxy-4-hydroxy-1,8-naphthyridine (**16**) depending on the nature and position of R.



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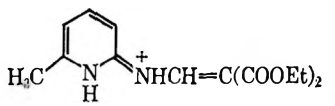
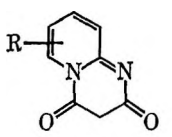
Lappin[8] found that pyrido[1,2-*a*]pyrimidin-4-ones (**13**) were formed except when the substituent in position 6 of the 2-aminopyridine was an electron-releasing group, when the naphthyridine (**15**) was obtained instead. The fact that ethyl (6-methyl-2-pyridylamino)methylenemalonate when cyclized with PPA gave a pyrimidin-4-one and not a naphthyridine may be accounted for on the supposition that the pyridylaminomethylenemalonate is protonated to give the cation



which is not possible when just heated alone. Cyclization would thus occur at the ring nitrogen rather than at position 3. We found that pyrido[1,2-*a*]pyrimidin-4-ones were obtained in all cases using PPA, except with 2,6-diaminopyridine when a tar was obtained. The 3-carbethoxy-4H-pyrido[1,2-*a*]pyrimidin-4-ones (**14**) prepared and cyclized are given in Table III.

When diethyl malonate was heated with 2-aminopyridines at 160° for 2 hr with PPA, good yields of 2,3-dihydro-4H-pyrido[1,2-*a*]pyrimidine-2,4-diones (**17**) were obtained. Chichibabin[23] reported the formation of 2,3-dihydro-4H-pyrido[1,2-*a*]pyrimidine-2,4-dione (**17**, R = H) in unspecified yield by heating 2-aminopyridine and diethyl malonate. When the latter compounds were heated with PPA at 130° during 1 hr, the malonamide (**18**, R = H) was obtained instead which was cyclized at 160° with PPA to the pyrimidine-2,4-dione (**17**, R = H).



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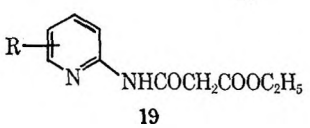

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R = H, 4-CH_3, 5-CH_3

3-Methyl-2-aminopyridine was sufficiently reactive to give the pyrimidinedione (**17**, R = 9-CH_3) merely on heating in the absence of PPA, no malonamide being

(22) O. Seide, *Chem. Ber.*, **58**, 352 (1925).
(23) A. E. Chichibabin, *ibid.*, **57**, 1168 (1924).
(24) G. R. Lappin, Q. R. Peterson, and C. E. Wheeler, *J. Org. Chem.*, **15**, 377 (1950).

isolated. In certain cases a malonamate (**19**) was isolated along with a malonamide which was also obtained by heating the former with PPA.

It would therefore seem reasonable to suggest that the mechanism for the one-stage synthesis of the pyridopyrimidinedione is as shown in the following route.

2-aminopyridine + diethyl malonate ⟶
malonamate (19) —(2-aminopyridine)→ malonamide (18) ⟶
pyridopyrimidine-2,4-dione (17)

This mechanism is more likely than that proposed by Khalifa[25] which postulates a rearrangement of the malonamate to a hypothetical 2-imino-N-carbethoxyacetopyridine as an intermediate.

When 6-methyl- and 5-halo-2-aminopyridines were heated with diethyl malonate up to 170° in PPA, only the malonamide was obtained; neither a 1,8-naphthyridine nor a pyridopyrimidinedione was isolated; *cf.* report by Lappin.[24]

Experimental Section

All melting points were determined on an electrically heated copper block and are uncorrected.

Alkyl β-(2-Pyridylamino)crotonates (11).—A mixture containing 0.03 mol of the 2-aminopyridine and 0.03 mol of ethyl β-aminocrotonate was heated at 140° for 1 hr. The reaction product was cooled and treated with dilute ethanol. The crude product (yields varying from 50 to 65%) was crystallized from ethanol to give colorless needles. The same products, in similar yields were obtained using Kucherov's method.[14] The following are new alkyl β-(2-pyridylamino)crotonates (**11**) obtained. R_1 and R_3 substituent, % yield, melting point, and analysis are given: 5-Cl, CH_3, 52%, 89–90° (Calcd for $C_{10}H_{11}ClN_2O_2$: C, 52.97; H, 4.86. Found: C, 53.03; H, 5.01); 3-CH_3, C_2H_5, 48% 63–64° (Calcd for $C_{12}H_{16}N_2O_2$: C, 65.46; H, 7.27. Found: C, 65.36; H, 7.12); 3-CH_3, CH_3, 45%, 83–84° (Calcd for $C_{11}H_{14}N_2O_2$: C, 64.08; H, 6.79. Found: C, 64.05; H, 6.83), 3,5-di-Br, CH_3, 61%, 115–116° (Calcd for $C_{10}H_{10}Br_2N_2O_2$: C, 34.29; H, 2.86. Found: C, 34.35; H, 2.96).

Cyclization of Alkyl β-(2-Pyridylamino)crotonates.—About 1.0 g of the crotonate **11** and 8.0 g of PPA were heated for 30 min at 140° with frequent stirring. The reaction product was cooled and neutralized with 2 *N* NaOH to give the pyrido[1,2-*a*]-pyrimidin-4-one (crude yield 70–90%) crystallized from petroleum ether (bp 80–100°) or dilute ethanol as colorless needles.

2-Acylacetamidopyridines (12).—A mixture of 0.1 mol of the 2-aminopyridine and 0.2 mol of β-keto ester was heated for 1 hr at 150–160°. On cooling, the product solidified. The solid was triturated with 1% NaOH to remove unchanged reactants. The crude product (yields 75–95%) was crystallized from either water or dilute ethanol as colorless needles. The compound gave a purple color with an ethanolic solution of ferric chloride. New acylacetamidopyridines were obtained. Substituents, % yield, melting point, and analysis are given: group 1, R_1 = 4-CH_3, R_2 = CH_3, 75%, 122–123° (Calcd for $C_{10}H_{12}N_2O_2$; C, 62.50; H, 6.25. Found: C, 62.39; H, 6.34.); R_1 = 5-CH_3, R_2 = CH_3, 78%, 152–153° (Calcd for $C_{10}H_{12}N_2O_2$: C, 62.50; H, 6.25. Found: C, 62.54; H, 6.31); R_1 = 6-CH_3, R_2 = CH_3, 65%, 104° (Calcd for $C_{10}H_{12}N_2O_2$: C, 62.50; H, 6.25. Found: C, 62.51; H, 6.29); group 2, R_1 = 4-CH_3, R_2 = C_6H_5, 76%, 134° (Calcd for $C_{15}H_{14}N_2O_2$: N, 11.02. Found: N, 11.20); R_1 = 5-CH_3, R_2 = C_6H_5, 74%, 162–163° (Calcd for $C_{15}H_{14}N_2O_2$: N, 11.02. Found: N, 10.93); R_1 = 6-CH_3, R_2 = C_6H_5, 84%, 78–79° (Calcd for $C_{15}H_{14}N_2O_2$: N, 11.02. Found: N, 10.98); R_1 = 5-Cl, R_2 = C_6H_5, 98%, 161–162° (Calcd for $C_{14}H_{11}ClN_2O_2$: N, 10.20. Found: N, 10.39); R_1 = 5-Br, R_2 = C_6H_5, 89%, 159–160° (Calcd for $C_{14}H_{11}BrN_2O_2$: N, 8.77. Found: N, 8.65).

Cyclization of 2-Acylacetamidopyridines to Pyrido[1,2-*a*]-primidin-4-ones (2).—A mixture of 0.01 mol of the 2-acylacetamidopyridine and ten times the weight of PPA was heated at 140° with frequent stirring until the mixture became a dark red. It was then cooled and neutralized with 2 *N* NaOH and recooled in ice. The product was filtered, and the crude product was crystallized from petroleum ether (bp 60–80°) yielding colorless needles.

N-(2-Pyridyl)-β-(2′-pyridylamino)crotonamides (4). A. Symmetrical Crotonamides.—A mixture of 0.1 mol of 2-aminopyridine and 0.05 mol of β-keto ester was heated at 140° for 3 hr. The reaction, after solidifying, was triturated with hot water. The crude material was crystallized from ethanol yielding colorless needles. The hot washings gave a small quantity of the 2-acylacetamidopyridine on cooling.

B. Unsymmetrical Crotonamides.—A mixture of 0.02 mol of a 2-aminopyridine and 0.02 mol of an acetoacetamidopyridine derived from a different 2-aminopyridine was refluxed in alcohol containing 1 drop of concentrated H_2SO_4 for 3 hr. On cooling, the crotonamide separated and crystallized from ethanol as colorless needles.

Conversion of Crotonamides (4) into Pyrido[1,2-*a*]pyrimidin-4-ones (2).—A mixture of 0.005 mol of **4** and ten times that weight of PPA was heated at 150° with frequent stirring for 1 hr. After cooling and neutralizing with 2 *N* NaOH, the resulting solution was extracted with chloroform. The pyrimidin-4-one was obtained from the chloroform layer and crystallized from petroleum ether (bp 60–80°). Mixture melting points with pyrimidin-4-ones obtained by other methods were not depressed.

The aqueous layer on extraction with ether yielded a small quantity of the 2-aminopyridine (**5**).

Direct Synthesis of Pyrido[1,2-*a*]pyrimidin-4-ones (2) from 2-Aminopyridines and β-Keto Esters Using PPA.—A mixture of 0.1 mol of a 2-aminopyridine, 0.15 mol of β-keto ester, and six times the weight of the former of PPA was heated at 100° with frequent stirring (the 4- and 5-halo-2-aminopyridines required temperatures of up to 160°). After 1 hr the reaction mixture, which was a deep red color, was cooled and neutralized with 2 *N* NaOH to give, after cooling in ice, the pyrimidin-4-one. Crystallization from petroleum ether (bp 60–80°) or ethanol gave colorless needles. Uv spectra of the 2-methyl compounds showed maxima at 350 and 245 mμ, while the 2-phenyl analogs showed maxima at 350 and about 260 mμ.

Cyclization of Ethyl 2-Pyridylaminomethylenemalonates.—A mixture of 0.005 mol of ethyl 2-pyridylaminomethylenemalonate[26] as prepared by Lappin[8] and ten times its weight of PPA was heated for 4 hr at 110° with frequent stirring. The cooled reaction product was carefully neutralized with dilute ammonia. On cooling in ice for several hours a 3-carbethoxy-4H-pyrido-[1,2-*a*]pyrimidin-4-one separated in 70–90% yields. Crystallization from ethanol gave colorless needles.

Direct Synthesis of 3-Carbethoxy-4H-pyrido[1,2-*a*]pyrimidin-4-ones (14) Using PPA.—A mixture of 0.01 mol of the 2-aminopyridine, 0.01 mol of EMME, and eight times the weight of the 2-aminopyridine of PPA was heated at 110–120° for 2–3 hr with stirring. The cooled reaction product was neutralized with dilute ammonia to give **14**, crystallized from ethanol. A mixture melting point with the product obtained by the cyclization of the malonate was not depressed.

Direct Synthesis of 2,3-Dihydro-4H-pyrido[1,2-*a*]pyrimidine-2,4-diones (17).—A mixture of 0.02 mol of the 2-aminopyridine, 0.02 mol of diethyl malonate, and six times the weight of 2-aminopyridine of PPA was heated for 2 hr at 170° with stirring and the reaction product was neutralized with 2 *N* NaOH to give **17** in 60–70% yields. The melting point of two pyrimidine-2,4-diones were found to be different from those quoted in the literature, *viz.*, R = H, mp 305–308° (lit. mp 295–298° [24]), and R = 8-CH_3, mp 253–255° dec (lit. mp 270° dec[25]).

Di(2-pyridyl)malonamides (18).—A mixture of 0.02 mol of the 2-aminopyridine, 0.02 mol of diethyl malonate, and eight times the weight of the amine of PPA was heated at 130° with stirring. The cooled reaction product was neutralized with 2 *N* NaOH to give **18** in 30–40% yields. Crystallization from ethanol gave colorless needles. Three malonamides were found to have melting points different from those given by Lappin,[25] *viz.*, R = H, 226–227° dec (235°); R = 5-CH_3, 207–209° dec (200° dec); and R = 6-CH_3, 161–162° (145–146°).

(25) M. Khalifa, *Bull. Fac. Pharm.* (Cairo University), **1**, 149 (1961); *Chem. Abstr.*, **61**, 5643 (1964).

(26) The melting points given by Lappin[8] for ethyl (5-chloro-2-pyridylamino)methylenemalonate and the corresponding 5-bromo- were found to be incorrect. They should be, respectively, 131–132 and 135–136° (Calcd for $C_{12}H_{15}ClN_2O_4$: C, 52.26; H, 5.03. Found: C, 52.38; H, 5.24. Calcd for $C_{12}H_{15}BrN_2O_4$: C, 45.47; H, 4.38. Found: C, 45.71; H, 4.40).

Registry No.—**11** (R_1 = 5-Cl; R_3 = CH_3), 16867-42-8; **11** (R_1 = 3-CH_3; R_3 = C_2H_5), 16867-43-9; **11** (R_1 = 3-CH_3; R_3 = CH_3), 16878-13-0; **11** (R_1 = 3,5-di-Br; R_3 = CH_3), 16867-44-0; **12** (R_1 = 4-CH_3; R_2 = CH_3), 16867-45-1; **12** (R_1 = 5-CH_3; R_2 = CH_3), 16867-46-2; **12** (R_1 = 6-CH_3; R_2 = CH_3), 16867-47-3; **12** (R_1 = 4-CH_3; R_2 = C_6H_5), 16867-48-4; **12** (R_1 = 5-CH_3; (R_2 = C_6H_5), 16867-49-5; **12** (R_1 = 6-CH_3; R_2 = C_6H_5), 16867-50-8; **12** (R_1 = 5-Cl; R_2 = C_6H_5), 16867-51-9; **12** (R_1 = 5-Br; R_2 = C_6H_5), 16867-52-0; **15** (R = 3-CH_3), 16878-15-2; **15** (R = 5-Cl), 16867-57-5; **15** (R = 5-Br), 16867-58-6.

Acknowledgment.—One of us (S. S. I.) wishes to thank the South African Council for Scientific and Industrial Research for the award of an assistantship.

Unsaturated Heterocyclic Systems. XL. Evaluation of Spiro[9,10-ethanoanthracene-11,2′-thietane] S,S-Dioxides and 2-α-Dialkylaminoalkyl-3-dialkylaminothietane 1,1-Dioxides as Precursors of 2-Methylenethiete 1,1-Dioxide Derivatives[1,2]

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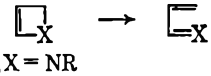
Received March 14, 1968

Three synthetic approaches to the highly strained 2-methylenethiete 1,1-dioxide ring system have been evaluated. The retro Diels–Alder route wherein the 9,10-ethanoanthracene moiety was employed as a blocking group for the exocyclic double bond met with failure when it was recognized that the temperatures required to liberate anthracene were well above those at which the desired tetravalent sulfur heterocycles decomposed. The Hofmann degradation approach suffered from the fact that 2α-dialkylaminoalkyl-3-dialkylaminothietane 1,1-dioxides such as **13** and **14** displayed a propensity for ring cleavage when treated with methyl iodide. Two intermediate methiodides, could, however, be isolated. When subjected in turn to the conditions of Hofmann elimination, these methiodides were found to be especially prone to demethylation. Alternatively, N-oxide degradation of 2α-dialkylaminoalkyl-3-dialkylaminothietane 1,1-dioxides, although not an entirely general procedure, was found to give rise to two methylenethiete dioxides. Pertinent mechanistic implications of the above reactions and the physical and spectral properties of the title sulfones are presented in some detail.

A common and fundamental property of unsaturated four-membered-ring heterocycles such as **1a–c** is the



1a, X = NR
b, X = O
c, X = S
d, X = SO_2

ease with which these molecules undergo electrocyclic bond reorganization with ring cleavage. Numerous past investigations have suggested the intermediacy of molecules such as **1** in a variety of chemical and photochemical transformations, but, in general, attempts at isolation have been unsuccessful and rearrangement products have resulted. Recently, however, the isolation of thiete (**1c**)[5a] and a bicyclic thiete derivative[5b] has been described; as expected, both substances have proven to be quite reactive at ambient temperatures.

It was recognized several years ago that the heterocyclic system in question, **1**, was uniquely stabilized when the hetero ring substituent was the sulfone group. Since the preparation of thiete 1,1-dioxide (**1d**) was first described and its chemical behavior examined in a preliminary fashion,[6] the chemistry of this ring system has received considerable attention[7] and a number of stable derivatives are now known.[7,8] It was our intent to investigate in some detail the synthesis and properties of exocyclic methylene derivatives of thiete dioxide, *e.g.*, **2**, in order to examine the effects which are produced by extension of the π-electron system in the indicated manner. That molecules such as **2** would be

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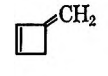
reactive and be subject to diverse types of reactions was anticipated on the basis of analogy to the chemical behavior of methylenecyclobutenes. For example, hydrocarbons **3–5** are known to polymerize readily and



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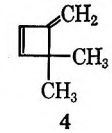

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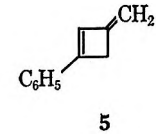

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(1) For paper XXXIX of this series, see L. A. Paquette and M. K. Scott, *J. Org. Chem.*, **33**, 2379 (1968).

(2) This work was generously supported by Grant GP-5977 from the National Science Foundation.

(3) Alfred P. Sloan Foundation Research Fellow.

(4) National Science Foundation Undergraduate Research Participant, summer 1966.

(5) (a) D. C. Dittmer, K. Takahashi, and F. A. Davis, *Tetrahedron Lett.*, 4061 (1967); (b) D. C. Dittmer and F. A. Davis, *J. Amer. Chem. Soc.*, **87**, 2064 (1965).

(6) (a) D. C. Dittmer and M. E. Christy, *J. Org. Chem.*, **26**, 1324 (1961); (b) D. C. Dittmer and M. E. Christy, *J. Amer. Chem. Soc.*, **84**, 399 (1962).

(7) (a) D. C. Dittmer and N. Takashina, *Tetrahedron Lett.*, 3809 (1964); (b) L. A. Paquette, *J. Org. Chem.*, **30**, 629 (1965); (c) L. A. Paquette and T. R. Phillips, *ibid.*, **30**, 3883 (1965); (d) L. A. Paquette and M. Rosen, unpublished results; (e) D. C. Dittmer and F. A. Davis, *ibid.*, **32**, 3872 (1967).

(8) (a) W. E. Truce, J. R. Norell, J. E. Richman, and J. P. Walsh, *Tetrahedron Lett.*, 1677 (1963); (b) R. H. Hasek, P. G. Gott, R. H. Meen, and J. C. Martin, *J. Org. Chem.*, **28**, 2496 (1963); (c) G. Opitz and H. Schempp, *Z. Naturforsch.*, **19b**, 78 (1964); (d) W. E. Truce and J. R. Norell, *J. Amer. Chem. Soc.*, **85**, 3236 (1963); (e) D. C. Dittmer and F. A. Davis, *J. Org. Chem.*, **29**, 3131 (1964); (f) G. Opitz and H. Schempp, *Ann.*, **684**, 103 (1965); (g) R. H. Hasek, R. H. Meen, and J. C. Martin, *J. Org. Chem.*, **30**, 1495 (1965); (h) J. N. Wells and F. S. Abbott, *J. Med. Chem.*, **9**, 489 (1966); (i) L. A. Paquette and M. Rosen, *J. Amer. Chem. Soc.*, **89**, 4102 (1967); (j) L. A. Paquette and M. Rosen, *J. Org. Chem.*, **33**, 2130 (1968).

spontaneously at room temperature.[9] As the degree of substitution on **3** is significantly increased, however, the carbocycle is seen to acquire moderate stability as gauged by the behavior of 3-methylene-1,4-diphenyl-2-methylcyclobutene.[10]

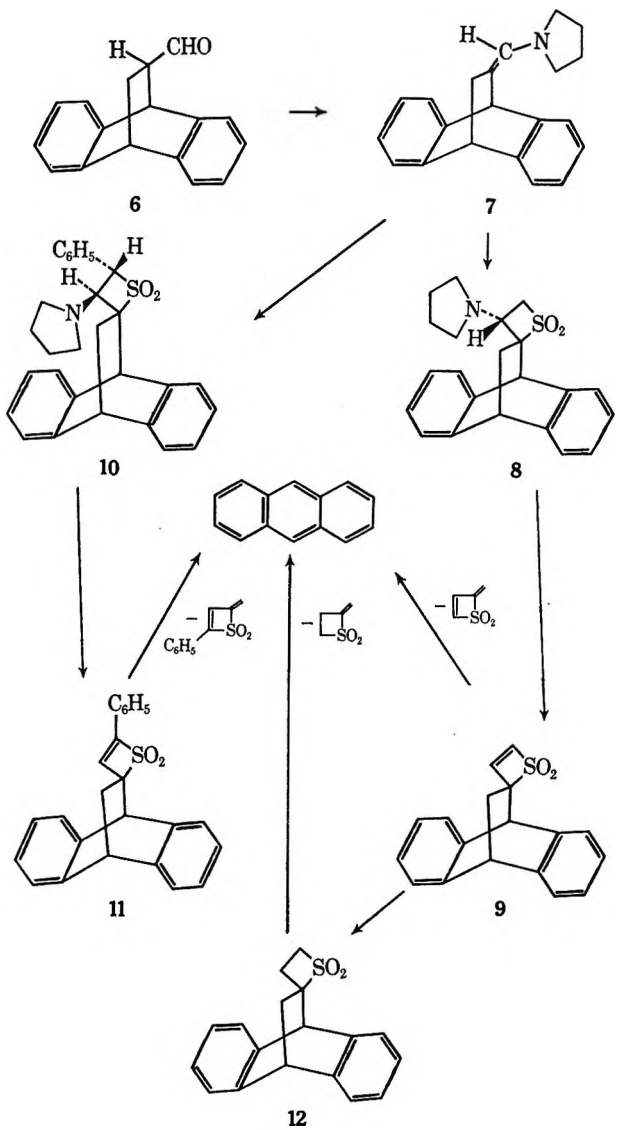
The present paper delineates the various synthetic approaches which have been examined in the preparation of **2** and its derivatives, whereas the ensuing article[11] describes various chemical reactions of this unsaturated heterocyclic system.[12]

Results

The Retro Diels–Alder Route.—Our initial approach was designed to take advantage of the fact that 9,10-ethanoanthracene derivatives decompose at somewhat elevated temperatures to generate anthracene and unsaturated compounds. Specifically, the intent was to construct a thiete dioxide derivative which incorporated the partially reduced anthracene ring as a blocking group for the exocyclic double bond. This reactive site of unsaturation was then to be introduced at the final stage of the synthesis. The synthesis is outlined in Scheme I. The stereochemistry of **8** was assigned subsequent to consideration of nonbonded strain minimization available to each of the two possible transition states leading to cycloaddition. The *trans* relationship of the pyrrolidino and phenyl groups in **10** is assigned on the basis of the nmr coupling constant (10.0 Hz) of the four-membered sulfone ring protons. Earlier, application of the Karplus correlation[13] to the thietane dioxide ring system was shown to be reliable.[14] The stereochemical assignment depends further upon recognition of the fact that the small heterocyclic ring exists in a puckered coformation[15] with the two substituents in question occupying *trans* equatorial positions and the protons exhibiting a dihedral angle of approximately 180°.[16] The spatial arrangement of the pyrrolidino and phenyl groups relative to the ethanoanthracene superstructure in **10**, although somewhat less convincing, is believed to be as indicated in Scheme I on the basis of steric factors operating in the cycloaddition process and because **10** does not form a methiodide salt.

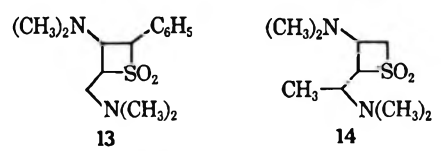
Sulfones **9**, **11**, and **12** were found to be quite stable to 250°. Pyrolysis of **9** and **11** at approximately 300° under a nitrogen atmosphere at various reduced pressures resulted in the vigorous liberation of anthracene and sulfur dioxide, and formation of an intractable yellow solid (in the cold traps) and a brittle, black glassy residue. Under these conditions, **12** merely distilled with slight decomposition; at 400°, however, similar decomposition products were observed. As will become apparent, the failure of this synthetic

SCHEME I



scheme can be traced to the instability of the four-membered-ring sulfones at the temperatures required to remove the anthracene blocking group.

The Hofmann Degradation Approach.—The reaction of sulfenes with 1,3-bis(dialkylamio)-1-alkenes is now recognized to produce a mixture of products from which 2-α-dialkylaminoalkyl-3-dialkylaminothietane 1,1-dioxides such as **13** and **14** can be isolated under strictly



controlled conditions.[8i] In view of the disposition of the tertiary amino groups in these sulfones, a study of the Hofmann degradation of their derived methiodides was initiated in the expectation that derivatives of methylenethiete dioxide would result.

Exposure of **13** to methyl iodide in methanol solution at room temperature resulted in a gradual exothermic reaction and precipitation of a yellow crystalline solid (*ca.* 41% yield) which consisted of a mixture of monomethiodide **15** and tetramethylammonium iodide (see Scheme II). Chromatographic work-up of the non-

(9) (a) D. R. Howton and E. R. Buchman, *J. Amer. Chem. Soc.*, **78**, 4011 (1956); (b) D. E. Applequist and J. D. Roberts, *ibid.*, **78**, 4012 (1956).

(10) A. T. Blomquist and Y. C. Meinwald, *ibid.*, **81**, 667 (1959).

(11) L. A. Paquette and M. Rosen, *J. Org. Chem.*, **33**, 3027 (1968).

(12) Portions of this work were presented at the 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1967, p S14.

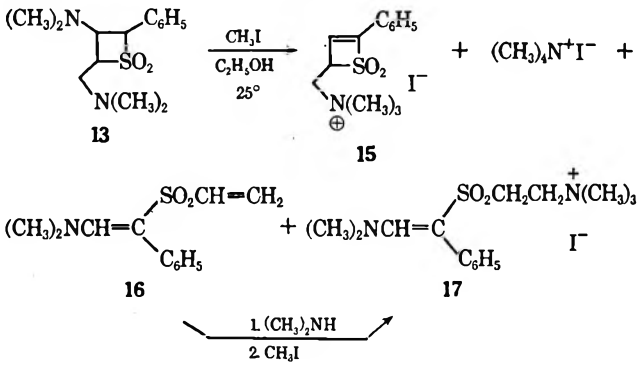
(13) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); M. Karplus, *J. Amer. Chem. Soc.*, **85**, 2871 (1963).

(14) L. A. Paquette, *J. Org. Chem.*, **29**, 2854 (1964).

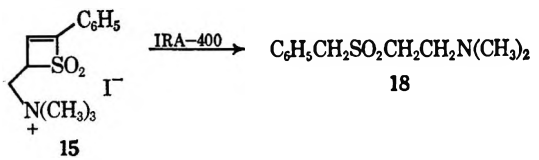
(15) For a summary of the data pertaining to this question, see footnotes 17–21 of ref 8i.

(16) Because of the fact that puckering of the thietane dioxide ring had not been conclusively established when ref 14 appeared, the assignments of configuration in this paper (structures V and VI) should be reversed to compensate for this conformational bias.

SCHEME II

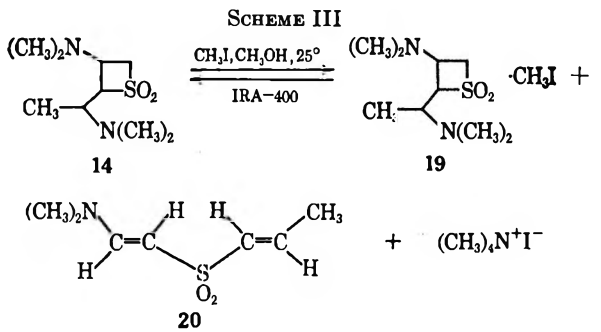


crystalline residue on neutral alumina afforded two additional crystalline solids, **16** (17%) and **17** (6.5%). Elution of **15** through an Amberlite IRA-400 ion-exchange column (hydroxide form) and careful removal of water gave 2-(benzylsulfonyl)-N,N-dimethylethylamine (**18**) as the only characterizable product.



A similar ring cleavage was noted in the attempted quaternizaton of **14** with methyl iodide. In addition to a crystalline monomethiodide (**19**) which was deposited from the solution in 67% yield, careful chromatography of the noncrystalline residue also permitted isolation of the known vinyl enamino sulfone **20** (15%) and a small quantity of tetramethylammonium iodide (Scheme III). Hofmann degradation of **19** afforded only the demethylation product **14**.

SCHEME III

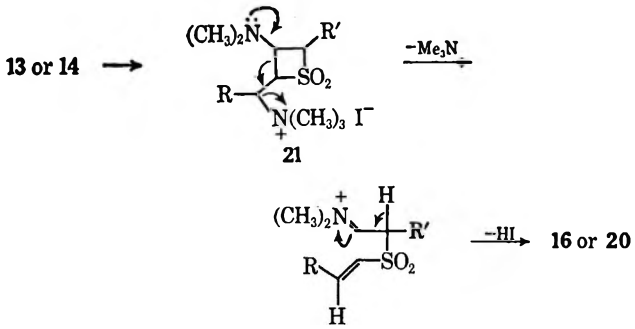


Such results indicate that **13** and **14** exhibit a marked propensity for ring cleavage under the conditions of quaternization. A mechanistic rationalization of this phenomenon demands that the 2α-amino substituent be the more nucleophilic nitrogen center and thus be subject to more rapid quaternization. This newly generated electron-deficient site (see **21**) is now subject to ready ejection (as trimethylamine) by migration of electrons from the 3-amino substituent with synchronous rupture of the four-membered ring as shown in Scheme IV.[17]

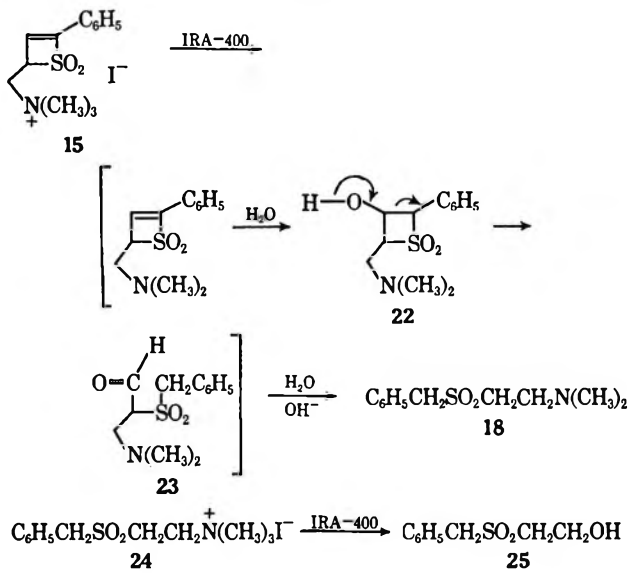
Undoubtedly the most surprising result was the strong preference exhibited by **15** and **19** for demethylation under the Hofmann elimination conditions. In this regard, we propose that **18** arises by loss of methanol directly from **15** or from the methiodides of intermediates **22** and **23** and not from **24** since the latter is rapidly transformed into alcohol **25** under the reaction conditions (see Scheme V). The remainder of the proposed mechanism receives support from the fact that thiete dioxide and 3-hydroxythietane 1,1-dioxide likewise undergo ring cleavage to dimethyl sulfone in basic solution.[6b]

(17) Precedent for this mechanism has been described recently: L. A. Paquette and M. Rosen, *Tetrahedron Lett.*, 311 (1966).

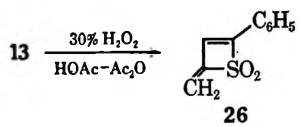
SCHEME IV



SCHEME V



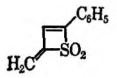
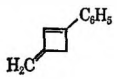
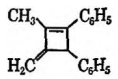
The N-Oxide Route.—Treatment of either **13** or **14** with hydrogen peroxide in methanol solution gave in each case a brown oily liquid which could not be converted into a picrate and decomposed when heated *in vacuo*. However, when **13** was treated with excess 30% hydrogen peroxide in acetic acid–acetic anhydride solution at room temperature for 1 day, there resulted an oily residue which after chromatography on neutral alumina gave the methylenethiete dioxide **26** in 37%



yield. All spectra were recorded on freshly prepared samples of **26** for this sulfone gradually becomes colored at room temperature and polymerizes to a solid which is insoluble in all of the common organic solvents. We have observed that **26** is soluble in chloroform and acetonitrile but only slightly soluble in carbon tetrachloride; however, these solutions quickly turn red in color on standing and the sulfone cannot be recovered. De-

composition was noted to be minimal in ether from which **26** can be recrystallized. The ultraviolet spectrum of this material was consistent with a 1-phenylbutadienyl chromophore and is compared in Table I with the reported values of two carbocyclic analogs.

TABLE I
COMPARISON OF THE ULTRAVIOLET SPECTRA OF 26 WITH TWO METHYLENECYCLOBUTENES

 **26** λ_{max}^{ether}, mμ (ε)	 **5** $\lambda_{max}^{isooctane}$, [a] mμ (ε)	 **27** $\lambda_{max}^{isooctane}$, [b] mμ (ε)
...	212 (4,600)	...
...	219 (3,760)	...
...	225 (3,960)	228 (12,000)
...	233 (3,640)	235 (9,120)
291 (33,400)	291 (7,250)	292 (26,900)
...	...	302 (25,100)
...	...	316.5 (sh) (13,200)

[a] Reference 9. [b] Reference 10.

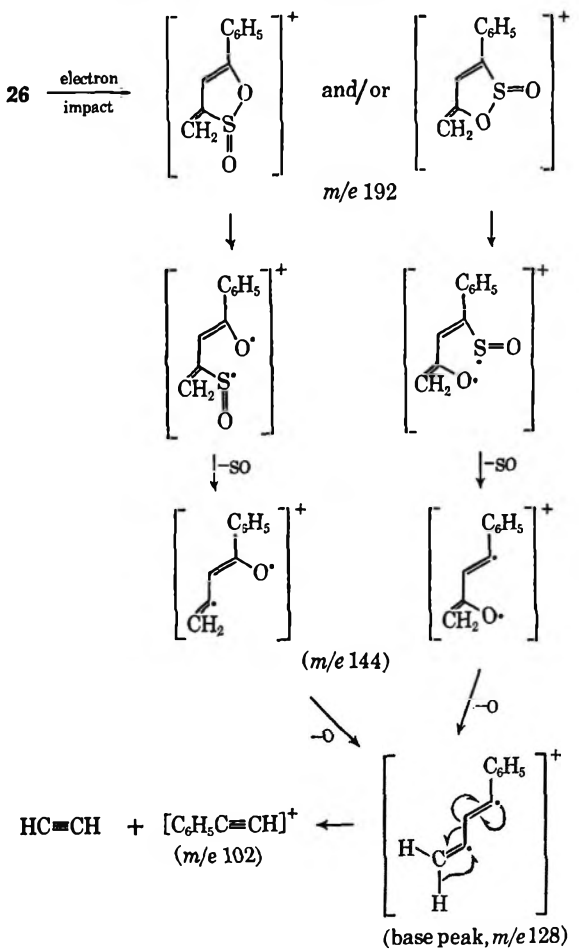
The mass spectrum of **26** (see Table II) shows a molecular ion (*m/e* 192) and a base peak at *m/e* 128. This fragmentation can be explained by the sequential loss of the elements of sulfur monoxide (*m/e* 144) and oxygen from an intermediate cyclic sulfinate such as **28** or **29** (see Scheme VI). The ion corresponding to the base peak appears to fragment to acetylene and phenylacetylene. Precedence for the intervention of a cyclic sulfinate ester has been found in the pyrolysis and electron impact of dibenzothiophene 5,5-dioxide[18] and in the thermal rearrangement of two thiete dioxides.[19]

TABLE II
PRINCIPAL MASS SPECTRAL PEAKS IN 2-METHYLENETHIETE 1,1-DIOXIDES 26 AND 32

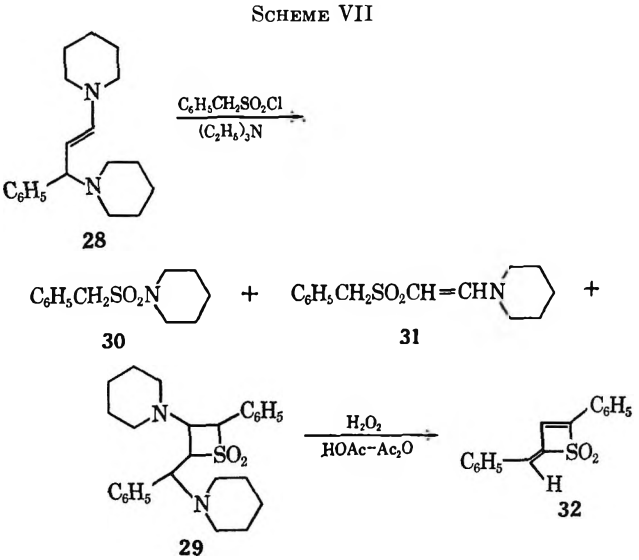
26		32	
m/e	Relative abundance, %	*m/e*	Relative abundance, %
192	34	268	23
144	68	220	10
129	12	204	32
128	100	203	15
127	26	202	20
126	10	105	30
105	28	103	10
102	43	102	100
		101	10

The successful preparation of methylenethiete dioxide **26** by the N-oxide route prompted an examination of the generality of the procedure. Accordingly, our attention was next turned to the degradation of thietane dioxide **29**. The synthesis of **29** was achieved by treating 1,3-bis(1-piperidino)-3-phenyl-1-propene (**28**) with phenylsulfene; it should be noted that 1-(benzylsulfonyl)piperidine (**30**) and the enamino sulfone **31** accompanied the production of **29**, as anticipated from earlier work[8i] (see Scheme VII). When an acetic acid–acetic anhydride solution of **29** was treated with 30% hydrogen peroxide, the methylenethiete dioxide **32** was produced in 85% yield. This strained heterocycle is quite stable under normal laboratory conditions. The sulfone is insoluble in ether and carbon tetrachloride but soluble in chloroform, and is easily crystallized from tetrahydrofuran. The nmr spectrum of **32** is consistent with the gross structure; however, because the ring vinyl proton resides under the aromatic envelope and the second vinyl proton is a broad singlet, a definitive

SCHEME VI
MASS SPECTRAL CRACKING PATTERN FOR 26



SCHEME VII

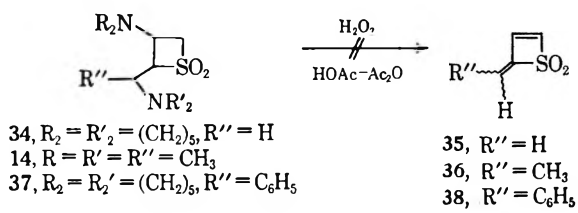


(18) E. K. Fields and S. Meyerson, *J. Amer. Chem. Soc.*, **88**, 2836 (1966); *cf.* also ref 7e.

(19) (a) D. C. Dittmer, R. S. Henion, and N. Takashina, Abstracts, 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967, p O101; (b) R. W. Hoffmann and W. Sieber, *Ann.*, **703**, 96 (1967).

assignment of the geometric configuration about the exocyclic double bond was not possible on the basis of such a spectral analysis. However, consideration of steric factors at play in the elimination step, coupled with an analysis of the nmr spectral properties of the Diels–Alder adduct of **32** with 1,3-diphenylisobenzofuran,[11] permit the conclusion that **32** is of the indicated stereochemistry. That this methylenethiete dioxide possesses a diphenylbutadienyl chromophore is apparent from its ultraviolet spectrum in chloroform (see Experimental Section); this spectrum is roughly comparable with that reported for *trans,trans*-1,4-diphenyl-1,3-butadiene.[20] The mass spectrum of **32** displays a fragmentation pattern analogous to that of **26** (see Table II).

The first indication that the N-oxide degradation pathway was not completely general came from an attempt to prepare the parent of the methylenethiete dioxide series (**35**). The synthesis of the requisite thietane dioxide **34** was effected from the known 1,3-bis(1-piperidino)-1-propene (**33**) and sulfene; treatment of **34** with hydrogen peroxide in the usual manner gave a small amount of yellow oil which displayed an infrared spectrum indicative of the presence of an enamine function and nmr absorptions consistent with the presence of a piperidino group. This material could not be obtained crystalline and was not characterized further.



34, $R_2 = R'_2 = (CH_2)_5$, $R'' = H$
14, $R = R' = R'' = CH_3$
37, $R_2 = R_2' = (CH_2)_5$, $R'' = C_6H_5$

35, $R'' = H$
36, $R'' = CH_3$
38, $R'' = C_6H_5$

In the same way, **14** and **37** afforded oily mixtures, the components of which still contained nitrogen. In these latter examples, the ring system is apparently cleaved in a manner analogous to the sequence of events triggered by methyl iodide. A reasonable hypothesis is that N-oxide formation occurs initially at the 2α-nitrogen atom; if the resulting N-oxide is endowed with appreciable stability, the remaining nitrogen is subsequently oxidized and the methylenethiete dioxide ultimately formed. If the intermediate mono-N-oxide is prone to cleavage in order to relieve the strain inherent in the four-membered ring, then the desired unsaturated heterocycles are not produced.

In summary, the synthesis of the first derivatives of the highly strained methylenethiete dioxide system has been achieved. It is apparent that the stability of this group of heterocycles is markedly dependent upon substitution, particularly phenyl substitution. In this respect, a favorable comparison with the properties of methylenecyclobutenes can be seen.[9,10] Methylenethiete dioxides now join thiirene dioxides[21] in the growing list of strained and reactive tetravalent sulfur heterocycles which have been recently synthesized or recognized as reaction intermediates.

Experimental Section[22]

1-[(9,10-Dihydro-9,10-ethanoanthracen-11-ylidene)methyl]-pyrrolidine (7).—A solution of 150.0 g (0.64 mol) of 9,10-dihydro-9,10-ethanoanthracene-11-carboxaldehyde (**6**)[23] and 58.0 g (0.96 mol) of pyrrolidine in 550 ml of toluene was heated under a Dean–Stark trap at reflux for 2 hr. The mixture was cooled and concentrated *in vacuo* to give a yellow solid which was dissolved in 1200 ml of anhydrous ether. This solution was concentrated to *ca.* 600 ml and cooled to give 140.2 g (76.3%) of a light yellow crystalline solid, mp 118–120°. Recrystallization from ether yielded flakes of **7**: mp 125–127°; $\lambda_{max}^{CCl_4}$ 6.02 μ (>C=C–N<); $\tau_{TMS}^{CDCl_3}$ 8.26–8.56 (complex pattern, 4 H, $-CH_2-$ of pyrrolidino group), 7.48 and 7.43 (merging doublets, J = 2.5 Hz, 2 H, $-CH_2-C=C$), 6.86–7.19 (complex pattern, 4 H, $(-CH_2-)_2N-$ of pyrrolidino group), 5.66 (triplet, J = 2.5 Hz, 1 H, >CH–CH_2–), 5.51 (singlet, 1 H, >CH–C=CH–N<), 3.83 (broad singlet, 1 H, vinyl proton), and 2.46–3.06 (complex pattern, 8 H, aromatic ring protons).

Anal. Calcd for $C_{21}H_{21}N$: C, 87.76; H, 7.37. Found: C, 87.41; H, 7.30.

1-(9,10-Dihydrospiro[9,10-ethanoanthracene-11,2′-thietan]-3′-yl)pyrrolidine S,S-Dioxide (8).—A stirred solution of 90.0 g (0.314 mol) of **7** and 33.0 g (0.327 mol) of triethylamine in 500 ml of dry tetrahydrofuran under a nitrogen atmosphere was treated dropwise at −10° with a solution of 37.0 g (0.323 mol) of methanesulfonyl chloride in 120 ml of the same solvent during 45 min. Upon completion of the addition, the mixture was allowed to warm slowly to room temperature and was stirred at that temperature for 6 hr. Filtration of the slurry afforded a solid mixture of triethylamine hydrochloride and adduct. The solid mixture was dissolved in water and the insoluble material was filtered and washed with water, methanol, and ether to yield 71.2 g of a slightly colored solid, mp 232–233° dec. The reaction filtrate was concentrated *in vacuo* and the resulting solid was slurried with methanol, filtered, and washed further with methanol, acetone, and ether to afford 27.8 g of a light brown solid, mp 192–194° dec. The total yield of crude **8** was 99.0 g (86.1%). One recrystallization of the combined solids from acetone–methanol gave 85.0 g (74.1%) of colorless **8**, mp 237–238° dec. An analytical sample was obtained from acetone as fine white crystals: mp 246.5° dec; λ_{max}^{Nujol} 7.70 and 8.80 μ ($-SO_2-$). The compound was too insoluble in organic solvents for useful nmr studies.

Anal. Calcd for $C_{22}H_{23}NO_2S$: C, 72.03; H, 6.34; S, 8.77. Found: C, 72.29; H, 6.32; S, 8.71.

9,10-Dihydrospiro[9,10-ethanoanthracene-11,2′[2H]-thiete] 1′,1′-Dioxide (9).—The methiodide of **8** was prepared by reaction with excess methyl iodide in refluxing acetone. The salt was filtered from the warm reaction mixture and was obtained as a light brown solid, mp 186–188° dec (frothing). Concentration of the filtrate *in vacuo* gave unreacted starting material which was reutilized in the methiodide preparation. The methiodide was not purified for analysis and was used directly for the next reaction.

A stirred slurry of 10.0 g (0.019 mol) of this methiodide, *ca.* 5 g (0.022 mol) of freshly prepared silver oxide, and 600 of water was refluxed for 2 hr. A reaction was evidenced by the presence of free amine and a color change from brown to black in the reaction vessel. The mixture was cooled and the solid was filtered and extracted with chloroform. The chloroform solution was dried and filtered through Celite to afford, after removal of the

(20) λ_{max} 328 mμ (ϵ 41,000); see R. A. Friedel and M. Orchin, "Ultraviolet Spectra of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1951, Spectrum No. 129; E. A. Braude, *Ann. Rept. Progr. Chem.* (Chem. Soc. London), **42**, 105 (1945).

(21) (a) L. A. Carpino and L. V. McAdams, III, *J. Amer. Chem. Soc.*, **87**, 5804 (1965); (b) L. A. Carpino and R. H. Rynbrandt, *ibid.*, **88**, 5682 (1966); (c) see also L. A. Paquette and L. S. Wittenbrook, *Chem. Commun.*, 471 (1966); L. A. Paquette and L. S. Wittenbrook, *J. Amer. Chem. Soc.*, **89**, 4483 (1967); L. A. Paquette, L. S. Wittenbrook, and V. V. Kane, *ibid.*, **89**, 4487 (1967).

(22) Melting points were determined with a Thomas–Hoover melting point apparatus and are corrected. Infrared spectra were recorded with a Perkin-Elmer Infracord Model 137 spectrometer fitted with sodium chloride prisms. Ultraviolet spectra were determined with a Cary 14 recording spectrometer. Nuclear magnetic resonance spectra were obtained with a Varian A-60 spectrometer purchased with funds made available through the National Science Foundation. The mass spectrum was measured with an AEI MS-9 mass spectrometer at an ionizing energy of 70 eV. The microanalyses were performed by the Scandinavian Microanalytical Laboratory, Herlev, Denmark.

(23) F. Weiss and R. Rusch, *Bull. Soc. Chim. Fr.*, 550 (1964).

chloroform, a light brown solid. Recrystallization of this solid from acetone gave 4.95 g (88.7%) of **9**, mp 220–222° dec. An analytical sample was obtained from acetone: mp 226–228° dec; $\lambda_{max}^{CHCl_3}$ 7.69 and 8.65 μ ($-SO_2-$); $\tau_{TMS}^{CDCl_3}$ 8.04 and 7.30 [AB quartet (further split by J = 2.5 Hz), J = 14.0 Hz, 2 H, $-CH_2-$], 5.59 (triplet, J = 2.5 Hz, 1 H, >CH–CH_2–), 5.24 (singlet, 1 H, >CH–C<), 3.59 (doublet, J = 4.0 Hz, 1 H, non-α-sulfonyl vinyl proton), 3.32 (doublet, J = 4.0 Hz, 1 H, α-sulfonyl vinyl proton), and 2.42–2.97 (complex pattern, 8 H, aromatic ring protons).

Anal. Calcd for $C_{18}H_{14}O_2S$: C, 73.44; H, 4.79; S, 10.87. Found: C, 73.60; H, 4.89; S, 11.00.

1-(9,10-Dihydro-4′-phenylspiro[9,10-ethanoanthracene-11,2′-thietan]-3′-yl)pyrrolidine S,S-Dioxide (10).—To a rapidly stirred solution of 26.0 g (0.091 mol) of **7** and 9.5 g (0.094 mol) of triethylamine in 150 ml of dry tetrahydrofuran cooled to −10° was added dropwise under a nitrogen atmosphere during 30 min a solution of 17.5 g (0.092 mol) of phenylmethanesulfonyl chloride in 75 ml of the same solvent. After the addition, the mixture was warmed to room temperature and stirred for 6 hr. The triethylamine hydrochloride[24] was filtered and the filtrate was concentrated *in vacuo* to give a yellow froth which, when slurried with 250 ml of methanol at room temperature, gave 28.0 g of **10** as a light brown solid, mp 178–180° dec (second crop, 4.70 g, mp 165–177° dec, total yield 81.8%). An analytical sample was obtained from acetone–methanol: mp 184–185° dec; $\lambda_{max}^{CHCl_3}$ 7.65, 8.70, and 9.00 μ ($-SO_2-$); $\tau_{TMS}^{CDCl_3}$ 8.25–9.00 (multiplet with a superimposed singlet at ~8.9, 8 H, pyrrolidino group), 7.24 and 7.19 (merging doublets, J = 2.5 Hz, 2 H, >CH–CH_2–C<), 6.40 (doublet, J = 10.0 Hz, 1 H, >N–CH<), 5.50 (triplet, J = 2.5 Hz, 1 H, >CH–CH_2–), 5.00 (singlet, 1 H, >CH–C<), 4.58 (doublet, J = 10.0 Hz, 1 H, α-sulfonyl proton), and 2.28–2.98 (complex pattern, 13 H, aromatic ring protons).

Anal. Calcd for $C_{28}H_{27}NO_2S$: C, 76.15; H, 6.16; N, 3.17; S, 7.26. Found: C, 75.82; H, 6.30; N, 2.98; S, 7.30.

9,10-Dihydro-4′-phenylspiro[9,10-ethanoanthracene-11,2′[2H]-thiete] 1′,1′-Dioxide (11).—A stirred mixture of **10** (12.0 g, 0.027 mol) in 100 ml of glacial acetic acid and 100 ml of acetic anhydride was treated dropwise during 15 min at −10° with 18.0 g (0.16 mol) of 30% hydrogen peroxide solution. The homogeneous reaction mixture was warmed to room temperature and stirred for 18 hr during which time a colorless solid was seen to crystallize from the solution. The solid was filtered and washed with methanol and ether to yield 7.7 g (76.5%) of colorless **11**, mp 240–242° dec. An analytical sample was obtained from acetone–methanol: mp 250–251° dec; $\lambda_{max}^{CHCl_3}$ 7.69 and 8.71 μ ($-SO_2-$); $\tau_{TMS}^{CDCl_3}$ 5.16 (singlet, 1 H, >CH–C<), 3.62 (singlet, 1 H, vinyl proton), and 2.50–2.95 (complex pattern, 13 H, aromatic ring protons).

Anal. Calcd for $C_{24}H_{18}O_2S$: C, 77.81; H, 4.90; S, 8.66. Found: C, 77.69; H, 4.96; S, 8.58.

9,10-Dihydrospiro[9,10-ethanoanthracene-11,2′-thiethane] 1′,1′-Dioxide (12).—A mixture of 6.0 g (0.02 mol) of **9**, 250 ml of acetone, and 1.0 g of 10% palladium on carbon was shaken under 50 psig of hydrogen for 25 hr at room temperature. The catalyst was filtered, and the filtrate was evaporated to give a colorless solid. Recrystallization from methanol gave 5.50 g (91.3%) of **12**, mp 207–208°. Pure **12** was obtained from methanol: mp 207.5–208.5° (slight coloration); $\lambda_{max}^{CHCl_3}$ 7.62, 8.63 and 8.85 μ ($-SO_2-$); $\tau_{TMS}^{CDCl_3}$ 7.72–8.72 [complex pattern, 3 H, >CH–CH_2–C< (one such proton) and $-CH_2-CH_2-SO_2-$], 7.17 [low field portion of an AB quartet (further split by J = 2.5 Hz), J = 14.0 Hz, 1 H, >CH–CH_2–C< (one such proton)], 6.29 (doublet of triplets, J = 9.0 and 2.5 Hz, 2 H, α-sulfonyl protons), 5.63 (multiplet, 1 H, >CH–CH_2–), 5.22 (singlet, 1 H, >CH–C<), and 2.41–3.09 (complex pattern, 8 H, aromatic ring protons).

Anal. Calcd for $C_{18}H_{16}O_2S$: C, 72.94; H, 5.44; S, 10.82. Found: C, 72.89; H, 5.49; S, 10.76.

Reaction of 2-Phenyl-3-dimethylamino-4-dimethylaminomethylthietane 1,1-Dioxide (13) with Methyl Iodide.—Addition of 4.5 g (0.032 mol) of methyl iodide to a stirred solution of 3.0 g (0.0105 mol) of **13** in 20 ml of methanol resulted in a gradual exothermic reaction. After the initial reaction had subsided, the mixture was kept at room temperature for 1 day during which time there precipitated 1.7 g (40.8% based on pure **15**) of a yellow crystalline solid, mp 204–205° dec. Recrystallization of this material from aqueous methanol yielded pure **2-phenyl-4-dimethylaminomethyl-2-thiete 1,1-dioxide methiodide monohydrate (15)** as a colorless highly crystalline solid: mp 204–205° dec; λ_{max}^{Nujol} 2.90 (H_2O) and 7.55 and 8.85 μ ($-SO_2-$); λ_{max}^{EtOH} 266 mμ (ϵ 8080). Examination of the filtrates afforded tetramethylammonium iodide, mp >250°.

Anal. Calcd for $C_{13}H_{18}INO_2S \cdot H_2O$: C, 39.30; H, 5.07; N, 3.53; S, 8.07. Found: C, 39.09; H, 5.38; N, 3.33; S, 8.14.

The filtrate from the removal of **15** and tetramethylammonium iodide was concentrated under reduced pressure and chromatographed on neutral alumina. Elution of the column with ether yielded 0.45 g (17.4%) of **1-dimethylamino-2-phenyl-3-thia-1,4-pentadiene 3,3-dioxide (16)**, mp 101–103° from carbon tetrachloride (lit.[8i] mp 102–103°).

Continued elution with methanol–chloroform (1:1) gave an oily solid which afforded 0.3 g (6.46%) of pure **1,5-bis(dimethylamino)-2-phenyl-3-thia-1-pentene 3,3-dioxide 5-methiodide monohydrate (17)** upon trituration with ether: mp 220–221° (methanol); λ_{max}^{Nujol} 2.90 (H_2O), 6.10 (–C=C–N<), 7.70, and 8.90 μ ($-SO_2-$); λ_{max}^{EtOH} 2.47 mμ (ϵ 14,140), 266 sh (10,450) and end absorption.

Anal. Calcd for $C_{15}H_{25}IN_2O_2S \cdot H_2O$: C, 40.72; H, 6.15; N, 6.33; S, 7.25. Found: C, 39.91; H, 6.03; N, 6.52; S, 7.06.

Unequivocal Synthesis of 17.—A cooled (−10°) solution of 0.02 g (0.08 mol) of **16** in 5 ml of dry tetrahydrofuran was treated with excess dimethylamine. After remaining at 0° for 1 day, the mixture was concentrated to give an oil which was immediately treated with methyl iodide in refluxing methanol solution for 2 hr. On cooling, there was deposited 0.03 g (84.0%) of a crystalline material, mp 220–221° (methanol), identical in all respects with **17**.

Hofmann Degradation of 15.—A solution of 6.45 g (0.016 mol based on pure **15**) of the mixture of **15** and tetramethylammonium iodide in hot water was passed through a column of Amberlite IRA-400 ion-exchange resin (hydroxide form). The total eluate was concentrated to *ca.* 50 ml *in vacuo* and extracted with chloroform to yield 1.7 g (46.1% based on pure **15**) of an oily crystalline solid. Recrystallization of this material from ether–petroleum ether (bp 60–80°) gave rodlike crystals of **2-(benzylsulfonyl)-N,N-dimethylethylamine (18)**, mp 69–70° (lit.[8i] mp 68–69°).

Anal. Calcd for $C_{11}H_{17}NO_2S$: C, 58.11; H, 7.54; N, 6.16; S, 14.11. Found: C, 58.27; H, 7.60; N, 6.10; S, 13.99.

Reaction of 2-(α-Dimethylaminoethyl)-3-dimethylaminothietane 1,1-Dioxide (14) with Methyl Iodide.—Addition of 10.0 g (0.07 mol) of methyl iodide to a solution of 5.0 g (0.022 mol) of **14** in 50 ml of methanol resulted in a gradual exothermic reaction. After the initial reaction had subsided, the mixture was kept at room temperature for one day during which time there precipitated a colorless solid. This solid [5.5 g (67.1%), mp 168–169° dec] was filtered and the filtrate was saved. All attempts to recrystallize this material from aqueous methanol–ether gave poor (10%) recovery of the solid, mp 173–175° dec. Analysis of the unpurified material for iodine identified it as the monomethiodide **19**.

Anal. Calcd for $C_{10}H_{23}IN_2O_2S$: I, 35.03. Found: I, 35.49.

The above filtrate was concentrated *in vacuo* and chromatographed on neutral alumina. Elution of the column with ether afforded 0.6 g (15.1%) of an oil which was identical in all respects with **1-dimethylamino-3-thia-1,4-hexadiene 3,3-dioxide (20)**. The crude oil was hydrogenated over 10% palladium on carbon and a methiodide was prepared from the hydrogenated material, mp 166° (lit.[8i] mp 166° dec).

Continued elution with methanol–chloroform (1:4) gave 0.1 g of tetramethylammonium iodide, mp 250°.

Attempted Hofmann Degradation of 19.—A solution of 4.0 g (0.011 mol) of **19** in hot water was passed through a column of Amberlite IRA-400 ion-exchange resin (hydroxide form). The total alkaline eluate was reduced to one-half its volume *in vacuo* at 60–70°. The remaining solution was concentrated under reduced pressure at −70° to 1.5 g (61.6%) of a brown oil. The oil was similar in all respects to **14** (with the exception that its infrared spectrum displayed a medium intensity absorption at 6.1 μ due to small amounts of an enamine impurity). A methanol solution of this material gave on reaction with methyl iodide the above methiodide (**19**), mp 165–166° dec, in good yield.

(24) Dissolution of this salt in water and extraction of the aqueous solution with methylene chloride gave no additional material. Basification of the aqueous phase and reextraction likewise gave no additional product(s).

Hofmann Degradation of 18.—The methiodide salt of **18** was prepared with methyl iodide in refluxing methanol in 93.4% yield, mp 212–213° dec (from aqueous methanol).

A solution of 10.0 g (0.027 mol) of this methiodide (**24**) in hot water was passed through a column of Amberlite IRA-400 ion exchange resin (hydroxide form). The total eluate was concentrated *in vacuo* and extracted with chloroform to yield 2.3 g (43.4%) of colorless solid. Recrystallization from ethyl acetate–petroleum ether gave flakes of 2-(benzylsulfonyl)ethanol (**25**): mp 74° (lit.[25] mp 97°, needles from water); $\lambda_{max}^{CHCl_3}$ 2.90 (–OH) and 7.60 and 8.96 μ ($-SO_2-$); $\tau_{TMS}^{CHCl_3}$ 6.98 (triplet, J = 5.5 Hz, 2 H, $-SO_2CH_2CH_2-$), 6.80 (singlet, 1 H, $-CH_2OH$), 6.05 (triplet, J = 5.5 Hz, 2 H, $-CH_2OH$), 5.70 (singlet, 2 H, benzylic protons), and 2.67 (singlet, 5 H, phenyl group).

Anal. Calcd for $C_9H_{12}O_3S$: C, 53.98; H, 6.03; S, 16.02. Found: C, 54.14; H, 6.05; S, 15.71.

2-Methylene-4-phenyl-2H-thiete 1,1-Dioxide (26).—A solution of **13** (7.0 g, 0.025 mol) in 15 ml of glacial acetic acid and 15 ml of acetic anhydride contained in a 100-ml, round-bottomed flask equipped with a magnetic stirring bar and cooled to −10° was treated dropwise with stirring during 10 min with 14.0 g (0.123 mol) of 30% hydrogen peroxide. The reaction mixture was stirred at 0° for an additional 30 min and at room temperature for 17 hr, again cooled in ice, and neutralized with a 25% sodium hydroxide solution. Three runs as above were combined and concentrated *in vacuo* for 1.5 hr at 60° and at 30° to proximate dryness. The solid residue was dissolved in a minimum amount of water and the solution was extracted with chloroform. The organic extract was separated, dried over anhydrous potassium carbonate, and concentrated to a brown oil. Chromatography of this oil on neutral alumina yielded upon elution with ether–petroleum ether (1:1) and ether 5.40 g (37.6%) of a light yellow crystalline solid, mp 83–85° dec.[26] Rapid recrystallization from ether–petroleum ether gave pure **26** as a colorless, highly crystalline solid: mp 86–88° dec; λ_{max}^{Nujol} 7.66, 8.40, 8.67, and 8.90 μ ($-SO_2-$); λ_{max}^{ether} 291 mμ (ϵ 33,400); $\tau_{TMS}^{CDCl_3}$ 2.53 (singlet, 6 H, phenyl group and styrene proton), 4.45 (doublet of doublets, J = 4.0 and 1.0 Hz, 1 H, methylene proton), and 4.66 (doublet, J = 4.0 Hz, 1 H, methylene proton).

Anal. Calcd for $C_{10}H_8O_2S$: C, 62.48; H, 4.19; S, 16.68. Found: C 62.34; H, 4.47; S, 16.34.

2-Phenyl-3-(1-piperidino)-4-(1-piperidinophenylmethyl)thietane 1,1-Dioxide (29).—To a rapidly stirred solution of 18.6 g (0.065 mol) of **28**[27] and 6.8 g (0.067 mol) of triethylamine in 100 ml of dry tetrahydrofuran cooled to −10° was added dropwise under a nitrogen atmosphere a solution of 12.5 g (0.066 mol) of phenylmethanesulfonyl chloride in 100 ml of the same solvent. Upon completion of the addition, the mixture was permitted to warm to room temperature and was stirred at that temperature for 4 hr. The triethylamine hydrochloride[24] was filtered and the filtrate was evaporated to give a brown oily solid which was chromatographed on neutral alumina. Elution of the column with petroleum ether–ether (3:1) gave 9.45 g of a brown solid. Two recrystallizations of this material from ether afforded 6.0 g (20.7%) of **29** as a light brown solid, mp 156–157°. Further purification from ether gave pure **29**: mp 161–162°; $\lambda_{max}^{CCl_4}$ 7.59, 8.56, 8.84, and 9.06 μ ($-SO_2-$); $\tau_{TMS}^{CDCl_3}$ 8.57 (multiplet, 12 H, $-CH_2-$ of piperidino groups), 7.22–7.83 [multiplet, 8 H, $(-CH_2-)_2N-$ of piperidino groups], 6.32 (broad triplet, J = 8.0 Hz, 1 H, >CH–N<), 5.77 (broad doublet, J = 11.0 Hz, $C_6H_5-CH-N<$), 5.00 (complex pattern, 1 H, nonbenzylic α-sulfonyl proton), 4.62 (broad doublet, J = 8.0 Hz, 1 H, benzylic α-sulfonyl proton), and 2.70 (singlet, 10 H, phenyl groups).

Anal. Calcd for $C_{26}H_{34}N_2O_2S$: C, 71.19; H, 7.81; N, 6.39. Found: C, 71.21; H, 7.91; N, 6.23.

Continued elution with petroleum ether–ether (3:1 and 1:1) and ether yielded 7.0 g of an oil which contained some **29**. Recrystallization of this material from ether afforded 3.45 g (21.8%) of colorless flakes, mp 125–127°. Further purification from carbon tetrachloride gave pure 1-(benzylsulfonyl)piperidine (**30**), mp 137° (lit.[28] mp 136–138°).

(25) E. Fromm and H. Jörg, *Chem. Ber.*, **58B**, 304 (1925).

(26) The combined eluates were concentrated to a small volume and the solid was crystallized from the solution. Petroleum ether was added to cause further crystallization and the material was removed by filtration. In this way, pure **26** could be isolated and its decomposition minimized.

(27) C. Mannich, K. Handke, and K. Roth, *Chem. Ber.*, **69**, 2112 (1936).

(28) O. Eisleb, German Patent, 735,866 (April 22, 1943); *Chem. Abstr.*, **38**, 4101 (1944).

Further elution of the column with chloroform–ether (1:1) gave a brown oil which upon trituration with ether afforded 0.5 g (2.86%) of a brown crystalline solid, mp 86–88°. Recrystallization from ether gave analytically pure 2-(1-piperidino)-1-phenylmethanesulfonylethylene (**31**): mp 91–92°: $\lambda_{max}^{CCl_4}$ 6.16 (C=C–N<), 7.66 and 9.00 μ $-SO_2-$); $\tau_{TMS}^{CDCl_3}$ 8.47 (multiplet, 6 H, $-CH_2-$ of piperidino group), 6.96 (multiplet, 4 H, $(-CH_2-)N-$ of piperidino group), 5.83 (broad singlet, 2 H, benzylic protons), 5.32 and 3.30 (doublets, J = 13.0 Hz, 1 H each, vinyl protons), and 2.67 (singlet, 5 H, phenyl group).

Anal. Calcd for $C_{14}H_{19}NO_2S$: C, 63.36; H, 7.22; N, 5.28. Found: C, 63.41; H, 7.24; H, 5.17.

2-Benzylidene-4-phenyl-2H-thiete 1,1-Dioxide (32).—A stirred mixture of **29** (5.0 g, 11.4 mmol) in 20 ml of glacial acetic acid and 15 ml of acetic anhydride was treated dropwise during 5 min at −10° with 6.0 g (0.053 mol) of 30% hydrogen peroxide. The reaction mixture was permitted to warm to room temperature and was stirred for 19 hr, again cooled in ice, and neutralized with a 25% sodium hydroxide solution. The yellow oily solid which precipitated during neutralization was extracted with chloroform and the organic solution was dried over potassium carbonate. (The aqueous layer from the extraction afforded no additional material after concentration to dryness and extraction of the salt residue with chloroform.) The dried chloroform extract was filtered and concentrated *in vacuo* to give an oily solid which afforded, on trituration with ether, 1.82 g of a yellow solid, mp 209–210° dec. The filtrate was concentrated and chromatographed on neutral alumina. Elution of the column with ether gave 0.8 g of the same material (total yield 85.3%), mp 208–210° dec. Recrystallization of the combined solids from tetrahydrofuran–petroleum ether afforded pure **32**: mp 212–213° dec; $\lambda_{max}^{CHCl_3}$ 6.02 (>C=C<), 7.63 and 8.70 μ ($-SO_2-$); $\lambda_{max}^{CHCl_3}$ 366 (sh) mμ (ϵ 23,450), 349 (40,200), 337 (38,800), and 240 (12,850); $\tau_{TMS}^{CDCl_3}$ 3.49 (singlet, 1 H, exocyclic styrene proton), 2.31–2.79 (broad singlet, 11 H, phenyl groups and ring proton).

Anal. Calcd for $C_{16}H_{12}O_2S$: C, 71.61; H, 4.51; S, 11.95. Found: C, 71.39; H, 4.24; S, 12.26.

2-(1-Piperidinomethyl)-3-(1-piperidino)thietane 1,1-Dioxide (34).—A solution of 10.00 g (0.099 mol) of triethylamine and 20.0 g (0.096 mol) of 1,3-bis(1-piperidino)-1-propene (**33**)[27] in 50 ml of dry tetrahydrofuran was treated in the usual manner with 11.0 g (0.096 mol) of methanesulfonyl chloride in 50 ml of the same solvent. Removal of the triethylamine hydrochloride and concentration of the filtrate yielded an oily liquid which afforded, on trituration with ether at 0°, 16.0 g of a brown crystalline solid, mp 62–64° (second crop, 2.5 g, mp 58–60°, total yield 67.3%). Recrystallization from ether–petroleum ether gave pure **34**: mp 67–68°; $\lambda_{max}^{CCl_4}$ 7.54, 8.39, 8.78, and 9.07 μ ($-SO_2-$); $\tau_{TMS}^{CDCl_3}$ 8.50 (broad singlet, 12 H, $-CH_2-$ or piperidino groups), 7.58 [multiplet, 8 H, $(-CH_2-)_2N-$ of piperidino groups], 6.92–7.28 [complex pattern (five sharp lines), 3 H, $-CH_2N<$ and >CHN<], 6.08 (doublet, J = 8.0 Hz, 2 H, $-CH_2SO_2-$), and 5.45–5.85 (multiplet, 1 H, $>CHSO_2-$).

Anal. Calcd for $C_{14}H_{26}N_2O_2S$: C, 58.69; H, 9.15; N, 9.78. Found: C, 58.68; H, 9.23; N, 9.48.

Chromatography of the residues obtained from concentration of the above mother liquors on neutral alumina gave, on elution of the column with ether, a small quantity of additional **34**, mp 67–68°. Elution with petroleum ether–ether (1:1) gave a mixture of **34** and 1-(methylsulfonyl)piperidine (characteristic $\lambda_{max}^{CCl_4}$ 10.4 μ for sulfonamide but not characterized any further), mp 40–55°. Further elution with chloroform–ether (1:9) gave colored oils which displayed intense absorption in the infrared spectrum at 6.10 μ.

2-(1-Piperidinophenylmethyl)-3-(1-piperidino)thietane 1,1-Dioxide (37).—A stirred solution of 20.0 g (0.07 mol) of **28**[27] and 7.3 g (0.07 mol) of triethylamine in 60 ml of anhydrous tetrahydrofuran under a nitrogen atmosphere was treated dropwise at −10° with a solution of 8.1 g (0.07 mol) of methanesulfonyl chloride in 50 ml of the same solvent. The addition required 1 hr. Upon completion of the addition, the mixture was permitted to warm slowly to room temperature and was stirred at that temperature for 8 hr. The mixture was filtered to remove the precipitated triethylamine hydrochloride, and evaporation of the filtrate afforded a brown viscous oil. The oil became crystalline after standing at room temperature for 1 day. The partially crystalline mixture was mixed with ether and cooled to 0° to afford 14.45 g of yellow solid, mp 125–127°. Further recrystallization of this material from ether–petroleum ether gave pure **37** as a colorless fluffy solid: mp 129–130°; $\lambda_{max}^{CCl_4}$ 7.50 8.40, and

9.10 μ ($-SO_2-$); $\tau_{TMS}^{CDCl_3}$ 8.11–8.92 (multiplet, 12 H, $-CH_2-$ of piperidino groups), 7.25–8.08 [multiplet, 8 H, $(-CH_2-)_2N-$ of piperidino groups], 6.56 (broad triplet, J = 6.0 Hz, H, >CHN<, 6.07 and 5.88 [singlet and doublet (J = 3.0 Hz), respectively, 3 H, $-CH_2-SO_2-$ and $C_6H_5-CH-N<$, respectively], 4.93 and 5.13 (doublet of doublets, J = 12.0 and 6.0 Hz, 1 H, $>CH-SO_2-$), and 2.75 (singlet, 5 H, phenyl group).

Anal. Calcd for $C_{20}H_{30}N_2O_2S$: C, 66.26; H, 8.34; N, 7.73; S, 8.85. Found: C, 66.49; H, 8.46; N, 7.69; S, 8.97.

All filtrates and insoluble residues were combined and chromatographed on neutral alumina. The only material isolated was **37** and the total weight obtained by direct crystallization and chromatography was 15.5 g (61.0%).

Registry No.—**7**, 16808-51-8; **8**, 16808-52-9; **9**, 16808-53-0; **10**, 16808-54-1; **11**, 16808-55-2; **12**, 16808-56-3; **15**, 16808-57-4; **17**, 16808-58-5; **19**, 16793-41-2; **25**, 16793-42-3; **26**, 16793-43-4; **29**, 16791-06-3; **31**, 16790-87-7; **32**, 16790-88-8; **34**, 16790-89-9; **37**, 16790-90-2.

Unsaturated Heterocyclic Systems. XLI. Selected Reactions of 2-Methylenethiete 1,1-Dioxides[1,2]

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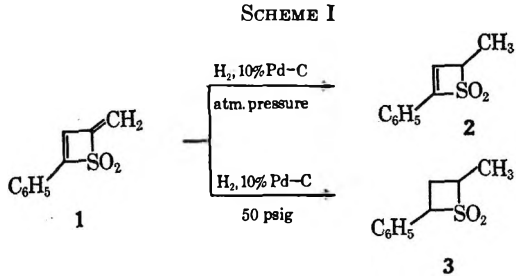
2-Methylene-4-phenyl-2H-thiete 1,1-dioxide (**1**) could be hydrogenated in two distinct stages to a dihydro and tetrahydro derivative, respectively. This strained sulfone (**1**) was also found to undergo ready Michael reaction with dimethylamine. When exposed to 1,3-diphenylisobenzofuran, both **1** and its phenyl congener **7** gave rise to Diels–Alder adducts. In each instance, a single adduct was formed. The stereochemistry of the adducts and the stereospecificity of the processes have been assigned on the basis of spectral data and steric considerations. Irradiation of **1** in diethyl ether leads to the formation of a lone ($2 + 2\pi$) dimer. Spectral analysis and dipole moment data establish the structure of the dimer as that of the *trans*-1,2-cyclobutane derivative **14**. The probable mechanistic pathways for the stereoselective photocycloaddition are discussed.

The preceding paper describes the first synthesis of highly unsaturated and reactive methylenethiete dioxides.[1] The "cross conjugation" of the butadiene chromophore with the sulfonyl group in such molecules, when considered together with the relatively high degree of ring strain, makes the system a particularly suitable subject for experimental evaluation of chemical reactivity, bond hybridization, and involvement of d orbitals at the heteroatom. Although the geometrical parameters (*i.e.*, interorbital and internuclear angles) for a molecule such as **1** have not yet been evaluated, a number of modified physical and chemical properties can be expected because of varied hybridization at the vinylic carbon atoms. Although the four carbon centers fall roughly into two sets of similarly hybridized atoms, their relative reactivities were anticipated to differ significantly and to lend to the molecule properties which are not normally seen in unstrained α,β-unsaturated sulfones or thiete dioxides. The present paper describes the chemical properties of **1** and **7**, of which reactions have been selected in an attempt to provide insight into the reactivity differences of the exocyclic and endocyclic double bonds.[4]

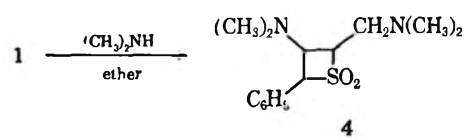
Results and Discussion

When a dilute solution of **1** was hydrogenated at atmospheric pressure over 10% palladium on charcoal, there resulted a rapid uptake of hydrogen which ceased before 1 equiv was consumed. The resulting dihydro derivative was easily identified as 2-methyl-4-phenyl-2H-thiete 1,1-dioxide (**2**) principally on the basis of its nmr spectrum (see Experimental Section). When the pressure of hydrogen was increased to 50 psig and the catalytic hydrogenation allowed to proceed for 58 hr, thietane dioxide **3** was formed in greater than 90% yield (Scheme I).

SCHEME I



Exposure of **1** to a cold ethereal solution of dimethylamine (eq 1) led to the formation of 2-dimethylaminomethyl-3-dimethylamino-4-phenylthietane 1,1-dioxide (**4**), mp 76–78°, isomeric with the sulfone of identical



(1)

gross structure, mp 91–93°,[5] utilized in the preparation of **1**.[1] The stereochemical relationship of the two isomers could not be established with certainty owing to unresolvable complexities of certain nmr absorptions and the lack of appropriate model compounds.

Reaction of equimolar quantities of **1** and 1,3-diphenylisobenzofuran (**5**) in refluxing benzene solu-

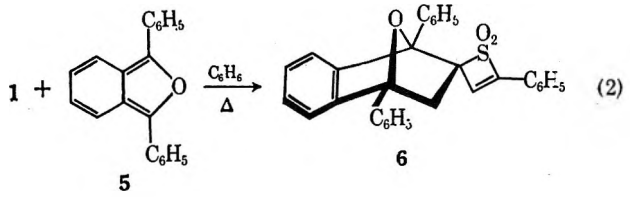
(1) For part XL of this series, see L. A. Paquette, M. Rosen, and H. Stucki, **33**, 3020 (1968).

(2) This work was generously supported by Grant GP-5977 from the National Science Foundation.

(3) Alfred P. Sloan Foundation Research Fellow.

(4) Our intended goal was somewhat beclouded by the fact that, of the two known and available methylenethiete dioxides (**1** and **7**), only **7** possesses two identically substituted (except for the ring) double bonds. However, as will be seen, the chemical behavior of **1** is sufficiently diagnostic of the divergence in reactivity between the two sites of unsaturation to be of interpretive value.

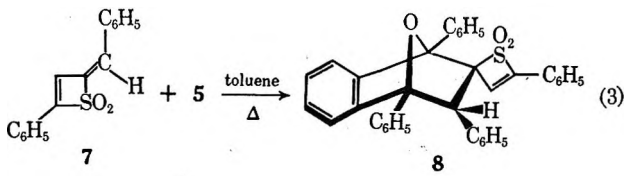
(5) L. A. Paquette and M. Rosen, *J. Amer. Chem. Soc.*, **89**, 4102 (1967).



5 6

tion (eq 2) for 16 hr afforded in 79% yield a *single* crystalline 1:1 adduct which had been assigned structure **6**. In confirmation of the structural assignment, the nmr spectrum of **6** displayed only an AB quartet (J = 13.0 Hz) at τ 6.67 and 7.17 (methylene protons) and a singlet at 3.38 (styrene proton) in addition to the aromatic proton absorption.

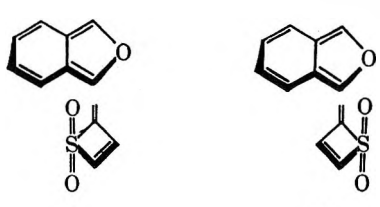
A similar Diels–Alder condensation of **5** with 2-benzylidene-4-phenyl-2H-thiete 1,1-dioxide (**7**) led to the spiro sulfone **8** (eq 3). The *cis* relationship of the



7 8

endoxy bridge and the sulfonyl group follows from the steric considerations presented below. A decision as to whether the phenyl group is of the *exo* or *endo* configuration was attained from a comparative analysis of the nmr spectra of **8** and **6**. Thus, whereas **6** exhibited a singlet at τ 3.38 for the styryl proton, the spectrum of **8** displays the same proton at 3.94. The magnitude of this upfield shift is most readily understood in terms of diamagnetic shielding experienced by the styryl proton in **8** because of its proximity to the face of the benzene ring in question. It follows therefore that this phenyl substituent occupies the *endo* position and that the structure of methylenethiete dioxide **7** is that in which the benzylidene phenyl group is *trans* to the sulfonyl function.[1]

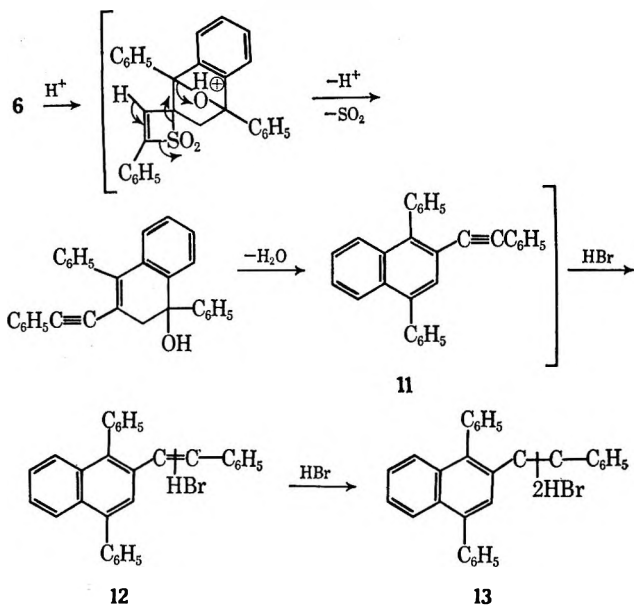
Diels–Alder additions to methylenethiete dioxides thus clearly prefer involvement of the exocyclic double bond. The formation of lone adducts in these cycloadditions is interesting and suggests steric control in the transition states leading to **6** and **8**. Inspection of diagrams **9** and **10** reveals that in the first transition state the bulky space-filling sulfonyl group is forced to lie in close proximity to the underface of the planar isobenzofuran molecule. Such nonbonded interaction can be expected to raise the energy associated with **9** to the point where transition state **10** becomes the only low energy pass available to the reacting components.



9 10

Endoxy sulfone **6** was reversibly protonated in hot polyphosphoric acid (80% recovery after quenching in water subsequent to 12-hr exposure at 100°). However, when **6** was refluxed in an acetic acid solution of anhydrous hydrogen bromide, there resulted a mixture consisting chiefly of monobromide **12** and traces of dibromide **13**. The gross structural assignment of **12** was substantiated by elemental analysis and spectral data (see Experimental Section); the exact position of attachment of the bromine was not established. On the basis of the above data and precedent concerning the acid-catalyzed dehydrative expulsion of sulfur dioxide from a thietane dioxide,[6] the pathway in Scheme II is proposed. Protonation of **6** at the endoxy bridge

SCHEME II



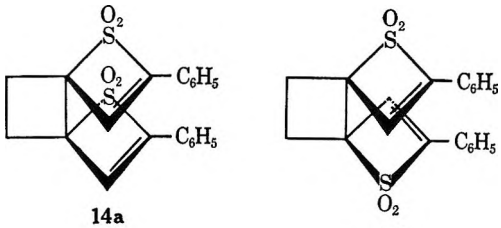
12 13

can lead with the proper migration of electrons (as shown) to the expulsion of sulfur dioxide. The resulting tertiary carbinol is without doubt rapidly dehydrated to attain the additional resonance energy of the naphthalene ring. Electrophilic addition of hydrogen bromide to the resulting acetylene (**11**) produces the observed products.

Irradiation of a dilute ether solution of **1** with an Hanovia 200 W mercury arc for 5 days gave in 12% yield a *lone* crystalline photodimer (**4**). The dimeric nature of this material was derived from its elemental analysis and mass spectrum. The latter displayed a molecular ion at m/e 384 (18% of base), a peak at m/e 192 (47% of base) corresponding to the molecular ion of the monomer, and peaks at m/e 144 (base) and 128 (86% of base) which result from the loss of sulfur monoxide and oxygen, respectively and consecutively, from the monomer unit. The nmr spectrum of **4** denoted the presence of two vinyl protons, and the ultraviolet absorption curve confirmed the presence of two α-sulfonyl styrene chromophores. These data established the fact that dimerization had occurred exclusively at the exocyclic double bond. On the basis of this analysis, four possible structures for the dimer are theoretically possible: *cis*-1,2 (**14a**), *trans*-1,2 (**14b**), *cis*-1,3 (**14c**), and *trans*-1,3 (**14d**).

The nmr spectrum of **14d** can be expected to display a sharp singlet for the cyclobutane protons since rapid inversion of the puckered cyclobutane ring at room temperature would effectively average the four protons and cause them to be magnetically equivalent. In contrast, the cyclobutane methylene groups of dimer

(6) L. A. Paquette and T. R. Phillips, *J. Org. Chem.*, **30**, 3883 (1965).



14a

14b

14c

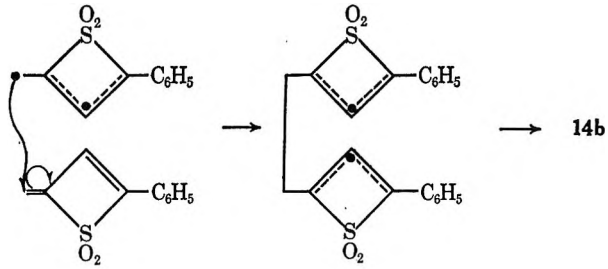
14d

14c would very likely give rise to a symmetrical AB pattern in which the individual peaks would probably be further split by transannular coupling. Precedent for this analysis has been derived from the spectra of the isomeric 1,3-dihalo-1,3-dimethylcyclobutanes.[7] In the *cis*-1,2 structure (**14a**), one hydrogen of each methylene group is seen to be *cis* to a sulfonyl group and therefore subject to its field effect; a significant difference in chemical shift between the two types of protons would very likely result. With regard to the corresponding *trans* compound (**14b**), these effects would be somewhat minimized and large chemical-shift differences would perhaps not be seen. In actuality, the photodimer shows a broad temperature-independent multiplet centered at τ 7.27 ($W_{1/2}$ = 3.7 Hz) for the methylene protons. Although this observation eliminated the 1,1,3,3-tetrasubstituted cyclobutane formulations (**14c** and **d**) from consideration, it remained to differentiate between **14a** and **b**.

The dipole moment of the dimer was 2.7 ± 0.5 D. in benzene solution. Whereas the dipole moments of *cis* isomers **14a** and **14c** can be expected to be very large (8–10 D.),[8] those of *trans* isomers **14b** and **14d** would be expected to have canceling bond moments. Since **14d** had already been eliminated as the correct structure, it became clear that the photodimerization of **1** had given rise exclusively to the *trans*-1,2 dimer (**14b**). The substance possesses a small, but significant, dipole moment since the two hetero rings probably cannot attain the conformation where the two dipoles are completely opposed.

Irradiation of **7** under analogous conditions for varying lengths of time gave no characterized products. The viscous yellow oils which resulted in these attempts contained no sulfonyl absorption in their infrared spectra.

The photodimerization of **1** to **14b** represents yet another example of a symmetry-allowed photochemical 2 + 2 cycloaddition.[9] The question of whether the formation of the cyclobutane ring is concerted or proceeds by means of attack of a photochemically excited ($\pi \rightarrow \pi^*$) molecule of **1** upon a ground-state counterpart (as illustrated) cannot be answered on the basis of the available data. It should be noted, however, that the two odd electrons in **15** enjoy appreciable resonance



15

delocalization. The high degree of stereoselectivity observed in the photodimerization process can be seen to result from minimal steric interference of the two sulfonyl groups in the most favorable transition state.

Both **1** and **7** failed to react when refluxed in benzene or toluene with diiron enneacarbonyl. No characterizable products were found on attempted cyclopropanation with trimethylsulfonium bromide and potassium *t*-butoxide in dimethyl sulfoxide solution at room temperature.[10]

Experimental Section[11]

Partial Hydrogenation of 1.—A solution of 0.5 g (2.6 mmol) of **1** in 50 ml of ether containing 300 mg of 10% palladium on carbon was placed in an atmospheric hydrogenation apparatus. The uptake of hydrogen was rapid but ceased before 1 equiv was consumed. The catalyst was removed by filtration, and the filtrate was concentrated to give a colorless solid which possessed an unpleasant odor and contained starting material. Recrystallization of this mixture from ether–petroleum ether afforded 0.25 g (49.5%) of **2-methyl-4-phenyl-2H-thiete 1,1-dioxide** (**2**) as a slightly colored solid, mp 104–107°. An analytical sample of **2** was obtained from ether: mp 111–112°; $\lambda_{max}^{CCl_4}$ 7.62, 8.47, and 8.80 μ (–SO_2–); λ_{max}^{EtOH} 255 mμ (ϵ 17,270); $\tau_{TMS}^{CCl_4}$ 8.48 (doublet, J = 7.0 Hz, 3 H, methyl group), 5.25 (broad quartet, J = 7.0 Hz, 1 H, α-sulfonyl proton), 3.10 [singlet (slightly split), J = 2.0 Hz, 1 H, styrene proton], and 2.60 (singlet, 5 H, phenyl group).

Anal. Calcd for $C_{10}H_{10}O_2S$: C, 61.83; H, 5.18; S, 16.51. Found: C, 61.95; H, 5.32; S, 16.45.

Complete Hydrogenation of 1.—A solution of 0.2 g (1.05 mmol) of **1** in 30 ml ether containing 100 mg of 10% palladium on charcoal was shaken under 50 psig of hydrogen for 54 hr at room temperature. The catalyst was removed by filtration and the filtrate was concentrated to give 0.2 g (>90%) of a colorless solid, mp 95–97°. Recrystallization from ether–petroleum ether (bp 60–80°) afforded pure **2-methyl-4-phenylthietane 1,1-dioxide** (**3**): mp 107–109°; $\lambda_{max}^{CCl_4}$ 7.62, 8.47, and 8.80 μ (–SO_2–); $\tau_{max}^{CDCl_3}$ 8.48 (broad doublet, J = 7.0 Hz, 3 H, methyl group), 7.25–7.75 (multiplet, 2 H, ring methylene protons), 5.55–5.95 (multiplet, 1 H, nonbenzylic α-sulfonyl proton), 4.68 (multiplet, 1 H, benzylic α-sulfonyl proton), and 2.60 (singlet, 5 H, phenyl group).

(7) K. Griesbaum, W. Naegele, and G. G. Wanless, *J. Amer. Chem. Soc.*, **87**, 3151 (1965).

(8) For an excellent discussion of sulfone dipole moments, see C. C. Price and S. Oae, "Sulfur Bonding," The Ronald Press Co., New York, N. Y., 1962, pp 67–73.

(9) R. Hoffmann and R. B. Woodward, *J. Amer. Chem. Soc.*, **87**, 2046 (1965).

(10) W. E. Truce and V. V. Badiger, *J. Org. Chem.*, **29**, 3277 (1964).

(11) Melting points were determined with a Thomas–Hoover melting point apparatus and are corrected. Infrared spectra were recorded with a Perkin-Elmer Infracord Model 137 spectrometer fitted with sodium chloride prisms. Ultraviolet spectra were determined with a Cary 14 recording spectrometer. Nuclear magnetic resonance spectra were obtained with a Varian A-60 spectrometer purchased with funds made available through the National Science Foundation. The mass spectrum was measured with an AEI MS-9 mass spectrometer at an ionizing energy of 70 eV. The microanalyses were performed by the Scandinavian Microanalytical Laboratory, Herlev, Denmark.

Anal. Calcd for $C_{10}H_{12}O_2S$: C, 61.19; H, 6.16; S, 16.34. Found: C, 61.18; H, 6.17; S, 16.22.

Reaction of 2-Methylene-4-phenyl-2H-thiete 1,1-Dioxide (1) with Dimethylamine.—Into a cold (−20°) solution of 0.30 g (1.6 mmol) of 1 in 20 ml ether was distilled excess dimethylamine and the resulting brown mixture was left overnight at 0°. Evaporation of the solution and trituration of the residual brown oil with ether afforded on cooling 0.20 g (45.5%) of 2-dimethylaminomethyl-3-dimethylamino-4-phenylthietane 1,1-dioxide (4), mp 76–78°. Recrystallization from ether gave pure 4 (unassigned isomer): mp 84–85°; $\lambda_{max}^{CCl_4}$ 7.50, 8.55, and 8.67 μ (–SO_2–); $\tau_{max}^{CDCl_3}$ 7.83 and 7.60 (two singlets, 6 H each, dimethylamino groups), 6.90 (doublet, J = 6.0 Hz, 2 H, –CH_2NMe_2), 6.43 (doublet, J = 10.0 Hz, 1 H, >$CHNMe_2$), 5.55–5.95 (multiplet, 1 H, nonbenzylic α-sulfonyl proton), 4.82 (doublet, J = 10.0 Hz, 1 H, benzylic proton), and 2.52 (singlet, 5 H, phenyl group).

Anal. Calcd for $C_{14}H_{22}N_2O_2S$: C, 59.54; H, 7.85; N, 9.92. Found: C, 59.63; H, 7.85; N, 9.57.

3,4-Dihydro-1,4,4′-triphenylspiro[1,4-epoxynaphthalene-2(1H),-2′[2H-]thiete] 1′,1′-Dioxide (6).—A solution of 0.7 g (2.6 mmol) of 1,3-diphenylisobenzofuran (5)[12] and 0.5 g (2.6 mmol) of 1 in 10 ml of benzene was refluxed for 16 hr under an atmosphere of nitrogen. The resulting brown solution was concentrated to an oil which was chromatographed on neutral alumina. Elution of the column with ether–petroleum ether (1:2) afforded 1.15 g (79.2%) of colorless adduct, mp 210–212° dec. An analytical sample of 6 was obtained from benzene–petroleum ether: mp 207–209°, with prior formation of yellow color at 165°; $\lambda_{max}^{CHCl_3}$ 7.67 and 8.69 μ (–SO_2–); λ_{max}^{EtOH} 262 mμ (ϵ 27,900); $\tau_{TMS}^{CDCl_3}$ 6.67 and 7.17 (AB quartet, J = 13.0 Hz, 2 H, methylene protons), 3.38 (singlet, 1 H, styrene proton), 2.20–3.15 (complex pattern with singlet at 2.68, 17 H, fused aromatic ring protons and phenyl groups), and 1.88 (complex pattern, 2 H, fused aromatic ring protons).

Anal. Calcd for $C_{30}H_{22}O_3S$: C, 77.89; H, 4.80; S, 6.93. Found: C, 78.21; H, 4.92; S, 6.74.

3,4-Dihydro-1,3,4,4′-tetraphenylspiro[1,4-epoxynaphthalene-2(1H),2′[2H-]thiete] 1′,1′-Dioxide (8).—A solution of 1.05 g (3.8 mmol) of 1,3-diphenylisobenzofuran (5) and 1.0 g (3.7 mmol) of 7 in 15 ml of toluene was refluxed for one day under an atmosphere of nitrogen. The toluene was removed *in vacuo* and the yellow residue was chromatographed on neutral alumina. Elution of the column with ether–petroleum ether (1:3) gave 0.4 g (20.0%) of yellow adduct, mp 211–213° dec. Recrystallization of this material from benzene–petroleum ether gave colorless crystals of 8: mp 216°, with prior formation of yellow color at 190°; $\lambda_{max}^{CHCl_3}$ 7.66 and 8.69 μ (–SO_2–); λ_{max}^{EtOH} 263 mμ (ϵ 12,970) and end absorption; $\tau_{max}^{CDCl_3}$ 5.40 (multiplet, 1 H, benzylic proton), 3.94 (broad singlet, 1 H, styrene proton), 2.28–3.18 (complex pattern with singlet superimposed at 2.92, 22 H, fused aromatic ring protons and phenyl groups), and 1.68–1.91 (complex pattern, 2 H, fused aromatic ring protons).

Anal. Calcd for $C_{38}H_{26}O_3S$: C, 80.27; H, 4.87; S, 5.95. Found: C, 80.20; H, 4.95; S, 5.94.

Further elution of the column with ether–petroleum ether (1:1) and ether gave 1.5 g of an oily solid. Recrystallization of this material from benzene–petroleum ether afforded 0.45 g of a mixture of 8, dibenzoyl ethylene, and 7, mp 162–165°.

Treatment of 6 with Hydrogen Bromide.—A stirred mixture of 0.65 g (1.4 mmol) of 6 and 10 ml of glacial acetic acid containing 0.5 ml of acetic anhydride was treated with gaseous hydrogen bromide for 5 min. The resulting red solution was refluxed for 16 hr whereupon it turned dark brown. The solution was cooled and poured into water, and the organic components were extracted with chloroform. Usual work-up of this solution gave 0.9 g of a brown oil. Chromatography of this material on neutral alumina afforded, on elution with petroleum ether–ether (3:1), 0.5 g (77.0%) of 12, as a colorless waxy solid, mp *ca.* 73° (prior softening at 63°). Molecular distillation of this material at *ca.* 120° (0.02 mm) and recrystallization from methanol gave pure 12: mp 68–70°; $\lambda_{max}^{CCl_4}$ 14.33 μ (aromatic system); λ_{max}^{EtOH} 310 (ϵ 20,150), 285 (32,750), and 236 mμ (37,400); $\tau_{TMS}^{CCl_4}$ 3.16 (singlet, 1 H, vinyl proton), and 2.10–3.05 (complex pattern, 20 H, aromatic protons).

Anal. Calcd for $C_{30}H_{21}Br$: C, 78.09; H, 4.59. Found: C, 77.63; H, 4.21.

Photolysis of 1. *trans*-**2,7-Diphenyl-1,6-dithiadispiro[3.0.3.2]-deca-2,7-diene 1,1,6,6-Tetraoxide (14b).**—A stirred solution of 5.1 g (0.027 mol) of 1 in 450 ml of ether was irradiated under nitrogen with a Hanovia 200 W mercury arc for 5 days. Work-up gave a black oily solid which was chromatographed on neutral alumina. Elution of the column with ether–petroleum ether (1:1) afforded 0.9 g of starting material and 0.5 g (11.9% based on unrecovered 1) of photodimer 14b, mp 231° dec. An analytical sample of 14b was obtained from acetone: mp 232° dec (sintering at *ca.* 205°); $\lambda_{max}^{CHCl_3}$ 7.62 and 8.64 μ (–SO_2–); λ_{max}^{EtOH} 258 mμ (ϵ 36,900), slight shoulder at 266, and end absorption; $\tau_{TMS}^{DMSO\text{-}d_6}$ 7.27 [multiplet, 4 H, –$(CH_2)_2$–], 2.47 (singlet, 10 H, phenyl groups), and 2.10 (singlet, 2 H, vinyl protons).

Anal. Calcd for $C_{20}H_{16}O_4S_2$: C, 62.48; H, 4.20; S, 16.68. Found: C, 62.31; H, 4.29; S, 16.65.

Registry No.—2, 16791-00-7; 3, 16791-01-8; 4, 16791-02-9; 6, 16791-03-0; 8, 16791-04-1; 14b, 16791-05-2.

Acknowledgment.—The authors are especially indebted to Professor N. L. Allinger for the dipole moment data.

(12) M. S. Newman, *J. Org. Chem.*, **26**, 2630 (1961).

Conversion of Triphenylamine and Acylated Triphenylamines into 9,10-Diaryl-9-acridanols

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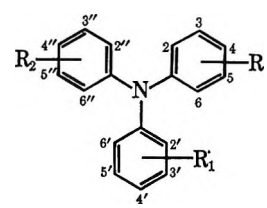
Reaction of triphenylamine with an aromatic carboxylic acid in polyphosphoric acid (PPA) gave 9-aryl-10-phenyl-9-acridanol (**2**) in yields as high as 50%, together with a mixture of *para*-acylated triphenylamines; acridanol **2** arises by cyclization of an intermediate *ortho*-acylated triphenylamine. Certain *para*-monoacylated triphenylamines were rearranged in PPA at 190° into the corresponding acridanols **2** in ~50% yield; *p*-di- and -tribenzoyltriphenylamines under similar conditions gave nuclear-substituted acridanols. The intermolecularity of the above transformations is supported. Acylation of triphenylamine with acid anhydrides and acid chlorides in the presence of anhydrous stannic chloride proceeded readily in benzene solution and provided *para*-acylated triphenylamines.

The Friedel–Crafts and other electrophilic substitution reactions of triphenylamine have been recently studied.[1-4] A consideration of the findings that the products were *para*-substituted derivatives led Baker, *et al.*,[4] to conclude that the *ortho* positions in triphenylamine were sterically hindered. However, a preliminary account[1] of the formation of 9,10-diphenyl-9-acridanol (**2a**) from triphenylamine and benzoic acid in polyphosphoric acid (PPA) indicated otherwise. This synthesis has now been developed and extended to provide a convenient new route to the little-known acridanols **2**, in which *ortho* acylation of triphenylamine features prominently.

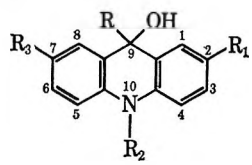
From equimolar amounts of triphenylamine and an aromatic acid in PPA at 120–125° for 0.5 hr, under which conditions rearrangement of *para*-acylated triphenylamines into acridanols did not occur (see below), the corresponding 9-aryl-10-phenyl-9-acridanol (**2**), essentially free of ketone impurity, was afforded in about 10% yield (Table I). The acid-soluble products were formulated as acridanol **2** on the basis of their properties, analysis, and infrared spectra; in several instances the assigned structures were confirmed by comparison with authentic material prepared from N-phenylacridone and the appropriate arylmagnesium bromide.[5]

Compensating for the poor yields of acridanol in the direct synthesis were the advantages of rapidity and apparent general applicability of the method, and the ease of isolation of the product, as compared with the procedure[5] utilizing Grignard reagents. However, not all aromatic acids were successfully employed in the new method, and 4-nitrobenzoic acid, for example, failed to yield acridanol. Glacial acetic acid gave a trace of what may have been the corresponding acridanol, but the reaction with aliphatic acids was not generally examined.

The direct synthesis, which resembles Popp's modification of the Bernthsen acridine reaction[6] with triphenylamine in place of diphenylamine, undoubtedly involves preliminary formation of 2-acyltriphenylamine as an intermediate. That such an *ortho* acylation is sterically feasible was demonstrated by forming 2,7-dimethyl-9-phenyl-10-(*p*-tolyl)-9-acridanol (**2m**) in nearly quantitative yield from 4,4′,4″-tritolylamine (**1h**) and benzoic acid in PPA. In support of the suggested intermediate, 2-benzoyltriphenylamine (**1a**) underwent facile and quantitative conversion into **2a** in PPA at 120°; this cyclization was effected also by anhydrous aluminum chloride, anhydrous stannic chloride, boron trifluoride etherate, and concentrated sulfuric acid.



1a, R = 2-C_6H_5CO; $R_1 = R_2$ = H
b, R = 3-C_6H_5CO; $R_1 = R_2$ = H
c, R = 4-C_6H_5CO; $R_1 = R_2$ = H
d, R = 2-C_6H_5CO; R_1 = 4′-C_6H_5CO; R_2 = H
e, R = 4-C_6H_5CO; R_1 = 4′-C_6H_5CO; R_2 = H
f, R = 2-C_6H_5CO; R_1 = 4′-C_6H_5CO; R_2 = 4″-C_6H_5CO
g, R = 4-C_6H_5CO; R_1 = 4′-C_6H_5CO; R_2 = 4″-C_6H_5CO
h, R = 4-CH_3; R_1 = 4′-CH_3; R_2 = 4″-CH_3
i, R = 2-C_6H_5CO; R_1 = 4′-CH_3; R_2 = 4″-CH_3
j, R = 3-C_6H_5CO; R_1 = 4′-CH_3; R_2 = 4″-CH_3
k, R = 4-*p*-$CH_3C_6H_4CO$; $R_1 = R_2$ = H
l, R = 4-*p*-$CH_3C_6H_4CO$; R_1 = 4′-*p*-$CH_3C_6H_4CO$; R_2 = H
m, R = 4-CH_3CO; $R_1 = R_2$ = H
n, R = 4-*n*-$C_5H_{11}CO$; $R_1 = R_2$ = H



2a, R = $R_2 = C_6H_5$; $R_1 = R_3$ = H
b, R = *o*-$CH_3C_6H_4$; $R_1 = R_3$ = H; $R_2 = C_6H_5$
c, R = *m*-$CH_3C_6H_4$; $R_1 = R_3$ = H; $R_2 = C_6H_5$
d, R = *p*-$CH_3C_6H_4$; $R_1 = R_3$ = H; $R_2 = C_6H_5$
e, R = *o*-BrC_6H_4; $R_1 = R_3$ = H; $R_2 = C_6H_5$
f, R = *m*-BrC_6H_4; $R_1 = R_3$ = H; $R_2 = C_6H_5$
g, R = *p*-BrC_6H_4; $R_1 = R_3$ = H; $R_2 = C_6H_5$
h, R = *o*-IC_6H_4; $R_1 = R_3$ = H; $R_2 = C_6H_5$
i, R = *p*-FC_6H_4; $R_1 = R_3$ = H; $R_2 = C_6H_5$
j, R = C_6H_5; $R_1 = R_3$ = H; R_2 = *p*-$C_6H_5COC_6H_4$
k, R = C_6H_5; $R_1 = C_6H_5CO$; R_2 = *p*-$C_6H_5COC_6H_4$; R_3 = H
l, R = C_6H_5; $R_1 = CH_3$; R_2 = *p*-$CH_3C_6H_4$; R_3 = H
m, R = C_6H_5; $R_1 = R_3 = CH_3$; R_2 = *p*-$CH_3C_6H_4$
n, R = *p*-$CH_3C_6H_4$; $R_1 = R_3$ = H; R_2 = *p*-$CH_3C_6H_4COC_6H_4$

In addition to acridanol **2a**, the acylation of triphenylamine with benzoic acid afforded an acid-insoluble mixture of unreacted triphenylamine, 4-benzoyltriphenylamine (**1c**), 4,4′-dibenzoyltriphenylamine (**1e**), and 4,4′,4″-tribenzoyltriphenylamine (**1g**); each acyl derivative was identified unequivocally by comparison with authentic material prepared by an appropriate

(1) B. Staskun, *J. Org. Chem.*, **29**, 2856 (1964).
(2) C. J. Fox and A. L. Johnson, *ibid.*, **29**, 3536 (1964).
(3) C. J. Fox and A. L. Johnson, *Makromol. Chem.*, **82**, 53 (1965).
(4) T. N. Baker, W. P. Doherty, W. S. Kelly, W. Newmeyer, J. E. Rogers, R. E. Spalding, and R. I. Walter, *J. Org. Chem.*, **30**, 3714 (1965).
(5) L. H. Cone, *J. Amer. Chem. Soc.*, **36**, 2101 (1914).
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TABLE I

DIRECT SYNTHESIS OF SUBSTITUTED 9-ACRIDANOLS (2) FROM TRIPHENYLAMINE (1.2 g, 0.005 mol)

Aromatic acid	Weight of aromatic acid, g	Molar ratio[a]	Reacn temp, °C	Method[b]	Acridanol product	Yield, %[c]	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
Benzoic	0.3	1:0.5	120–125	A		12[d,e]								
	0.6	1:1	120–125	A		12[d]								
	1.2	1:2	120–125	A		17[d]								
	2.4	1:4	120–125	A		17[d]	175–177[f]							
	0.3	1:0.5	155–160	A	**2a**[g]	34[d,e]								
	0.6	1:1	155–160	A		15–25[h]		$C_{26}H_{19}NO$	85.93	5.48	4.01	86.00	5.62	3.89
	0.6	1:1	155–160	B		23[d]								
	0.3	1:0.5	190–195	A		48[d,e]								
	0.6	1:1	190–195	A		25–35[h]								
	0.6	1:1	190–195	B		47[d]								
2-Toluic	0.35	1:0.5	160	A		35[d,e]								
	0.7	1:1	155–160	A	**2b**[g]	14[h]	191–192	$C_{26}H_{21}NO$	85.92	5.82	3.85	85.80	5.70	3.58
	0.7	1:1	160	B		28[d]								
3-Toluic	0.7	1:1	190	B	**2c**[g]	38[d]	143–144	$C_{26}H_{21}NO$	85.92	5.82	3.85	85.90	5.75	3.75
4-Toluic	0.7	1:1	120–125	A		10[d]								
	0.7	1:1	155–160	A	**2d**[g]	25[g]	174–176	$C_{26}H_{21}NO$	85.92	5.82	3.85	85.81	5.91	3.75
	0.35	1:0.5	190	A		48[d,e]								
	0.7	1:1	190	B		45–50[d]								
2-Bromobenzoic	1.0	1:1	160	A		12[d]								
	1.0	1:1	195	A	**2e**	26[d]	187–189	$C_{26}H_{18}BrNO$	70.10	4.23	3.27	70.30	4.23	3.38
	1.0	1:1	190	B		22[d]								
3-Bromobenzoic	1.0	1:1	195	B	**2f**	23[d]	*i*	$C_{26}H_{18}BrNO$						
4-Bromobenzoic	1.0	1:1	120–125	A	**2g**	7[d]	197–199	$C_{26}H_{18}BrNO$	70.10	4.23	3.27	70.11	4.23	3.34
	1.0	1:1	190	B		19[d]								
2-Iodobenzoic	1.2	1:1	190	B	**2h**	9[d]	200–203	$C_{26}H_{18}INO$	63.17	3.82	2.95	63.15	3.94	2.87
4-Fluorobenzoic	0.7	1:1	120–125	A		10[d]								
	0.7	1:1	190–195	A	**2i**	15[h]	176–179	$C_{26}H_{18}FNO$	81.72	4.94	3.81	81.33	4.96	3.69
	0.7	1:1	190	B		21[d]								

[a] Triphenylamine/aromatic acid. [b] Method A, reactants were stirred together in PPA (10 g) for 0.5 hr. Method B, aromatic acid was added portionwise over 0.25 hr to a solution of amine in PPA and stirring was continued for an additional 0.25 hr. [c] Crude acridanol. [d] Negligible ketone impurity present. [e] Yield based on aromatic acid. [f] Lit.[5] mp 178°. [g] Structure established by comparison with product of Cone[5] synthesis. [h] Product contaminated with acylated acridanol; purification proved troublesome and required a number of recrystallizations. [i] Acridanol not purified.

TABLE II

SUBSTITUTED TRIPHENYLAMINES (1) PREPARED BY ULLMANN REACTION

Reactants[a] (weight, g)	Yield, %[b]	Product	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
Diphenylamine (1[c]), 2-iodobenzophenone (1.5)	40	**1a**	127–128	$C_{25}H_{19}NO$	85.93	5.48	4.01	85.87	5.42	4.11
Diphenylamine (1[c]), 3-iodobenzophenone (1.5)	40	**1b**	139–140	$C_{25}H_{19}NO$	85.93	5.48	4.01	85.82	5.54	4.29
Diphenylamine (1[c]), 4-iodobenzophenone (1.5)	60	**1c**	127–128	$C_{25}H_{19}NO$	85.93	5.48	4.01	85.74	5.69	4.20
4,4′-Dibenzoyldiphenylamine (0.3), iodobenzene (0.7[c])	50	**1e**	143–144	$C_{32}H_{23}NO_2$	(81.50	5.34	2.97)[d]	81.83	5.40	3.31
4,4′-Dibenzoyldiphenylamine (1.2), 2-iodobenzophenone (1.5[c])	70	**1f**	150–151	$C_{39}H_{27}NO_3$	84.00	4.88	2.51	84.07	4.91	2.61
4,4′-Dibenzoyldiphenylamine (0.8), 4-iodobenzophenone (1.5[c])	50	**1g**	176–177[e]	$C_{39}H_{27}NO_3$	84.00	4.88	2.51	83.98	4.83	2.69
4,4′-Ditolylamine (1), 4-iodotoluene (1.1)	20	**1h**	115–116[f]	$C_{21}H_{21}N$	87.76	7.37	4.87	87.84	7.41	4.82
4,4′-Ditolylamine (1), 2-iodobenzophenone (1.5)	50	**1i**	140	$C_{27}H_{23}NO$	85.91	6.14	3.71	85.66	6.15	3.88
4,4′-Ditolylamine (1), 3-iodobenzophenone (1.5)	50	**1j**	105–107	$C_{27}H_{23}NO$	85.91	6.14	3.71	85.89	6.20	3.51
Aniline (5[c]), 4-iodobenzophenone (1.5)	30	*g*	148–149	$C_{19}H_{15}NO$	83.49	5.53	5.13	83.51	5.58	5.22

[a] Amine, iodo compound. [b] Pure compound; recrystallizations from aqueous acetone. The crude yields are not maximal and improvements may well be possible. All the products were obtained as yellow crystals, except 4-benzoyltriphenylamine (**1c**, colorless) and 4,4′,4″-tritolylamine (**1h**, buff). [c] Excess of reactant. [d] Calcd for $C_{32}H_{23}NO_2 \cdot H_2O$. Compound **1e** crystallized from aqueous acetone as the monohydrate, mp 143–144°, as was indicated by analysis and by the (weak) absorption at 2.70 and 2.77 μ in the infrared spectrum. [e] Lit.[2] mp 173.5–175.5°. [f] H. Wieland [*Ber.*, **40**, 4279 (1907)] reports mp 117°. [g] 4-Benzoyldiphenylamine.

Ullmann[7] reaction (Table II). The composition of the acid-insoluble product varied with the molar ratio of reactants employed. Thus, with benzoic acid in large excess (4:1), 4,4′,4″-tribenzoyltriphenylamine (**1g**), was obtained in 80% yield [together with **2a** in improved and apparently maximal yield (17%)]; this is a much more convenient preparation of **1g** than that from benzoyl chloride and aluminum chloride.[2]

When the synthesis of acridanol 2a from equimolar amounts of reactants was conducted at 160 and 190°, the yield of acid-soluble product was increased, but this now showed (weak–medium) carbonyl absorption in the infrared and was, as found subsequently, contaminated with C-acylated acridanol. Certain other aromatic acids, however, furnished the acridanol **2** virtually free of ketone impurity, even at these elevated reaction temperatures (Table I).

That the C-acylated acridanols were not derived by nuclear acylation of acridanol **2** was shown by recovering acridanol **2a** unchanged after treatment with benzoic acid in PPA at 190°. Their presence became explicable when it was found that certain of the *para*-acylated triphenylamines could be transformed by PPA into acylated acridanols.

A variety of pure acylated triphenylamines were treated with PPA at 190–195° for 0.5 hr with the following results; other observations pertaining to a mechanism are included.

(7) F. Ullmann, *Ber.*, **36**, 2382 (1903).

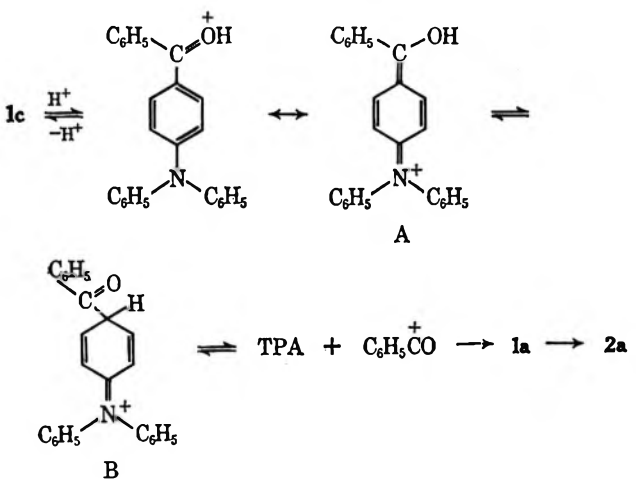
4-Benzoyltriphenylamine (**1c**), although unaffected at 120–125°, was rearranged at the higher reaction temperature into 9,10-diphenyl-9-acridanol (**2a**) in 45% yield; also formed was triphenylamine and other material of unknown constitution. 4-(*p*-Toluoyl)triphenylamine (**1k**) likewise afforded 9-(*p*-tolyl)-10-phenyl-9-acridanol (**2d**) in 55% yield. It was of preparative and mechanistic significance that the acridanols derived in this manner were contaminated with minor amounts only of ketone impurity. In support of an intermolecular process, reaction **1c** → **2a** when conducted in the presence of 4,4′,4″-tritolylamine (**1h**) gave acridanol **2a** together with 2,7-dimethyl-9-phenyl-10-(*p*-tolyl)-9-acridanol (**2m**).

Nuclear-acylated acridanols were obtained on subjecting *p*-di-and triacylated triphenylamines to the action of PPA at 190–195° for 0.5 hr. Thus, 4,4′-dibenzoyltriphenylamine (**1e**) was converted (50%) into a mixture of acridanol **2a** and 10-(*p*-benzoylphenyl)-9-phenyl-9-acridanol (**2j**); benzoic acid sublimed during reaction; its presence was indicative of an intermolecular process. The acid was liberated also when 4,4′,4″-tribenzoyltriphenylamine (**1g**) was transformed (40%) into acridanol **2j** and 2-benzoyl-10-(*p*-benzoylphenyl)-9-phenyl-9-acridanol (**2k**). The products **2j** and **2k** were identified by comparison with samples derived by cyclization of the appropriate 2-benzoyltriphenylamine in PPA or concentrated sulfuric acid. In this respect, the reaction of 2,4′,4″-tribenzoyltriphenylamine (**1f**), to give acridanol **2k**, which involved electrophilic attack on a deactivated nucleus, was noticeably slow compared with that of 2-benzoyltriphenylamine (**1a**) under similar conditions.

Although the acyl groups in 4,4′,4″-tribenzoyltriphenylamine (**1g**) were not sterically hindered, the compound nevertheless suffered extensive deacylation in PPA at 190° (*cf.* Balaban, *et al.*[8]) as was demonstrated by heating in the presence of excess triphenylamine to give 9,10-diphenyl-9-acridanol (**2a**) as the sole acid-soluble product of reaction.

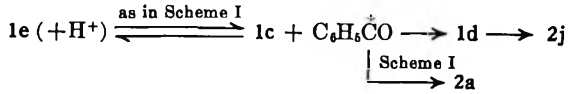
The above observations and results may be rationalized in terms of the tentative intermolecular processes assumed to occur at 190–195° and depicted in Schemes I (**1c** → **2a**), II (**1e** → **2a** + **2j**), and III (**1g** → **2j** + **2k**).

SCHEME I

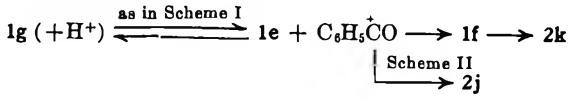


(8) M. Frangopol, A. Genunche, N. Negoita, P. T. Frangopol, and A. T. Balaban, *Tetrahedron*, **23**, 841 (1967).

SCHEME II



SCHEME III

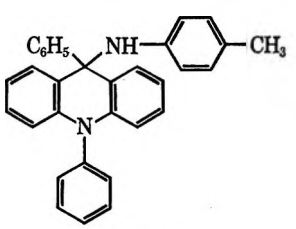


4-Benzoyltriphenylamine (**1c**) and benzoic acid in PPA at 120–125°, however, gave the *para*-acylated derivatives **1e** and **1g**, and negligible acridanol **2j** (and thus **1d**); competitive *ortho* acylation is inhibited presumably because of the proximity to the reaction site of the positively polarized N atom. The production of acridanol **2j** *via* **1c** as in Scheme II may become feasible at 190° if **1c** is less extensively protonated at the higher temperature.

It is noteworthy that the *meta*-acylated bases, *viz.*, 3-benzoyltriphenylamine (**1b**) and 3-benzoyl-4′,4″-dimethyltriphenylamine (**1j**), failed to rearrange into acridanols in PPA at 190–195; in this respect it is significant that these substances are incapable of providing structural contributions analogous to A and B (Scheme I).

In the light of the behavior of the various *para*-acylated triphenylamines in PPA, a modified procedure for acylating triphenylamine with aromatic acids was adopted and led to improved yields (10–50%, depending on the nature of the aromatic acid) of acridanol **2** practically free of ketone impurity (Table I). Thus, addition portionwise, of benzoic acid to a solution of an equimolar amount of triphenylamine in PPA at 190–195°, gave acridanol **2a** in 47% yield. A similar improvement was achieved more conveniently by mixing the amine and benzoic acid in the molar ratio 2:1 and heating with PPA. In these reactions triphenylamine, the least deactivated and hence most reactive substrate competing for acylium ion, $RC\overset{+}{O}$, was present in excess throughout, with the result that those processes giving rise to C-acylated acridanols (Schemes II and III) were effectively curtailed; moreover, the yield of product was augmented by rearrangement of 4-benzoyltriphenylamine (**1c**) under the reaction conditions prevailing.

When treated with 4-toluidine in PPA acridanol **2a** was converted into what appeared to be 9,10-diphenyl-9-*p*-tolylaminoacridan (**3**).



3

The facility with which triphenylamine undergoes electrophilic substitution has been noted.[1,2,4] It is possible in fact to acylate the amine with acid anhydrides and acid chlorides using benzene as the solvent. Refluxing a benzene solution of equimolar amounts of triphenylamine and benzoic anhydride (or benzoyl chloride) and excess anhydrous stannic chloride for 1 hr, for

TABLE III

ACYLATION OF TRIPHENYLAMINE (1.2 g, 0.005 mol) IN BENZENE SOLVENT (15 ml)

Acylating agent	Lewis acid	Molar ratio of reactants[a]	Reaction products[b] (yield, %)[c]
Benzoyl chloride	Anhydrous stannic chloride	1:1.05:4	TPA[d] (~15), 1c (70), 1e (<5), 1g (negligible)
		1:2.4:8	TPA (negligible), 1c (small), 1e (~40), 1g (~25)
4-Toluoyl chloride		1:1:4	TPA (25), 1k[e] (65)
Benzoic anhydride		1:1.1:8	TPA (5), 1c (69), 1e (6), 1g (<5), 2a (<5)
		1:3.3:12	TPA (negligible), 1c (negligible), 1e (~50), 1g (~20)
n-Hexanoic anhydride		1:1.1:4	1n[f] (60)
Acetic anhydride		1:1.1:4	1m[g] (65)
Benzoyl chloride	Anhydrous aluminum chloride		
		1:1:2.7	TPA (~40), 1c (~15), 1e (~15)
		1:4:4.5	TPA (~10), 1c + 1e (small), 1g (65–70)
4-Toluoyl chloride		1:2.2:2.5	TPA (negligible), 1k (~3), 1l[h] (>30)

[a] Triphenylamine/acylating agent/Lewis acid. [b] Separated on a silica gel column; identity confirmed by comparison with Ullmann product (Table II). [c] Crude yield reported, based on triphenylamine. [d] Triphenylamine. [e] Pale yellow crystals from aqueous acetone, mp 92–93°. *Anal.* Calcd for $C_{26}H_{21}NO$: C, 85.92; H, 5.82; N, 3.85. Found: C, 85.63; H, 5.72; N, 3.76. [f] Colorless, viscous gum, bp 200–209 (0.1 mm) [lit.[2] bp 230–235° (0.5 mm)]. *Anal.* Calcd for $C_{24}H_{25}NO$: C, 83.92; H, 7.34; N, 4.08. Found: C, 84.05; H, 7.32; N, 4.03. [g] Colorless crystals from aqueous acetone, mp 143–144° (lit.[2] mp 142–143°). [h] Yellow crystals from aqueous acetone, mp 205–206°. *Anal.* Calcd for $C_{34}H_{27}NO_2$: C, 84.79; H, 5.65; N, 2.91. Found: C, 84.47; H, 5.70; N, 2.91.

example, afforded 4-benzoyltriphenylamine (**1c**) in 70% yield. This method was likewise successful for other *para*-monoacylated triphenylamines (Table III). Utilization of an excess of benzoyl chloride in the presence of anhydrous aluminum chloride under similar conditions, led to 4,4′,4″-tribenzoyltriphenylamine (**1g**) in ~70% yield. Products containing a high proportion of *para*-diacylated triphenylamine resulted from use of other molar proportions of reactants (Table III).

Experimental Section[9]

Direct Synthesis of 9-Aryl-10-phenyl-9-acridanols (2) from Triphenylamine and Aromatic Acids (Table I). General Procedure.—Equimolar amounts of triphenylamine (1.2 g, 0.005 mol) and aromatic acid were stirred together with PPA (10 g, Riedel-de Haën) at 120–125° for 0.5 hr. After cooling and addition of water (~50 ml), acid-insoluble material A was removed, and the (charcoaled) filtrate made alkaline with 5 *N* sodium hydroxide to deposit acridanol **2** (7–12%; negligible carbonyl absorption at 6.0–6.05 μ in the infrared), which was purified by reprecipitation from dilute hydrochloric acid and subsequent recrystallization from either aqueous acetone, aqueous pyridine, or petroleum ether (bp 80–100°). A mixture of **2** and nuclear-acylated acridanol resulted from reaction at 160 or 190° (Table I).

Improved yields of acridanol **2**, likewise virtually free of ketone impurity, were afforded (i) by stirring triphenylamine (1.2 g) and aromatic acid in the molar ratio 2:1, with PPA (10 g) at 190–195° for 0.5 hr, and also (ii) by adding the aromatic acid portionwise over a period of 0.25 hr to a stirred solution of an equimolar amount of triphenylamine (1.2 g) in PPA (10 g) at 190–195° and continuing the heating for an additional 0.25 hr.

Details of the synthesis performed under a variety of conditions as well as other relevant data are given in Table I.

The acridanols **2** dissolved readily in dilute mineral acids and in dilute acetic acid and formed green solutions which exhibited a striking "Flourescein"-like fluorescence in ordinary light. The infrared spectra of the acridanols **2** (listed in Table I) and compounds **2l** and **2m** were very similar in the 2.7–8.6-μ region and all showed sharp peaks at or near 2.80 (m) (OH stretching), 6.20 (s) (medium peak in **2m**), 6.60 (m), 6.70 (s), 6.85 (s), 7.40 (s), 7.60 (m), 7.80 (m–s), 8.60 (m), and 9.7–9.8 (s) μ. The mass spectra of the acridanols **2** (**2a**, **c**, and **m**) all showed a parent peak M, and peaks at M − OH, M − R, and (M − OH − R + 1).

Examination (tlc[9]) of the acid-insoluble material A above, derived from benzoic acid, showed it to contain triphenylamine, 4-benzoyltriphenylamine (**1c**), 4,4′-dibenzoyltriphenylamine (**1e**), 4,4′,4″-tribenzoyltriphenylamine (**1g**), and other (uncharacterized) compounds. When acid-insoluble A (1.4 g) was dissolved in a minimal amount of benzene and chromatographed on silica gel (30 g) with benzene as the eluent, it afforded triphenylamine (fraction 1, purple fluorescence[9]), 0.48 g (40% recovery); compound **1c** (fraction 2, blue fluorescence), 0.30 g (~17%); compound **1e** (fraction 3, blue-purple fluorescence), 0.30 g (~15%); and compound **1g** (fraction 4, blue-purple fluorescence), 0.10 (~4%). The latter (base **1g**) could be readily eluted from the column by means of benzene–acetone (20:1).

With increase of benzoic acid in the acylation the content of di- and triacylated derivatives **1e** and **1g** in the acid-insoluble product A was enhanced at the expense of triphenylamine and compound **1c**. Treatment of triphenylamine (1.2 g) with a 4 *M* proportion of benzoic acid (2.4 g) in PPA (10 g) at 120–125° for 0.5 hr, gave, in addition to acridanol **2a** (0.30 g, 17%), crude 4,4′,4″-tribenzoyltriphenylamine (**1g**, 2.3 g, 80%) contaminated (tlc) by a small amount of compound **1e** and free of triphenylamine and base **1c**.

2,7-Dimethyl-9-phenyl-10-(*p*-tolyl)-9-acridanol (**2m**) was prepared by stirring 4,4′,4″-tritolylamine (**1h**, 0.25 g) with excess benzoic acid (0.15 g) in PPA (5 g) at 110–130° for 0.5 hr. After addition of water, the mixture was filtered, and the green fluorescent solution was made alkaline to deposit acridanol **2m** (0.30 g, ~90%). Recrystallization of this from aqueous acetone gave colorless crystals, mp 149–150°.

Anal. Calcd for $C_{28}H_{25}NO$: C, 85.90; H, 6.44; N, 3.58. Found: C, 85.74; H, 6.49; N, 3.53.

9,10-Diphenyl-9-(*p*-tolylamino)acridan (**3**).—Acridanol **2a** (0.2 g) was reacted with an excess of 4-toluidine (0.2 g) in PPA (4 g) at 120–125° for 0.5 hr. Addition of water afforded a yellow-green fluorescent solution; this was filtered from negligible insoluble impurity and made alkaline to deposit crude **3** contaminated with 4-toluidine. Recrystallization from aqueous acetone gave colorless crystals, mp 199–201°, soluble in dilute mineral acid affording a green fluorescent solution.

Anal. Calcd for $C_{32}H_{26}N_2$: C, 87.63; H, 5.98; N, 6.39. Found: C, 87.05; H, 5.92; N, 6.14.

The infrared spectrum of **3** revealed acridanol **2a** to be absent and displayed a weak absorption at 2.95 (NH stretching) and a medium peak at 12.2 μ (*para* substitution).

Preparation of Substituted Triphenylamines by the Ullmann Reaction (Table II).—The general procedure is illustrated for 2-benzoyltriphenylamine (**1a**). A mixture of diphenylamine (1 g, excess), 2-iodobenzophenone (1.5 g), anhydrous potassium carbonate (0.8 g), and copper powder (50 mg) in nitrobenzene (10 ml) was refluxed for 5–6 hr. After removal of the solvent by steam distillation, the insoluble residue was extracted with benzene and the dried, concentrated extract was chromatographed on silica gel (40 g) using benzene as the eluent. A

(9) Melting points are uncorrected. Infrared spectra consistent with the proposed structures were obtained for all new compounds and were recorded on a Perkin-Elmer Infracord Model 137 spectrophotometer using a 1-mg sample per 300 mg of potassium bromide. Mass spectra were determined from an AEI Model MS-9 mass spectrometer (70 eV). Thin layer chromatography (tlc) was carried out with silica gel G; the mobile phase was benzene containing 1% acetone, and spots were located by visual inspection and/or by their fluorescence in ultraviolet light (350 mμ). Column chromatography was performed with silica gel (Kieselgel, Merck; 0.05–0.20 mm) used without pretreatment; the progress of the separations was followed in ultraviolet light (350 mμ).

fraction with a strong yellow fluorescence[9] was evaporated to afford crude **1a**, recrystallized as yellow crystals from aqueous acetone, mp 127–128°.

Details of the various acylations are collected in Table II.

4,4′-Dibenzoyldiphenylamine.—Ullmann reaction of 4-iodobenzophenone (1.5 g) with 4-aminobenzophenone (1.2 g, excess) as above gave, after removal of nitrobenzene solvent, a dark brown insoluble product. This was extracted successively with 2 *N* hydrochloric acid and with methanol to remove undesirable material, and the residue of 4,4′-dibenzoyldiphenylamine (1 g, ~54%) was recrystallized from 90% (v/v) acetic acid; the pale green crystals, mp 241–242°, were identical (mixture melting point and infrared spectrum) with those from the acylation of diphenylamine with benzoic acid in PPA.[1]

Acylation of Triphenylamine in Benzene Solution (Table III).—The following preparation illustrates the general procedure. A solution of triphenylamine (1.2 g, 0.005 mol) and benzoic anhydride (1.25 g, 0.0055 mol) in benzene (15 ml) was treated with anhydrous stannic chloride (10.5 g, 0.04 mol) and refluxed for 1 hr during which period hydrogen chloride was evolved and some crystalline material separated. Water and benzene were added and a substance B, sparingly soluble in both the aqueous and organic phases, was filtered off. The benzene layer (~50 ml) was washed with 2 *N* sodium hydroxide and water, dried (anhydrous magnesium sulfate), concentrated (rotary evaporator), and chromatographed[9] on silica gel (30 g) using benzene as the eluent to afford the following products (crude yield): triphenylamine (0.06 g, 5%), **1c** (1.2 g, 69%), **1e** (0.14 g, 6%), and **1g** (<0.1 g).

Product B above appeared to be a complex of acridanol **2a** and $SnCl_4$ (or H_2SnCl_6) (see below) and dissolvedg radually on warming with 1 *N* hydrochloric acid; addition of alkali to the green fluorescent solution gave acridanol **2a** (0.06 g, 4%) identified by its infrared spectrum.

Other acid anhydrides and also acid chlorides were treated similarly with triphenylamine in the presence of anhydrous stannic chloride or anhydrous aluminum chloride, and the relevant details and results are shown in Table III.

Formation of 9-Acridanols by Cyclization of 2-Benzoyltriphenylamines. 9,10-Diphenyl-9-acridanol (2a).—The crude product, obtained in methods A–E below, was in each case identified as acridanol **2a** by its infrared spectrum.

A.—2-Benzoyltriphenylamine (**1a**, 0.2 g) dissolved readily in concentrated sulfuric acid (1.5 ml) with an exothermic effect, and a green fluorescent solution was obtained instantly. After remaining at ~20° for 0.5 hr, this was poured into water and the solution made alkaline to deposit crude acridanol **2a** in quantitative yield (0.2 g).

B.—Compound **1a** (0.3 g) and anhydrous aluminum chloride (0.4 g) were intimately mixed and heated at ~120°; a vigorous reaction set in with evolution of hydrogen chloride and yellow fumes. The temperature was kept at 120–140° for 5 min, warm 1 *N* acid HCl was added, and the filtered solution made alkaline to furnish acridanol **2a** in quantitative yield (0.29 g).

C.—2-Benzoyltriphenylamine (**1a**, 0.1 g) was stirred with PPA (2 g) at 110–120° for 20 min. The mixture was treated with water and the solution was basified to give acridanol **2a** (0.09 g, ~90%). When conducted at 20° for 0.5 hr, the reaction led to acridanol **2a** in ~20% yield.

D.—Addition of boron trifluoride etherate (2 ml) to amine **1a** (0.2 g) resulted in a green fluorescent solution. After 0.5 hr, this was treated with water which caused a yellow solid to deposit. The ether was evaporated and the insoluble material (suspected of being a complex of acridanol **2a** and HBF_4 or BF_3) was warmed with hot 2 *N* hydrochloric acid until dissolved; basification of the solution yielded acridanol **2a** (0.18 g, ~90%). A similar sparingly soluble complex was precipitated on addition of an aqueous solution of $NaBF_4$ to a solution of acridanol **2a** in 2 *N* hydrochloric acid.

E.—A solution of amine **1a** (0.1 g) in anhydrous stannic chloride (2 ml, excess) after remaining at ~20° for 1 hr was poured into 1 *N* hydrochloric acid to afford a yellow fluorescent mixture with much insoluble material. The latter was filtered off and warmed with 1 *N* hydrochloric acid when it dissolved; basification of the solution gave acridanol **2a** (~50%). A similar complex was deposited on mixing together 1 *N* hydrochloric acid solutions of acridanol **2a** and stannic chloride.

2-Methyl-9-phenyl-10-(*p*-tolyl)-9-acridanol (2l).—2-Benzoyl-4′,4″-dimethyltriphenylamine (**1i**, 0.5 g) dissolved readily in concentrated sulfuric acid (4 ml) with an exothermic effect. After 0.25 hr at ~20°, water was added and the green fluorescent solution basified to give crude **2l** (0.48 g, ~95%) which was recrystallized as colorless crystals from aqueous acetone, mp 139–140°.

Anal. Calcd for $C_{27}H_{23}NO$: C, 85.91; H, 6.14; N, 3.71. Found: C, 86.04; H, 6.16; N, 3.74.

Formation of 9-Acridanols by Rearrangement of 4-Acylated Triphenylamines. 9,10-Diphenyl-9-acridanol (2a).—4-Benzoyltriphenylamine (**1c**, 1.0 g) was stirred with PPA (10 g) at 190–195° for 0.5 hr and the mixture was treated with water. Acid-insoluble material C (0.5 g) was removed, and the green fluorescent filtrate was made alkaline to deposit acridanol **2a** (0.45 g, 45%; negligible carbonyl absorption) identified by its infrared spectrum. Product C was a mixture (tlc) of triphenylamine, trace amounts of bases **1c** and **1e**, and other substances (unidentified). The conversion into **2a** was less (15–20%) at 155–160°, and negligible at 120–125°.

10-Phenyl-9-(*p*-tolyl)-9-acridanol (2d) was formed (0.38 g, 55%) virtually free of ketone impurity, from 4-*p*-toluoyltriphenylamine (**1k**, 0.7 g) and PPA (7 g) at 190–195° for 0.5 hr, and was identical (infrared spectrum) with acridanol **2d** derived from *p*-tolylmagnesium bromide and N-phenylacridone.

Under similar conditions 3-benzoyltriphenylamine (**1b**) and 3-benzoyl-4′,4″-dimethyltriphenylamine (**1j**) were each converted into an acid- and alkali-insoluble solid which showed weak carbonyl absorption in the infrared spectrum. A trace of suspected acridanol was formed from **1j** (as evidenced by the green fluorescence of the acid reaction solution).

4-Acetyltriphenylamine (**1m**) decomposed to an acid- and alkali-insoluble charcoal-like product; treatment with PPA at 140° for 0.5 hr afforded much unchanged **1m** and a trace of acridanol. An excess of anhydrous aluminum chloride (0.5 g) acting on 4-benzoyltriphenylamine (**1c**, 0.5 g) at 190° for 0.5 hr failed to yield acridanol **2a**; the acid-insoluble product (0.45 g) obtained after addition of water was a mixture (tlc) of triphenylamine, base **1c** (and perhaps **1e**), and other material (unidentified).

Equimolar amounts of amine **1c** (0.35 g) and benzoic acid (0.12 g) in PPA (4 g) were stirred at 120–125° for 0.5 hr. Addition of water afforded an acid-insoluble mixture (tlc) of compounds **1e** and **1g**, while the green fluorescent filtrate contained negligible base.

Intermolecularity of the Amine 1c → Acridanol 2a Rearrangement.—A mixture of 4-benzoyltriphenylamine (**1c**, 0.1 g) and 4,4′,4″-tritolylamine (**1h**, 0.05 g) in PPA (2 g) reacted at 195–200° for 0.5 hr to furnish ~50 mg of acid-soluble base. This was found (infrared and mass spectra) to consist of acridanol **2a** together with 2,7-dimethyl-9-phenyl-10-(*p*-tolyl)-9-acridanol (**2m**).

Formation of Acylated Acridanols by Rearrangement of Di- and Triacylated Triphenylamines. 10-(*p*-Benzoylphenyl)-9-phenyl-9-acridanol (2j).—4,4′-Dibenzoyltriphenylamine (**1e**, 0.8 g, free of mono- and tribenzoyltriphenylamine impurity by tlc) was stirred with PPA (15 g) at 190–195° for 0.5 hr, during which period a trace of benzoic acid (identified by its infrared spectrum) sublimed. After cooling and addition of water, insoluble material D (0.4 g; tlc showed negligible base **1e** present) was removed, and the filtrate was made alkaline to afford a buff-colored product (0.3 g) composed (infrared and mass spectra) of acridanols **2a** and **2j**. The solution of product D in glacial acetic acid (5 ml) was diluted with 1 *N* hydrochloric acid, the mixture was filtered hot (charcoal), and the green fluorescent filtrate was made alkaline to deposit crude **2j**. This was purified by reprecipitation from its (charcoaled) benzene solution with petroleum ether (bp 80–100°) and proved to be indentical (infrared spectrum) with acridanol **2j** prepared as follows. The Ullmann reaction of 4-benzoyldiphenylamine (0.05 g, Table II) with 2-iodobenzophenone (0.2 g, excess) as before gave, after removal of nitrobenzene, crude 2,4′-dibenzoyltriphenylamine (**1d**) which was warmed (90°) with concentrated sulfuric acid (1 ml) for 0.5 hr. Addition of water and filtration of the hot (charcoaled) mixture gave a green fluorescent solution, from which was obtained acridanol **2j** characterized by spectral analysis. Infrared absorption was at 2.85 (m) (OH stretching) and 6.0 μ (s) (CO stretching), and the spectrum which was similar to that of acridanol **2k** (see below) could be distinguished from the latter by comparison of the relative intensities of the respective absorptions at 6.85, 7.4–7.8, 13.0, and 13.85 μ. The mass spectrum (70 eV) showed a weak parent peak at *m/e* 453, a medium peak at *m/e* 436 (M − OH), a medium peak at *m/e* 376 (M − C_6H_5), and a base peak at *m/e* 360 (M − OH − C_6H_5 + 1).

2-Benzoyl-10-(*p*-benzoylphenyl)-9-phenyl-9-acridanol (2k).—4,4′,4″-Tribenzoyltriphenylamine [1g, free (tlc) of mono- and dibenzoytriphenylamine impurity] was stirred with PPA (20 g) at 190–195° for 0.5 hr; a small amount of benzoic acid (identified by its infrared spectrum) sublimed. After cooling, water (~50 ml) was added, acid-insoluble material E (0.6–0.7 g, tlc showed negligible base 1g) was removed, and the filtrate was made alkaline to deposit a pale yellow solid (0.2 g) shown by its infrared and mass spectra to be a mixture of acridanols 2j and 2k. Product E was dissolved in glacial acetic acid (5 ml) and treated as for D above to provide crude acridanol 2k (0.2 g) which was purified by dissolving in benzene and adding petroleum ether (bp 80–100°) to afford a buff-colored solid, mp 115–120°.

Anal. Calcd for $C_{39}H_{27}NO_3 \cdot H_2O$: C, 81.37; H, 5.08; N, 2.43. Found: C, 81.70; H, 5.31; N, 2.46.

The mass spectrum showed a very weak parent peak at *m/e* 557, a weak peak at *m/e* 540 (M − OH), a weak peak at *m/e* 481 (M − C_6H_5 +1), a weak peak at *m/e* 464 (M − OH − C_6H_5 + 1), a base peak at *m/e* 436 (M − OH − C_6H_5CO + 1), and a medium peak at *m/e* 360 (M − OH − $C_6H_5COC_6H_4$ + 1).

A sample of acridanol 2k was prepared unambiguously by cyclization of 2,4′,4″-tribenzoyltriphenylamine (1f, 0.15 g) with PPA (5 g) at 120–125° for 0.5 hr. Addition of water (~100 ml) to the orange fluorescent solution gave a sparingly soluble gum which was separated by decantation and dissolved in glacial acetic acid (5 ml). The acid solutions were combined, warmed to dissolve the sparingly soluble acridanol 2k, filtered hot (charcoal), and made alkaline to afford crude 2k (0.18, ~70%) which was identical (infrared and mass spectra) with the rearrangement product of 1g. In concentrated sulfuric acid (1 ml) conversion of amine 1f (0.2 g) into acridanol 2k proceeded very slowly at 20° compared with the conversion amines 1c and 1i; reaction at 90° for 1 hr afforded base 2k in ~20% yield.

Deacylation of 4,4′,4″-Tribenzoyltriphenylamine (1g).—A mixture of the amine (1g, 0.3 g) and excess of triphenylamine (1 g) in PPA (10 g) was stirred at 190° for 0.5 hr. After addition of water and removal of acid-insoluble material, the green fluorescent filtrate was made alkaline to give 9,10-diphenyl-9-acridanol (2a, 0.25 g, 45% yield, based on complete deacylation of amine 1g) which showed no carbonyl absorption in its infrared spectrum.

Registry No.—1a, 16911-31-2; 1b, 16911-32-3; 1c, 16911-33-4; 1e, 16911-34-5; 1f, 16911-35-6; 1g, 1183-66-0; 1h, 1159-53-1; 1i, 16959-98-1; 1j, 16959-99-2; 4-benzoyldiphenylamine, 4058-17-7; 2a, 16911-37-8; 2b, 16911-38-9; 2c, 16911-39-0; 2d, 16911-40-3; 2e, 16960-00-2; 2f, 16960-01-3; 2g, 16911-41-4; 2h, 16911-42-5; 2i, 16911-43-6; 2j, 16911-44-7; 2k, 16911-45-8; 2l, 16911-46-9; 2m, 16911-47-0; 3, 16911-48-1; triphenylamine, 603-34-9.

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The Reaction of Chlorosulfonyl Isocyanate with Allenes and Olefins[1-3]

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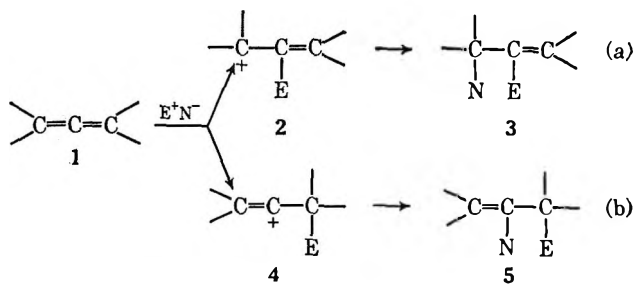
The addition of chlorosulfonyl isocyanate to allenes (2,4-dimethyl-2,3-pentadiene, 2-methyl-2,3-pentadiene, 2,3-pentadiene, 3-methyl-1,2-butadiene, pentamethyleneallene, 1,3-diphenylpropadiene, phenylpropadiene, and cyclononadiene) has been studied. In all cases, initial electrophilic attack occurred at the central carbon atom of the allenic system to produce, in the transition state, an allyl-type stabilized carbonium ion. Structures of the N-chlorosulfonyl-β-lactam cycloadducts and/or 2-carboxamido-1,3-butadiene products have been established on the basis of nmr spectroscopy and conversion into authentic derivatives prepared independently by the reaction of chlorosulfonyl isocyanate with the appropriate olefin. In the case of 3-methyl-1,2-butadiene, a third product identified by degradation and synthesis as 1-chlorosulfonyl-1-(2-carboxy-3-methyl-2-butenyl)urea was obtained. Chlorosulfonyl isocyanate added stereospecifically to *cis*- and *trans*-β-methylstyrene to lead to the *cis*- and *trans*-β-lactam, respectively, hydrolysis of which led to *erythro*- and *threo*-3-amino-2-methyl-3-phenylpropanoic acid hydrochloride. This experimentally determined relationship permitted assignment of the geometry of a number of β-lactam, carboxamido-1,3-butadiene, and amino acid products.

With a few exceptions, the principal mode of electrophilic (E^+) addition to cyclic and 1,3-disubstituted, straight-chain allenes has been *via* path a, while allene itself and monosubstituted allenes react predominantly *via* the vinyl carbonium (4) route (path b).[4] Attack by the nucleophile (N^-) on carbonium ions 2



and 4 complete the reaction to observed products 3 and 5, respectively.

Recently we reported that the stepwise 1,2-dipolar cycloaddition of chlorosulfonyl isocyante (CSI) to allenes [2,4-dimethyl-2,3-pentadiene (6a), 3-methyl-1,2-butadiene (6d), pentamethyleneallene (6e) and 1,2-cyclononadiene (6h)] proceeded *via* path a to produce initially, in the transition state, an allyl-type stabilized carbonium ion (7) leading ultimately to β-lactams (8, 9) and/or from the aqueous extract, 2-carboxamido-1,3-

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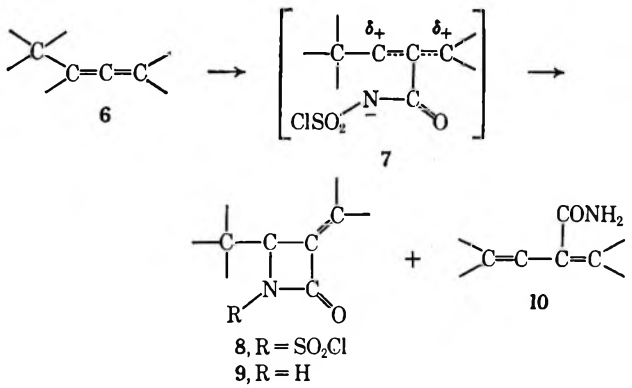
(2) Presented in part before the Organic Division, 151st National Meeting of the American Chemical Society, Pittsburgh, Pa., March 1966, Abstracts, p K76, and at the First International Congress of Heterocyclic Chemistry, the University of New Mexico, Albuquerque, N. M., June 12–15, 1967, Paper No. 76.

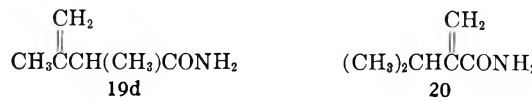
(3) Taken entirely from the Ph.D. Thesis of J. F. Kelly, 1969.

(4) For relevant references, including exceptions, *cf.* R. K. Sharma, B. A. Shoulders, and P. D. Gardner, *J. Org. Chem.*, **32**, 241 (1967); W. A. Waters and E. F. Kiefer, *J. Amer. Chem. Soc.*, **89**, 6261 (1968); and two recent reviews of allene chemistry: A. A. Petrov and A. V. Fedorova, *Russ. Chem. Rev.*, **33**, 1 (1964); H. Fischer in "Cumulenes," S. Patei, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, pp 1060–1083.



butadienes (**10**).[5] The reaction between CSI and **6d** produced a third product (**11**) which seemed to be an adduct of 2 equiv of CSI with one of **6d**.[5] In this paper, we (i) report on CSI addition to allenes 2-methyl-2,3-pentadiene (**6b**), 2,3-pentadiene (**6c**), 1,3-diphenylpropadiene (**6f**), and phenylpropadiene (**6g**); (ii) provide experimental details of the reaction between CSI and **6a–h**, with proof of structure of both β-lactam and diene amide products; (iii) identify **11** by degradation and independent synthesis; (iv) provide experimental evidence for the stereospecific cycloaddition of CSI to *cis*- and *trans*-β-methylstyrene (*cis* and *trans* **16g**),[6] and (v) use this information to establish the geometry of a number of products.

Addition of CSI to allenes **6a**, **b**, **d**, and **e** led to both N-chlorosulfonyl-β-lactams and dienes: respectively, 1-chlorosulfonyl-4,4-dimethyl-3-isopropylidene-2-azetidinone (**8a**, 67%) and 3-methyl-2-isopropylidene-3-butenamide (**10a**, 28%); 1-chlorosulfonyl-3-ethylidene-4,4-dimethyl-2-azetidinone (37%) (a 13:87 *cis* **8b**–*trans* **8b** mixture)[7] and 2-ethylidene-3-methyl-3-butenamide (25%) (a 29:71 *cis* **10b**–*trans* **10b** mixture);[7b] 1-chlorosulfonyl-3-methylene-4,4-dimethyl-2-azetidinone (**8d**, 23%), 3-methyl-2-methylene-3-butenamide (**10d**, 36%), and 1-chlorosulfonyl-1-(2-carboxy-3-methyl-2-butenyl)urea (**11**, 23%); and 1-chlorosulfonyl-3-methylene-1-azaspiro[3.5]nonan-2-one (**8e**, 40%) and 2-(1-cyclohexenyl)-2-propenamide (**10e**, 32%) (Chart I). Allene **6c** produced only diene 2-ethylidene-3-butenamide (**10c**, 31%), whereas **6f**, **g**, and **h** led only to N-chlorosulfonyl-β-lactams, 3-benzylidene-1-chlorosulfonyl-4-phenyl-2-azetidinone (**8f**, 63%), 1-chlorosulfonyl-3-methylene-4-phenyl-2-azetidinone (**8g**), and 10-chlorosulfonyl-10-azabicyclo[7.2.0]undec-1-ene-11-one (**8h**, 89%) (Chart I). No isolable products were obtained from the reaction of 1,2-heptadiene or 4-phenyl-1,2-butadiene with CSI. Cycloadduct **8g** was obtained in good yield as evidenced by the infrared spectrum, but polymerized within minutes *via* ring opening (since the carbonyl band at 5.5 μ shifted rapidly to *ca* 5.9 μ). Immediate benzenethiol–pyridine reduction of **8g** permitted the isolation of the stable β-lactam (**9g**) in 8% over-all yield. Similarly, reduction of **8a**, **b**, **d–f**, and **h** provided the unsubstituted β-lactams, **9a**, **b**, **d–f**, and **h**, respectively, in yields of 55–91%. In general, proof of β-lactam structures **9a**, **b**, and **d–h** was established by acid hydrolysis to unsaturated amino acid hydrochlorides **12a**, **b**, and **d–h**, which on hydrogenation led respectively, to **13a**, **b**, and **d–h**. Amino acid hydrochlorides **13a**, **b**, and **d–g** were independently prepared by the following sequence of reactions: (i) cycloaddition of CSI to 2,4-dimethyl-2-pentene (**16a**), 2-methyl-2-pentene (**16b**), 2-methyl-2-butene (**16d**), ethylidenecyclohexane (**16e**), *trans*-1,3-diphenylpropene (**16f**), and *cis*- and *trans*-β-methylstyrenes (*cis* **16g** and *trans* **16g**) led to the N-chlorosulfonyl-β-lactam products (**17a**, **b**, and **d–g**, respectively); (ii) reduction to β-lactams **18a**, **b**, and **d–g**, respectively; and (iii) acid hydrolysis to **13a**, **b**, and **d–g**. Proof of structure of diene amides **10a–e** was achieved by reduction to the following saturated derivatives: diisopropylacetamide (**15a**),[8] 2-isopropylbutanamide (**15b**),[9] 2-ethylbutanamide (**15c**),[10] 2,3-dimethylbutanamide (**15d**),[5,11] and 2-cyclohexylpropanamide (**15e**),[12] respectively. In the case of **10d**, hydrogenation over Pd–C gave an 85% yield of partially reduced 2,3-dimethyl-2-butenamide (**14d**) and 15% of **15d**. We must revise our earlier suggestion[13] and now conclude that the conversion **10d** → **14d** must involve 1,4 reduction since neither of the independently prepared "1,2-reduction" products 2-methyl-3-methylenebutanamide (**19d**) and 3-methyl-2-methylenebutanamide (**20**) isomerize to **14d** under the catalytic conditions (5% Pd–C) employed. Finally, minor products (4–8%) of the addition of CSI to **16a**, **b**, and **d** included 3-methyl-2-isopropyl-3-butenamide (**19a**), 2-ethyl-3-methyl-3-butenamide (**19b**), and **19d**, respectively. Hydrogenation of **19a** and **b** led to quantitative conversion into **15a** and **b**, respectively, as did **14d**, **19d**, and **20** into **15d**.



Structure of 11 (Chart II).—The identity of **11** was established as 1-chlorosulfonyl-1-(2-carboxy-3-methyl-2-butenyl)urea by benzenethiol–pyridine reduction to 1-(2-carboxy-3-methyl-2-butenyl)urea (**22**). Both the ozonation of **11** and permanganate–periodate oxidation of **22** produced acetone, isolated as the 2,4-DNP derivative, thus suggesting the same isopropylidene moiety in each. Catalytic reduction of **22** led to 1-(2-carboxy-3-methylbutyl)urea (**23**), alkaline hydrolysis of which gave 2-carboxy-3-methylbutylamine (**24**). Benzoylation of **24** under Schotten–Bauman conditions led to crystalline 1-benzamido-2-carboxy-3-methylbutane (**25**). A parallel sequence of reactions on **22** → **26** → **27** with a final catalytic reduction also led to **25**. Although **23** and **24** were isolated, purified, and characterized, the reaction sequence **22** → **23** → **24** → **25** could be accomplished in 47% over-all yield without isolation of intermediates. Authentic **25** was prepared from diethyl isopropylmalonate (**28**) *via* the half-ester (**29**), followed by a Mannich reaction to ethyl 3-methyl-2-methylenebutanoate (**30**) and its hydrolysis to **31**. A Michael addition of HBr to **31** led to 2-bromomethyl-3-

(5) E. J. Moriconi and J. F. Kelly, *J. Amer. Chem. Soc.*, **88**, 3657 (1966).
(6) E. J. Moriconi and J. F. Kelly, *Tetrahedron Lett.*, 1435 (1968).
(7) (a) Based on nmr analysis of the unsubstituted β-lactam product mixture *cis* **9b** and *trans* **9b**; (b) the *cis* or *trans* designation refers to the position of the olefinic methyl group *cis* or *trans* to the adjacent C=O group.
(8) F. C. B. Marshall, *J. Chem. Soc.*, 2754 (1930).
(9) G. S. Slomp, Jr., and J. L. Johnson, *J. Amer. Chem. Soc.*, **80**, 915 (1958).
(10) H. Koch and F. Hillberath, *Ber.*, **73**, 1171 (1940).
(11) C. D. Nenitzescu and I. Chicos, *ibid.*, **68**, 1584 (1935).
(12) R. S. Thakur, *J. Chem. Soc.*, 1481 (1933).
(13) Reference 5, footnote 11.

CHART I

6a, $R_1 = R_2 = R_3 = R_4 = CH_3$
b, $R_1 = R_2 = R_3 = CH_3$; $R_4 = H$
c, $R_1 = R_4 = H$; $R_2 = R_3 = CH_3$
d, $R_1 = R_2 = CH_3$; $R_3 - R_4 - H$
e, $R_1R_2 = -(CH_2)_5-$; $R_3 = R_4 = H$
f, $R_1 = R_3 = H$; $R_2 = R_4 = C_6H_5$
g, $R_1 = R_3 = R_4 = H$; $R_2 = C_6H_5$
h, $R_2R_3 = -(CH_2)_6-$; $R_1 = R_4 = H$

8a, $R_1 = R_2 = R_3 = R_4 = CH_3$; $R_5 = SO_2Cl$
9a, $R_1 = R_2 = R_3 = R_4 = CH_3$; $R_5 = H$
cis **8b**,[7b] $R_1 = R_2 = R_4 = CH_3$; $R_3 = H$; $R_5 = SO_2Cl$
trans **8b**,[7b] $R_1 = R_2 = R_3 = CH_3$; $R_4 = H$; $R_5 = SO_2Cl$
cis **9b**,[7b] $R_1 = R_2 = R_4 = CH_3$; $R_3 = R_5 = H$
trans **9b**,[7b] $R_1 = R_2 = R_4 = CH_3$; $R_3 = R_5 = H$
8d, $R_1 = R_2 = CH_3$; $R_3 = R_4 = H$; $R_5 = SO_2Cl$
9d, $R_1 = R_2 = CH_3$; $R_3 = R_4 = R_5 = H$
8e, $R_1R_2 = -(CH_2)_5-$; $R_3 = R_4 = H$; $R_5 = SO_2Cl$
9e, $R_1R_2 = -(CH_2)_5-$; $R_3 = R_4 = R_5 = H$
8f, $R_1 = R_4 = H$; $R_2 = R_3 = C_6H_5$; $R_5 = SO_2Cl$
9f, $R_1 = R_4 = R_5 = H$; $R_2 = R_3 = C_6H_5$
8g, $R_1 = R_3 = R_4 = H$; $R_2 = C_6H_5$; $R_5 = SO_2Cl$
9g, $R_1 = R_3 = R_4 = R_5 = H$; $R_2 = C_6H_5$
8h, $R_2R_3 = -(CH_2)_6-$; $R_1 = R_4 = H$; $R_5 = SO_2Cl$
9h, $R_2R_3 = -(CH_2)_6-$; $R_1 = R_4 = R_5 = H$

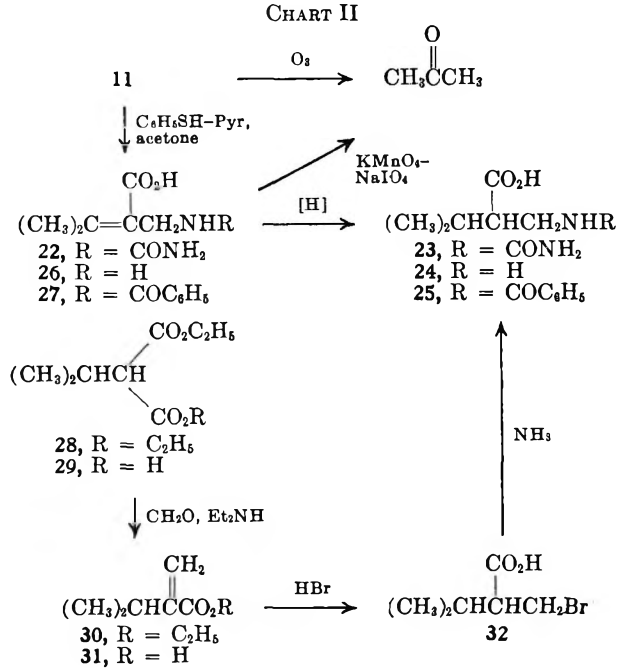
10a, $R_1 = H$; $R_2 = R_3 = R_4 = CH_3$
cis **b**, $R_1 = R_3 = H$; $R_2 = R_4 = CH_3$
trans **b**, $R_1 = R_4 = H$; $R_2 = R_3 = CH_3$
c, $R_1 = R_2 = R_3 = H$; $R_4 = CH_3$
d, $R_1 = R_3 = R_4 = H$; $R_2 = CH_3$
e, $R_1R_2 = -(CH_2)_5-$; $R_3 = R_4 = H$

12a, $R_1 = R_2 = R_3 = R_4 = CH_3$
b, $R_1 = R_2 = R_3 = CH_3$; $R_4 = H$
d, $R_1 = R_2 = CH_3$; $R_3 = R_4 = H$
e, $R_1R_2 = -(CH_2)_5-$; $R_3 = R_4 = H$
f, $R_1 = R_3 = H$; $R_2 = R_4 = C_6H_5$
g, $R_1 = R_3 = R_4 = H$; $R_2 = C_6H_5$
h, $R_2R_3 = -(CH_2)_6-$; $R_1 = R_4 = H$

15a, $R_1 = R_2 = CH(CH_3)_2$
b, $R_1 = CH(CH_3)_2$; $R_2 = C_2H_5$
c, $R_1 = R_2 = C_2H_5$
d, $R_1 = CH(CH_3)_2$; $R_2 = CH_3$
e, R_1 = cyclohexyl; $R_2 = CH_3$

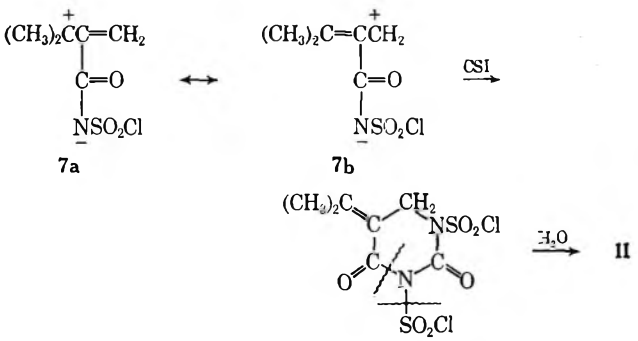
[H]
CO2H
R3
R2
H
R1
NH3 Cl−
13a, R1 = R2 = CH3; R3 = CH(CH3)2
b, R1 = R2 = CH3; R3 = C2H5
d, R1 = R2 = R3 = CH3
e, R1R2 = −(CH2)5−; R3 = CH3
erythro f, R1 = H; R2 = C6H5; R3 = CH2C6H5
threo f, R1 = C6H5; R2 = H; R3 = CH2C6H5
erythro g, R1 = H; R2 = C6H5; R3 = CH3
threo g, R1 = C6H5; R2 = H; R3 = CH3
h, R1 = H; R2R3 = −(CH2)4−
meso i, R1 = H; R2 = R3 = C2H5
dl i, R1 = R3 = C2H5; R2 = H
[H]
R2
R1CH=CCHCONH2
R3
19a, R1 = H; R2 = CH3; R3 = CH(CH3)2
b, R1 = H; R2 = CH3; R3 = C2H5
d, R1 = H; R2 = R3 = CH3
i, R1 = CH3; R2 = H; R3 = C2H5
+
HCl
R2 R3
R1 R4
N
R5
O
CSI
R3
R2
C=C
R4
R1
16a, R1 = R2 = CH3; R3 = H; R4 = CH(CH3)2
b, R1 = R2 = CH3; R3 = H; R4 = C2H5
d, R1 = R2 = R3 = CH3; R4 = H
e, R1R2 = −(CH2)5−; R3 = H; R4 = CH3
trans f, R1 = R3 = H; R2 = C6H5; R4 = CH2C6H5
cis g, R1 = R4 = H; R2 = C6H5; R3 = CH3
trans g, R1 = R3 = H; R2 = C6H5; R4 = CH3
cis i, R1 = R4 = H; R2 = R3 = C2H5
trans i, R1 = R3 = H; R2 = R4 = C2H5
17a, R1 = R2 = CH3; R3 = H; R4 = CH(CH3)2; R5 = SO2Cl
18a, R1 = R2 = CH3; R3 = R5 = H; R4 = CH(CH3)2
17b, R1 = R2 = CH3; R3 = H; R4 = C2H5; R5 = SO2Cl
18b, R1 = R2 = CH3; R3 = R5 = H; R4 = C2H5
17d, R1 = R2 = R3 = CH3; R4 = H; R5 = SO2Cl
18d, R1 = R2 = R3 = CH3; R4 = R5 = H
17e, R1R2 = −(CH2)5−; R3 = H; R4 = CH3; R5 = SO2Cl
18e, R1R2 = −(CH2)5−; R3 = R5 = H; R4 = CH2
trans 17f, R1 = R3 = H; R2 = C6H5; R4 = CH2C6H5; R5 = SO2Cl
cis 18f, R1 = R5 = H; R2 = C6H5; R3 = CH2C6H5
trans 18f, R1 = R5 = H; R2 = C6H5; R4 = CH2C6H5
cis 17g, R1 = R4 = H; R2 = C6H5; R3 = CH3; R5 = SO2Cl
trans 17g, R1 = R3 = H; R2 = C6H5; R4 = CH3; R5 = SO2Cl
cis 18g, R1 = R4 = R5 = H; R2 = C6H5; R3 = CH3
trans 18g, R1 = R3 = R5 = H; R2 = C6H5; R4 = CH3
cis 17i, R1 = R4 = H; R2 = R3 = C2H5; R5 = SO2Cl
trans 17i, R1 = R3 = H; R2 = R4 = C2H5; R5 = SO2Cl
cis 18i, R1 = R4 = R5 = H; R2 = R3 = C2H5
trans 18i, R1 = R3 = R5 = H; R2 = R4 = C2H5

CHART II



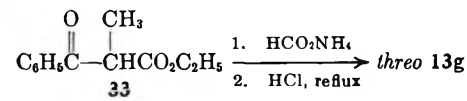
methylbutanoic acid (**32**), treatment of which with aqueous ammonia led to the primary amine **24** and ultimately **25**.

The mechanism of formation of **11** is consistent with the initial formation of the allyl carbonium ion **7** (path a), followed successively by the 1,4-dipolar cycloaddition of **7b** to a second molecule of the electrophilic dipolarophile CSI and hydrolytic cleavage to **11**.[14]

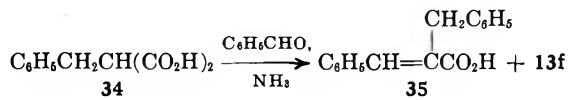


Product Geometry.—We recently reported the stereospecific *cis* addition of CSI to *cis*- (*cis* **16g**) and *trans*-β-methylstyrene (*trans* **16g**) to yield 2 + 2 cycloadducts, N-chlorosulfonyl-*cis*- (*cis* **17g**) and -*trans*-3-methyl-4-phenyl-2-azetidinone (*trans* **17g**).[6] The retention of configuration of R_1–R_4 in *cis* and *trans* **17g** is unequivocally supported by nmr data. Thus the eclipsed *cis* protons in *cis* **17g** show the expected vicinal coupling of 7.25 Hz while the *trans*-skewed protons in *trans* **17g** displayed vicinal coupling of 4.00 Hz. Furthermore, the methyl protons (R_3) in *cis* **17g** are in the shielding region of the *cis*-phenyl ring (R_2) and appear as a doublet upfield (0.54 ppm) relative to the *trans*-methyl protons (R_4) in *trans* **17g**.[15,16]

Benzenethiol–pyridine reduction of *cis* and *trans* **17g**, respectively, led to *cis* and *trans* **18g**; acid hydrolysis quantitatively converted the *cis*-β-lactam into *erythro*-3-amino-2-methyl-3-phenylpropanoic acid hydrochloride (*erythro* **13g**), whereas the *trans*-β-lactam led to the *threo* isomer (*threo* **13g**). This experimentally established relationship (*cis*-β-lactam → *erythro*-amino acid and *trans*-β-lactam → *threo*-amino acid) permitted the identification and assignment of the geometry of a number of products. (i) The reduced, acid hydrolysis product of **9g** was spectroscopically determined to consist of a 63:37 mixture of *erythro* **13g** and *threo* **13g**. (ii) Leuckart reduction of ethyl 2-benzoylpropanoate (**33**) led to an 18% yield of **13g** identified as *threo* **13g**.



(iii) The reaction sequence commencing with allene **6f** → **8f** → **9f** → **18f** led solely to the *cis* isomer of 3-benzyl-4-phenyl-2-azetidinone (*cis* **18f**) since acid hydrolysis of *cis* **18f** quantitatively converted it into *erythro*-3-amino-2-benzyl-3-phenylpropanoic acid hydrochloride (*erythro* **13f**). The alternative route to this amino acid (*via* **9f** → **12f** → **13f**) also produced only *erythro* **13f**. The homogeneity of *cis* **18f** further suggested that the olefinic phenyl substituent (R_3) in the N-chlorosulfonyl-β-lactam precursor **8f** is *trans* to the carbonyl group.[7b] (iv) The reaction sequence commencing with the olefin *trans* **16f** → **17f** → **18f** led solely to the *trans* isomer of 3-benzyl-4-phenyl-2-azetidinone (*trans* **18f**) since acid hydrolysis quantitatively converted it into *threo*-3-amino-2-benzyl-3-phenylpropanoic acid hydrochloride (*threo* **13f**). (v) Finally, a Mannich reaction on benzylmalonic acid (**34**) led to 2-benzylcinnamic acid (**35**, 19%) and an 18% yield of a 58:42 *erythro*–*threo* mixture of **13f**. Earlier in this



paper, we had noted that the addition of CSI to 2-methyl-2,3-pentadiene (**6b**) had led to *cis*–*trans* isomers of both **8b** and **10b** in which the less sterically hindered *trans* isomer predominated.[7b] These conclusions were based on an nmr analysis of **9b** (reduction product of **8b**) and **10b**. Thus, in both *cis* **9b** and *cis* **10b**, the olefinic methyl group is in the plane of and proximate to the adjacent C=O group, and appears downfield (0.21 and 0.44 ppm, respectively) in the nmr spectrum, relative to the same substituent in *trans* **9b** and *trans* **10b**.

(14) At the First International Congress of Heterocyclic Chemistry,[2] R. Huisgen reported on "1,4-Dipolar Cycloaddition. A General Principle of Heterocyclic Syntheses." The formation of **11** is a specific example of this synthetic principle. A related example has recently been reported [H. Ulrich, B. Tucker, and A. A. R. Sayigh, *J. Amer. Chem. Soc.*, **90**, 528 (1968)].

(15) K. D. Barrow and T. M. Spotswood, *Tetrahedron Lett.*, 3326 (1965).

(16) Similar stereospecificity was observed in the cycloaddition of CSI to *cis*- (*cis* **16i**) and *trans*-3-hexene (*trans* **16i**). Analytical and spectral data, and results of decoupling experiments for *cis* and *trans* **17g**, and *cis* and *trans* **17i** are summarized in the Experimental Section.

Experimental Section[17-22]

Reaction of CSI with Allenes (16).—The general procedure used was as follows. A solution of the allene in anhydrous ether (15 ml/0.1 mol) was added dropwise to an ice bath cooled, stirred solution of an equimolar amount of CSI in the same solvent (20 ml/0.1 mol). The solution was stirred until the ir spectrum showed the absence of the allene and isocyanate peaks (*ca.* 5.1 and 4.4 μ, respectively) (15 min to 3 hr) and poured onto 10–20 g of ice. The ether layer was extracted with eight 15-ml portions of water and the aqueous extracts were combined with the water layer. The ether moiety was dried (Na_2SO_4) and evaporated to dryness under a N_2 stream. The residue was extracted or dissolved in boiling solvent; the solution was decolorized (charcoal) and cooled to −20° to give the N-chlorosulfonyl-β-lactam product (**8**). Concentration of the filtrate occasionally gave additional amounts of product.

The combined aqueous extracts were extracted for 4–5 days (Raab extractor) with CH_2Cl_2. The methylene chloride solution after work-up led to the unsaturated amide product (**10**).

Variations in isolation procedure for **8** and **10** are noted under each allene.

2,4-Dimethyl-2,3-pentadiene (6a) (10.0 g, 0.10 mol) gave 16.3 g (67%) of **1-chlorosulfonyl-4,4-dimethyl-3-isopropylidene-2-azetidinone (8a)**: mp 71–72° (from hexane); uv max (CH_3OH), 241 mμ (ϵ 22,000); ir (KBr), 5.58 μ (C=O).

Anal. Calcd for $C_8H_{12}NO_3SCl$: C, 40.45; H, 5.09; N, 5.89. Found: C, 40.55; H, 5.13; N, 6.20.

Evaporation of the CH_2Cl_2 extract led to crude **3-methyl-2-isopropylidene-3-butenamide (10a)** which was dissolved in 50 ml of ether and decolorized (charcoal), and 50 ml of hexane was added. The solution was boiled until the temperature reached 50° and then cooled to give 4.0 g (29%) of pure **10a** as needles: mp 134–135° dec and sublimes; ir (KBr), 6.09 μ (C=O).

Anal. Calcd for $C_8H_{13}NO$: C, 69.04; H, 9.41; N, 10.01. Found: C, 68.88; H, 9.37; N, 10.11.

2-Methyl-2,3-pentadiene (6b) (8.2 g, 0.1 mol) gave 8.3 g (37%) of **1-chlorosulfonyl-3-ethylidene-4,4-dimethyl-2-azetidinone (8b)** after extraction with five 30-ml portions of boiling pentane: mp 92–93° (from pentane); uv max (CH_3OH), 229 mμ (ϵ 23,500); ir (KBr), 5.58 μ (C=O).

Anal. Calcd for $C_7H_{10}NO_3SCl$: C, 37.59; H, 4.51; N, 6.26. Found: C, 37.72; H, 4.73; N, 6.10.

The methylene chloride extract was evaporated to 25 ml *in vacuo* and poured slowly into 150 ml of boiling hexane. The boiling was continued until the CH_2Cl_2 had evaporated. The hexane was decanted and the residual oil was further extracted with three 25-ml portions of boiling hexane. The hexane extracts were combined and were evaporated to 100 ml, cooled, and filtered to give 3.2 g (25%) of a 29% *cis*–71% *trans* mixture of **2-ethylidene-3-methyl-3-butenamide (10b)**: mp 55–57°; uv max (CH_3OH), 227 mμ (ϵ 23,100); ir (KBr), 6.08 μ (C=O); nmr ($CDCl_3$), for *cis* **10b**, δ 6.40 (broad singlet, 2, NH_2), 5.67 (q, 1, J = 7 Hz, $=CHCH_3$), 5.05 and 4.85 (two broad singlets, 2, $=CH_2$), 1.84 (s, 3, CH_3), and 1.78 (doublet with one peak under methyl singlet, 3, $=CHCH_3$); for *trans* **10b**, δ 7.20 (broad singlet, 2, NH_2), 6.65 (q, 1, J = 7 Hz, $=CHCH_3$), 5.23 and 4.95 (two broad singlets, 2, $=CH_2$), 1.84 (s, 3, CH_3), and 1.71 (d, 3, J = 7 Hz, $=CHCH_3$).

Anal. Calcd for $C_7H_{11}NO$: C, 67.17; H, 8.86; N, 11.19. Found: C, 66.81; H, 9.13; N, 10.81.

2,3-Pentadiene (6c) (4.2 g, 0.062 mol) gave 2.1 g (31%) of **3-carboxamido-1,3-pentadiene (10c)**. After extraction of the ether layer with water, the combined aqueous extracts were then extracted with methylene chloride (Raab extractor) for 5 days. The methylene chloride extract was evaporated to dryness, and the residue was extracted with three 20-ml portions of boiling hexane to give, on cooling, **10c**: mp 100–102°; uv max (CH_3OH), 220 mμ (ϵ 20,200); ir (KBr), 6.08 μ (C=O).

Anal. Calcd for C_6H_9NO: C, 64.85; H, 8.15; N, 12.60. Found: C, 64.52; H, 8.19; N, 12.35.

3-Methyl-1,2-butadiene (6d) (5.0 g, 0.074 mol) gave 3.5 g (23%) of **1-chlorosulfonyl-4,4-dimethyl-3-methylene-2-azetidinone (8d)** after extraction with three 30-ml portions of boiling pentane: mp 51–52° (from pentane); uv max (CH_3OH), 218 mμ (ϵ 10,000); ir (KBr), 5.52 μ (C=O).

Anal. Calcd for $C_6H_8NO_3SCl$: C, 34.37; H, 3.85; N, 6.68. Found: C, 34.51; H, 4.03; N, 6.80.

After the boiling pentane extraction, the yellow, semisolid residue was extracted with three 30-ml portions of boiling ether. Hexane was added to the hot combined ether extracts to the cloud point. The solution was boiled again, decolorized (charcoal), and filtered. Additional hexane was added (total *ca.* 50 ml), and the solution was boiled until **1-chlorosulfonyl-1-(2-carboxy-3-methyl-2-butenyl)urea (11)** began to precipitate. After cooling, **11** was filtered. Further concentration of the filtrate led to additional **11**: total yield 2.3 g (23%) (from ether–hexane); mp 126–127°; uv max (CH_3OH), 215 mμ (ϵ 12,000); ir (KBr), 5.95 and 6.13 μ (C=O).

Anal. Calcd for $C_7H_{11}N_2O_5SCl$: C, 31.06; H, 4.10; N, 10.35; mol wt, 271. Found: C, 31.66; H, 4.38; N, 10.36; mol wt (isothermal distillation), 288.

The methylene chloride extract was evaporated to dryness and the residue was recrystallized from ether–hexane to give 2.9 g (36%) of **3-methyl-2-methylene-3-butenamide (10d)**, mp 70° (with polymerization). Amide **10d** polymerizes on standing in the solid state within 1 day, but it is stable for several days in ether solution: uv max (CH_3OH), 223 mμ (ϵ 7800); ir (KBr), 6.09 μ (C=O).

Anal. Calcd for C_6H_9NO: C, 64.85; H, 8.15; N, 12.60. Found: C, 64.93; H, 8.24; N, 12.32.

Pentamethyleneallene (6e) (10.0 g, 0.09 mol) gave 9.15 g (40%) of **1-chlorosulfonyl-3-methylene-1-azaspiro[3.5]nonan-2-one (8e)**: mp 96–97° (from hexane); uv max (CH_3OH), 215 mμ (ϵ 2200); ir (KBr), 5.56 μ (C=O).

Anal. Calcd for $C_9H_{12}NO_3SCl$: C, 43.28; H, 4.85; N, 5.61. Found: C, 43.44; H, 5.02; N, 5.86.

The methylene chloride extract was evaporated *in vacuo* to dryness, and the residue was recrystallized from ether–hexane to give 2.4 g (32%) of **2-(1-cyclohexenyl)-2-propenamide (10e)**: mp 135–137°; uv max (CH_3OH), 234 mμ (ϵ 8,500); ir (KBr), 6.05 μ (C=O).

Anal. Calcd for $C_9H_{13}NO$: C, 71.48; H, 8.66; N, 9.27. Found: C, 71.78; H, 8.76; N, 9.38.

1,3-Diphenylpropadiene (6f) (2.0 g, 0.01 mol) gave 2.2 g (63%) of **3-benzylidene-1-chlorosulfonyl-4-phenyl-2-azetidinone (8f)**. After addition of **6f** to CSI, the mixture was stirred for 1 hr at room temperature, after which it was poured into 50 ml of hexane. Crude **8f** was filtered and recrystallized from ether–hexane to give **8f** as needles: mp 98–99°; uv max (CH_3OH), 219 mμ (ϵ 6100) and 304 (13,000); ir (KBr), 5.58 μ (C=O).

Anal. Calcd for $C_{16}H_{12}NO_3SCl$: C, 57.57; H, 3.62; N, 4.20. Found: C, 57.31; H, 3.64; N, 4.24.

Phenylpropadiene (6g) (6.4 g, 0.06 mol) gave 0.62 g (8%) of **3-methylene-4-phenyl-2-azetidinone (9g)**. After addition of **6g** to CSI, the mixture was stirred for 2 hr and cooled to −40°; 10.5 g (0.095 mol) of thiophenol was added quickly, followed by slower addition (30 min) of 4.5 g (0.055 mol) of pyridine. The mixture was stirred for an additional hr at −40°, after which 75 ml of ethanol were added. The solution was evaporated *in vacuo* to a volume of 50 ml and then cooled to −20°. The precipitated diphenyl disulfide was filtered, and the filtrate was evaporated

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(17) Melting points are corrected; boiling points are uncorrected. The infrared spectra were recorded on a Perkin-Elmer 337 grating spectrophotometer; ultraviolet spectra were recorded on a Cary 15 spectrophotometer. Nmr spectra were obtained on a Varian Associates A-60A spectrometer using TMS as an internal standard in organic solvents and the DOH peak (δ 4.67) in D_2O solutions. Double resonance experiments on *cis* and *trans* **17g** and *cis* and *trans* **17i** (Table I) were conducted with a Varian Associates 6058A spin decoupler. Full nmr data are available in ref 3. Gas chromatograms were run on a Perkin-Elmer 880 instrument with a flame ionization detector and using a column packed with 10% SE 30 on Chromosorb W. Microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. CSI was obtained from American Hoechst Corp. **2-Methyl-2,3-pentadiene (6b)**, **2,3-pentadiene (6c)**, and **phenylpropadiene (6g)** were prepared from the appropriate olefin using Skattebøl's general two-step procedure;[18] **3-methyl-1,2-butadiene (6d)** and **pentamethylene allene (6e)** were synthesized by reduction of 3-chloro-3-methyl-1-butyne and 1-ethnyl-1-chlorocyclohexane, respectively, using lithium aluminum hydride in tetrahydrofuran;[19] **1,2-cyclononadiene (6h)** was prepared in the one-step procedure from cyclooctene.[20] **1,3-Diphenylpropadiene (6f)** was synthesized *via* prototropic rearrangement of 1,3-diphenylpropyne by adsorption on a basic alumina column;[21] ***trans*-1,3-diphenylpropene (16f)** was prepared by the Bamford–Stevens procedure.[22] **2,4-Dimethyl-2,3-pentadiene (6a)** and all other olefins (**16a–e, g,** and **i**) were obtained from the Chemical Samples Co.

(18) L. Skattebøl, *Acta Chem. Scand.*, **17**, 1683 (1963).

(19) W. J. Bailey and C. R. Pfeifer, *J. Org. Chem.*, **20**, 95 (1955).

(20) K. G. Untch, D. J. Martin, and N. T. Castellucci, *ibid.*, **30**, 3572 (1965).

(21) T. L. Jacobs and D. Danker, *ibid.*, **22**, 1424 (1957).

(22) W. R. Bamford and T. S. Stevens, *J. Chem. Soc.*, 4735 (1952).

in vacuo. The residual oil was dissolved in the minimal amount of ether, deposited on a 2 × 25 cm column (Woelm neutral alumina, activity grade I), and eluted successively with equal volumes (200 ml) of hexane, CCl_4, and $CHCl_3$. Crude **9** appeared in the CCl_4 fraction, and after evaporation of the solvent, was recrystallized twice from hexane to give pure **9g**: mp 106–107°; ir (KBr), 5.75 and 5.84 μ (C=O).

Anal. Calcd for $C_{10}H_9NO$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.58; H, 5.68; N, 8.88.

1,2-Cyclononadiene (6h) (2.5 g, 0.02 mol) gave 4.7 g (89%) of **10-chlorosulfonyl-10-azabicyclo[7.2.0]undec-1-en-11-one (8h)** after extraction with three 20-ml portions of boiling pentane. Recrystallization several times by cooling in Dry Ice–acetone bath, filtering, redissolution in pentane, and cooling to Dry Ice–acetone temperature gave pure **8h**: mp 45–46°; uv max (CH_3OH), 234 mμ (ε 14,500); ir (KBr), 5.51 μ (C=O).

Anal. Calcd for $C_{10}H_{14}NO_3SCl$: C, 45.54; H, 5.35; N, 5.31. Found: C, 45.47; H, 5.47; N, 5.09.

Benzenethiol–Pyridine Reduction of N-Chlorosulfonyl-β-Lactams (8) to β-Lactams 9.—The general procedure used was as follows. A solution of pyridine (20% mol excess) in acetone (15 ml/0.1 mol) was added dropwise (30 min) to a stirred solution of **8** and benzenethiol (2 equiv) in acetone (25 ml/0.1 mol), maintained at −30°. After stirring for an additional 30 min, an amount of water, equal to the volume of solvent acetone, was added slowly with stirring. The precipitated diphenyl disulfide was filtered, and the filtrate was extracted with six 25-ml portions of ether. The combined ether extracts were dried (Na_2SO_4) and evaporated to dryness, and the residue was recrystallized to give **9**. Any variations in isolation procedures for **9** are noted under each β-lactam.

Compound **8a** (11.9 g, 0.05 mol) gave 7.0 g (77%) of **4,4-dimethyl-3-isopropylidene-2-azetidinone (9a)**: mp 99–100° (from hexane); uv max (CH_3OH), 217 mμ (ε 16,900); ir (KBr), 5.78 and 5.85 μ (C=O).

Anal. Calcd for $C_8H_{13}NO$: C, 69.04; H, 9.41; N, 10.01. Found: C, 68.78; H, 9.58; N, 9.82.

The *cis–trans* **8b** mixture (4.5 g, 0.03 mol) gave 2.4 g (64%) of a 13% *cis*–87% *trans* mixture of **3-ethylidene-4,4-dimethyl-2-azetidinone (9b)**: mp 56–57° (needles from hexane); ir (KBr), 5.71 μ (C=O); nmr ($CDCl_3$), for *trans* **9b**, δ 7.65 (broad singlet, 1, NH), 6.03 (q, 1, J = 7 Hz, =CH), 1.73 (d, 3, J = 7 Hz, $=CHCH_3$), and 1.47 (s, 6, CH_3), for *cis* **9b**, δ 7.65 (broad singlet, 1, NH), 5.61 (q, 1, J = 7 Hz, =CH), 1.94 (d, 3, J = 7 Hz, $=CHCH_3$), and 1.38 (s, 6, CH_3).

Anal. Calcd for $C_7H_{11}NO$: C, 67.17; H, 8.86; N, 11.19. Found: C, 67.33; H, 8.81; N, 11.47.

Compound **8d** (10 g, 0.125 mol) gave 6.15 g (55%) of **3-methylene-4,4-dimethyl-2-azetidinone (9d)**. After evaporation of the ether extracts to dryness, the residual yellow oil was extracted with six 40-ml portions of boiling pentane. On cooling, **9d** crystallized as long needles. Sublimation (50°, 1 mm) led to analytically pure **9d**: mp 64–65°; uv max (CH_3OH) 229 mμ (ε 2900); ir (CS_2), 5.63 and 5.69 μ (C=O); Raman ($CHCl_3$), 3.24 (=CH_2), 5.80 (monomer C=C), and 5.89 μ (dimer–polymer C=C).

Anal. Calcd for C_6H_9NO: C, 64.83; H, 8.17; N, 12.60. Found: C, 65.15; H, 8.42; N, 12.59.

Compound **8e** (11.1 g, 0.045 mol) gave 4.5 g (68%) of **3-methylene-1-azaspiro[3.5]nonan-2-one (9e)**: mp 114–115° (needles from hexane); uv max (CH_3OH), 227 mμ (ε 2300); ir (KBr), 5.73 and 5.83 μ (C=O).

Anal. Calcd for $C_9H_{13}NO$: C, 71.48; H, 8.66; N, 9.27. Found: C, 71.76; H, 8.69; N, 9.50.

Compound **8f** (2.0 g, 0.006 mol) gave 1.25 g (91%) of **3-benzylidene-4-phenyl-2-azetidinone (9f)**. After addition of water, the solid which precipitated contained both diphenyl disulfide and **9f**. This solid material was filtered and washed successively with three 30-ml portions of H_2O and five 30-ml portions of cold hexane. The residual crude β-lactam was recrystallized from acetone: mp 219–221°; uv max (CH_3OH), 222 mμ (ε 9000) and 272 (10,700); ir (KBr), 5.77 and 5.88 μ (C=O).

Anal. Calcd for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.95. Found: C, 81.97; H, 5.54; N, 6.16.

Compound **8h** (3.0 g, 0.011 mol) gave 1.15 g (40%) of **10-azabicyclo[7.2.0]undec-1-en-11-one (9h)**: mp 144–145° (from hexane); uv max (CH_3OH), 212 mμ (ε 11,400); ir (KBr), 5.71 and 5.81 μ (C=O).

Anal. Calcd for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.70; H, 9.24; N, 8.60.

Concentrated Hydrochloric Acid Hydrolysis of β-Lactams 9 to Amino Acid Hydrochlorides (12).—The general procedure used was as follows. Concentrated HCl (2 ml/g) was added to analytically pure **9** and stirred for 30 min. The excess H_2O and HCl was removed *in vacuo* to give a quantitative yield of pure **12**. In the specific cases noted, heating was required to effect hydrolysis and/or an acetone wash was used.

Compound **9a** gave **3-amino-3-methyl-2-isopropylidenebutanoic acid hydrochloride (12a)**: mp 215° dec; ir (KBr), 5.84 μ (C=O).

Anal. Calcd for $C_8H_{16}NO_2Cl$: C, 49.61; H, 8.33; N, 7.23. Found: C, 49.38; H, 8.24; N, 7.34.

Compound **9b** gave **3-amino-2-ethylidene-3-methylbutanoic acid hydrochloride (12b)**: mp 213° dec; ir (KBr), 5.97 μ (C=O).

Anal. Calcd for $C_7H_{14}NO_2Cl$: C, 46.80; H, 7.86; N, 7.79. Found: C, 46.59; H, 7.80; N, 7.55.

Compound **9d** gave **3-amino-2-methylene-3-methylbutanoic acid hydrochloride (12d)**: mp 168° dec; ir (KBr), 5.89 μ (C=O).

Anal. Calcd for $C_6H_{12}NO_2Cl$: C, 43.52; H, 7.30; N, 8.46. Found: C, 43.60; H, 7.29; N, 8.69.

Compound **9e** gave **2-(1-aminocyclohexyl)-2-propenoic acid hydrochloride (12e)** after washing with cold acetone: mp 211° dec; ir (KBr), 5.90 μ (C=O).

Anal. Calcd for $C_9H_{16}NO_2Cl$: C, 52.55; H, 7.84; N, 6.81. Found: C, 52.78; H, 8.09; N, 6.64.

Compound **9f** was heated at 80° in concentrated HCl for 30 min to give **3-amino-2-benzylidene-3-phenylpropanoic acid hydrochloride (12f)**. The residue was treated with 25 ml of boiling acetone and filtered: mp 251–252° dec; uv max (CH_3OH), 257 mμ (ε 18,600); ir (KBr), 5.92 μ (C=O).

Anal. Calcd for $C_{16}H_{16}NO_2Cl$: C, 66.32; H, 5.57; N, 4.83. Found: C, 66.15; H, 5.63; N, 5.16.

Compound **9g** gave **3-amino-2-methylene-3-phenylpropanoic acid hydrochloride (12g)** after washing with cold acetone: mp 197° dec; ir (KBr), 5.78 μ (C=O).

Anal. Calcd for $C_{10}H_{12}NO_2Cl$: C, 56.23; H, 5.66; N, 6.56. Found: C, 56.22; H, 5.64; N, 6.26.

Compound **9h** gave **3-amino-2-carboxy-1-cyclononene hydrochloride (12h)**: mp 145–146° dec; uv max (CH_3OH), 212 mμ (ε 12,500); ir (KBr), 5.81 μ (C=O).

Anal. Calcd for $C_{10}H_{18}NO_2Cl$: C, 54.67; H, 8.26; N, 6.38. Found: C, 54.58; H, 8.37; N, 6.64.

Catalytic Reduction of Amino Acid Hydrochlorides (12) to Amino Acid Hydrochlorides (13).—The general procedure used was as follows. A mixture of 1.0 g of **12** in 75 ml of ethanol and 0.2 g of catalyst was hydrogenated in a Paar apparatus under 50 psi H_2 for 3 hr. The catalyst was filtered and the solvent was evaporated to dryness. The residue was washed with warm acetone to leave a quantitative yield of **13**. The catalyst for each hydrogenation is parenthetically noted.

Hydrogenation (PtO_2) of **12a** gave **3-amino-3-methyl-2-isopropylbutanoic acid hydrochloride (13a)**: mp 209° dec; ir (KBr), 5.73 μ (C=O).

Anal. Calcd for $C_8H_{18}NO_2Cl$: C, 49.10; H, 9.28; N, 7.16. Found: C, 49.39; H, 9.15; N, 7.21.

Hydrogenation (PtO_2) of **12b** gave **3-amino-2-ethyl-3-methylbutanoic acid hydrochloride (13b)**: mp 111–115° dec; ir (KBr) 5.85 μ (C=O).

Anal. Calcd for $C_7H_{16}NO_2Cl$: C, 46.28; H, 8.88; N, 7.71. Found: C, 45.96; H, 9.24; N, 7.80.

Hydrogenation (5% Pd–C) of **12d** gave **3-amino-2,3-dimethylbutanoic acid hydrochloride (13d)**: mp 125–130° dec; ir (KBr), 5.88 μ (C=O).

Anal. Calcd for $C_6H_{14}NO_2Cl$: C, 42.99; H, 8.42; N, 8.36. Found: C, 42.52; H, 8.59; N, 8.31.

Hydrogenation (5% Pd–C) of **12e** gave **2-(1-aminocyclohexyl)-propanoic acid hydrochloride (13e)**: mp 209° dec; ir (KBr), 5.88 μ (C=O).

Anal. Calcd for $C_9H_{18}NO_2Cl$: C, 52.04; H, 8.74; N, 6.74. Found: C, 51.98; H, 8.88; N, 6.68.

Hydrogenation (10% Pd–C) of **12f** gave *erythro*-**3-amino-2-benzyl-3-phenylpropanoic acid hydrochloride** (*erythro* **13f**): mp 236–237° dec; ir (KBr), 5.80 and 5.88 μ (C=O). This compound could not be obtained sufficiently pure for analysis.

Compound **13f** was also obtained by hydrogenation (10% Pd–C) of **9f** to *cis*-**3-benzyl-4-phenyl-2-azetidinone** (*cis* **18f**) (95%) which was quantitatively converted into **13f** by treatment with concentrated HCl. Compound *cis* **18f** had the following properties: mp 121–122° (from hexane); ir (KBr), 5.70 μ

(C=O); nmr ($CDCl_3$), δ 8.40 (broad singlet, 1, NH) 7.50–6.70 (multiplet with main peak at 7.29, 10, C_6H_5), 4.82 (d, 1, J = 5.5 Hz, CH) 4.05–3.55 (m, 1, $CHCH_2$), 2.58 (eight lines, the AB portion of an ABX pattern, 2, J_{AB} = 15 Hz, J_{BX} = 7 Hz, J_{AX} = 9 Hz, $\Delta\nu_{AB}$ = 22 Hz, CH_2).

Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 81.05; H, 6.62; N, 5.90.

Hydrogenation (PtO_2) of **12g** gave a 63:37 mixture of *erythro*- and *threo*-**3-amino-2-methyl-3-phenylpropanoic acid hydrochloride** (**13g**) as shown by nmr comparison with authentic samples: mp 200–201° dec; ir (KBr) 5.80 μ (C=O).

Anal. Calcd for: $C_{10}H_{14}NO_2Cl$: C, 55.69; H, 6.54; N, 6.49. Found: C, 55.60; H, 6.40; N, 6.40.

Hydrogenation (PtO_2) of **12h** gave **2-aminocyclonanecarboxylic acid hydrochloride** (**13h**): mp 214–215°; ir (KBr), 5.88 μ (C=O).

Anal. Calcd for $C_{10}H_{20}NO_2Cl$: C, 9.09; H, 54.17; N, 6.32. Found: C, 9.10; H, 53.80; N, 6.36.

Catalytic Reduction of Carboxamido-1,3-butadienes (10) to Saturated Amides (15).—Quantities of reactants and reductive and work-up procedures were the same as those in the quantitative conversion of **12** into **13**.

Hydrogenation (PtO_2) of **10a** gave **diisopropylacetamide** (**15a**): mp 147–148° (from ether–hexane) (lit.[8] mp 148–148.5°); ir (KBr), 6.06 μ (C=O).

Hydrogenation (PtO) of **10b** gave **2-isopropylbutanamide** (**15b**): mp 130–131° (from ether–hexane) (lit.[9] mp 133–134°); ir (KBr), 6.08 μ (C=O).

Hydrogenation (PtO_2) of **10c** gave **2-ethylbutanamide** (**15c**): mp 107–108° (from ether–hexane) (lit.[10] mp 107°); ir (KBr) 6.06 μ (C=O).

Hydrogenation (5% Pd–C) of **10d** gave 2,3-dimethyl-2-butenamide (**14d**) (85%) and **2,3-dimethylbutanamide** (**15d**) (15%). Both **10d** and **14d** were quantitatively reduced to **15d** using PtO_2 catalyst. Compound **14d** had the following properties: mp 128–129° (from ether–hexane) (lit.[23] mp 130.5°); uv max (CH_3OH), 218 mμ (ε 3700); ir (KBr), 6.02 μ (C=O). Evaporation to dryness of the mother liquors from the ether–hexane recrystallization gave **15d**: mp 129° (from ether–hexane) (lit.[11] mp 129°); ir (KBr), 6.03 μ (C=O).

Hydrogenation (5% Pd–C) of **10e** gave **2-cyclohexylpropanamide** (**15e**): mp 156–157° (from ether–hexane) (lit.[12] mp 156–157°); ir (KBr), 6.06 μ (C=O).

Reactions of CSI with Olefins (16).—The general procedure used was the same as for the reaction of CSI with allenes. Solid residues were recrystallized while the purity of liquids was checked by gas chromatography.

The combined aqueous extracts were extracted for 4–5 days (Raab extractor) with CH_2Cl_2. The CH_2Cl_2 extract was evaporated to dryness, and the residue was recrystallized to give **19**.

Variations in solvents and work-up procedure are noted under each olefin.

2,4-Dimethyl-2-pentene (**16a**) (10 g, 0.10 mol) gave 20.6 g (87%) of **1-chlorosulfonyl-4,4-dimethyl-3-isopropyl-2-azetidinone** (**17a**): mp 55–56° (from hexane); ir (KBr), 5.57 μ (C=O).

Anal. Calcd for $C_8H_{14}NO_3Cl$: C, 40.08; H, 5.89; N, 5.84. Found: C, 40.50; H, 5.83; N, 6.36.

3-Methyl-2-iospropyl-3-butenamide (**19a**) (0.5 g, 4%) had mp 123–124° (from ether–hexane); ir (KBr), 6.04 μ (C=O).

Anal. Calcd for $C_8H_{15}NO$: C, 67.98; H, 10.71; N, 9.92. Found: C, 68.04; H, 10.97; N, 10.06.

2-Methyl-2-pentene (**16b**) (20 g, 0.24 mol) gave 46 g (87%) of **1-chlorosulfonyl 3-ethyl-4,4-dimethyl-2-azetidinone** (**17b**), a liquid which showed a single peak on vpc but decomposed before elemental analyses could be obtained: ir (neat), 5.50 μ (C=O).

2-Ethyl-3-methyl-3-butenamide (**19b**) (3.0 g, 6%) had mp 58–60° (from ether–hexane); ir (KBr), 6.05 μ (C=O).

Anal. Calcd for $C_7H_{13}NO$: C, 66.10; H, 10.30; N, 11.01. Found: C, 65.91; H, 10.52; N, 11.29.

2-Methyl-2-butene (**16d**) (10 g, 0.14 mol) gave 21.1 g (70%) of **1-chlorosulfonyl-3,4,4-trimethyl-2-azetidinone** (**17d**): mp 44–45° (from 30–60° petroleum ether) (lit.[24] mp 44–45°); ir (KBr), 5.52 μ (C=O).

2-Methyl-3-methylenebutanamide (**19d**) (1.3 g, 8%) had mp 100–101° (from ether–hexane) (lit.[23] mp 104–105°); ir (KBr), 6.02 μ (C=O).

Ethylidenecyclohexane (**16e**) (11 g, 0.10 mol) gave 23.5 g (94%) of **1-chlorosulfonyl-3-methyl-1-azaspiro[3.5]nonan-2-one** (**17e**). After the addition of **16e** to CSI, both in ether solvent, **17e** precipitated and was filtered. Evaporation of the filtrate gave additional amounts of **17e**: mp 89–90° (from hexane); ir (KBr), 5.51 μ (C=O).

Anal. Calcd for $C_9H_{14}NO_3SCl$: C, 42.94; H, 5.61; N, 5.56. Found: C, 43.15; H, 5.62; N, 5.60.

trans-**1,3-Diphenylpropene** (**16f**) (4.0 g, 0.028 mol) gave 6.2 g (68%) of **1-chlorosulfonyl-*trans*-3-benzyl-4-phenyl-2-azetidinone** (**17f**). The solvent used was methylene chloride. After the usual work-up, the residue was extracted with seven 20-ml portions of boiling pentane and cooled: mp 65–66° (from pentane); ir (KBr), 5.50 μ (C=O).

Anal. Calcd for $C_{16}H_{14}NO_3SCl$: C, 57.23; H, 4.20; N, 4.17. Found: C, 57.04; H, 4.54; N, 4.33.

1-Chlorosulfonyl-*cis*-3-methyl-4-phenyl-2-azetidinone (*cis* **17g**). —A solution of 6.0 g (0.05 mol) of *cis*-β-methylstyrene (*cis* **16g**) in 10 ml of CH_2Cl_2 was added to a stirred solution of 7.1 g (0.05 mol) of CSI in 20 ml of CH_2Cl_2 at room temperature. The solution was stirred for an additional 5 hr and then poured onto 20 g of ice. The CH_2Cl_2 layer was separated and evaporated under a N_2 stream. The residue was dissolved in 50 ml of ether, decolorized twice with charcoal and filtered. Hexane (50 ml) was added to the filtrate and the solution was boiled until the temperature rose to 45°. Cooling led to the precipitation of the major portion of *cis* **17g** while further concentration of the mother liquor and cooling, yielded an additional amount: total yield 10.6 g (82%): mp 54–55°; ir (KBr), 5.51 μ (C=O).[25]

Anal. Calcd for $C_{10}H_{10}NO_3Cl$: C, 46.25; H, 3.88; N, 5.39. Found: C, 46.48; H, 4.09; N, 5.26.

1-Chlorosulfonyl-*trans*-3-methyl-4-phenyl-2-azetidinone (*trans* **17g**).—Similar treatment of *trans*-β-methylstyrene (*trans* **16g**) (6.0 g, 0.05 mol) gave 11.1 g (85%) of *trans* **17g**: mp 45–46°; ir (neat), 5.50 μ (C=O).[25]

Anal. Calcd for $C_{10}H_{10}NO_3SCl$: C, 46.25; H, 3.88; N, 5.39. Found: C, 46.49; H, 3.90; N, 5.71.

1-Chlorosulfonyl-*cis*-3,4-diethyl-2-azetidinone (*cis* **17i**).—The procedure used for the preparation of *cis* **17i** from *cis*-**3-hexane** (*cis* **16i**) was similar to that for *cis* **17g**, except for the reaction time (2 days) and solvent (50 ml of ether). The ether solution was extracted with seven 15-ml portions of water. The ether solution was dried (Na_2SO_4) and evaporated to dryness. The residue was extracted with four 30-ml portions of boiling petroleum ether (30–60°), and the resulting solution, cooling to −20°, deposited a major portion of *cis* **17i**. Concentration of the filtrate and again cooling to −20° led to additional amounts of *cis* **17i**. Thus 5.0 g (0.06 mol) of *cis* **16i** gave 6.3 g (47%) of *cis* **17i**. **N-chlorosulfonyl-β-lactam** *cis* **17i** is a liquid at room temperature; although vpc and nmr spectra of freshly prepared samples indicated a single product,[25] all attempts to obtain a sample of elemental analysis were frustrated by its ease of decomposition: ir (CCl_4), 5.49 μ (C=O).

1-Chlorosulfonyl-*trans*-3,4-diethyl-2-azetidinone (*trans* **17i**).—*trans*-**3-Hexene** (*trans* **16i**) (10 g, 0.12 mol) gave, after a reaction time of 48 hr (24 hr at room temperature and 24 hr at a gentle reflux), 20.1 g (74%) of liquid *trans* **17i**: ir (CCl_4), 5.49 μ (C=O).[25]

The aqueous extracts from *cis* and *trans* **17i** gave, respectively, 0.3 g (4%) and 0.5 g (3%) of **2-ethyl-3-pentenamide** (**19i**): mp 76–77° (from hexane); ir (KBr), 6.01 μ (C=O).

Anal. Calcd for $C_7H_{13}NO$: C, 66.10; H, 10.30; N, 11.01. Found: C, 66.21; H, 10.45; N, 11.26.

Benzenethiol–Pyridine Reduction of N-Chlorosulfonyl-β-Lactams (17) to β-Lactams (18).—The procedure used was similar to that employed in the reduction of **8** to **9**.

Compound **17a** (19 g, 0.077 mol) gave 7.7 g (72%) of **4,4-dimethyl-3-isopropyl-2-azetidinone** (**18a**): mp 58–59° (from hexane); ir (KBr), 5.69 and 5.82 μ (C=O).

Anal. Calcd for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 68.21; H, 10.87; N, 9.86.

Compound **17b** (22 g, 0.20 mol) gave 8.3 g (65%) of **3-ethyl-4,4-dimethyl-2-azetidinone** (**18b**): bp 64–66° (0.2 mm); ir (neat), 5.75 μ (C=O).

Anal. Calcd for $C_7H_{13}NO$: C, 66.10; H, 10.30; N, 11.01. Found: C, 65.91; H, 10.26; N, 11.12.

Compound **17d** (10.6 g, 0.05 mol) gave 3.1 g (50%) of **3,4,4-trimethyl-2-azetidinone** (**18d**): bp 62–63° (0.4 mm) (lit.[24] bp 74–75° (0.5 mm)); ir, 5.78 μ (C=O).

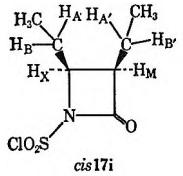
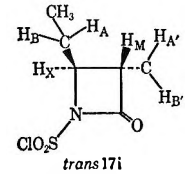
(23) E. J. Corey, *J. Amer. Chem. Soc.*, **75**, 1163 (1955).

(24) R. Graf, *Ann.*, **661**, 111 (1963).

(25) All nmr data are summarized in Table I.

TABLE I

NMR DATA OF *cis* AND *trans* **17g** AND *cis* AND *trans* **17i**[a]

Compd	Substituent	Chemical shift (δ)	Area	Multiplicity	Coupling constant, Hz
cis **17g**	R_1 (H_X)	5.52	1	Doublet	$J_{MX} = 7.25$
	R_2	7.42	5	Singlet	
	R_3	0.94	3	Doublet	$J_{AM} = 7.50$
	R_4 (H_M)	3.92	1	Pentet	
trans **17g**	R_1 (H_X)	4.89	1	Doublet	$J_{MX} = 4.00$
	R_2	7.49	5	Singlet	
	R_3 (H_M)	3.51	1	Quartet of doublets	
	R_4	1.50	3	Doublet	$J_{AM} = 7.60$
 *cis* **17i**	R_1 (H_X)	4.32	1	Six peaks[b]	$J_{AX} = J_{MX} = 7.50$, $J_{BX} = 5.75$
	CH_2's in R_2, R_3	2.20–1.50	4	Multiplet	
	CH_3's in R_2, R_3	1.30–0.80	6	Multiplet	
	R_4 (H_M)	3.52	1	Quartet[c]	$J_{A'M} = J_{B'M} = J_{MX} = 7.50$
 *trans* **17i**	R_1 (H_X)	4.00	1	Pentet[d]	$J_{AX} = 7.50$, $J_{BX} = J_{MX} = 3.75$
	CH_2's in R_2, R_4	2.30–1.60	4	Multiplet	
	CH_3's in R_2, R_4	1.40–0.80	6	Multiplet	
	R_3 (H_M)	3.16	1	Triplet of doublets	$J_{A'M} = J_{B'M} = 7.50$

[a] Spectra were determined in $CDCl_3$ (*cis* and *trans* **17g**) and CCl_4 (*cis* and *trans* **17i**); δ values are reported with an accuracy of ± 0.005 ppm while J values have an accuracy of ± 0.05 Hz. [b] Actually an ABMX pattern where two pairs of lines overlap giving the observed six lines. [c] Actually an A_2MX pattern where $J_{AM} = J_{MX}$; thus the eight expected lines overlap to give the observed quartet. [d] Actually an ABMX pattern where $J_{BX} = J_{MX} = J_{AX/2}$; thus the eight expected lines overlap to give the observed pentet.

Compound **17e** (20 g, 0.08 mol) gave 10.8 g (71%) of **3-methyl-1-azaspiro[3.5]nonan-2-one** (**18e**): mp 62–63° (from hexane); ir (KBr), 5.68 and 5.75 μ (C=O).

Anal. Calcd for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.14. Found: C, 70.85; H, 9.82; N, 8.96.

Compound *trans* **17f** (1.0 g, 0.003 mol) gave 0.65 g (93%) of ***trans*-3-benzyl-4-phenyl-2-azetidinone** (*trans* **18f**): mp 141–142° from ether–hexane); ir (KBr), 5.71 and 5.82 μ (C=O); nmr (DMSO-d_6), δ 7.75–6.90 (multiplet with main peak at 7.27, 11, C_6H_5 and NH), 4.42 (d, 1, J = 2 Hz, CHC_6H_5), 3.50–2.85 (m, 1, CH), and 3.18 (d, 2, J = 2 Hz, CH_2).

Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 81.27; H, 6.26; N, 5.70.

Compound *cis* **17g** (3.9 g, 0.015 mol) gave 2.3 g (96%) of ***cis*-3-methyl-4-phenyl-2-azetidinone** (*cis* **18g**) after extraction of the residue with four 15-ml portions of boiling hexane followed by cooling of the extracts to −20°: mp 105–106°; ir (KBr), 5.68 and 5.88 μ (C=O).

Anal. Calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.37; H, 7.07; N, 8.68.

Compound *trans* **17g** (3.9 g, 0.015 mol) gave 2.1 g (87.5%) of ***trans*-3-methyl-4-phenyl-2-azetidinone** (*trans* **18g**) using the same isolation procedure as for *cis* **18g**: mp 99–100°; ir (KBr), 5.68 and 5.82 μ (C=O).

Anal. Calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.63; H, 6.91; N, 8.47.

Compound *cis* **17i** (4.5 g, 0.02 mol) gave 1.7 g (68%) of ***cis*-3,4-diethyl-2-azetidinone** (*cis* **18i**) after extraction of the residue with five 30-ml portions of boiling hexane followed by evaporation of the hexane extracts to a volume of 40 ml and cooling to −20°: mp 49–50°; ir (CCl_4), 5.67 and 5.70 μ (C=O).

Anal. Calcd for $C_7H_{13}NO$: C, 66.10; H, 10.30; N, 11.01. Found: C, 65.91; H, 10.28; N, 10.75.

Compound *trans* **17i** (4.5 g, 0.02 mol) gave 2.1 g (80%) of ***trans*-3,4-diethyl-2-azetidinone** (*trans* **18i**) after evaporation of the hexane extracts followed by distillation *in vacuo*: bp 72–73° (0.3 mm); ir (CCl_4), 5.63 and 5.70 μ (C=O).

Anal. Calcd for $C_7H_{13}NO$: C, 66.10; H, 10.30; N, 11.01. Found: C, 65.88; H, 10.33; N, 11.34.

Concentrated Hydrochloric Acid Hydrolysis of β-Lactams 18 to Amino Acid Hydrochlorides (13).—The general procedure used was the same as that for the conversion of **9** into **12**. Thus **18a, 18b, 18d, 18e,** *trans* **18f,** *cis* **18g,** *trans* **18g,** *cis* **18i,** and *trans* **18i** were quantitatively and respectively converted into **13a, 13b, 13d, 13e,** *threo* **13f,** *erythro* **13g,** *threo* **13g,** *meso* **13i,** and *dl* **13i**.

***threo*-3-Amino-2-benzyl-3-phenylpropanoic acid hydrochloride** (*threo* **13f**) had mp 227° dec (after boiling acetone wash); ir (KBr), 5.83 μ (C=O).

Anal. Calcd for $C_{16}H_{18}NO_2Cl$: C, 65.86; H, 6.22; N, 4.80. Found: C, 65.71; H, 6.44; N, 4.72.

***erythro*-3-Amino-2-methyl-3-phenylpropanoic acid hydrochloride** (*erythro* **13g**) had the following properties: mp 221–223° dec; ir (KBr), 5.85 and 6.03 μ (C=O); nmr (D_2O), δ 7.41 (s, 5, C_6H_5), 4.50 (d, 1, J = 8 Hz, CHC_6H_5) 3.20 (rough pentet, 1 J = 7 Hz, $CHCH_3$), and 1.23 (d, 3, J = 7 Hz, CH_3).

Anal. Calcd for $C_{10}H_{14}NO_2Cl$: C, 55.69; H, 6.54; N, 6.49. Found: C, 55.44; H, 6.68; N, 6.50.

***threo*-3-Amino-2-methyl-3-phenylpropanoic acid hydrochloride** (*threo* **13g**) had the following properties: mp 243–244° dec; ir (KBr), 5.80 μ (C=O); nmr (D_2O), δ 7.48 (s, 5, C_6H_5), 4.53 (d, 1, J = 10 Hz, CHC_6H_5), 3.40–2.80 (m, 1, $CHCH_3$), and 1.00 (d, 3, J = 7 Hz, CH_3).

Anal. Calcd for $C_{10}H_{14}NO_2Cl$: C, 55.69; H, 6.54; N, 6.49. Found: C, 55.71; H, 6.76; N, 6.26.

***meso*-3-Amino-2-ethylpentanoic acid hydrochloride** (*meso* **13i**) had mp 175–176° dec; ir (KBr), 5.89 μ (C=O).

Anal. Calcd for $C_7H_{16}NO_2Cl$: C, 46.28; H, 8.88; N, 7.71. Found: C, 45.98; H, 8.87; N, 7.50.

***dl*-3-Amino-2-ethylpentanoic acid hydrochloride** (*dl* **13i**) had mp 215–216° dec; ir (KBr), 5.86 μ (C=O).

Catalytic Reduction of β,γ-Unsaturated Amides (19) to Amides (15).—The general procedure used was the same as that for the conversion of **10** into **15**. Thus **9a, b, d,** and **i** were quantitatively and respectively converted into **15a, b, d,** and **i**.

Preparation of 3-Methyl-2-methylenebutanamide (20).—3-Methyl-2-methylenebutanoic acid (5.0 g) and thionyl chloride (7 g) were refluxed for 1 hr, followed by evaporation of the excess $SOCl_2$. The crude acid chloride was slowly added to 15 ml of 28% aqueous NH_3 maintaining the reaction temperature at 0°. The crude amide was filtered and dissolved in ether; the ethereal solution was dried ($MgSO_4$) and filtered, and 40 ml of hexane was added. The resulting solution was boiled until crystallization commenced, and then cooled to give 3.1 g (62%) of **20**: mp 103–104° (lit.[26] mp 104–105°); ir (KBr) 6.07 μ (C=O).

(26) V. P. Golmov and N. M. Afan'ev, *Zh. Obshch. Khim.*, **22**, 1953 (1952); *Chem. Abstr.*, **47**, 9269*b* (1953).

Treatment of either **19d** or **20** (1 g) in 10 ml of ethanol with 0.2 g of 5% Pd–C for 5 hr led only to recovery of starting material. Introduction of hydrogen into the system (50 psi) resulted in the quantitative conversion of both **19d** and **20** into **15d** in 15 min.

Ozonation of 1-Chlorosulfonyl-4,4-dimethyl-3-methylene-2-azetidinone (8d).—Excess ozone was bubbled through a cooled (−78°) solution of 0.523 g (2.50 mmol) of **8d** in 100 ml of CH_2Cl_2 with absorption of only 1.37 mmol of ozone. The solution was warmed to ambient temp, 25 ml of water was added and the two-phase system was refluxed overnight. The water layer was separated and added to 75 ml of a 10% alcoholic solution of 2,4-DNP·HCl. The precipitated product was filtered and recrystallized from methanol–water to give formaldehyde 2,4-dinitrophenylhydrazone, mp 166° (lit.[27a] mp 166°).

Diels–Alder Adduct of 3-Methyl-2-methylene-3-butenamide (10d).—An admixture of solutions of 1.1 g (0.01 mol) of **10d** in 20 ml of ether and 1.1 g (0.01 mol) of maleic anhydride in 30 ml of ether precipitated, after standing overnight, 1.9 g (90%) of **1-carboxamido-2-methyl-1-cyclohexene-4,5-dicarboxylic anhydride**: mp 160–161° (after cold acetone wash); ir (KBr), 5.41 and 5.73 (anhydride C=O) and 6.10 μ (amide C=O).

Anal. Calcd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.50; H, 5.43; N, 6.44.

1-(2-Carboxy-3-methyl-2-butenyl)urea (22).—Pyridine (4.0 g, 0.05 mol) in 20 ml of acetone was added (30 min) to a cooled (−30°) and stirred solution of 10.4 g (0.04 mol) of **1-chlorosulfonyl-1-(2-carboxy-3-methyl-2-butenyl)urea (11)** and 8.8 g (0.08 mol) of benzenethiol in 100 ml of acetone. The solution was stirred for an additional 30 min at −30°. Addition of 150 ml of petroleum ether (30–60°) precipitated a semisolid product which was filtered and washed several times with petroleum ether and then dissolved in 40 ml of hot water. The hot solution was decolorized (charcoal) and cooled to crystallize 4.5 g (70%) of **22**. One recrystallization from acetone gave **22**: mp 177–178°; uv max (CH_3OH), 217 mμ (ε 8000); ir (KBr) 5.98 and 6.10 μ (C=O).

Anal. Calcd for $C_7H_{12}N_2O_3$: C, 48.83; H, 7.02; N, 16.27. Found: C, 49.00; H, 7.19; N, 15.98.

Ozonation of 11.—Excess ozone (6 mmol) was bubbled through a cooled solution (−78°) of 1.4 g (5.2 mmol) of **11** in 100 ml of ethyl acetate. The solution was then flushed with nitrogen and warmed to ambient temperature; 25 ml of water was added and the two phase system was refluxed overnight. After cooling, the water layer was separated and added to a 10% ethanolic solution of 2,4-DNP·HCl. After 1 hr, the crude hydrazone was filtered and recrystallized from methanol–water to give 0.25 g (20%) of acetone 2,4-dinitrophenylhydrazone, mp 128° (lit.[27b] mp 126°).

Oxidation of 22 with $KMnO_4$–$NaIO_4$.—To a potassium carbonate buffered (pH ~8) solution of 0.86 (0.005 mol) of **22** in 75 ml of water was added 80 ml of an oxidation mixture composed of 0.31 g of $KMnO_4$ and 21.0 g of $NaIO_4$ in 200 ml of water. The mixture was stirred for 90 min at room temperature after which 15 g of $NaHSO_3$ was added to destroy excess oxidant. The solution was warmed to 80° and a nitrogen stream was dispersed into the solution exiting into 25 ml of 10% ethanolic 2,4-DNP·HCl solution. The stream was continued until no more precipitate formed. The crude material was filtered and recrystallized from methanol–water to give 0.9 g (74%) of acetone 2,4-dinitrophenylhydrazone, mp 127–128°.

1-(2-Carboxy-3-methylbutyl)urea (23).—Hydrogenation (0.1 g PtO_2) of **22** (2 g) in 100 ml of ethanol in a Paar apparatus under 50 psi of hydrogen (4 hr) gave **23**: mp 131–132° (from acetone); ir (KBr), 5.83 and 6.09 μ (C=O).

Anal. Calcd for $C_7H_{14}N_2O_3$: C, 48.26; H, 8.10; N, 16.08. Found: C, 48.57; H, 8.08; N, 15.91.

2-Carboxy-3-methylbutylamine (24).—A solution of **23** in 30 ml of 25% aqueous KOH was refluxed 12 hr. After cooling and neutralization with concentrated HCl, the solution was evaporated to dryness *in vacuo*. The residue was extracted with two 25-ml portions of boiling absolute ethanol and the ethanol extracts also were evaporated to dryness. The residue was again extracted with boiling absolute ethanol. Evaporation of this ethanolic solution led to **24** (0.40 g, 15%): mp 215° dec; ir (KBr), 6.18, 6.40, and 6.68 μ (CO_2^- and $^+NH_3$).

1-Benzamido-2-carboxy-3-methylbutane (25).—A 25% aqueous KOH solution (30 ml) was added (15 min) to a stirred solution composed of 1.0 g of **24** and 1.5 g of benzoyl chloride. Stirring was continued for an additional 15 min, after which the solution was acidified to pH 4 (congo red) and cooled. The solution was extracted with three 20-ml portions of ether; the combined ether extracts were dried ($MgSO_4$) and 40 ml of hexane was added. The solution was evaporated slowly (steam bath) until the cloud point. On cooling 0.9 g (51%) of **25** crystallized: mp 174–175°; ir (KBr), 5.91 (acid C=O) and 6.12 μ (amide C=O).

Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.33; H, 7.47; N, 6.11.

1-Benzamido-2-carboxy-3-methyl-2-butene (27).—Urea **22** (2.4 g) was refluxed (12 hr) in 25 ml of 30% aqueous KOH to give an aqueous solution of the salt of **1-amino-2-carboxy-3-methyl-2-butene (26)**.[28] Benzoylation of **26** was accomplished in the same manner as the preparation of **25** to give 2.4 g of **27**. Benzoylation of the water layer (after the ether extraction) ultimately led to an additional 0.2 g of **27**: total yield 77%; mp 149–150°; uv max (CH_3OH), 225 mμ (ε 18,000); ir (KBr), 5.98 and 6.20 μ (C=O).

Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.93; H, 6.72; N, 5.98.

Hydrogenation (PtO_2) of **27** quantitatively converted it into **25**. Further, hydrogenation (PtO_2) of **22**, followed successively by saponification with aqueous KOH and treatment with benzoyl chloride, also led to **25** in 47% over-all yield.

Preparation of 25 from Diethyl Isopropylmalonate (28).—Saponification of 200 g (0.99 mol) of **28** in 650 ml of absolute ethanol with 60 g (1.07 mol) of KOH in an equal volume of the same solvent led ultimately to 151 g (88%) of ethyl isopropylmalonic acid ester (**29**) as an oil[29] which was used without further purification.

Diethylamine (62 g, 0.85 mol) was added slowly with stirring to 146 g (0.85 mol) of **29** at 0° followed by more rapid addition of 85 ml of 40% aqueous CH_2O solution (1.0 mol). After several hours, the solution clouded and CO_2 began to evolve slowly. After 24 hr, the two-phase system was separated, and the lighter moiety was dissolved in 50 ml of ether and dried ($MgSO_4$). Evaporation of the ether followed by distillation *in vacuo* gave 73 g (60%) of **ethyl 3-methyl-2-methylenebutanoate (30)**, bp 57–58° (932 mm) (lit.[30] bp 150°). Saponification of 20 g (0.16 mol) of **30** with 20 g of KOH in 125 ml of water led, after acidification, to 15.5 g (97%) of **3-methyl-2-methylenebutanoic acid (31)**, bp 71–72° (4 mm) (lit.[30] bp 100° (19 mm)).

Anhydrous hydrogen bromide was bubbled slowly into a solution of 5.0 g of **31** in 30 ml of $CHCl_3$ until an ir spectrum of the solution showed the absence of the C=C absorption at 6.15 μ (*ca.* 6 hr). The chloroform solution was evaporated *in vacuo* leaving the crude **2-bromomethyl-3-methylbutanoic acid (32)** as an oil which was used without further purification. This crude material was dissolved in 50 ml of aqueous NH_3 (28%) and the tightly capped flask was stirred for 24 hr at 45–50°. The mixture was then evaporated to dryness *in vacuo;* the residue was extracted with two 30-ml portions of boiling absolute ethanol. This too was evaporated to dryness, and the resulting residue was dissolved in a minimum volume of hot absolute ethanol. Addition of ether to the cloud point of the ethanolic solution, followed by cooling, gave 3.7 g (65%) of **24**, mp 215°. Benzoylation of **24** gave **25**, identical in all respects with that obtained *via* the degradation of **11**.

Leuckart Reduction of Ethyl 2-Benzoylpropanoate (33).—A mixture of 20 g (0.097 mol) of **33**[31] and 25 g (0.40 mol) of ammonium formate was slowly heated in an oil bath to 185–190°, at which temperature it was maintained for 4 hr. The water formed was removed with a Dean–Stark apparatus. After cooling, the mixture was dissolved in 40 ml of ether and washed with four 50-ml portions of H_2O. The ether layer was then evaporated to dryness and 50 ml of concentrated HCl added to the residue. This mixture was refluxed 4 hr and evaporated *in vacuo*, and the residue was recrystallized from methanol–ether to give 4.1 g (18%) of *threo* **13g**, identical in all respects with that obtained from the hydrolysis of *trans* **18g**.

(27) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "Systematic Identification of Organic Compounds," 4th ed., John Wiley and Sons, Inc., New York, N. Y., 1958: (a) p 283; (b) p 316.

(28) This could be isolated in conventional fashion as the zwitterion of **26**, mp 238° dec.

(29) E. J. Corey, *J. Amer. Chem. Soc.*, **74**, 5897 (1952).

(30) G. Darzens, *Compt. Rend.*, **152**, 445 (1911).

(31) R. H. Kimball, G. D. Jefferson, and A. B. Pike, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p 284.

Mannich Reaction on Benzylmalonic Acid (34).—A mixture of 30 g (0.16 mol) of **34** (K & K Laboratories), 16.6 g (0.20 mol) of benzaldehyde, and 20 ml of 10% alcoholic NH_3 was heated for 1 hr on a steam bath and then 3 hr at 130° in an autoclave. The mixture was then added to 100 ml of 30% aqueous K_2CO_3 solution and the whole was extracted with three 70-ml portions of ether. The aqueous residue was slowly acidified with concentrated HCl and, on cooling, precipitated 7 g (19%) of **2-benzylcinnamic acid (35)**, mp 159–160° (from ethanol–water) (lit.[32] mp 160°). The aqueous filtrate was extracted with three 50-ml portions of ether. The ether extracts were dried ($MgSO_4$) and evaporated to dryness and the residue was recrystallized from ethanol–ether to give 8 g (18%) of a 58:42 *erythro–threo* mixture of **13f** as determined by nmr spectroscopy: mp 226–227° dec; ir (KBr), 5.87 and 5.90 μ (C=O).

Registry No.—**8a**, 13086-19-6; **8b**, 16934-01-3; **8d**, 13088-65-8; **8e**, 13085-96-6; **8f**, 16934-04-6; **8h**, 13085-97-7; **9a**, 13085-98-8; **9b** (*cis*), 16933-57-6; **9b** (*trans*), 16933-58-7; **9d**, 13085-95-5; **9e**, 13085-99-9; **9f**, 16933-61-2; **9g**, 16933-62-3; **9h**, 13086-00-5; **10a**, 16933-64-5; **10b** (*cis*), 16933-65-6; **10b** (*trans*), 16933-66-7; **10c**, 16933-67-8; **10d**, 13088-60-3; **10e**, 16933-69-0; **11**, 16933-70-3; **12a**, 16933-71-4; **12b**, 16933-72-5; **12d**, 16933-73-6; **12e**, 16933-74-7; **12f**, 16933-75-8; **12g**, 16933-76-9; **12h**, 16933-77-0; **13a**, 16933-78-1; **13b**, 16933-79-2; **13d**, 16933-80-5; **13e**, 16933-81-6; **13f** (*threo*), 16933-82-7; **13f** (*erythro*), 16933-83-8; **13g** (*threo*), 16933-84-9; **13g** (*erythro*), 16933-85-0; **13i** (*meso*), 16933-86-1; **13i** (*dl*), 16933-87-2; **17a**, 16933-88-3; **17e**, 16933-89-4; **17f**, 16933-90-7; **17g** (*cis*), 16933-91-8; **17g** (*trans*), 16933-92-9; **17i** (*cis*), 16933-93-0; **17i** (*trans*), 16933-94-1; **18a**, 16933-95-2; **18b**, 16933-96-3; **18e**, 16933-97-4; **18f** (*cis*), 16933-98-5; **18f** (*trans*), 16933-99-6; **18g** (*cis*), 16934-12-6; **18g** (*trans*), 16934-13-7; **18i** (*cis*), 16934-14-8; **18i** (*trans*), 16934-15-9; **19a**, 16934-16-0; **19b**, 16934-17-1; **19i**, 16934-18-2; **22**, 16934-19-3; **23**, 16934-20-6; **24**, 16934-21-7; **25**, 16934-22-8; **27**, 16934-23-9; 1-carboxamido-2-methyl-1-cyclohexene-4,5-dicarboxylic anhydride, 16934-24-0; chlorosulfonyl isocyanate, 1189-71-5.

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(32) W. M. Radionov and E. A. Postovskaja, *J. Amer. Chem. Soc.*, **51**, 841 (1929).

Azetidines. IV. The Reaction of 1,1-Dimethyl-, 1-Benzyl-1-methyl-, and 1,1-Dibenzyl-3,3-dimethylazetidinium Salts with Alkali Metal Amides in Liquid Ammonia[1-3]

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Of several possibilities, only the Stevens rearrangement product arising from enlargement of the azetidine ring was obtained from the reaction of 1,1,3,3-tetramethylazetidinium iodide (**1**) with potassium amide in liquid ammonia. Similarly, 1-benzyl-1,3,3-trimethylazetidinium iodide (**8**) gave only the ring-enlarged Stevens product even though, in this case, a Sommelet product was also possible. In contrast, 1,1-dibenzyl-3,3-dimethylazetidinium bromide (**13**) gave a 98% yield of the Sommelet product plus a small amount of the Stevens product with the azetidine ring retained. Ion-pair mechanisms best account for these results.

The reaction with sodium amide in liquid ammonia of tetraalkylammonium halides possessing a benzylic hydrogen was found by Kantor and Hauser[4] to be an excellent method for effecting the Sommelet rearrangement.[5] Subsequently Hauser and coworkers established, by two independent proofs,[6] that the mechanism for this reaction involved nucleophilic attack by an ylide carbon at the *ortho* position of the aromatic ring followed by tautomeric rearomatization.

The investigation of a number of quaternary salts of this type led to the implication that sodium amide in liquid ammonia was quite selective and gave exclusively either the Sommelet or the Stevens[7] (*e.g.*, with benzhydrylbenzyldimethylammonium ion[8]) rearrangement. More recent studies have shown that these early results were, at least in part, caused by a fortuitous choice of quaternary salts. Thus Jones, *et al.*,[9] Fery and Wilputte-Steinert,[10] Bumgardner,[11] and Jenny and Druey[12] have found examples in which the Stevens rearrangement accompanies the Sommelet rearrangement, and Klein and Hauser[13] have discovered that benzhydryltrimethylammonium ion, which had previously been reported to give only the Sommelet product, actually forms *ca.* 15% Stevens product.

The behavior of quaternary ammonium salts which do not possess a benzylic or similarly activated methylene group with alkali metal amides in liquid ammonia

(1) Part III: A. G. Anderson, Jr., and M. T. Wills, *J. Org. Chem.*, **33**, 2123 (1968).

(2) From the Ph.D. Thesis of M. T. Wills, University of Washington.

(3) Supported in part by State of Washington Initiative 171 Funds for Research in Biology and Medicine.

(4) S. W. Kantor and C. R. Hauser, *J. Amer. Chem. Soc.*, **73**, 4122 (1951).

(5) (a) M. Sommelet, *Compt. Rend.*, **205**, 56 (1937); (b) H. E. Zimmerman, "Molecular Rearrangements," part I, P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, pp 345–406; (c) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press Inc., New York, N. Y., 1965, pp 223–229.

(6) F. N. Jones and C. R. Hauser, *J. Org. Chem.*, **26**, 2979 (1961); C. R. Hauser and D. N. van Eanam, *J. Amer. Chem. Soc.*, **79**, 5512, 6280 (1957); *J. Org. Chem.*, **23**, 865 (1958).

(7) T. S. Stevens, E. M. Creighton, A. B. Gordon, and M. MacNicol, *J. Chem. Soc.*, 3193 (1928); T. S. Stevens, *ibid.*, 2107 (1930). The mechanistic relationship of the Stevens and Sommelet rearrangements have been discussed by D. J. Cram[5c] and H. E. Zimmerman.[5b]

(8) C. R. Hauser, R. L. Manyik, W. R. Brasen, and P. L. Bayless, *J. Org. Chem.*, **30**, 1119 (1955).

(9) G. C. Jones, W. Q. Beard, and C. R. Hauser, *ibid.*, **26**, 199 (1963).

(10) L. P. A. Fery and L. Wilputte-Steinert, *Bull. Soc. Chim. Belges*, **73**, 154 (1964).

(11) C. L. Bumgardner, *J. Amer. Chem. Soc.*, **85**, 73 (1963).

(12) E. F. Jenny and J. Druey, *Angew. Chem.*, **74**, 152 (1962).

(13) K. P. Klein and C. R. Hauser, *J. Org. Chem.*, **31**, 4275 (1966).

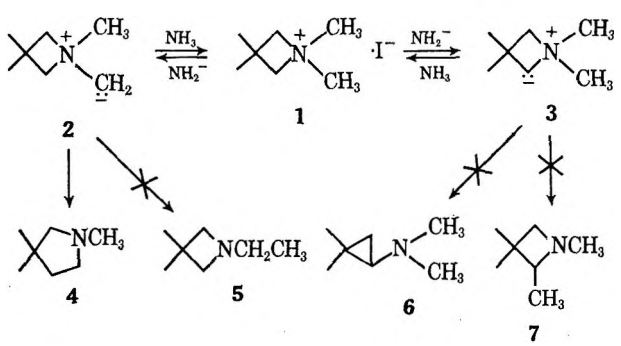
has been relatively little studied. Wittig and Burger[14] found that dimethylpyrrolidinium bromide gave Hofmann elimination products, dimethylpiperidinium bromide gave elimination and displacement products, and dimethylhexamethyleneammonium bromide gave a single elimination product. Thus no rearrangements were detected. The only rearrangement of such a system, to our knowledge, was found accidentally by Grovenstein and Rogers[15] to occur in the sodium–ammonia reduction of 2,2,2-triphenylethyltrimethylammonium iodide. A 93% yield of the Stevens product, 3,3,3-triphenylpropyldimethylamine, was obtained. The migration of the triphenylethyl (rather than a methyl) group was attributed to steric and electronic effects.

As a part of a study of tertiary and quaternary azetidines, we have examined the reactions of a series of methyl and benzyl quaternary azetidinium salts with alkali metal amides in liquid ammonia and have found that essentially exclusively Stevens or Sommelet rearrangements occur, depending on the structure of the quaternary ions.

Results and Discussion

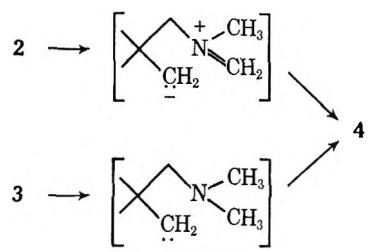
1,1,3,3-Tetramethylazetidinium Iodide (1).—The quaternary ion of this salt has two different types of α-hydrogens: those on the methyl and those on the ring methylene groups. The carbon–hydrogen bonds in the former would be sp^3 or nearly so, but the bonds in the latter would have relatively more S character and therefore would be more acidic.[16] The methylene hydrogens would be more sterically hindered, however, and thus the actual difference between the acidities of these and of the methyl hydrogens could be small. Qualitatively, therefore, both possible ylides (2 and 3) would be expected to be formed in appreciable amounts and four Stevens rearrangement products (4, 5, 6, and 7) could result *via* the usual ionic mechanism (Scheme I).

SCHEME I



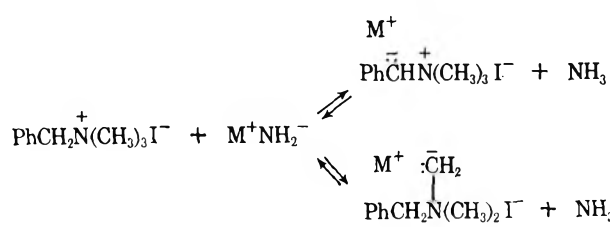
The reaction of 1 with potassium amide and liquid ammonia gave the Stevens product (4) in 70% yield. A small quantity (<1%) of higher molecular weight material of the same empirical formula was also obtained. The structure of 4 was indicated by the formation of a methiodide and a picrate, and by the nmr spectrum which consisted of a six-proton singlet at 1.03 ppm[17] (geminal methyls), two two-proton triplets (J = 3.5 cps) at 1.49 and 2.44 ppm (adjacent methylenes), a two-proton singlet at 2.14 ppm (isolated methylene), and a three-proton singlet at 2.17 ppm (N-methyl). None of the other three rearrangement products was found, nor were products derived from the nucleophilic attack on 1 by amide ion.

Thus the mechanism for this reaction must strongly favor the formation of 4 relative to the formation of 5, 6, or 7. Concerted processes did not appear to do this. An ion-pair mechanism, however, would release the strain of the four-membered ring only in the transition of 2 to the ion-pair intermediate leading to 4 (eq 1). A further possibility was the rearrangement of ylide 3 to 4 by a carbene mechanism.[18] The addition of a 5 molar excess of cyclohexene to one run, however, did not produce a detectable amount of a norcarane product.



(1)

1-Benzyl-1,3,3-trimethylazetidinium Iodide (8).—This salt possesses three types of α hydrogens including a benzylic group. Thus three ylides are possible and, from these, seven Stevens and two Sommelet products are possible. Although the benzylic hydrogens are the most acidic and the corresponding ylide can undergo only a Stevens rearrangement, a number of examples are known[5,9–13] where the Sommelet rearrangement is dominant even though it involves a more basic ylide than the competing Stevens. Puterbaugh and Hauser[19] have obtained evidence for the conversion of the less basic into the more basic ylide in such a case, and have suggested that the second ylide is in *direct* equilibrium with the first *via* a cyclic 1,3-prototropic shift or similar process. Although quantitative data on the acidities of the species involved is not available, qualitative considerations[20] point to proton transfer by equilibria with the ammonia solvent as an alternative possibility. In either scheme (eq 2) the more basic ylide is irre-



(2)

(14) G. Wittig and T. F. Burger, *Ann.*, **632**, 85 (1960).

(15) E. Grovenstein and L. C. Rogers, *J. Amer. Chem. Soc.*, **86**, 854 (1964).

(16) C. Juan and H. S. Gutowsky, *J. Chem. Phys.*, **37**, 2198 (1962).

(17) Chemical-shift values are reported as δ values in parts per million relative to tetramethylsilane as an internal standard.

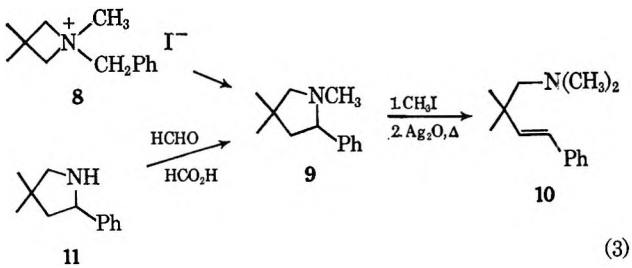
(18) G. Wittig and R. Polster, *Ann.*, **599**, 1 (1956); V. Franzen and G. Wittig, *Angew. Chem.*, **72**, 417 (1960); G. Wittig and D. Krause, *Ann.*, **679**, 34 (1964); F. Weygand, H. Daniel, and A. Schroll, *Ber.*, **97**, 1217 (1964).

(19) W. H. Puterbaugh and C. R. Hauser, *J. Amer. Chem. Soc.*, **86**, 1105 (1964).

(20) Tetramethylammonium iodide is metalated by phenyllithium [G. Wittig and M. H. Wetterling, *Ann.*, **557**, 193 (1947)] but not by benzylsodium [W. Schlenk and J. Holtz, *Ber.*, **50**, 274 (1917)]. These findings would place the acidity of the compound between those of benzene and toluene, and give an estimated pK_A of 36 on the McEwen–Streitwieser–Applequist–Dessy scale.[5c] A benzylic methylene group adjacent to the positive nitrogen would be expected to be *ca.* 2 pK_a units more acidic. Since the pK_a of ammonia is estimated to be 35 (R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959) or 36 [N. S. Wooding and W. C. Higginson, *J. Chem. Soc.*, 774 (1952)], the acidities of the α hydrogens and of the ammonia are not greatly different.

versibly removed by conversion into the Sommelet product, and it is not unlikely that both are operative.

When **8** was treated with potassium amide and liquid ammonia the solution became blood red in color and a 79% yield of a Stevens rearrangement product (**9**) was obtained. No Sommelet or other Stevens products were found (eq 3). The conversion of **9** into the methiodide derivative and then Hofmann degradation (eq 3)

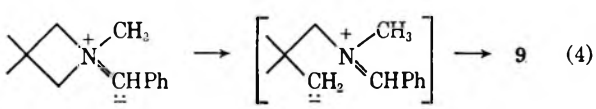


(3)

gave 4-dimethylamino-3,3-dimethyl-1-phenyl-1-butene (**10**), which was readily characterized by its nmr and ultraviolet spectra. The identification of **9** was confirmed by the Leuckart methylation of 2-phenyl-4,4-dimethylpyrrolidine (**11**).[21]

The reaction of **8** with sodium amide and liquid ammonia at a temperature (−50 to −45°) lower than that (−33°) used in the reaction with potassium amide resulted in the formation of a yellow-green color. There was obtained a 69% yield of **9** and a high boiling product which was not characterized.

As the benzylic hydrogens in **8** are probably about 100 times more acidic than the other α hydrogens,[5c] the benzylic ylide (**12**) would be formed the most readily. In addition, the rate of rearrangement of **12** must also be relatively fast since neither of the other possible rearrangement products from the methyl ylide (the Stevens as from **2** or the Sommelet as from **17**) was found. Again, no compounds which could have arisen from the ring carbanion ylide were detected and it is felt that an ion-pair mechanism as shown (eq 4) best accounts for the results.

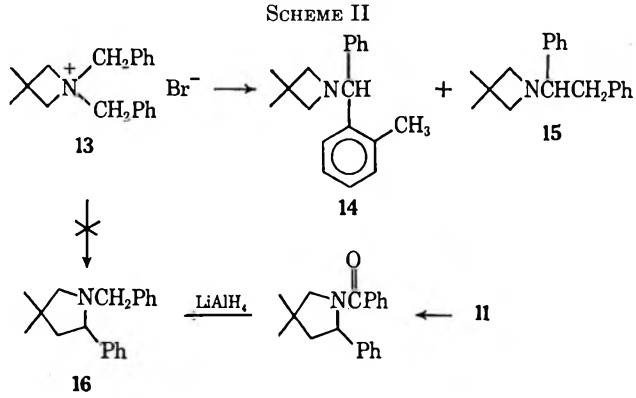


(4)

1,1-Dibenzyl-3,3-dimethylazetidinium Bromide (13).—From the reaction of **13** with either potassium amide or lithium amide in liquid ammonia were obtained a 98% yield of a Sommelet rearrangement product (**14**) and 2% yield of a Stevens rearrangement product (**15**) (see Scheme II). Potassium amide caused the reaction mixture to become red-brown in color whereas no color was produced with lithium amide. The expected ring-expanded Stevens product (**16**) was not found. To be certain that **16** was not present, it was synthesized by the lithium aluminum hydride reduction of the benzamide derivative of **11** and its gas chromatographic properties were determined and compared with those of **14** and **15**. The identity of the Sommelet product (**14**) was shown by its nmr spectrum and the comparison of the nmr spectrum of its methiodide derivative with that of the independently synthesized methobromide. The latter was prepared by the reaction

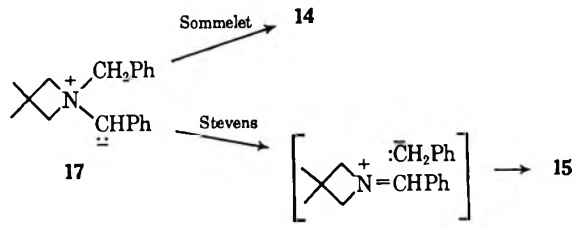
(21) A. G. Anderson, Jr., and M. T. Wills, *J. Org. Chem.*, **32**, 3241 (1967).

SCHEME II



of 1,3,3-trimethylazetidine with bromophenyl-*o*-tolylmethane.

The exclusive Stevens rearrangement with ring expansion found for both **1** and **8** made the results with **13** somewhat unexpected. This was especially true with respect to formation of **15** rather than **16**. Thus both products obtained must arise from the benzyl carbanion ylide (**17**), and the ion pair shown is considered to be the most likely intermediate in the Stevens rearrangement. In a separate experiment the reaction of **13** with sodium ethoxide in ethanol appeared to give selective (96%) nucleophilic displacement at a ring methylene rather than at a benzylic or *ortho* carbon.



Experimental Section[22]

Reaction of 1,1,3,3-Tetramethylazetidinium Iodide (1)[1] with Potassium Amide in Liquid Ammonia.—A solution of 59 mmol of KNH_2 in 150 ml of liquid NH_3 was prepared in the manner described by Hauser and Harris[23] from 2.3 g (59 mg-atom) of K metal which had been washed free of mineral oil with isooctane. Commercial anhydrous NH_3 was dried by allowing it to vaporize through a tube filled with solid NaOH. Freshly distilled cyclohexene (10 ml)[24] and then 4.2 g (17.5 mmol) of pulverized **1** were added, the latter in portions over a period of 10 min with stirring. No color developed. Stirring was continued at the boiling point (−33°) for 10 hr. After the careful addition of 3 g (59 mmol) of solid NH_4Cl, 100 ml of ether was added slowly and the NH_3 was allowed to evaporate (overnight). The residual mixture was filtered, the solid salts were washed with ether, and the total filtrate was extracted with two 50-ml portions of 5% H_2SO_4. The acidic extract was washed with two 50-ml portions of ether, then cooled and made strongly basic with 50% NaOH solution.

(22) Melting points were taken on a Thomas–Hoover capillary melting point apparatus and are uncorrected. Ultraviolet spectra were recorded with a Cary Model 14 recording spectrophotometer. Infrared spectra were recorded with a Perkin-Elmer Model 21 infrared spectrophotometer. Mass spectra were recorded by Mr. R. Buddemeier on a Consolidated Engineering Corp. mass spectrometer, Type 21-103. Nuclear magnetic resonance spectra were recorded on a Varian Associates Model A-60 analytical nmr spectrometer and values are reported in parts per million (δ) relative to tetramethylsilane as an internal standard. Vapor phase chromatographic analyses were performed on an Aerograph Model 600 (Hy-Fi) apparatus using a 0.125-in. by 5-ft column of 20% cyanosilicone (XF-1150) on 60–80 mesh Chromosorb W unless otherwise indicated. Elemental analyses were performed by Dr. A. Bernhardt, Max Planck Institute, Mülheim (Ruhr), Germany.

(23) C. R. Hauser and T. M. Harris, *J. Amer. Chem. Soc.*, **80**, 6360 (1958).

(24) Other runs were identical except that no cyclohexene was added.

A solution of the organic layer in 70 ml of ether was dried ($CaSO_4$), concentrated by distillation through a 50-cm glass helices packed column, and the residue was transferred to a small one-piece distillation apparatus. 1,3,3-Trimethylpyrrolidine (**4**) was collected (0.95 g) as a colorless liquid: bp 110–111°; $n^{25}D$ 1.4192.[25] The ethereal forerun on treatment with picric acid gave 1 g of the picrate salt of **4**, corresponding to 0.31 g of the amine. The total yield was thus 1.26 g (70%). The methiodide derivative was obtained as granular crystals, mp 330–332°. A sample of **4** gave a single peak on vapor phase chromatography over silicone (20 ft), Ucon Polar, and polyester columns: nmr (CCl_4), δ 1.03 (s, 6), 2.14 (s, 2), 2.17 (s, 3), 1.49 (t, 2, J = 3.5 Hz), and 2.44 (t, 2, J = 3.5 Hz).

Anal. Calcd for $C_7H_{15}N$: mol wt, 113. Found (mass spectroscopy): mol wt, 113.

Recrystallization of the picrate twice from absolute ethanol afforded the analytical sample, mp 220–224° dec (lit.[25] mp 226–227°).

Anal. Calcd for $C_{13}H_{18}N_4O_7$: C, 45.61; H, 5.30; N, 16.35. Found: C, 45.63; H, 5.29; N, 16.32.

The residue from the distillation yielded 15 mg of colorless plates: mp 103–104°; nmr (CCl_4), δ 0.84 (s, 9 or 10), 1.99 (s, 2), and 2.44 (s, 4). A picrate, after recrystallization from ethanol, melted at 263–266° dec. The substance was not characterized further.

Anal. Calcd for $(C_{13}H_{18}N_4O_7)_n$: C, 45.61; H, 5.30; N, 16.35. Found: C, 45.79; H, 5.38; N, 16.36.

2-Phenyl-1,4,4-trimethylpyrrolidine (**9**).—A mixture of 0.7 g (4 mmol) of 4,4-dimethyl-2-phenylpyrrolidine,[21] 1 g (20 mmol) of formic acid, and 0.5 ml (6 mmol) of aqueous 37% formaldehyde was heated to 95° and maintained at this temperature for 8 hr. The mixture was cooled, 3 ml of 4 *N* aqueous HCl was added, and the whole was then evaporated to dryness under reduced pressure. The brown, crystalline residue was dissolved in water and the basified (NaOH) solution was extracted with ether. The ethereal extract was dried (Na_2SO_4), concentrated, and distilled, giving 0.6 g (80%) of **9** as a colorless oil: bp 100–101° (6 mm), bp 43–44° (0.2 mm); $n^{25}D$ 1.5030. Vapor phase chromatography at 120° of a sample gave a single peak with a retention time of 3 min. After recrystallization from ethanol, the picrate melted at 111–113° and the methiodide, obtained as tiny, tan needles, melted at 201–202°. The infrared and nmr spectra were recorded.

Anal. Calcd for $C_{13}H_{19}N$: C, 82.47; H, 10.12; N, 7.40. Found: C, 82.54; H, 10.00; N, 7.47.

4-Dimethylamino-3,3-dimethyl-1-phenyl-1-butene (**10**).—A solution of 0.58 g (3.07 mmol) of 2-phenyl-1,4,4-trimethylpyrrolidine (**9**) in 3 ml of acetonitrile was treated with excess CH_3I and then stirred for 2 hr. After evaporation of the solvent and excess CH_3I, 2 ml of H_2O and 0.46 g (6 mmol) of Ag_2O were added and the mixture was stirred for 3 hr. After filtration and evaporation of the filtrate to dryness under reduced pressure, the residue (presumed to be the quaternary ammonium hydroxide) was heated at 100–150° (0.5–0.1 mm). There was obtained 0.2 g (33%) of **10** as a colorless oil, bp 89–90° (1 mm). Vapor phase chromatography on a Craig polyester column at 175° gave a single peak with a retention time of 10 min; ir (CCl_4), 6.22 μ (weak, conjugated double bond); uv max (95% EtOH) mμ (log ε) at 250 (4.04), 284 (2.98), and 292 (2.79); nmr (CCl_4), δ 1.07 (s, 6), 2.16 (s, 2), 2.20 (s, 6), 6.16 (s, 2), and 7.13 (m, 5).

The methiodide, after three recrystallizations from ethanol, melted at 185–186°.

Anal. Calcd for $C_{15}H_{24}NI$: C, 52.15; H, 7.01; N, 4.06. Found: C, 52.08; H, 7.14; N, 3.93.

Reaction of 1-Benzyl-1,3,3-trimethylazetidinium Iodide (8) with Alkali Amide and Liquid Ammonia. A. With Potassium Amide.—To a solution of 60 mmol of KNH_2[23] in 150 ml of liquid NH_3 was added 6.4 g (20 mmol) of **8** in portions over a period of 1 hr and the mixture was then stirred at −33° for 2 hr. During the addition the solution became deep red in color. The addition of 4 g of solid NH_4Cl discharged the color. Ether (65 ml) was added and then the NH_3 was evaporated. Filtration and evaporation of the ether gave 3.2 g of reddish oil. Distillation of 2.7 g of this product afforded 2.5 g (corresponding to 79%) of 2-phenyl-1,4,4-trimethylpyrrolidine (**9**) as a colorless oil, bp 105–106° (10 mm). Vapor phase chromatography of the product showed only one component and the substance was identical (infrared and nmr spectra, vpc retention time, and mixture melting point of picrate) with an authentic sample.

Treatment of **9** with excess CH_3I, then with Ag_2O, and, finally, heating under reduced pressure as described for the preparation of **10** gave a product which was identical (ultraviolet, infrared, and nmr spectra) with an authentic sample of **10**.

B. With Sodium Amide.—To a cooled (−50°), stirred suspension of 5.85 g (0.15 mol) of $NaNH_2$ in 300 ml of liquid NH_3 was added 15.9 g (0.05 mol) of **8** in portions over a period of 1.5 hr and then stirring was continued at −50 to −45° for 1 hr. The color of the reaction mixture was yellow-green. After the addition of 7.4 g of solid NH_4Cl the mixture was worked up as described in part A and there was obtained 6.52 g (69%) of **9**, bp 43–44° (0.2 mm), plus some higher boiling material which was not identified.

1-(Phenyl-*o*-tolylmethyl)-1,3,3-trimethylazetidinium Bromide.—An equimolar (6 mmol) mixture of phenyl-*o*-tolylmethyl bromide [bp 141–145° (0.8 mm), lit.[26] bp 136–138° (0.3 mm); $n^{25}D$ 1.6154], prepared from the treatment of the corresponding carbinol[27] with HBr,[28] and 1,3,3-trimethylazetidine[1] in CH_3CN (5 ml) was stirred at room temperature for 4 hr and then diluted with ether. The precipitated bromide salt was recrystallized from ethanol–ether, mp 124–130°. The nmr spectrum was identical with that of the corresponding iodide obtained from **14**.

Reaction of 1,1-Dibenzyl-3,3-dimethylazetidinium Bromide (13) with Alkali Amide in Liquid Ammonia. A. Potassium Amide.—To 60 mmol of KNH_2[23] in 150 ml of liquid NH_3 was added 7 g (20 mmoles) of **13** in portions over a period of 1 hr and the mixture was stirred at −33° for 2.5 hr. The red-brown color which developed was discharged when 4 g of solid NH_4Cl was added. After the addition of 75 ml of ether, the NH_3 was allowed to evaporate. Filtration and then evaporation of the ether left 5.6 g of a viscous yellow oil which solidified on standing. Distillation gave 5.2 g (98%) of a colorless oil [bp 108–110° (0.15 mm), $n^{25}D$ 1.5519] which solidified on standing, mp 48–51°. The nmr spectrum corresponded to that expected for 3,3-dimethyl-1-(phenyl-*o*-tolylmethyl)azetidine (**14**).

Anal. Calcd for $C_{19}H_{23}N$: C, 85.99; H, 8.73; N, 5.28. Found: C, 85.96; H, 8.71; N, 5.38.

The picrate after one recrystallization from ethanol melted at 233–234°. The structure of **14** was confirmed by the identity of the nmr spectrum of its methiodide, mp 150–156° dec (after recrystallization from ethanol), with that of a synthetic sample of the corresponding methobromide.

Anal. Calcd for $C_{20}H_{26}NI$: C, 58.97; H, 6.43; N, 3.44. Found: C, 59.10; H, 6.48; N, 3.56.

Vapor phase chromatography of the product at 190° indicated it to consist of 98% **14** and 2% a substance which was identified by its retention time as 3,3-dimethyl-1-(1,2-diphenylethyl)-azetidine (**15**).[21] No evidence for the presence of **16** was found.

B. With Lithium Amide.—To the $LiNH_2$ formed from 0.105 g (15 mg-atoms) of Li wire and 50 ml of dry liquid NH_3 as given in the literature[29] was added with stirring 1.73 g (5 mmol) of **13** over a 20-min period and stirring was continued at −33° for 4 hr. No color developed. The mixture was worked up as described under part A and afforded 1.28 g (97%) of product as a yellow oil which was identical (picrate, mp 233–234°; vapor phase chromatographic analysis showed 98% **14** and 2% **15**) with that obtained in A. No **16** was found.

1-Benzyl-4,4-dimethyl-2-phenylpyrrolidine (**16**).—Benzoyl chloride (1.4 g, 10 mmol) was slowly added to 0.85 g (5 mmol) of 4,4-dimethyl-2-phenylpyrrolidone,[21] with stirring, followed by 4 ml of 10% NaOH. Stirring was continued for 30 min and the mixture was then extracted with 50 ml of ether. The ethereal extract, after being washed with dilute sodium hydroxide and then water, was evaporated to dryness. Recrystallization of the residue from aqueous ethanol and then from absolute methanol gave 1.3 g (61%) of a product presumed to be the benzoyl derivative, mp 104–106°.

A solution of the derivative in 30 ml of dry ether was added over a 5-min period to 30 ml of ether containing 0.5 g of $LiAlH_4$.

(25) N. J. Leonard and V. W. Gash, *J. Amer. Chem. Soc.*, **76**, 2781 (1954). These authors reported bp 77–79° and $n^{20}D$ 1.3842 for **4**. The discrepancy between these values and those of the present work led to the further characterization of our product.

(26) I. Lapkin and O. M. Lapkina, *J. Gen. Chem. USSR* (Eng. transl.), **25**, 911 (1955).

(27) J. F. Norris and J. T. Blake, *J. Amer. Chem. Soc.*, **50**, 1808 (1928).

(28) A. H. Wragg, T. S. Stevens, and D. M. Ostle, *J. Chem. Soc.*, 4057 (1958).

(29) C. R. Hauser and W. H. Puterbaugh, *J. Amer. Chem. Soc.*, **75**, 1068 (1953).

The mixture was refluxed for 4 hr, treated with 2 ml of saturated Na_2CO_3, filtered, and finally extracted with 30 ml of 5% aqueous HCl. The acidic extract was extracted with ether and then basified with excess 50% NaOH. The organic layer which formed was taken up in ether and the dried (Na_2SO_4) ether solution was evaporated to dryness. Distillation of the residue under reduced pressure gave 0.72 g (55%) of **16** as a colorless oil [bp 119–120° (0.2 mm), $n^{24}D$ 1.5467] which solidified on standing, mp 48.5–49.5°. The nmr spectrum was consistent with the structure assigned.

Anal. Calcd for $C_{19}H_{23}N$: C, 85.99; H, 8.73; N, 5.28. Found: C, 86.14; H, 8.84; N, 5.36.

The picrate melted at 125–127° after recrystallization from ethanol.

Reaction of 1,1-Dibenzyl-3,3-dimethylazetidinium Bromide (13) with Sodium Ethoxide.—Compound **13** (5 mmol, 1.73 g) was added to 50 ml of ethanol containing 20 mmol (1.36 g) of sodium ethoxide and the homogeneous solution was refluxed for 10 hr. Water (25 ml) was then added and the ethanol was removed by distillation. An ethereal extract of the residue was dried over Na_2SO_4 and the solvent was then evaporated. The yellow oil (1.5 g, 96%) which remained, $n^{25}D$ 1.5268, was indicated to be 3-dibenzylamino-2,2-dimethyl-1-ethoxypropane by its relatively long (10.5 min) retention time on vapor phase chromatography at 195°, by its infrared spectrum, and by its nmr spectrum (CCl_4): δ 0.75 (s, 6), 2.42 (s, 2), 3.02 (s, 2), 3.54 (s, 4), 1.05 (t, 3, J = 3.5 Hz), 3.26 (q, 2, J = 3.5 Hz), and 7.20 (m, 10).

Registry No.—**4,** 16911-20-9; **4** methiodide, 16959-96-9; **9,** 16911-21-0; **9** picrate, 16911-22-1; **9** methiodide, 16957-22-5; **10,** 16911-23-2; **10** methiodide, 16911-24-3; **14,** 16911-25-4; **14** methiodide, 16911-26-5; **14** picrate, 16911-27-6; **16,** 16911-28-7; **16** picrate, 16911-29-8; 3-dibenzylamino-2,2-dimethyl-1-ethoxypropane, 16911-30-1; ammonia, 7664-41-7.

Pyrrolo[1,2-*a*]indole Chemistry. Reactions of a Tridentate Carbanion[1]

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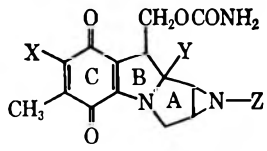
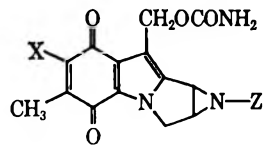
The pyrrolo[1,2-*a*]indole anion **8** has been acylated by a group of electrophiles, including ethyl carbonate, ethyl chloroformate, dimethyl oxalate, phenyl isocyanate, and carbon dioxide. Its tridentate character has been demonstrated by the isolation of products arising from attack at the 1, 3, and 9 positions. One product, the ester **11**, is the first simple example of the 3H-pyrrolo[1,2-*a*]indole system. The chemistry of ester **11** was studied, to no avail, as a possible route to the mitomycin structural array **1** or **2**.

The tetracyclic array of the mitomycins **1** and the stereochemically simpler aziridinomitosenes **2** is a



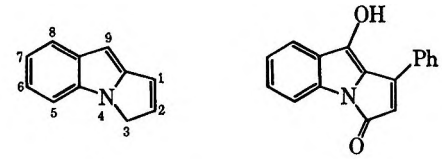
1



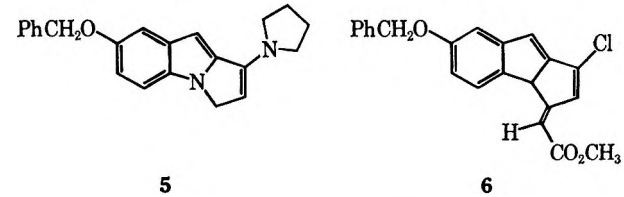
2

unique heterocyclic system with potent biological activity.[2] Substantial progress has been made by a Lederle group[3] in the elaboration of synthetic pathways to various tricyclic derivatives in the pyrrolo[1,2-*a*]indole series. However, the final attainment of a tetracyclic product by attaching an aziridine moiety to the tricyclics using a variety of cyclization methods was not achieved.

Our paper approach to the synthetic problem of aziridine annelation was to obtain a tricyclic compound **3** with unsaturation in the position appropriate for ring addition *via* the elegant method of dipolar addition of azide[4] followed by subsequent photochemical decomposition of the resultant triazoline.[5] The major drawback to our scheme was that the simple 3H-pyrrolo[1,2-*a*]indole structure **3** was not known. The early report of a dehydrative acetylation of N-phenacylanthranilic acid to afford 9-hydroxy-3-keto-1-phenyl-3H-pyrrolo[1,2-*a*]indole (**4**) is not correct.[6,7] The enamine **5**, not completely characterized, may be an example of the desired system.[3b] An authentic, but more complex, 3 H derivative, the 3-methylenecarboxylate **6**, has

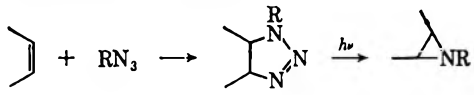


3 **4**



5 **6**

been characterized as well.[8] Two independent syntheses directed toward the preparation of the simple heterocycle **3** both afforded the isomeric 9H-pyrrolo[1,2-*a*]indole (**7**). The Hofmann elimination route (Scheme I, path 1)[3b] and the elegant and general heterocyclic synthesis *via* a vinylphosphonium salt (Scheme I, path 2)[9] are usually unambiguous, position-specific



(1) (a) Presented at the Third Middle Atlantic Meeting of the American Chemical Society, Philadelphia, Pa., Feb 2, 1968, Abstracts, p H74. (b) Taken from the Ph.D. Thesis of K. F. B., Fordham University, 1968. (c) This research was supported by a grant from the Public Health Service, NIH GM 12758, for which we are most grateful.

(2) (a) J. S. Webb, D. B. Cosulich, J. H. Mowat, J. B. Patrick, R. W. Broschard, W. E. Meyer, R. P. Williams, C. F. Wolf, W. Fulmor, C. Pidacks, and J. E. Lancaster, *J. Amer. Chem. Soc.*, **84**, 3187 (1962); (b) J. B. Patrick, R. P. Williams, W. E. Meyer, W. Fulmor, D. B. Cosulich, R. W. Broschard, and J. S. Webb, *ibid.*, **86**, 1889 (1964).

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(7) R. W. Franck and J. Usilton, Fordham University, unpublished results, 1966.

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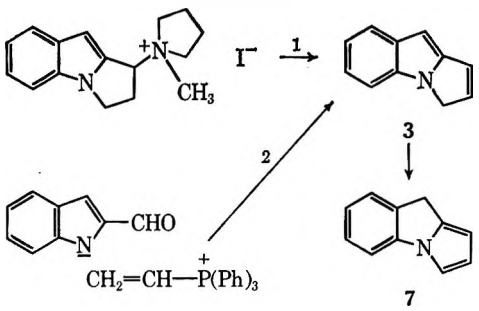
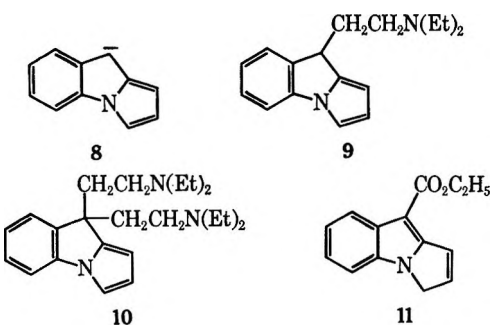
SCHEME I

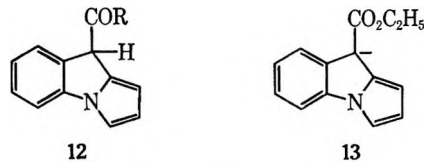


methods. Thus, it must be concluded that the 3 H product is less stable than the 9 H isomer, a fact which is supported by Hückel molecular orbital calculations.[3b,8,10] Our attention was directed toward obtaining a 3 H isomer that was stabilized relative to the 9 H compound. We proposed to accomplish this goal *via* utilization of the anion **8** of heterocycle **7**, previously described by Huisgen.[11] The reported alkylation of the anion with diethylaminoethyl chloride apparently gave exclusively the 9-alkyl product **9**. It was our plan to study the introduction of acyl groups in a similar manner.

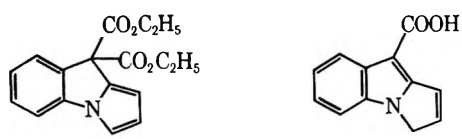
The anion **8** is prepared by treating the heterocycle **7** with butyllithium. When the reaction with diethylaminoethyl chloride was repeated, the discharge of the green anion (estimated visually) took 20 hr. Three products were detected by vapor phase chromatography (vpc) of the reaction mixture. The major product (85%) was the 9-alkyl compound **9**, its structural assignment based on an nmr spectrum with 3 pyrrole protons. Also, the 9,9-dialkyl product **10** (12%) was isolated, its characterization based on its nmr with 3 pyrrole and 28 diethylaminoethyl protons. The third product (3%) was not characterized. The formation of bisalkyl product can be explained by invoking equilibration of anion **8** with monoalkyl **9** to afford neutral **7** and the anion of **9**. When the anion **8** was added to excess diethyl carbonate, instantaneous reaction was observed. Immediate work-up of the mixture afforded material which could be purified by silica gel chromatography to yield recovered **7** (33%) and 9-carbethoxy-3H-pyrrolo[1,2-*a*]indole (**11**) (18%). Strong evidence



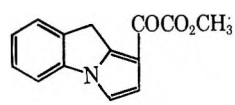
for the proposed structure is the appearance of 2 vinyl protons in the nmr spectrum of **11**; the lines appeared as doubled triplets at δ 6.32 and 6.77 (J_{12} = 6.0 and J_{13} = J_{23} = 2.0 Hz, the J_{12} being far outside the limit for vicinal coupling in pyrroles).[12] The grouping of uv maxima in the 240-and 320-mμ region with a minimum at 280 mμ (compare pyrrole **7**, uv max 265 mμ) is in agreement with every 2-vinylindole that we know of.[13] That the 3 H isomer in this system could be more stable than the 9 H isomer is supported by molecular orbital calculations.[10] The recovery of starting heterocycle **7** can be explained by considering that the intermediate acylation product **12**, more acidic than **7**, reacts with anion **8** to form anion **13** and neutral **7**. This



proton transfer must occur more rapidly than condensation of **8** with diethyl carbonate. Eventual work-up by protonation of **13** affords the product **11**. A more reactive acylating agent, ethyl chloroformate, was used so that the acylation of **8** would be a faster process. The products isolated were the 9,9-bis acylated product **14** (13%) (3 pyrrole and 10 ethyl protons in the nmr) and recovered starting material **7** (35%). This course must come from further acylation of anion **13**, with ethyl chloroformate being more reactive than diethyl carbonate which does not give bis acylation with short reaction time. When carbon dioxide was employed as the electrophile with anion **8**, 9-carboxy-3H-pyrrolo-[1,2-*a*]indole (**15**) was isolated in 7% yield and starting



7 was recovered in 74% yield. The acid **15** lost CO_2 on melting and also upon column chromatography. When dimethyl oxalate was the electrophile in the condensation, the major product isolated by chromatography was the 1-substituted 9 H compound **16** (13%). Its struc-



(12) A. R. Katritzky in "Physical Methods in Heterocyclic Chemistry," Vol. II, A. R. Katritzky, Ed., Academic Press Inc., New York, N. Y., 1963, p 128.

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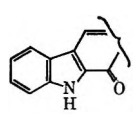
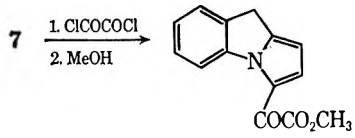


(10) C. Sherr, R. Cloney, K. Bernady, E. Leser, and R. W. Franck, Fordham University, unpublished results, 1967.

(11) E. Laschtuvka and R. Huisgen, *Chem. Ber.*, **93**, 81 (1960).

tural assignment is based on the nmr showing two pyrrole protons and no deshielded aromatic proton (at C_8) characteristic of the anisotropic effect of a carbonyl at the 9 position. Also a 1% yield of the 3-oxalylated compound **17** was obtained. A sample of **17** was independently prepared *via* oxalylation of **7**. In addition,



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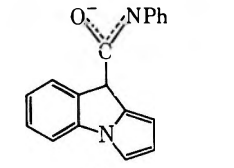
34% recovery of **7** was obtained. The anion **8** was condensed with phenyl isocyanate, since the initial condensation product **18**, being anionic, would not participate in a proton transfer with **8** since the result would be a dianion. In the event, the products isolated were the 9,9-diacylated compound **19** (3%), the 1-acyl product **20** (1%), the 3-acyl isomer **21** (14%), and recovered **7** (13%). All the products had nmr spectra consistent with the 9H-pyrrolo system. The products isolated are an example of the trapping of all three positions of the tridentate anion **8** in a single reaction.



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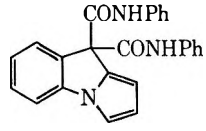

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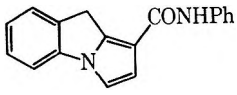

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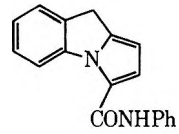

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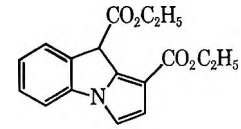
All the acylations appeared to be instantaneous reactions whereas the alkylation first described was slow. Since the alkylating agent contained a tertiary amine grouping, it was hypothesized that this amine function was forming a stable coordination complex with anion **8**, a well-known phenomenon of tertiary amines and organolithiums.[14] Further, we felt that the complex was unreactive and only its dissociation to free organolithium would provide a species that would alkylate or acylate. Thus the acylation with diethyl carbonate was repeated with prior addition of triethylamine to preformed anion **8**. The reaction was slowed markedly with incomplete discharge of the color of anion **8** after 4 hr. Work-up of the mixture at this point afforded the previously obtained 3 H ester **11** (9%), the 1,9 diester **22** (3%), and recovered **7** (76%). The diester **22** was clearly in the 9 H, or pyrrole, series, with its longest wavelength uv maximum at 272 mμ and with two typical pyrrole protons at δ 6.89 and 7.15 (J = 3 Hz). In a similar experiment where the reaction mixture was allowed to



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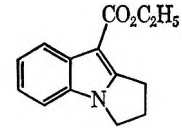
stand for 24 hr prior to work-up, the yield of diester **22** increased to 6% and monoester **11** was present in less than isolable quantity (detected only by tlc). The difference in structure of the bis acyl product obtained under these conditions compared with the rapid reaction with ethyl chloroformate suggests that the latter case is one of kinetic control of product formation, while the former is a case where thermodynamic factors determine the product formed. The conclusions that we can draw about the reactions of the carbanion **8** are that the nature of the acylating agent does play some role in the determination of the product in a way that we cannot as yet interpret. Also, we note that this system is a case of a demonstrably tridentate carbanion.

With ester **11**, the first simple member of the 3H-pyrrolo[1,2-*a*]indole class, in hand, we set out to study its chemistry to determine whether an aziridine function could be introduced as had been planned originally. Hydrogenation of the vinylic double bond of **11** to afford indole ester **23** proceeded in 99% yield. This was



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the only usable reaction we could perform with **11**. Our first attempts at aziridine introduction at the vinylic bond were based on the method of triazoline formation (*vide supra*).[4,5] No useful result was obtained upon reaction of **11** with methyl azide, *p*-bromophenyl azide, or carbethoxy azide, over a gamut of conditions and solvents. Since the dipolar addition reaction of azides has been shown to be sensitive to steric effects, ring strain features, and bond polarities,[4] and since none of the favorable sort of features is incorporated in **11**, the failure of this approach was not totally unexpected. We then turned to the less discriminate method of nitrene insertion as a means of aziridine synthesis.[15] Both photochemical and ordinary methods of nitrene generation were used. Many products were detected by tlc. One preparative tlc fraction was isolated which had ir and uv spectra (see Experimental Section) which were in agreement with what one would have predicted for the desired product, but a satisfactory nmr spectrum could not be obtained. The iodine isocyanate method of aziridine synthesis was examined[16] and found wanting. This was expected since the simpler electrophilic attack of ester **11** by bromine had given a very complex mixture. Our investigations with ester **11** have been suspended at this point while our laboratory turns to other varieties of unsaturated tricyclics.

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Experimental Section[17,18]

9H-Pyrrolo[1,2-*a*]indole (7).—Material of mp 90–91°, prepared as previously described, was used in the following experiments.[19]

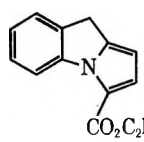
Lithium Anion of 9H-Pyrrolo[1,2-*a*]indole (8).—The anion employed in the subsequent condensations was prepared by addition of a 10 *M* % excess of a hexane solution of *n*-butyllithium (Foote) to an approximately 0.3 *M* solution of 9H-pyrrolo[1,2-*a*]indole in anhydrous diethyl ether. The solution was stirred for 15 min before further reaction at which time it appeared a Brunswick green.

Condensation of the Anion with β-Chloroethyldiethylamine.[11]—To a solution of the anion (3.00 mmol) in 20 ml of anhydrous diethyl ether was added a solution of 410 mg (3.02 mmol) of β-chloroethyldiethylamine in 2 ml of diethyl ether. The mixture was stirred for 20 hr after which the lithium chloride was filtered off and the solvent was removed. The resulting oil was evaporatively distilled at 140–150° (0.30 mm) yielding 20 mg of starting hydrocarbon followed by 645 mg of a pale yellow distillate whose tlc, vpc, and nmr spectrum revealed it to contain a trace of **7** and a mixture of alkylated products. A benzene solution of the distillate was subjected to gas chromatography at 247°. The mixture was resolved into three components of retention times of 4.4, 5.5, and 7.7 min in a ratio of 15:1:3.5, respectively. Samples of each component were collected and analyzed by nmr. The first component appeared to be the monoalkylated product **9-β-diethylaminoethyl-9H-pyrrolo[1,2-*a*]indole (9)**: nmr (CCl_4), δ 0.95 (t, 6, CH_3CH_2), 1.97 (m, 2, CH_2CH), 2.50 (m, 6, CH_2N), 3.98 (m, 1, HC-9), 6.03 (dd, 1, HC-1), 6.28 (t, 1, HC-2), 6.95 (dd, 1, HC-3), 7.00–7.33 (m, 4, aromatic). Insufficient amounts of the second component were collected to permit identification. The third component appeared to be the dialkylated product, **9,9-di-β-diethylaminoethyl-9H-pyrrolo[1,2-*a*]indole (10)**: nmr (CCl_4), δ 0.78 (t, 12, CH_3), 2.00 (broad s, 4, CH_2), 2.29 (m, 12, CH_2N), 6.02 (m, 1, HC-1), 6.32 (m, 1, HC-2), 6.98 (m, 1, HC-3), 7.05–7.38 (m, 4, aromatic).

Condensation of the Anion with Diethyl Carbonate. 9-Carbethoxy-3H-pyrrolo[1,2-*a*]indole (11).—A solution of the anion **8** (33.82 mmol) in 110 ml of anhydrous ether was added as rapidly as possible to an ice-cooled solution of 4.0 g (34 mmol) of diethyl carbonate, redistilled from P_2O_5, in 40 ml of diethyl ether. The resulting mixture was immediately hydrolyzed with ice and dilute hydrochloric acid. Standard work-up afforded a deep red oil. Tlc of the oil displayed the presence of starting hydrocarbon and one major new product: ir (CCl_4), 1705 cm^{-1} (C=O). The oil was chromatographed on a column of 180 g of alumina. Elution with hexane yielded 1.723 g (32.8%) of starting hydrocarbon. Elution with 1:4 benzene–hexane followed by 1:1 benzene–hexane afforded 2.111 g of a reddish oil which crystallized from hexane–benzene to give 1.158 g of tan crystals, mp 74.5–76.5°. The mother liquors gave a second crop of 0.19 g, mp 75.0–76.5°, for a total yield of 17.6%. An analytical sample of the ester, **9-carbethoxy-3H-pyrrolo[1,2-*a*]indole**, was prepared by evaporative distillation at 140–160° (0.15 mm) and crystallization from hexane: mp 76.5–78.5°; ir (CCl_4), 1700 cm^{-1} (C=O); ir (CS_2), 692 and 684 cm^{-1} (*cis* C=C); uv max (isooctane), 227 mμ (ε 28,000), 248 (16,000), 253 (16,000), 265 sh (3000), 310 sh (12,000), 320 (13,000), 336 sh (9200), 357 (4200); uv max (95% C_2H_5OH), 229 mμ (ε 33,000), 237 (32,000), 318 (17,000); nmr (CCl_4), δ 1.35 (t, 3, CH_3), 4.02 (t, 2, $J_{13} = J_{23} = 2$ Hz, CH_2N), 4.23 (q, 2, CH_2O), 6.32 (dt, 1, $J_{12} = 6.0$, $J_{23} = 2.0$ Hz, HC-2), 6.77 (dt, 1, $J_{12} = 6.0$, $J_{23} = 2.0$ Hz, HC-1), 6.85–7.13 (m, 3, HC-5, HC-6, HC-7), 8.02 (m, 1, HC-8); nmr (acetone-d_6), δ 1.38 (t, 3, CH_3), 4.33 (q, 2, CH_2O), 4.64 (t, 2, $J_{13} = J_{23} = 2.0$ Hz, NCH_2), 6.87 (dt, 1, $J_{12} = 6$, $J_{23} = 2.0$ Hz, HC-2), 6.98–7.29 (m, 4, HC-1, three aromatic), 8.17 (m, 1, HC-8).

Anal. Calcd for $C_{14}H_{13}NO_2$: C, 74.0; H, 5.8; N, 6.2. Found: C, 74.0; H, 5.8; N, 6.1.

In a subsequent experiment, the crude red oil was analyzed by vpc which indicated the presence of starting **7** and one major product, namely **11**. Several minor peaks were also noted in the chromatogram, but these were small in area relative to the two components noted above. In experiments in which the anion was added over a longer period of time, or in which the anion was added rapidly, but the mixture was allowed to stir with ice cooling for several hr, the amount of ester **11** was found to decrease with time, until it was no longer evident in the reaction mixture upon vpc analysis. No new volatile product developed during this time. In one scaled-up experiment, the anion **8** was added to a large excess of diethyl carbonate. Upon chromatography of the reaction mixture on silica gel, a new ester was eluted from the column after starting **7** had been removed but before the major product **11** was recovered. Evaporative distillation of this new fraction at 120–130° (0.15 mm) produced 40 mg of a pale yellow oil which could not be induced to crystallize. This ester appeared to be **3-carbethoxy-9H-pyrrolo[1,2-*a*]indole**:



ir (CCl_4), 1712 cm^{-1} (ester C=O); nmr (CCl_4), δ 1.33 (t, 3, CH_3), 3.61 (broad s, 2, $ArCH_2$), 4.25 (q, 2, OCH_2), 5.93 (dt, 1, $J_{12} = 3.4$ Hz, $J_{19} < 0.5$ Hz, HC-1), 6.93–7.27 (m, 4, HC-2, three aromatic), 8.63 (m, 1, HC-5).

9-Carbethoxy-1,2-dihydro-1H-pyrrolo[1,2-*a*]indole (23).—A solution of 166 mg (0.730 mmol) of ester **11** in 20 ml of absolute ethanol was hydrogenated over 54 mg of a 5% palladium-on-carbon catalyst at room temperature and atmospheric pressure. Hydrogen (1 equiv) was consumed in 2 min and the mixture was stirred for 12 min with no additional gas uptake. Upon removal of the catalyst and solvent, there was obtained 166 mg (99%) of crystals, mp 95–95.5°. An analytical sample was prepared by crystallization from hexane: mp 95.5–96.0°; ir (CCl_4), 1698 cm^{-1} (ester C=O); ir (CS_2), absence of *cis* C=C at 692 and 684 cm^{-1}; uv max (isooctane), 217 mμ (ε 34,000), 229 (26,000), 245 sh (11,000), 275 sh (9700), 283 (12,000), 292 (11,000); nmr (CCl_4), δ 1.30 (t, 3, CH_3), 2.27 (m, 2, NCH_2CH_2), 2.78 (m, 2, $NCH_2CH_2CH_2$), 3.53 (t, 2, $J_{23} = 7$ Hz, NCH_2), 4.17 (q, 2, OCH_2), 6.75–7.11 (m, 3, aromatic), 7.95 (m, 1, HC-8).

Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.3; H, 6.6; N, 6.1. Found: C, 73.3; H, 6.6; N, 6.2.

Condensation of the Anion 8 with Ethyl Chloroformate. 9,9-Biscarbethoxy-9H-pyrrolo[1,2-*a*]indole (14).—A solution of 12.9 mmol of the anion **8** was added to an ice-cooled solution of 2.8 g (26 mmol) of redistilled ethyl chloroformate in 50 ml of diethyl ether. The mixture was stirred for 20 min and then poured into water. The organic layer was worked up in the usual manner and the solvent was removed to yield a red oil, ir (CCl_4) 1750 cm^{-1}, the vpc of which showed one major product other than regenerated **7**. The reaction product was chromatographed on 100 g of silica gel. Elution with CCl_4 afforded 700 mg (35%) of **7**. Elution with $CHCl_3$ yielded a red oil which was evaporatively distilled at 125–145° (0.01 mm) to afford 573 mg of a pale yellow oil. This oil, diester **14**, was crystallized from hexane–chloroform to yield 475 mg (13%) of crystals, mp 111–113°. An analytical sample was prepared by crystallization from hexane–chloroform: mp 115.0–115.5°; ir (CCl_4), 1755 cm^{-1} (unconjugated ester C=O); uv max (isooctane), 212 mμ (ε 21,000), 269 (13,000); nmr ($CDCl_3$), δ 1.23 (t, 6, CH_3), 4.24 (q, 4, OCH_2), 6.46 (m, 2, HC-1, HC-2), 7.10 (dd, 1, $J_{13} = 1.5$, $J_{23} = 2.6$ Hz, N-HC-3), 7.15–7.43 (m, 3, aromatic), 7.80 (m, 1, HC-8).

Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.2; H, 5.7; N, 4.7. Found: C, 68.2; H, 5.8; N, 4.7.

(17) All reactions described within were conducted under an atmosphere of nitrogen using the apparatus of Johnson and Schneider.[18] The standard reaction work-up, unless otherwise noted, involved washing the organic reaction solvent with dilute sodium bicarbonate solution, distilled water, and saturated sodium chloride. The organic solvent was then dried with anhydrous sodium sulfate and evaporated at reduced pressure. Column chromatography was performed with neutral Woelm alumina, activity III, and with Davison silica gel (100–200 mesh). Melting points were determined on a Fisher–Johns apparatus and are uncorrected. Analyses were done by Spang Microanalytical Laboratory, Ann Arbor, Mich. Vpc analyses were determined with an F & M instrument on a 6 ft × 0.125 in. 10% SE-30 on a firebrick column. Infrared spectra were obtained with a Perkin-Elmer 337 grating spectrophotometer. Ultraviolet spectra were taken with a Cary 15 spectrophotometer. Nmr spectra were measured with a Varian A-60 instrument, probe temperature 38°, with signals reported relative to internal tetramethylsilane, δ 0.00 ppm.

(18) W. S. Johnson and W. P. Schneider, *Org. Syn.*, **30**, 18 (1950).

(19) V. J. Mazzola, K. F. Bernady, and R. W. Franck, *J. Org. Chem.*, **32**, 486 (1967).

Condensation of Anion 8 with Carbon Dioxide. 9-Carboxy-3H-pyrrolo[1,2-*a*]indole (15).—To a stirred, ice-cooled solution of 32.9 mmol of the anion **8** in 110 ml of diethyl ether was added gaseous CO_2, dried by passing it through a column of molecular sieves, until the green color of the anion was discharged. The mixture was then poured into water and the ethereal layer separated. The aqueous layer was extracted with ether; the combined ether layers were worked up in the usual way to afford 3.36 g of **7**, mp 86–90°. The aqueous layer was acidified with cold, dilute HCl and the resulting precipitate was extracted into ether and worked up as usual to yield 2.20 g of an acid mixture, shown by tlc to consist of one major product. The mixture was chromatographed on silica gel. Elution with $CHCl_3$ yielded 525 mg of **7** (decarboxylation on the column?) to make a total of 74% recovered starting material. Elution with 1:49 acetic acid–chloroform yielded 478 mg (7%) of acid **15** homogeneous on tlc, mp 180–210° (decarboxylation). No other product could be eluted from the column. Acid **15** was sublimed at 165° (0.14 mm) and crystallized from ethanol: mp 213–215° (decarboxylation): ir (KBr), 1645 cm^{-1} (acid C=O); uv max (95% C_2H_5OH), 225 mμ (ε 22,000), 253 (17,000), 318 (12,000).

Anal. Calcd for $C_{12}H_9NO_2$: C, 72.4; H, 4.6; N, 7.0. Found: C, 72.5; H, 4.6; N, 7.0.

Condensation of the Anion 8 with Dimethyl Oxalate.—A solution of 19.3 mmol of the anion **8** was added as rapidly as possible to an ice-cooled solution of 2.36 g (20 mmol) of dimethyl oxalate in 60 ml of ether. After complete addition of the anion, the mixture was hydrolyzed with ice and dilute HCl. The usual work-up gave a red oil, whose tlc showed the presence of **7** and several new spots: ir (CCl_4), 1740 (ester C=O), 1685 cm^{-1} (conjugated C=O). The crude product was chromatographed on a column of 100 g of silica gel. Elution with hexane and 1:1 hexane–benzene yielded 1.01 g (33.6%) of **7**. Elution with benzene afforded 1.13 g of a red oil which crystallized from benzene to yield ester **16** as 320 mg of black crystals, mp 133.5–136°. The mother liquors were chromatographed on alumina with benzene as eluent. Two yellow bands developed. The first one removed afforded 60 mg of an oil which crystallized from hexane–benzene to give 45 mg of crystals, mp 78–81°. The second band gave 320 mg of an oil which could be crystallized from hexane–benzene to afford 280 mg of material, mp 135–136°, which was identical with ester **16** obtained in the initial chromatography. The combined yield of methyl **9H-pyrrolo[1,2-*a*]indole-1-glyoxalate (16)** was 600 mg (13%). The analytical sample was recrystallized from hexane–benzene: mp 136.5–138.0°; ir (CCl_4), 1745 (ester C=O), 1675 cm^{-1} (conjugated C=O); uv max (isooctane), 239 mμ (ε 13,000), 282 (11,000), 289 (13,000), 299 (13,000); nmr ($CDCl_3$), δ 3.95 (s, 3, OCH_3), 4.08 (s, 2, $ArCH_2$), 6.93 (d, 1, J_{23} = 3.0 Hz, HC-2), 7.20–7.70 (m, 5, HC-3, aromatics).

Anal. Calcd for $C_{14}H_{11}NO_3$: C, 69.7; H, 4.6; N, 5.8. Found: C, 69.6; H, 4.7; N, 5.9.

The lower melting column fraction was evaporatively distilled at 120–140° (0.20 mm) and crystallized from hexane to afford 35 mg of yellow crystals, mp 98.0–98.5°, which were identical in their ir, uv, mp, and tlc characteristics with **methyl 9H-pyrrolo-[1,2-*a*]indole-3-glyoxalate (17)** prepared independently. The yield of this ester in this reaction was 1%.

Methyl 9H-Pyrrolo[1,2-*a*]indole-3-glyoxalate (17).—Following the procedure of Remers,[18] 254 mg (2.0 mmol) of oxalyl chloride was added to an ice-cooled, stirred solution of 310 mg (2.0 mmol) of **7** in 5 ml of CH_2Cl_2. After stirring for 15 min, the solvent was removed and the yellow-brown acid chloride was treated with 3 ml of methanol and 300 mg of Na_2CO_3. The mixture was stirred at room temperature for 2.5 hr and then at reflux for 2 min. Insoluble material was filtered off and the solvent was removed. The crude residue was chromatographed through alumina using benzene as eluent. Crystallization of the material from the column with methanol afforded 166 mg (34.4%) of ester **17**, mp 96.5–98.5°. The analytical sample was prepared *via* crystallization from hexane as long, pale yellow needles: mp 98.5–99.5°; ir (CCl_4), 1743 (ester C=O), 1662 cm^{-1} (conjugated C=O); uv max (isooctane), 233 mμ (ε 9500), 279 (7700), 286 (8800), 312 (13,000); nmr (acetone-d_6), δ 3.43 (s, 5, $ArCH_2$, OCH_3), 5.85 (dt, 1, J_{12} = 4.0, J_{19} = 1.0 Hz, HC-1), 6.62–7.05 (m, 4, HC-2, aromatic), 8.15 (m, 1, HC-5).

Anal. Calcd for $C_{14}H_{11}NO_3$: C, 69.7; H, 4.6; N, 5.8. Found: C, 69.7; H, 4.5; N, 5.9.

Condensation of the Anion 8 with Phenyl Isocyanate.—A solution of 3 mmol of anion **8** was added rapidly to an ice-cooled solution of 640 mg (5.37 mmol) of redistilled phenyl isocyanate in 10 ml of ether. The mixture was stirred for 5 min and then hydrolyzed with ice and dilute HCl. Work-up afforded a crude product, ir (CCl_4) 1721 and 1683 cm^{-1}, whose tlc indicated the presence of at least three new compounds. The crude product was chromatographed on alumina. Elution with hexane afforded 57 mg (13%) of **7**. Elution with 1:1 hexane–benzene gave 158 mg of a product which could be crystallized from benzene–ethanol to afford 117 mg (14%) of **N-phenyl-9H-pyrrolo-[1,2-*a*]indole-3-carboxamide (21)**, mp 200–202°. The analytical sample was prepared from benzene–ethanol: mp 202–203°; ir (KBr), 3305 (NH) and 1654 cm^{-1} (C=O); uv max (isooctane), 241 mμ (ε 9700), 287 sh (23,000), 293 (24,000); nmr (DMSO), δ 3.95 (broad s, 2, CH_2Ar), 6.30 (dt, 1, J_{12} = 3.5 Hz, J_{19} = 1.0, HC-1), 7.15–7.65 (m, 8, HC-2, NH, aromatics), 7.92 (m, 2, aromatics), 8.57 (m, 1, HC-5).

Anal. Calcd for $C_{18}H_{14}N_2O$: C, 78.8; H, 5.1; N, 10.2. Found: C, 78.9; H, 5.1; N, 10.1.

Elution of the column with benzene afforded 99 mg of a mixture which was fractionally crystallized from ethanol. The product isolated in this manner was 10 mg of **N-phenyl-9H-pyrrolo[1,2-*a*]indole-1-carboxamide (20)** (1% yield), mp 154–156°. An analytical sample was prepared by recrystallization from ethanol: mp 155–156°; ir (KBr), 1712 cm^{-1} (C=O); uv max (isooctane), 235 mμ (ε 14,000), 278 (16,000), 284 (16,000), 288 (15,000); nmr ($CDCl_3$), δ 4.19 (s, 2, CH_2Ar), 6.71 (d, 1, J_{23} = 2.5 Hz, HC-2), 7.00–7.80 (m, 11, HC-3, NH, aromatics).

Anal. Calcd for $C_{18}H_{14}N_2O$: C, 78.8; H, 5.1; N, 10.2. Found: C, 78.9; H, 4.9; N, 10.5.

The mother liquors from the above fractional crystallization were evaporated, and the residue was crystallized from hexane–benzene to afford 30 mg (3%) of **N,N′-diphenyl-9H-pyrrolo-[1,2-*a*]indole-9,9-dicarboxamide (19)**, mp 180–184°. An analytical sample was prepared from benzene–hexane: mp 186.5–188.0°; ir (KBr), 1680 cm^{-1} (C=O); uv max (isooctane), 248 mμ (ε 44,700); nmr ($CDCl_3$), δ 6.67 (m, 2, HC-1, HC-2), 7.14–7.72 (m, 16, HC-3, NH, aromatics), 8.08 (m, 1, HC-5).

Anal. Calcd for $C_{25}H_{19}N_3O_2$: C, 76.3; H, 4.9; N, 10.7. Found: C, 76.3; H, 4.9; N, 10.7.

Condensation of the Anion 8, Complexed with Triethylamine, with Diethyl Carbonate.—To a solution of 3.0 mmol of the anion **8** was added 310 mg (3.1 mmol) of triethylamine, and the resulting solution was allowed to stand for 2.5 hr. Then 390 mg (3.3 mmol) of diethyl carbonate was added to the solution. The usual discharge of the deep green color did not take place. The solution was stirred for 2.5 hr and then it was treated with ice and dilute HCl. Work-up yielded an oil whose tlc showed the presence of **7**, **11**, and a new product. The oil was chromatographed on alumina. Benzene elution afforded, in order, 356 mg (76.3%) of **7**, 89 mg of crude **11**, and 60 mg of a new ester, **22**. The crude ester **11** was distilled at 140–160° (0.15 mm) and crystallized from pentane–benzene to yield 60 mg (9%) of pure ester, mp 76–77.5°. The new ester **22** was distilled at 140–160° (0.15 mm) and crystallized from pentane–benzene to yield 26 mg (3%) of **1,9-dicarbethoxy-9H-pyrrolo[1,2-*a*]indole**, mp 92–93°. The analytical sample was recrystallized from pentane–benzene: mp 92.5–93.5°; ir (CCl_4), 1755, 1740, and 1725 cm^{-1} (C=O); uv max (isooctane), 212 mμ (ε 33,000), 230 (17,000), 237 sh (15,000), 272 (17,000); nmr ($CDCl_3$), δ 1.25 (t, 3, CH_3), 1.33 (t, 3, CH_3), 4.33 (q, 4, OCH_2), 5.07 (s, 1, HC-9), 6.89 (d, 1, J_{23} = 3.0 Hz, HC-2), 7.15 (d, 1, J_{23} = 3.0 Hz, HC-3), 7.31–7.59 (m, 4, aromatic).

Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.2; H, 5.7; N, 4.7. Found: C, 68.1; H, 5.8; N, 4.9.

In a similar experiment, the reaction solution was allowed to stir for 24 hr after the addition of diethyl carbonate. At this time, the green color was discharged. Work-up and chromatography gave 70% of recovered **7** and diester **22** in 6% yield, mp 92.5–93.5°. Only traces of **11** were detected.

Nitrene Addition to 9-Carbethoxy-3H-pyrrolo[1,2-*a*]indole-(11).—A solution of 227 mg (1.00 mmol) of ester **11** and 1.20 g (10.4 mmol) of ethyl azidoformate in 3.8 ml of methylene chloride was irradiated in a Pyrex tube under an atmosphere of N_2 with a Hanovia 100-W high-pressure lamp until 35 ml of N_2 was evolved.[16] The reaction mixture was then worked up by chromatography on alumina. Benzene elution gave recovered **11** (22%). Then 16 mg of material was obtained which exhibited carbonyl bands in the ir different from **11**. This product was chromatographed on tlc plates using silica gel G and 9:1 benzene–ether as developing solvent. A fraction (4 mg) was ob-

tained: mp 164–165.5°; ir (CCl_4), 1735 (carbamate C=O), and 1705 cm^{-1} (conjugated ester C=O); uv max (isooctane), 209 mμ (ε 28,000), 217 sh (26,000), 232 (22,000), 277 (6400), 287 (7100), 294 (6800). An interpretable nmr using a computer of average transients could not be obtained. The compound was not further characterized.

Registry No.—**9**, 16916-03-3; **10**, 16916-04-4; **11**, 16916-05-5; **14**, 16960-03-5; **15**, 16916-07-7; **16**, 16916-08-8; **17**, 16916-09-9; **19**, 16916-10-2; **20**, 16916-11-3; **21**, 16916-12-4; **22**, 16916-13-5; **23**, 16916-14-6; 3-carbethoxy-9H-pyrrolo[1,2-*a*]indole, 16916-06-6.

Displacement Reactions of Dibutyl Iodomethaneboronate and the Synthesis of Boron-Substituted Pyrimidines[1a,b]

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Dibutyl iodomethaneboronate has been synthesized by reaction of iodomethylmercuric iodide with boron tribromide followed by esterification with 1-butanol. Nucleophiles including alkoxides, amines, carbanions, and mercaptides displace iodide from dibutyl iodomethaneboronate to yield the corresponding substituted methaneboronic acid derivatives. Several boron-containing pyrimidines have been prepared by the reaction of the iodomethaneboronic ester with mercaptopyrimidines.

Reasons for studying carbon-functional boronic esters include observations of strong neighboring-group effects of boron[2–4] and the possibility of finding an effective compound for the ^{10}B neutron capture therapy of brain tumors.[5] Displacement of halide from an α-haloalkaneboronic ester is a potentially useful approach to a wide variety of substituted boronic esters.[3,4] However, it turned out that alkoxide ion often reacts much faster than more highly desired other nucleophiles, even mercaptides, in displacement of bromide from such compounds as dibutyl 2-bromopropane-2-boronate, owing to preliminary attack of the more basic anion on the boron atom. We thought it likely that reagents more nucleophilic toward carbon would react faster than those more basic toward boron if the transition state could be given more "SN2 character." Reduction of chain branching would accomplish this end, and a halomethaneboronic ester, $XCH_2B(OR)_2$, was therefore desired. A second advantage of such a compound would be the incorporation of a minimum of extraneous carbon along with the boron in compounds synthesized for potential biological properties.

Synthesis of $ICH_2B(OBu)_2$.—Our previous syntheses of α-haloalkaneboronic esters involved radical[2] or ionic[3] additions to alkeneboronic esters. An entirely new approach was therefore needed to make a halomethaneboronic ester. Chlorination of di-*t*-butyl methaneboronate with *t*-butyl hypochlorite yielded a little chloromethaneboronic ester after a lot of effort.[6] We therefore tried treating iodomethylmercuric iodide[7] with boron tribromide. After esterification of the product with 1-butanol, a low yield of dibutyl iodomethaneboronate (**1**) was obtained. Sodium iodide greatly improved the yield, evidently because it complexes with the mercury atom and makes it a better leaving electrophile.

$$ICH_2HgI + BBr_3 + NaI \longrightarrow HgI_2 + NaBr + ICH_2BBr_2 \xrightarrow{BuOH} \underset{\mathbf{1}}{ICH_2B(OBu)_2}$$

After trying numerous variations, it was found that the best reaction conditions were about 1 day of vigorous stirring at 25°, with a large excess of boron tribromide and a moderate amount of methylene iodide, the quantity trapped in the iodomethylmercuric iodide on recrystallization (~20%) being about right. Careful vacuum drying of the ICH_2HgI cut the yield in half, though increasing the amount of methylene iodide did not seem to help. It is possible that the CH_2I_2 functions by increasing the slight solubility of the ICH_2HgI in the boron tribromide or by modifying the surface or mechanical properties of the mercury compound.

Although we are not sure that our yield (40% based on crude ICH_2HgI) is the best possible, it appears that instability of either the iodomethylmercury or boron compound may be a limiting factor. Heat or ultraviolet light increased the amounts of various by-products containing the $B–CH_2–B$ linkage, as shown by the appearance of several nmr peaks at τ 9.5–10. The boron tribromide treatment worked better for conversion of methylenedimercuric iodide,[7] $CH_2(HgI)_2$, into bis(dibromoboryl)methane, $CH_2(BBr_2)_2$,[1a] but this approach to methanediboronic acid has now been superseded by the much more efficient direct reaction of methylene chloride, lithium, and dimethoxyboron chloride.[8]

The crude dibutyl iodomethaneboronate (**1**) contained variable amounts of bromomethaneboronic ester, revealed by the $Br–CH_2–B$ nmr peak at τ 7.6. (For comparison, the corresponding $Cl–CH_2–B$ peak is at τ 7.2,[6] the $I–CH_2–B$ peak at τ 7.95.) The bromo compound has about the same boiling point as tributyl borate and was not isolated. Sodium iodide in acetone converted into the iodo compound (**1**).

Displacement Reactions.—As anticipated, dibutyl iodomethaneboronate (**1**), when treated with a wide

(1) (a) Preliminary communication: D. S. Matteson and T. C. Cheng, *J. Organomental Chem.*, **6**, 100 (1966). (b) Supported by U.S. Public Health Service Grant CA-05513 from the National Cancer Institute. (c) Alfred P. Sloan Foundation Fellow. (d) Abstracted in part from the Ph.D. Thesis of T.-C. Cheng, 1968.

(2) D. S. Matteson and R. W. H. Mah, *J. Amer. Chem. Soc.*, **85**, 2599 (1963).

(3) D. S. Matteson and G. D. Schaumberg, *J. Org. Chem.*, **31**, 726 (1966).

(4) D. S. Matteson, *Organometal. Chem. Rev.*, **1**, 1 (1966).

(5) A. H. Soloway in "Progress in Boron Chemistry," Vol. 1, H. Steinberg and A. L. McCloskey, Ed., The Macmillan Co., New York, N. Y., 1964, p 203.

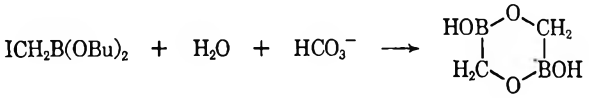
(6) D. S. Matteson, *J. Org. Chem.*, **29**, 3399 (1964).

(7) E. P. Blanchard, Jr., D. C. Blomstrom, and H. E. Simmons, *J. Organometal. Chem.*, **3**, 97 (1965).

(8) R. B. Castle and D. S. Matteson, *J. Amer. Chem. Soc.*, **90**, 2194 (1968).

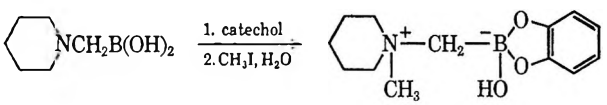
variety of nucleophilic reagents, gave simple displacement products. Reagents having nucleophilic sites on oxygen, nitrogen, carbon, and sulfur were tested.

Hydroxymethaneboronic acid presented the problem of high water solubility. To avoid the need for separating it from inorganic salts and to avoid conversion of the boronic acid into a salt, an ion-exchange resin was used in the bicarbonate form as the source of base to displace iodide from the iodomethyl compound (**1**). The dimeric cyclic ester (**2**) was isolated. We have previously prepared the analogous derivative from solvolysis of 2-bromopropane-2-boronic acid,[3] and the preparation of **2** from borane carbonyl has been reported.[9]



1 **2**

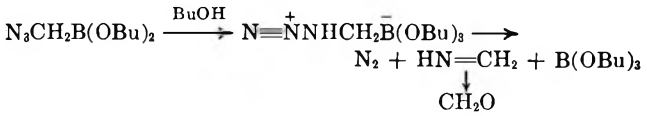
Ammonia and amines react readily with **1**. We were unable to isolate aminomethaneboronic acid from inorganic salts and boric acid, a usual by-product from reactions of **1**. Dimethylaminomethaneboronic acid, $(CH_3)_2N-CH_2B(OH)_2$, was obtained in partially purified form and was characterized as the catechol ester. Piperidine yielded a much easier product to handle. Piperidinomethaneboronic acid (**3**) was converted into the catechol ester and methylated with methyl iodide to yield a quaternary ammonium derivative postulated to have the zwitterion structure (**4**). Thus, it appears



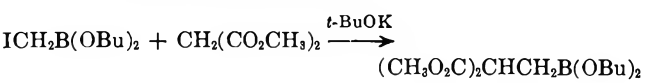
3 **4**

that the group $N-CH_2-B$ in various forms does not hydrolyze unduly readily. Phthalimidomethaneboronic acid was also prepared very easily from **1**, but were unable to isolate any aminomethaneboronic acid after basic hydrolysis.

Schaeffer and Todd have reported the reaction of chloromethyldimethylborane, $ClCH_2B(CH_3)_2$, with sodium azide.[10] We treated our iodomethaneboronic ester with sodium azide in 1-butanol, but degradation to formaldehyde (isolated as the 2,4-dinitrophenylhydrazone) and butyl borate (isolated as boric acid after hydrolysis) occurred. The instability of the azide is probably due to a β elimination of boron and nitrogen.



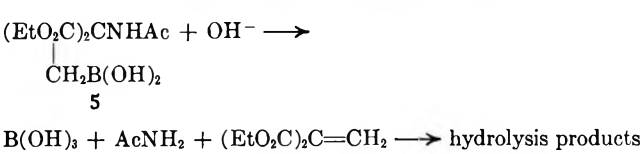
Carbanions from active methylene compounds are readily alkylated by dibutyl iodomethaneboronate (**1**). Successful reactions have been carried out with malononitrile,[1a] methyl cyanoacetate, dimethyl malonate, and diethyl acetamidomalonate. Products were also obtained from diethyl malonate and dibutyl malonate, but these appeared to decompose partially on distillation and were not obtained pure.



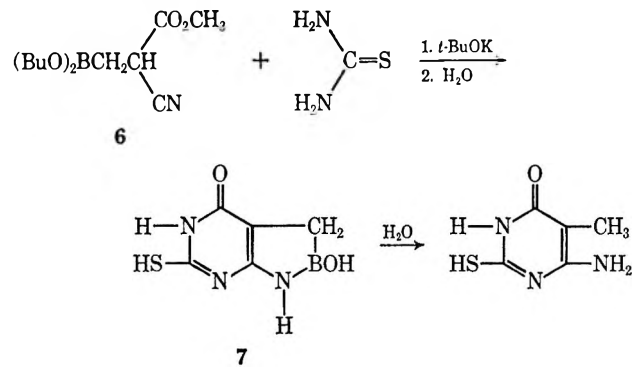
(9) L. J. Malone and M. R. Manley, *Inorg. Chem.*, **6**, 2260 (1967).

(10) R. Schaeffer and L. J. Todd, *J. Amer. Chem. Soc.*, **87**, 488 (1965).

It was hoped that the diethyl acetamidomalonate derivative (**5**) could be converted into a borono-substituted amino acid by hydrolysis. However, treatment with acid or base resulted in deboronation. The β relationship of the boronic acid and acetamido groups probably results in an elimination reaction. Several examples of related eliminations are known.[4]



Reaction of the methyl cyanoacetate derivative, methyl α-cyano-β-dibutoxyborylpropionate (**6**), with thiourea in the presence of potassium *t*-butoxide followed by treatment with water yielded the expected 2-mercapto-4-oxy-5-oxyboromethyl-6-iminopyrimidine (**7**). However, two molecules of this compound crystallized in a tight complex with one molecule of boric acid plus the elements of water. Distillation of methanol from a suspension of **7** did not alter the elemental composition, indicating that the boric acid was tightly chelated. Several structures might be written for such a chelate. To prove that **7** contained carbon-bound boron, it was boiled in 50% methanol to cause hydrolytic deboronation. The nmr spectrum in dimethyl sulfoxide-d_6 showed the disappearance of the CH_2B peak at τ 8.46 and its replacement by a methyl peak at τ 6.90 which was partially accomplished after 2 hr and complete after 17 hr.



6

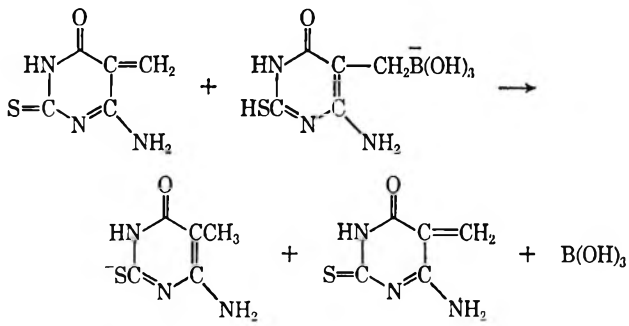
7

The product of the reaction of the cyanoacetic ester derivative (**6**) with guanidine was even more labile, and we were not able to obtain it except as a mixture with its deboronation product. Attempts to condense thiourea with the malononitrile derivative, $(BuO)_2BCH_2CH(CN)_2$, gave only deboronated pyrimidine.[11] Reaction of dibutyl 1-iodoethaneboronate, $(BuO)_2BCHICH_3$,[3] with malononitrile and potassium *t*-butoxide gave a rather low yield of the alkylated malononitrile, $(BuO)_2BCH(CH_3)CH(CN)_2$, and the product from reaction of this compound with thiourea appeared to be pyrimidine analogous to **7**. However, recrystallization seemed to cause either loss of boron or concentration of deboronation product, and we were unable to obtain a satisfactory analysis.[11]

The ease of deboronation of these compounds is totally unexpected. No satisfactory scheme for hydrolytic deboronation is possible, since a carbanion electron pair on the carbon from which the boron departs cannot be delocalized into the pyrimidine ring. It does no

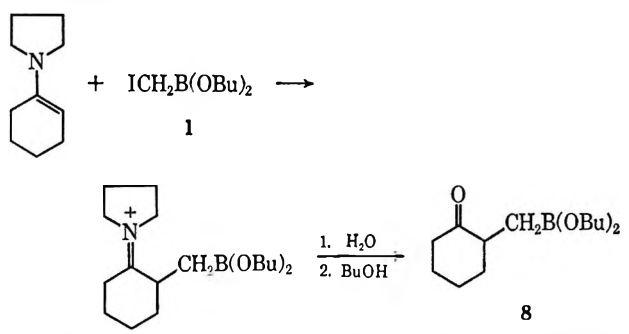
(11) Unpublished work with J. Ebbert.

good to assume that the pyrimidine structures are wrong for this purpose, since the charge cannot be delocalized in any reasonable alternative structure. Base-catalyzed elimination of boron and cyanide from the starting cyano compounds such as $(BuO)_2BCH_2CH(CN)_2$ is conceivable and may help cause the low yields, but there is good evidence that the carbon–boron bond survives in compounds such as **7** which contain no cyano group. Some sort of oxidative cleavage to a quinoidal structure is a speculative possibility, since the quinoidal material could serve as the oxidizing agent in a chain process.



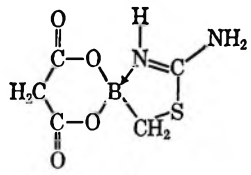
An unusual mechanism of this general type is not unreasonable in view of the highly exothermic character (perhaps 30 kcal/mol or more[4]) of deboronation.

Dibutyl iodomethaneboronate (**1**) also alkylates enamines, as shown by the conversion of 1-(1-pyrrolidinyl)cyclohexene into 2-(dibutoxyborylmethyl)cyclohexanone (**8**).



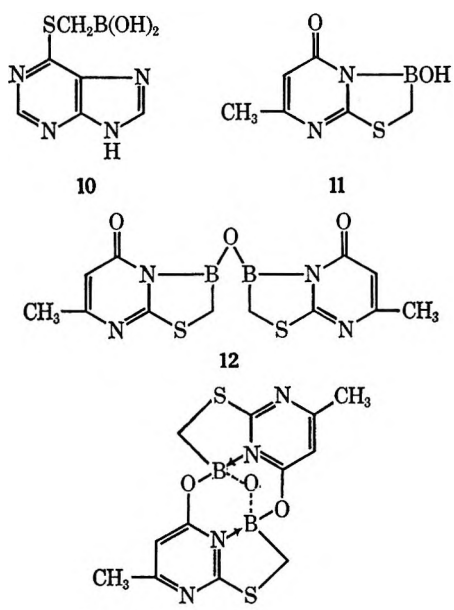
Mercaptide ions displace halide from all but the most highly branched α-haloalkaneboronic esters;[2-4] so it is hardly surprising that iodomethaneboronic ester (**1**) reacts efficiently with thiolacetate ion. Acetylthiomethaneboronic acid, $CH_3COSCH_2B(OH)_2$, has been obtained by hydrolysis of the ester. However, a number of attempts to hydrolyze the acetyl group with acid or base to obtain mercaptomethaneboronic acid, $HSCH_2B(OH)_2$, resulted in deboronation. The instability of this compound was as much unexpected as that of the pyrimidines described in a preceding paragraph. A somewhat similar mechanism, involving oxidation of $HSCH_2B(OH)_2$ to $S{=}CH_2$ with the latter serving as the oxidizing agent for the next step in a chain mechanism, is plausible. The exclusion of air from the reactions was not rigorous enough to preclude direct air oxidation, if that was unusually rapid. It is doubtful that the deboronation is purely hydrolytic, in view of the apparent stability of analogous alkylthioboron compounds.[3]

Thiourea underwent reaction with the iodomethaneboronic ester (**1**) in the usual manner.[3] The thioureidomethaneboronic acid was isolated as its catechol ester and also as the chelated anhydride with malonic acid (**9**). Similar chelates, which are surprisingly stable toward hydrolysis, have been reported previously.[12]



We had been totally unsuccessful in previous attempts to alkylate mercaptopyrimidines with α-haloalkaneboronic esters.[3] However, dibutyl iodomethaneboronate (**1**) underwent reaction readily with 2-thiobarbituric acid, 2-mercapto-4-oxy-6-methylpyrimidine, 2-mercapto-4-oxy-6-phenylpyrimidine, 2-mercapto-4-oxy-6-propylpyrimidine, 2-mercapto-4-oxy-6-carboxypyrimidine, and 6-mercaptopurine in refluxing acetonitrile to yield the S-boromethyl derivatives. These are not the usual conditions for alkylating mercaptopyrimidines,[13] and methyl iodide does not react with 2-mercapto-4-oxy-6-methylpyrimidine in acetonitrile. Although it is well established that S-alkylation occurs in preference to N-alkylation in alkaline solution,[13] data which support S-alkylation under neutral conditions[14] are less common. To support the structural assignments, dibutyl iodomethaneboronate (**1**) was added to an aqueous alkaline solution of 2-mercapto-4-oxy-6-methylpyrimidine and an 80% yield of the same product that resulted from reaction in acetonitrile was obtained. (Nmr spectra were weak at best owing to low solubilities and do not distinguish $S{-}CH_2{-}B$ from $N{-}CH_2{-}B$.)

The S-boromethyl-substituted mercaptopyrimidines were obtained in varying degrees of hydration or dehydration. The boronic acid form of 6-(dihydroxyborylmethylthio)purine (**10**) crystallized with **1** mol



(12) D. S. Matteson and G. D. Schaumberg, *J. Organometal. Chem.*, **8**, 359 (1967).

(13) G. W. Kenner and A. Todd in "Heterocyclic Compounds," Vol. 6, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1957, p 283.

(14) M. Gordon, *J. Amer. Chem. Soc.*, **73**, 984 (1951).

of water. More often, the products had the composition of a boronic anhydride. For example, 2-mercapto-4-oxy-6-methylpyrimidine yielded a derivative formulated as 2-(hydroxyboromethylthio)-4-oxy-6-methylpyrimidine (11), and this could be dehydrated to material formulated as oxybis(2-boromethylthio-4-oxy-6-methylpyrimidine) (12). However, structure 12 probably does not give a complete picture of what happens, since the main changes in the infrared spectrum on dehydration include loss of the OH band near 2.9 μ together with loss of a strong band near 6.0 μ, which is probably the carbonyl group. Some sort of cage structure such as **13** is a likely possibility and would account for the observed spectral changes. There is no way to measure the actual molecular weight of these exceedingly insoluble compounds, nor to decide between these and other possible arrangements of the labile B–O and B–N bonds.

Dibutyl iodomethaneboronate and 2-mercapto-6-oxypurine yielded a bis(boromethyl) derivative, postulated to be S,7-bis(dihydroxyborylmethyl)-2-mercapto-6-oxypurine since the sulfur and the 7-nitrogen are probably the most nucleophilic sites.

Biological Tests.—The pyrimidine compounds reported here have been submitted to Dr. A. H. Soloway, Northeastern University, to test for possible boron concentration in brain tumors in mice. The insolubility of these materials presents problems, and none has shown desirable biological properties. Other compounds tested with negative results include methanediboronic acid, iodomethaneboronic acid, hydroxymethaneboronic acid, dimethylaminomethylmethaneboronic acid, S-thioureidomethaneboronic acid, and thioacetylmethaneboronic acid.

Experimental Section

Inert atmospheres (nitrogen or argon) were routinely used for all reactions.

Dibutyl Iodomethaneboronate (1).—Iodomethylmercuric iodide[7] was recrystallized once from methylene iodide, collected by suction filtration, and used directly without further drying. The methylene iodide content appeared to be about 20%; yields were much reduced if this was removed. Iodomethylmercuric iodide (100 g), dry sodium iodide (53 g), and boron tribromide (250 ml) were stirred vigorously under argon at 20–25° for 24 hr. The stirrer was a Trubore Teflon-paddle type lubricated with equal parts of Kel-F 90 chlorofluorocarbon grease and perchlorobutadiene, mixed hot, which withstood the boron bromide vapors. All liquid volatile up to ~130° (0.5 mm), as indicated by the residual mercuric iodide turning yellow, was distilled under vacuum and collected at −75°. (*CAUTION:* Methylene chloride was used for the Dry Ice bath, since this quantity of boron tribromide is extremely hazardous in case of accidental contact with most other solvents.) Most of the boron tribromide was recovered (suitable for recycling) by redistillation at atmospheric pressure through a short column, stopping the distillation as soon as it became slow to avoid overheating the residue, which consisted of bromomethylboron dibromide and iodomethylboron dibromide. These were distilled under vacuum up to about 40° (0.5 mm), then diluted with 50 ml of toluene, and stirred at −75° during the dropwise addition of 50 ml of *n*-butyl alcohol. The 1-butanol and toluene were removed under vacuum, and the residue of butyl borate, bromomethaneboronate, and iodomethaneboronate was stirred overnight with 50 ml of 1-butanol, 15 ml of acetone, and 15 g of sodium iodide. After simple vacuum distillation from the salts, the dibutyl iodomethaneboronate was isolated by careful fractionation with a spinning-band column: bp 61–63° (0.1 mm); yield 22–26 g (35–40%); nmr (neat) τ 7.95 (s, ICH_2B) plus C_4H_9O peaks.

Anal. Calcd for $C_9H_{20}BIO_2$: C, 36.30; H, 6.72; B, 3.63; I, 42.61. Found: C, 36.58; H, 6.76; B, 3.71; I, 42.86.

Iodomethaneboronic Acid.—Exposure of 1 g of dibutyl iodomethaneboronate to the air in a thin layer until it had all been converted into solid (3 days) yielded iodomethaneboronic acid: mp 70–71°; nmr (D_2O) τ ~5.43 (s, OH), ~7.75 (s, CH_2).

Anal. Calcd for CH_4BIO_2: C, 6.46; H, 2.15; B, 5.82; I, 68.33. Found: C, 6.68; H, 2.19; B, 5.61; I, 68.48.

Dibutyl butoxymethaneboronate was prepared from dibutyl iodomethaneboronate and sodium butoxide in 1-butanol as described for similar compounds:[3] bp 63–64° (0.1 mm); ir (neat) (5–16 μ) 7.04 (s), 7.48 (s), 8.00 (s), 9.00 (s), 10.28 (m), 12.01 (m), 13.56 (m).

Anal. Calcd for $C_{13}H_{29}BO_3$: C, 64.20; H, 11.93; B, 4.10. Found: C, 64.03; H, 12.10; B, 3.93.

B,B-Dihydroxy-2,5-dibora-1,4-dioxane (2), the cyclic semiester of hydroxymethaneboronic acid, was prepared by stirring 8.5 g of Dowex 1-X8 anion-exchange resin which had been converted to the bicarbonate form with 4 g of dibutyl iodomethaneboronate and 20 ml of water under argon for 3 days. The solution was filtered and concentrated under vacuum, and the solid residue was recrystallized from about 3 ml of water and 5 ml of acetone: yield 1.3 g (84%); mp 147–148°; nmr (D_2O) τ ~6.4 (s, CH_2), ~5.32 (s, OH).

Anal. Calcd for $C_2H_6B_2O_4$: C, 20.87; H, 5.23; B, 18.70. Found: C, 20.86; H, 5.29; B, 18.93.

Catechol Ester of Piperidinomethaneboronic Acid (3).—Dibutyl iodomethaneboronate (3 g) was added dropwise to 10 ml of piperidine in 20 ml of 1-butanol and stirred 10 min. The precipitated piperidine hydriodide was removed by filtration and the filtrate was concentrated. No way was found to crystallize the residue of piperidinomethanboronic acid, which was dissolved in 20 ml of acetonitrile and 5 ml of distilled water and treated with 1.08 g of catechol. The catechol derivative crystallized at once and was collected and washed repeatedly with water, ethanol, ether, and acetone. The yield was 1.2 g (50%): the product did not melt up to 250°; ir (KBr, 5–16 μ) 6.72 (s), 6.86 (w), 6.95 (w), 7.3 (w), 8.02 (s), 8.16 (w), 8.7 (w), 9.11 (w), 9.92 (w), 10.13–10.23 (w), 10.59–10.68 (w), 10.92–11.0 (w), 11.26–11.4 (w), 12.3–12.5 (w), 13.70 (w).

Anal. Calcd for $C_{12}H_{16}BNO_2 \cdot H_2O$: C, 61.05; H, 7.72; B, 4.60; N, 5.96. Found: C, 61.36; H, 7.53; B, 4.48; N, 5.76.

Dimethylaminomethaneboronic acid was prepared and isolated as the **catechol ester** in the same manner as the piperidine compound, substituting dimethylamine in the procedure. In this case the catechol ester did not crystallize until the acetonitrile was evaporated and the residue was dissolved in 20 ml of water and kept in the refrigerator several days. The yield was 1.2 g (85%): mp 123–124°; nmr (CD_3SOCD_3) τ 7.33 (s, CH_3), 7.96 (s, NCH_2B), plus aromatic and OH peaks.

Anal. Calcd for $C_9H_{12}BNO_2 \cdot 2H_2O$: C, 50.74; H, 7.56; B, 5.06; N, 6.57. Found: C, 50.87; H, 7.67; B, 4.89; N, 6.74.

The N-methyl derivative of the catechol ester of piperidinomethaneboronic acid (4) resulted when the piperidino compound was treated with methyl iodide in dimethyl sulfoxide. The methylated compound contained hydroxide (presumably coordinated to the boron) instead of iodide and was recrystallized from dimethyl sulfoxide: it did not melt up to 250°; nmr (CD_3SOCD_3), τ 3.64 (C_6H_4), 6.2 (s, N-CH_3), 7.9 (s, NCH_2B), plus piperidino and OH absorptions.

Anal. Calcd for $C_{13}H_{18}BNO_3 \cdot H_2O$: C, 60.49; H, 8.20; B, 4.19; N, 5.43. Found. C, 60.73; H, 8.11; B, 4.05; N, 5.03.

Phthalimidomethaneboronic acid was prepared by refluxing 2.8 g of potassium phthalimide and 4 g of dibutyl iodomethaneboronate in 35 ml of 1-butanol for 8 hr, adding water, extracting into ether, and crystallizing the product from water. The yield was 2.5 g (90%), mp 134–135°.

Anal. Calcd for $C_9H_8BNO_4$: C, 52.73; H, 3.93; B, 5.28; N, 6.83. Found: C, 52.87; H, 3.97; B, 5.10; N, 7.03.

Catechol Ester of S-Thioureidomethaneboronic Acid.—Dibutyl iodomethaneboronate (3 g) and 0.74 g of thiourea were refluxed in 50 ml of acetonitrile for 3 hr, treated with 50 ml of water, and concentrated under vacuum to yield a residue of crude, hygroscopic S-thioureidomethaneboronic acid hydriodide. Treatment with catechol in water precipitated the catechol ester in 83% yield: mp 259–260° dec; nmr (CD_3SOCD_3) τ 3.55 (s, C_6H_4), 6.66 (s, NH), 7.93 (s, SCH_2B).[15]

(15) The infrared curve of this compound recorded on a Beckman IR-8 is reproduced in T.-C. Cheng's Ph.D. Thesis, Washington State University, 1968, available from University Microfilms, Inc., Ann Arbor, Mich.

Anal. Calcd for $C_8H_9BN_2O_2S$: C, 46.18; H, 4.36; B, 5.20; N, 13.47; S, 15.41. Found: C, 46.14; H, 4.34; B, 5.33; N, 13.36; S, 15.56.

The **malonic acid chelate of S-thioureiodomethaneboronic acid** was prepared by treatment of the crude hydriodide salt with malonic acid in water,[3] decomposing near 325° without melting: nmr (CD_3SOCD_3) τ 6.75 (s, $COCH_2CO$), 7.85 (s, BCH_2S), 1.5 (broad, NH).[15]

Anal. Calcd for $C_5H_7BN_2O_4S$: C, 29.73; H, 3.49; B, 5.36; N, 13.87; S, 15.87. Found: C, 29.66; H, 3.70; B, 5.23; N, 13.86; S, 15.96.

Dibutyl Acetylthiomethaneboronate.—A solution of 15 mmol of sodium butoxide and 1.3 g of thiolacetic acid in 25 ml of 1-butanol was stirred with 5 g of dibutyl iodomethaneboronate for 2 hr, 50 ml of water, and 50 ml of ether were added, and the organic phase was washed with saturated aqueous NaCl and dried ($MgSO_4$). The product was distilled through a spinning-band column: 3 g (70%); bp 81–82° (0.1 mm); nmr (neat), τ 7.99 (s, $COCH_3$), 8.09 (s, BCH_2S), plus typical C_4H_9O pattern.

Anal. Calcd for $C_{11}H_{23}BO_3S$: C, 53.67; H, 9.42; B, 4.39; S, 13.03. Found: C, 53.93; H, 9.47; B, 4.18; S, 13.12.

Acetylthiomethaneboronic acid was prepared from 2 g of the butyl ester and 10 ml of water by vacuum distillation of the BuOH–H_2O azeotrope and recrystallized from 2 ml of water: mp 100–101°.

Anal. Calcd for $C_3H_7BO_3S$: C, 26.90; H, 5.72; B, 8.08; S, 23.93. Found: C, 27.15; H, 5.15; B, 8.25; S, 23.96.

Dimethyl (Dibutoxyborylmethyl)malonate.—A solution of the sodium salt of dimethyl malonate was prepared from 3.55 g of the ester and an equimolar amount of sodium *t*-butoxide (from NaH) in 50 ml of *t*-butyl alcohol and 8 g of dibutyl iodomethaneboronate was added dropwise. After 3 hr, 50 ml of water and 100 ml of ether were added, the water layer was washed with 50 ml of ether and 20 ml of 1-butanol, and the combined organic phase was dried ($MgSO_4$). Distillation through a spinning-band column yielded 4.4 g (55%): bp 115–117° (0.4 mm); ir (neat) 5.8 μ (C=O).

Anal. Calcd for $C_{14}H_{27}BO_6$: C, 55.64; H, 9.01; B, 3.58. Found: C, 55.90; H, 9.29; B, 3.56.

Methyl α-cyano-β-dibutoxyborylpropionate (6) was similarly prepared from methyl cyanoacetate: bp 100–101° (0.1 mm); ir (neat) 4.45 (C≡N), 5.72 μ (C=O).

Anal. Calcd for $C_{13}H_{24}BNO_4$: C, 58.01; H, 8.99; B, 4.02; N, 5.20. Found: C, 57.99; H, 9.01; B, 3.95; N, 4.99.

Diethyl Acetamido(catechylborylmethyl)malonate.—Reaction of diethyl acetamidomalonate gave a product which could not be distilled and did not yield a crystalline boronic acid on treatment with water. Aqueous catechol converted the boronic acid into the crystalline catechol derivative, which was recrystallized from acetone and did not melt below 200°: nmr (CD_3SOCD_3), τ ~3.3–3.5 (C_6H_4), ~8.1 (s, CH_3CO), ~8.4 (s, CH_2B), plus ethoxy pattern; ir (KBr, 5–16 μ) 5.71 (s), 5.80 (m), 6.2 (s), 6.42 (s), 6.73 (s), 7.03 (w), 7.24 (w), 7.32 (m), 7.5 (w), 7.67 (m), 7.78 (m), 8.05 (s), 8.13 (s), 8.32 (m), 8.40 (m), 8.95 (m), 9.1 (m), 9.35 (w), 9.71 (m), 9.85 (w), 9.92 (w), 10.6 (w), 11.10 (m), 11.51 (w), 12.15 (w), 13.10 (w), 13.20 (w), 13.41 (m), 13.63 (s).

Anal. Calcd for $C_{16}H_{20}BNO_7$: C, 55.04; H, 5.77; B, 3.10; N, 4.01. Found: C, 54.88; H, 5.77; B, 3.20; N, 4.16.

2-(Dibutoxyborylmethyl)cyclohexanone (8).—A solution of 2.03 g of the pyrrolidine enamine from cyclohexanone[16] and 4 g of dibutyl iodomethaneboronate in 50 ml of benzene was refluxed 18 hr. Water (20 ml) was added, and the mixture was refluxed another 0.5 hr. Sulfuric acid (10%, 10 ml) was added, and the product was extracted with three portions of ether (100 ml) mixed with 1-butanol (20 ml) and then was isolated by short-path distillation at *ca.* 65° (0.1 mm): ir (neat) 3.43 (s, C–H), 5.93 (s, C=O), 7.6 μ (s, B–O).[15]

Anal. Calcd for $C_{15}H_{29}BO_3$: C, 67.17; H, 10.90; B, 4.03. Found: C, 67.19; H, 10.77; B, 3.96.

2-(S-Hydroxyboromethyl)thiobarbituric Acid.—Dibutyl iodomethaneboronate (3 g) and 1.33 g of 2-thiobarbituric acid were refluxed in 50 ml of acetonitrile for 3 hr, cooled, and treated with 40 ml of water to cause crystallization of the product, 1.6 g (87%). The analytical sample was recrystallized from a mixture of dimethylformamide, dimethyl sulfoxide, and water and decomposed without melting at 300°: ir (KBr) 2.9 (OH), 3.25 (NH or OH), 3.4, 3.5 (CH), 6.0, 6.2 μ (C=O, C=N).[15]

Anal. Calcd for $C_5H_5BN_2O_3S$: C, 32.46; H, 2.72; B, 5.85; N, 15.14; S, 17.33. Found: C, 33.00; H, 2.74; B, 5.65; N, 15.28; S, 17.43.

Oxybis[2-(S-boromethyl)thiobarbituric acid] resulted when the foregoing compound was recrystallized from ethanol (1 l./g): uv max (EtOH), 275 mμ (ϵ 12,700), 256 (19,400), 230 (12,800); ir spectrum (KBr) identical with hydrated precursor.[15]

Anal. Calcd for $C_{10}H_8B_2N_4O_5S_2$: C, 34.12; H, 2.29; B, 6.16; N, 15.91; S, 18.22. Found: C, 34.09; H, 2.43; B, 5.96; N, 15.90; S, 18.08.

2-Hydroxyboromethylthio-4-oxy-6-methylpyrimidine (11) was prepared in the same manner as the thiobarbituric acid analog, substituting 2-mercapto-4-oxy-6-methylpyrimidine in the ingredients. The first fraction which crystallized, mp ~260°, gave an analysis which was not quite correct for $C_6H_7BN_2O_2S$ (C 2% low). After 2 days storage at 5°, a second crop was collected from the aqueous acetonitrile mother liquor, 1 g (45%), mp 326–334° dec, correct analysis for the dihydrate (or monohydrate of the boronic acid having the ring opened). The infrared spectra (KBr) of the two forms were the same: 2.90, 2.98, 3.10 (OH, NH), 6.02 (C=O), 6.20, 6.27, 6.37, 6.48, 6.58 μ (pyrimidine).[15]

Anal. Calcd for $C_6H_7BN_2O_2S\cdot 2H_2O$: C, 33.05; H, 5.09; B, 4.96; N, 12.85; S, 14.71. Found: C, 33.00; H, 5.10; B, 5.01; N, 13.03; S, 14.47.

Oxybis(2-boromethylthio-4-oxy-6-methylpyrimidine) (12 or 13) was prepared by heating either of the two hydrates described in the preceding paragraph to ~100° under vacuum (0.1 mm) for 2–4 hr. The analytical sample was recrystallized from a large volume of ethanol: uv max (EtOH) 274 mμ (ϵ 22,900), 237 (66,500); ir (KBr) 2.9 (weak, residual OH), 6.0 (weak, residual C=O), 6.2–6.3, 6.50, 6.70 μ (pyrimidine), numerous other differences from hydrated form.[15]

Anal. Calcd for $C_{12}H_{12}B_2N_4O_3S_2$: C, 41.65; H, 3.50; B, 6.25; N, 16.17; S, 18.53. Found: C, 41.84; H, 3.51; B, 6.08; N, 15.95; S, 18.25.

The **catechol ester of 2-hydroxyboromethylthio-4-oxy-6-methylpyrimidine** was prepared by stirring a suspension of 0.5 g of the pyrimidine in 25 ml of water with 0.3 g of catechol for 1.5 hr at 25°. The crystalline product (0.7 g) was washed repeatedly with water, and acetone: mp 265–270°.

Anal. Calcd for $C_{12}H_{13}BN_2O_4S$: C, 49.33; H, 4.48; B, 3.70; N, 9.59; S, 10.97. Found: C, 49.69; H, 4.57; B, 3.57; N, 9.75; S, 11.02.

Oxybis(2-boromethylthio-4-oxy-6-phenylpyrimidine) was prepared by the same method described for the thiobarbituric acid analog, substituting 2-mercapto-4-oxy-6-phenylpyrimidine in the ingredients: mp 328–331° dec.[15]

Anal. Calcd for $C_{22}H_{16}B_2N_4O_3S_2$: C, 56.20; H, 3.41; B, 4.60; N, 11.92; S, 13.64. Found: C, 56.09; H, 3.40; B, 4.57; N, 11.94; S, 13.51.

Oxybis(2-boromethylthio-4-oxy-6-propylpyrimidine) was similarly prepared from 2-mercapto-4-oxy-6-propylpyrimidine and did not melt below 250°.[15]

Anal. Calcd for $C_{16}H_{20}B_2N_4O_3S_2$: C, 47.79; H, 5.01; B, 5.38; N, 13.93; S, 15.95. Found: C, 47.61; H, 4.88; B, 5.15; N, 14.13; S, 15.70.

6-(Dihydroxyborylmethylthio)purine was similarly prepared from 6-mercaptopurine and recrystallized by dissolving in 50 ml of water and precipitating with 100 ml of acetone: mp 235–244° dec; ir (KBr) 2.9 (s), 6.27 (s), 6.79 (m), 6.90 (m), 7.15 (m), 7.50 (m), 7.65 (w), 7.95 (m), 8.20 (w), 8.74–9.30 (m), 9.8 (m), 10.6 (w), 11.30 (m), 12.0–12.5 (m), 12.7 (w), 14.5 (w), 15.50 μ (m).

Anal. Calcd for $C_6H_7BN_4O_2S\cdot H_2O$: C, 31.60; H, 3.97; B, 4.74; N, 24.56; S, 14.06. Found: C, 31.46; H, 4.04; B, 4.97; N, 24.13; S, 13.63.

S,7-Bis(dihydroxyborylmethyl)-2-mercapto-6-oxypurine was similarly prepared from 2-mercapto-6-oxypurine and recrystallized from ethanol–water and decomposed at 330° without melting.[15]

Anal. Calcd for $C_7H_{10}B_2N_4O_5S\cdot H_2O$: C, 27.85; H, 4.01; B, 7.16; N, 18.56; S, 10.62. Found: C, 28.14; H, 3.35; B, 7.18; N, 18.94; S, 10.61.

2-(Dihydroxyborylmethylthio)-4-carboxyuracil was similarly prepared from thioorotic acid, was not recrystallized, but was washed with water, acetone, and then boiling 1,2-dimethoxyethane, and decomposed at 250° without melting (up to 350°).[15]

(16) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Amer. Chem. Soc.*, **85**, 207 (1963).

Anal. Calcd for $C_6H_7BN_2O_5S$: C, 31.33; H, 3.07; B, 4.70; N, 12.18; S, 13.94. Found: C, 31.07; H, 2.69; B, 4.74; N, 11.89; S, 13.95.

2-Mercapto-4-oxy-5-(oxyboromethyl)-6-iminopyrimidine (7).—A solution of 0.85 g of thiourea, an equimolar quantity of potassium *t*-butoxide, and 3 g of methyl α-cyano-β-dibutoxyborylpropionate in 40 ml of *t*-butyl alcohol was kept at 70° for 2 hr, then neutralized (to pH paper, pH about 7) with glacial acetic acid, and diluted with 40 ml of water. The product crystallized together with some boric acid, evidently tightly held in a chelate since attempted removal as the methyl borate azeotrope did not change the composition: yield 0.57 g (21%), recrystallized from methanol–water; nmr (CD_3SOCD_3) τ 8.46 (s, CCH_2B), 6.16 (s, NH, SH); decomposed at 250° without melting up to 350°; ir (KBr) 3.0 (NH), 6.1–6.5 μ (pyrimidine).[15]

Anal. Calcd for $C_{10}H_{13}B_3N_6O_6S_2$: C, 29.30; H, 3.20; B, 7.92; N, 20.50; S, 15.65. Found: C, 29.29, 29.27; H, 3.79, 3.74; B, 7.95 7.75; N, 19.97, 20.27; S, 15.80, 15.68.

A sample of the pyrimidine 7 without chelated boric acid was obtained on one occasion, but we were unable to purify it to the usual analytical standard. The reaction mixture was treated with acetic acid and then water, as described in the preceding paragraph, and was then extracted with a mixture of 1-butanol and ether. The aqueous phase was concentrated, and the oily residue was treated with acetone and allowed to stand for 1 month in the refrigerator to crystallize it.

Registry No.—**1,** 13251-29-1; iodomethaneboronic acid, 16876-23-6; dibutyl butoxymethaneboronate, 16876-24-7; **2,** 13536-41-9; catechol ester of **3,** 13251-31-5; dimethylaminomethaneboronic acid catechol ester, 16876-27-0; **4,** 16973-90-3; phthalimidomethaneboronic acid, 16876-28-1; catechol ester of S-thioureidomethaneboronic acid, 16876-29-2; dibutyl acetylthiomethaneboronate, 16876-30-5; acetylthiomethaneboronic acid, 16876-31-6; dimethyl (dibutoxyborylmethyl)-malonate, 16876-32-7; **6,** 16876-33-8; diethyl acetamido-(catechylborylmethyl)malonate, 16876-34-9; **8,** 16876-35-0; **9,** 16876-36-1; 2-(S-hydroxyboromethyl)thiobarbituric acid, 16876-37-2; oxybis[2-(S-boromethyl)thiobarbituric acid], 16876-38-3; **10,** 16876-39-4; **11,** 16876-40-7; catechol ester of **11,** 16915-93-8; **12,** 16876-41-8; **13,** 16876-42-9; oxybis(2-boromethylthio-4-oxy-6-phenylpyrimidine), 16876-43-0; oxybis(2-boromethylthio-4-oxy-6-propylpyrimidine), 16876-44-1; S-7-bis(dihydroxyborylmethyl)-2-mercapto-6-oxypurine, 16876-45-2; 2-(dihydroxyborylmethylthio)-4-carboxyluracil, 16876-46-3.

The Mechanism of the Prins Reaction. VI. The Solvolysis of Optically Active *trans*-2-Hydroxymethylcyclohexyl Brosylate and Related Arenesulfonates[1]

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The solvolysis of optically active *trans*-2-hydroxymethylcyclohexyl brosylate yields *trans*-2-hydroxymethylcyclohexanol with complete retention of optical activity. This result may be attributed to the intervention of a four-membered oxonium ion intermediate or reaction of the carbonium ion with solvent before any conformational change. The solvolyses of *trans*-2-hydroxymethylcyclopentyl β-naphthalenesulfonate and *threo*-1-hydroxy-2-methyl-3-butyl β-naphthalenesulfonate proceed with elimination, rearrangement, and complete inversion of configuration which indicates that these compounds are not suitable for generating the intermediate responsible for *trans* addition in the Prins reaction. The solvolysis of *cis*-2-hydroxycyclohexylcarbinyl brosylate yields no *trans*-2-hydroxymethylcyclohexanol, a compound which would be expected if four-membered-ring oxonium-ion intermediates were important in these reactions.

One of the most interesting features of the Prins reaction is the highly stereoselective *trans* addition found with simple alicyclic and acylic olefins. The Prins reaction of cyclohexene has been studied most extensively and the major products of the reaction are derivatives of *trans*-2-hydroxymethylcyclohexanol with only traces of the *cis* isomers.[3–5] Similarly, the Prins reactions of *cis*- and *trans*-2-butene appear to yield mainly the products of *trans* addition[6] and we find only a trace of the *cis* addition product in the Prins reaction of *trans*-2-butene.

A case of nonstereospecific addition has been reported by LeBel, Liesemer, and Mehemedbasich who find that the Prins reactions of *cis*- and *trans*-4-octene yield products of both *cis* and *trans* addition.[7] Moreover, the two olefins give different ratios of *trans* to *cis* addition. However, this lack of stereoselectivity may be the result of working in dioxane solution since dioxane is known to alter the stereochemistry of solvolysis reactions.[8] This possibility is also supported by the observation that the Prins reaction with cyclohexene in dioxane solution affords a 20% yield of the *cis* addition product.[9]

Several mechanisms have been proposed to account for the stereoselectivity of the Prins reaction with simple olefins. The mechanism which has been mentioned most frequently involves an intermediate four-membered-ring oxonium ion.[3,7,10,11] The second mechanism involves a three-membered bridged ion similar to the intermediates suggested for other examples of electrophilic additions to double bonds.[5,12,13] It is fair to say that no data have been presented which un-

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(2) Alfred P. Sloan Research Fellow, 1965–1967.

(3) A. T. Blomquist and J. Wolinsky, *J. Amer. Chem. Soc.*, **79**, 6025 (1957).

(4) E. E. Smissman and R. E. Mode, *ibid.*, **79**, 3447 (1957).

(5) L. J. Dolby, C. N. Lieske, D. R. Rosencrantz, and M. J. Schwarz, *ibid.*, **85**, 47 (1963).

(6) M. Hellin, M. Davidson, D. Lumbroso, P. Giuliani, and F. Coussemant, *Bull. Soc. Chim. Fr.*, 2974 (1964).

(7) N. A. LeBel, R. N. Liesemer, and E. Mehemedbasich, *J. Org. Chem.*, **28**, 615 (1963).

(8) A. Streitwieser, Jr., and S. Andreadas *J. Amer. Chem. Soc.*, **80**, 6553 (1958); A. Streitwieser, Jr., and W. D. Schaeffer, *ibid.*, **79**, 6233 (1957); H. Weiner and R. Sneen, *ibid.*, **84**, 3599 (1962); **87**, 292 (1965).

(9) M. Schwarz, unpublished observation.

(10) L. Bernardi and A. Leone, *Tetrahedron Lett.*, No. 10, 499 (1964).

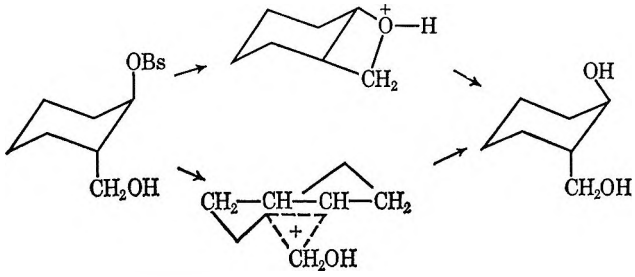
(11) E. Smissman, R. A. Schnettler, and P. S. Portoghese, *J. Org. Chem.*, **30**, 797 (1965).

(12) K. C. Murdock and R. B. Angier, *J. Amer. Chem. Soc.*, **84**, 3758 (1962).

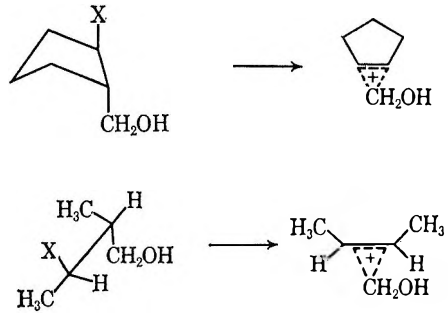
(13) G. Fodor and I. Tomoskozi, *Rev. Chim.* (Bucharest), **7**, 835 (1962).

ambiguously implicate either of these intermediates in the Prins reaction, but the stereospecific formation of two bicyclic alcohol side products in the Prins reaction with cyclohexene cannot be rationalized in terms of four-membered-ring oxonium ions.[14,15]

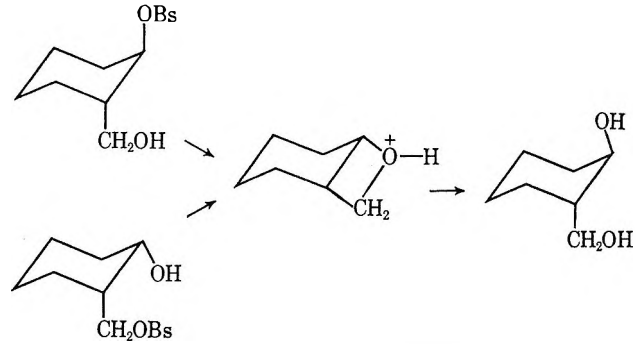
As a general approach to the mechanism of the Prins reaction we have attempted to generate the possible intermediates in solvolysis reactions and discern their intervention from the structures and distribution of the products. This approach was successful in demonstrating that the bicyclic alcohols formed in the Prins reaction of cyclohexene could arise from a common intermediate[15] and further that a mechanism for the Prins reaction in acetic acid involving six-membered acetoxonium ions is quite unlikely.[16] In an earlier study of the solvolysis of *trans*-2-hydroxymethylcyclohexyl brosylate, an unusually large fraction of retention of configuration was observed.[5] It was suggested that the diol of retained configuration could have been formed from the intermediate responsible for stereoselective *trans* addition in the Prins reaction.[5]



At the time these experiments were initiated it appeared that a distinction between the three-membered bridged ion and the four-membered oxonium ion should be possible since the oxonium ion would be capable of maintaining optical activity but the three-membered cyclic ion would not. This latter conclusion is now suspect. However, more promising compounds for displaying a racemic intermediate are *threo*-2-methyl-1-hydroxy-3-butyl arensulfonates and *trans*-2-hydroxymethylcyclopentyl arenesulfonates.



It was also of interest to examine the product from the solvolysis of *cis*-2-hydroxycyclohexylcarbinyl brosylate. If the solvolysis of *trans*-2-hydroxymethylcyclohexyl brosylate produces in part a four-membered cyclic oxonium ion which is responsible for the formation of the *trans*-2-hydroxymethylcyclohexanol, then it seems reasonable that *cis*-2-hydroxycyclohexylcarbinyl brosylate should give the same oxonium ion which



would be evidenced by the formation of some *trans*-2-hydroxymethylcyclohexanol.

Some of the above solvolysis reaction were examined in an effort to detect, in simplest terms, the 1,2 migration of a hydroxymethyl group. In an effort to find another system which might show this process we examined the solvolysis of the monotosylate of 2,2-dimethyl-1,3-propanediol. Although this neopentyl system is not one which would be derived by a Prins reaction, it offers the opportunity to measure the migratory aptitude of the hydroxymethyl group compared with that of a methyl group.

Synthesis.—Optically active *trans*-2-hydroxymethylcyclohexanol was obtained from the hydroboration of 1-hydroxymethylcyclohexene with the trialkyldiborane obtained from (−)-α-pinene followed by oxidation with hydrogen peroxide.[17] The absolute configuration of the (−)-*trans*-2-hydroxymethylcyclohexanol obtained in this manner was established as 1*R*:2*S*. A sample of *trans*-2-hydroxycyclohexanecarboxylic acid was partially resolved *via* the brucine salt.[18] The (+)-*trans*-2-hydroxycyclohexanecarboxylic acid, which has been shown to have the 1*S*:2*S* configuration,[18] was esterified with diazomethane and reduced with lithium aluminum hydride to yield (1*S*:2*R*)-(+)-*trans*-2-hydroxymethylcyclohexanol. The optically active *trans*-2-hydroxymethylcyclohexanol was converted into the required brosylate as previously described.[16]

The required arenesulfonate of *threo*-2-methyl-3-hydroxybutanol was prepared by a sequence involving the hydroboration of the benzyl ether of tiglic alcohol with triisopinocampheyldiborane followed by oxidation with hydrogen peroxide to afford *threo*-2-methyl-3-hydroxybutyl benzyl ether. The desired ether was contaminated with approximately 30% isomeric 2-hydroxy-2-methylbutyl benzyl ether from which it was separated by preparative vapor phase chromatography. Although the *threo*-2-methyl-3-hydroxybutyl benzyl ether obtained in this manner was optically active, treatment with β-naphthalenesulfonyl chloride afforded a crystalline naphthalenesulfonate which showed only a trace of optical activity. Hydrogenolysis of this material proceeded with some difficulty to afford the desired hydroxy β-naphthalenesulfonate as an oil.

The required *trans*-2-hydroxymethylcyclopentyl β-naphthalenesulfonate was prepared by the diborane reduction of the β-naphthalenesulfonate of methyl *trans*-

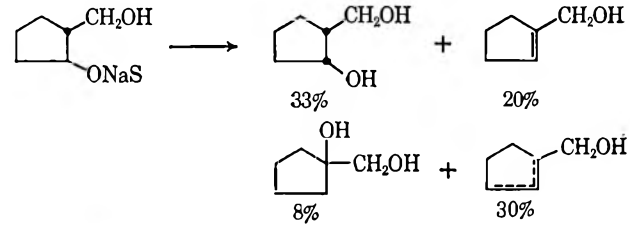
(14) L. J. Dolby, *J. Org. Chem.*, **27**, 2971 (1962).
(15) L. J. Dolby and M. J. Schwarz, *ibid.*, **28**, 1456 (1963).
(16) L. J. Dolby and M. J. Schwarz, *ibid.*, **30**, 3581 (1965).
(17) H. C. Brown, N. R. Ayyangar, and G. Zweifel, *J. Amer. Chem. Soc.*, **86**, 1071 (1964); H. C. Brown, N. R. Ayyangar, and G. Zweifel, *ibid.*, **86**, 397 (1964).
(18) J. Sanchez Real and J. Pascual, *An. Real Soc. Espan. Fis. Quim., Ser. B*, **49**, 445 (1953); J. Faixat, A. Fevrer, and J. Pascual, *ibid.*, **57**, 705 (1961); *Chem. Abstr.*, **57**, 5812 (1962).

2-hydroxycyclopentanecarboxylate. The methyl *trans*-2-hydroxycyclopentanecarboxylate was obtained by the sodium borohydride reduction of a mixture of 2-carboethoxycyclopentanone and 2-carbomethoxycyclopentanone which resulted in a mixture of the *cis*- and *trans*-hydroxy esters. The mixed hydroxy esters were separated by fractional distillation into *cis* and *trans* isomers and transesterification with methanol of the *trans*-hydroxy ester mixture afforded pure methyl *trans*-2-hydroxycyclopentanecarboxylate which was converted into the β-naphthalenesulfonate in the usual manner. The remaining arenesulfonate, 3-hydroxyl-2,2-dimethylpropyl tosylate, was prepared by treating the parent diol with a limited amount of *p*-toluenesulfonyl chloride.

Results

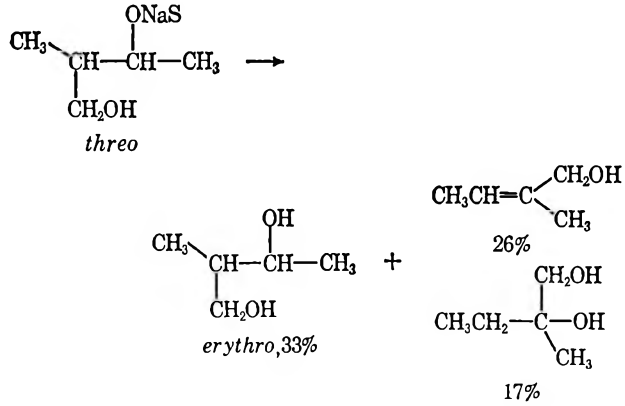
Optically active *trans*-2-hydroxymethylcyclohexyl brosylate was solvolyzed in aqueous acetone containing enough phosphate buffer to maintain the pH at 6 at the end of the reaction. The solvolysis gave 3-hydroxymethylcyclohexene in 60% yield and a mixture of *cis*- and *trans*-2-hydroxymethylcyclohexanols in 30% yield of which 35% was the *trans* isomer. Another component, 1-hydroxymethylcyclohexanol (8%) was identified by comparison with an authentic sample. The unsaturated alcohol and the two 1,3-diols were reported products from the solvolysis in aqueous dioxane and 1-hydroxymethylcyclohexanol is undoubtedly the unidentified compound previously reported.[5] The 1,3-diols were not directly separable by vapor phase chromatography but were collected as a mixture. The mixture of 1,3-diols was converted into the corresponding acetonides which are easily separated by vapor phase chromatography. Since this work was carried out with only partially resolved material, it was not possible to compare the optical activity of the *trans*-2-hydroxymethylcyclohexanol obtained from solvolysis with that of the starting *trans*-2-hydroxymethylcyclohexanol. Accordingly, a sample of the *trans*-2-hydroxymethylcyclohexyl brosylate used in the solvolysis experiment was cleaved with sodium amalgam[19] to regenerate optically active *trans*-2-hydroxymethylcyclohexanol which was converted into the acetonide and compared with the solvolysis product. The acetonides of the optically active *trans*-2-hydroxymethylcyclohexanols have specific rotations much smaller than and opposite in sign to those of the parent diols. Thus it was convenient to measure the rotations of the acetonides in aqueous ethanol which was 0.2 *M* in strong acid and resulted in rapid and quantitative hydrolysis of the acetonides to the parent diol. The specific rotations at four wavelengths of the hydrolyzed acetonides of *trans*-2-hydroxymethylcyclohexanol from the sodium amalgam cleavage and solvolysis of the optically active *trans*-2-hydroxymethylcyclohexyl brosylate were indistinguishable (see Experimental Section). This result establishes that the *trans*-2-hydroxymethylcyclohexanol obtained from the solvolysis of *trans*-2-hydroxymethylcyclohexyl brosylate is formed without the intervention of a racemic intermediate.

The solvolysis of *trans*-2-hydroxymethylcyclopentyl β-naphthalenesulfonate was carried out as described for *trans*-2-hydroxymethylcyclohexyl brosylate. Four of the ten peaks observed in the vapor phase chromatogram of the products accounted for 91% of the peak area. No *trans*-2-hydroxymethylcyclopentanol was found in the products although it was readily separated from the other products by vapor phase chromatography.



The *cis*-2-hydroxymethylcyclopentanol was identified by comparison with an authentic sample and the other products were identified from their spectral properties. The only significant feature of this result is that the substitution product is formed with complete inversion of configuration as expected in a normal solvolytic process.

The solvolysis of *threo*-2-methyl-1-hydroxy-3-butyl β-naphthalenesulfonate gave products similar to those obtained in the solvolysis of *trans*-2-hydroxymethylcyclopentyl β-naphthalenesulfonate.



The isomeric 1,3-diols were not directly separable by vapor phase chromatography and the 1,3-diol from the solvolysis reaction was collected by vapor phase chromatography and converted into the corresponding cyclopentanone ketal. Analysis of the cyclopentanone ketals which were readily separable by vapor phase chromatography indicated that the product 1,3-diol from the solvolysis reaction was 95% *erythro*-2-methyl-1,3-butanediol and 5% *threo*-diol. Sodium amalgam cleavage of the starting arenesulfonate gave a mixture of diols containing 97% *threo*-diol and 3% *erythro*-diol. Thus the solvolysis proceeds with essentially complete inversion of configuration.

The solvolysis of *cis*-2-hydroxycyclohexylcarbinyl brosylate affords 17% 2-methylcyclohexanone, 76% *cis*-2-hydroxymethylcyclohexanol, and 7% *trans*-1-methyl-1,2-cyclohexanediol identified by comparison with an authentic sample. No *trans*-2-hydroxymethylcyclohexanol was formed.

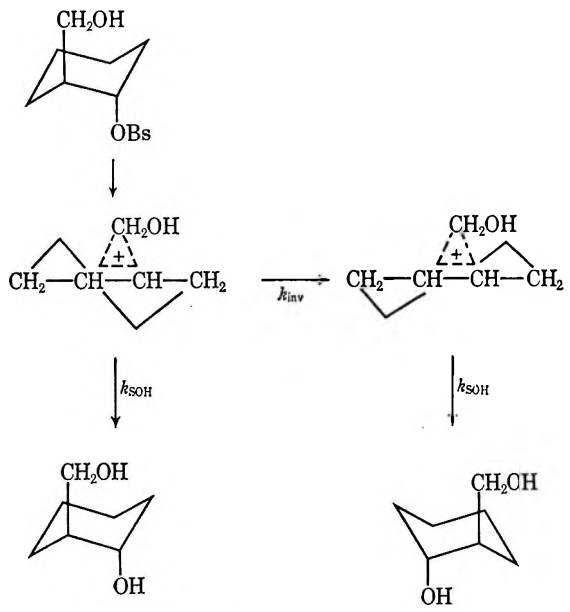
The solvolysis of 2,2-dimethyl-3-hydroxypropyl tosylate in water with an acetate buffer gave only 2-methylbutanal and a small amount of 2,2-dimethyl-1,3-propanediol. When the solvolysis was carried out

(19) P. Levine and J. Compton, *J. Amer. Chem. Soc.*, **57**, 2306 (1935); K. Freudenberg and F. Braums, *Ber.*, **55**, 3233 (1922); C. A. Grob and D. A. Prins, *Helv. Chim. Acta*, **28**, 840 (1945).

using a phosphate buffer at slightly higher pH, the reaction produced several more products. It appears that the solvolysis proceeds almost exclusively by methyl migration. It may be that the primary products of the reaction are mainly unsaturated alcohols which are rearranged to 2-methylbutanal in the more acidic acetate buffer system.

Discussion

The observation that the solvolysis of *trans*-2-hydroxymethylcyclohexyl brosylate affords the *trans*-diol with complete retention of optical activity may be taken as evidence for a four-membered oxonium-ion intermediate. However, another analysis is possible. Recent investigation by Berson and his collaborators[20] has established that a carbonium ion may be captured by solvent before it undergoes even a subtle conformational change. Thus in the case of *trans*-2-hydroxymethylcyclohexyl brosylate it is not certain that the three-membered bridged intermediate would result in racemization. The initially formed ion must undergo conformational change or capture by solvent would be expected to give the *trans*-diol by *trans*-diaxial opening resulting in optically active *trans*-diol of the same configuration as the starting hydroxy brosylate.



The corresponding bridged intermediates which could be formed from *trans*-2-hydroxymethylcyclopentyl and *threo*-1-hydroxy-2-methyl-3-butyl arenesulfonates would be racemic or present only a small barrier to racemization. However, since these arenesulfonates solvolyze with complete inversion of configuration, it is not possible to draw any further conclusions regarding the intervention of three-membered bridged intermediates in the solvolysis of *trans*-2-hydroxymethylcyclohexyl brosylate.

The solvolysis of the monotosylate of 2,2-dimethyl-1,3-propanediol also failed to reveal any products resulting from the 1,2 migration of a hydroxymethyl group. In this case, migration of a hydroxymethyl group would have resulted in the formation of unsaturated 3-methylbutanols or 3-methylbutanal which could not be detected among the solvolysis products.

The solvolysis of *cis*-2-hydrocyclohexylcarbinyl brosylate was examined to provide a direct test for the intervention of four-membered oxonium ions in the solvolysis of *trans*-2-hydroxymethylcyclohexyl brosylate. Both arenesulfonates could give in part the same four-membered cyclic oxonium ion and there should be some overlap in the products of the reaction. In particular, if the *trans*-2-hydroxymethylcyclohexanol obtained from *trans*-2-hydroxymethylcyclohexyl brosylate is properly ascribed to a four-membered cyclic oxonium ion, then the solvolysis of *cis*-2-hydroxycyclohexylcarbinyl brosylate should also afford some *trans*-diol.

In fact, the solvolysis of *cis*-2-hydroxycyclohexylcarbinyl brosylate does not give any of the *trans*-diol and this result weighs heavily against the intervention of four-membered cyclic oxonium ion intermediates in these reactions. It might be argued that *cis*-2-hydroxycyclohexylcarbinyl brosylate and *trans*-2-hydroxylmethylcyclohexyl brosylate give different oxonium ions. Presumably the difference would be in the degree of bonding between the oxygen and the two carbons involved. If this is the case, the four-membered cyclic oxonium ions are grossly different from five- and six-membered cyclic oxonium ions.[21]

Experimental Section[22]

Methyl (+)-*trans*-2-Hydroxycyclohexanecarboxylate.—A sample of (±)-*trans*-2-hydroxycyclohexanecarboxylic acid was partially resolved as described by Real and Pascual[18] to afford (+)-*trans*-2-hydroxycyclohexanecarboxylic acid: mp 104–106°; $[\alpha]_D$ 26.8 (*c* 0.155, chloroform). The acid (11.3 g) was esterified with diazomethane to afford 13.3 g of methyl (+)-*trans*-2-hydroxycyclohexanecarboxylate: bp 90–93° (2.5 mm) [lit.[5] bp 100–103° (6 mm)]; $[\alpha]_D$ 27.0 (*c* 0.426, ethanol).

Lithium Aluminum Hydride Reduction of Methyl (+)-*trans*-2-Hydroxycyclohexanecarboxylate.—The ester obtained above was reduced with lithium aluminum hydride as previously described[5] to afford (+)-*trans*-2-hydroxymethylcyclohexanol: bp 128–130° (2.3 mm) [lit.[5] bp 122–124° (2 mm)]; $[\alpha]_D$ 21.8 (*c* 0.913, ethanol).

(−)-*trans*-2-Hydroxymethylcyclohexanol.—In a dry 5-l. three-necked flask equipped with a thermometer, pressure-equalizing dropping funnel, stirrer, and a condenser was placed 1308 ml of 0.87 *M* diborane (1.13 mol) in tetrahydrofuran. The flask was cooled in a Dry Ice–acetone bath while 462 g (3.4 mol) of α-pinene in 420 ml of tetrahydrofuran was added dropwise during 20 min while purging with dry nitrogen. The reaction mixture was stirred at 0° for 3 hr after which a solution of 63 g (0.56 mol) of 1-hydroxymethylcyclohexene in 135 ml of tetrahydrofuran was slowly added (hydrogen evolution). The resulting solution was stirred at 5° for 10 hr, then treated with water to decompose the residual hydride.

The reaction mixture was treated with 453 g of 30% hydrogen peroxide at 30° while the pH was maintained at 7–9 by the concurrent addition of 3 *M* sodium hydroxide.[23] After stirring for 30 min, the mixture was refluxed overnight. Most of the solvent was removed by distillation and the organic layer was separated and dried over magnesium sulfate. Isopinocampheol and other

(20) J. A. Berson and M. S. Poonian, *J. Amer. Chem. Soc.*, **88**, 170 (1966); J. A. Berson and P. Reynolds-Warnhoff, *ibid.*, **86**, 595 (1964); J. A. Berson and D. Willner, *ibid.*, **86**, 609 (1964); J. A. Berson and J. J. Gajewski, *ibid.*, **86**, 5020 (1964).

(21) H. W. Heine, A. D. Miller, W. H. Barton, and R. W. Greiner, *ibid.*, **75**, 4778 (1953); D. S. Noyce and B. N. Bastian, *ibid.*, **82**, 1246 (1960); S. Winstein, E. Allred, R. Heck, and R. Glick, *Tetrahedron*, **3**, 1 (1958).

(22) All melting points and boiling points are uncorrected. Distillations were carried out with a 130-cm modified Podbielniak tantalum spiral column or a 92-cm spinning-band column. Proton magnetic resonance spectra were determined with a Varian A-60 spectrometer using tetramethylsilane as internal standard. Aerograph Models A-90-P and Autoprep A-700 gas chromatographs were used for vapor phase chromatography. Optical rotations were measured with a Perkin-Elmer Model 141 polarimeter.

(23) H. C. Brown and K. A. Kelbys, *J. Amer. Chem. Soc.*, **86**, 1791 (1964).

terpenoid material was distilled under reduced pressure to leave a pot residue which showed a postive flame test for boron. Methanol was added to the residue and its was distilled through a 50-cm Vigreux column until boron could not be detected in the distillate. Fractional distillation gave a forerun containing terpenoid materials and 47 g (65%) of (−)-*trans*-2-hydroxymethylcyclohexanol, bp 142–142.5° (13 mm) [lit. bp 122–124° (2 mm)]. The infrared and nmr spectra were identical with those of an authentic sample of *trans*-diol. The rotation of the diol was measured at five wavelengths: $[\alpha]_{578}$ −8.7°, $[\alpha]_{546}$ −10.0, $[\alpha]_{436}$ −17.4°, $[\alpha]_{365}$ −27.2°, and $[\alpha]_{313}$ −40.7° (*c* 0.541, ethanol).

Optically Active *trans*-2-Acetoxymethylcyclohexyl Brosylate.—A sample of (−)-*trans*-2-hydroxymethylcyclohexanol (5.40 g) was converted into the acetate brosylate as previously described.[16] Crystallization of the crude product afforded 7.0 g (43%) of *trans*-2-acetoxymethylcyclohexyl brosylate, mp 79–93°, which showed spectral properties identical with those of an authentic sample of racemic material. The broad melting range is undoubtedly caused by the fact that only partially resolved diol was used.

(−)-*trans*-2-Hydroxymethylcyclohexyl Brosylate.—The optically active *trans*-2-acetoxymethylcyclohexyl brosylate (7.0 g) obtained above was subjected to methanolysis as previously described.[5] Crystallization from ether–petroleum ether (bp 30–60°) yielded 4.52 g of the hydroxy brosylate (72%) in the first crop and a second small crop of much greater otpical activity. These two crops were combined and crystallized again to yield two crops. The first crop (5.06 g) showed mp 63–66°, $[\alpha]_{578}$ −2.25 (*c* 0.71, ethanol), and the second crop (0.5 g) showed mp 55–60°, $[\alpha]_{578}$ −30.9 (*c* 0.90, ethanol). These two crops were dissolved and combined to yield the (−)-*trans*-2-hydroxymethylcyclohexyl brosylate, $[\alpha]_{578}$ −3.07 (c 2.70, ethanol), employed in the solvolysis experiment.

***cis*- and *trans*-2-Carbomethoxycyclopentanols.**—A mixture of 2-carbomethoxycyclopentanone and 2-carbethoxycyclopentanone was reduced with sodium borohydride as described by Pascual.[24] The *cis* and *trans* mixed esters were separated using 5 ft × 0.25 in. column packed with 20% Carbowax 20M on firebrick. Fractionation of the crude product from the reduction of 16 g of mixed 2-carboalkoxycyclopentanones afford the following: fraction 1, 7.72 g, bp 92–100° (10 mm), 5.2% *trans;* fraction 2; bp 100–105° (10 mm), 14.5% *trans;* fraction 3, 8.34 g, bp 105–106° (10 mm), 48% *trans;* fraction 4, 4.90 g, bp 72–74° (0.35 mm), 95% *trans;* and pot residue, 9.0 g. A sample of *trans* rich hydroxy esters was transesterified with methanol–perchloric acid and separated by preparative vapor phase chromatography to afford pure *trans*-2-carbomethoxycyclopentanol, $n^{25}D$ 1.4582 (lit.[25] $n^{25}D$ 1.4569), and some *cis*-2-carbomethoxycyclopentanol. The 3,5-dinitrobenzoate of *cis*-2-carbomethoxycyclopentanol was prepared and melted at 98.5–99.5° [lit.[25] mp 103–103.5°].

***cis*-2-Hydroxymethylcyclopentanol** was prepared by lithium aluminum hydride reduction of the mixed ethyl and methyl esters of *cis*-2-hydroxycyclopentanecarboxylic acid. The material distilled at 123–125° (10 mm) [lit.[26] bp 160–165° (30 mm)] and melted at 31–33° after crystallization from ether.

Anal. Calcd for $C_6H_{12}O_2$: C, 62.00; H, 10.47. Found: C, 61.64; H, 10.36.

***trans*-2-Carbomethoxycyclopentyl β-Naphthalenesulfonate.**—A stirred solution of 10 g of *trans*-2-carbomethoxycyclopentanol in dry pyridine (100 ml) was cooled to 0° and treated with 28 g of β-naphthalenesulfonyl chloride. The reaction mixture was stirred overnight at room temperature and processed in the usual manner. The crude product was crystallized from ether to afford 12.0 g (52%) of *trans*-2-carbomethoxycyclopentyl β-naphthalenesulfonate, mp 69–79°, unchanged on further crystallizations.

Anal. Calcd for $C_{17}H_{18}SO_5$: C, 61.06; H, 5.39. Found: C, 60.87; H, 5.30.

***trans*-2-Hydroxymethylcyclopentyl β-Naphthalenesulfonate.**—In a three-necked flask fitted with a dropping funnel, condenser, and drying tube was placed 8.5 g of *trans*-2-carbomethoxycyclopentyl β-naphthalenesulfonate in dry tetrahydrofuran (40 ml). The reaction vessel was cooled in an ice bath and 125 ml of diborane (1 *M*) in tetrahydrofuran was added. The reaction mixture was refluxed for 2 hr and hydrolyzed with water followed by 15 ml of 6 *N* hydrochloric acid. Most of the solvent was evaporated, the organic layer was separated, and the aqueous layer was extracted with ether. The combined organic extracts were washed with water and dried over magnesium sulfate. The crude product obtained in nearly quantitative yield was crystallized at low temperature from carbon tetrachloride, but the material melted upon warming to room temperature.

***trans*-2-Acetoxymethylcyclopentyl β-naphthalenesulfonate** was prepared by acetylating some of the material obtained above with acetyl chloride and pyridine. The material crystallized from ether–hexane and showed mp 85.5–86.5°.

Anal. Calcd for $C_{18}H_{20}SO_6$: C, 62.06; H, 5.70. Found: C, 62.28; H, 5.93.

***erythro*-2-Methyl-1,3-butanediol.**—In a stainless steel bomb was placed 70 g of paraformaldehyde and a solution of 87 g of concentrated sulfuric acid and 206 ml of water. The sealed bomb was heated at 80° for 1 hr and then cooled in a Dry Ice–acetone bath. *trans*-2-Butene (88 g) was added and the sealed bomb was heated for 2 hr at 80–130° with rocking. The cooled bomb was opened and the reaction mixture was neutralized with aqueous sodium hydroxide after which it was continuously extracted with ether. Preparative vapor phase chromatography on a 10 ft × $^3/_8$ in. column packed with 10% cyanoethoxypropane on firebrick afforded *cis*-4,5-dimethyl-1,3-dioxane, which showed the same spectral properties noted previously.[6]

A 2.0-g sample of *cis*-4,5-dimethyl-1,3-dioxane was refluxed for 7 days with methanolic sulfuric acid (0.1 *N*). The sulfuric acid was neutralized with sodium bicarbonate and the mixture was filtered and concentrated. The residue was purified by vapor phase chromatography on a 10 ft × 0.25 in. column packed with cyanoethyl sucrose in Chromosorb G to afford *erythro*-2-methyl-1,3-butanediol. The nmr spectrum of the material obtained in this manner exhibited four signals ascribed to the two methyl groups (τ 8.77, 8.87, 9.07, and 9.18).

Anal. Calcd for $C_5H_{12}O_2$: C, 57.76; H, 11.54. Found: C, 57.51, H, 11.43.

Cyclopentanone Ketal of *erythro*-2-Methyl-1,3-butanediol.—A sample of the diol obtained above was heated with a 2 *M* excess of cyclopentanone at 80° overnight. Dry benzene was added and the water–benzene azeotrope was distilled through the Podbielniak column. The residue was subjected to glpc on a 20 ft × 0.25 in. column packed with silicone XF 1150 on Chromosorb P. The material contained 96% of the *cis* ketal (from the *erythro*-diol) and 4% of its epimer. The nmr spectrum of the *cis* ketal showed two signals at τ 8.92 and 9.01 (6 H) ascribed to the two methyl groups and a multiplet at τ 8.3 ascribed to the cyclopentane protons.

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.65; H, 10.67. Found: C, 70.55; H, 10.54.

Tiglic alcohol was prepared by the reduction of tiglaldehyde using aluminum hydride prepared *in situ* as described by Jorgenson.[27] Tiglic alcohol, bp 133–139° (lit.[28] bp 133–140°), was obtained in 74% yield.

***threo*-2-Methyl-1,3-butanediol.**—Hydroboration–oxidation of tiglic alcohol was carried out in the conventional manner.[29] The crude product was processed as described for (−)-*trans*-2-hydroxymethylcyclohexanol. Distillation afforded slightly impure diol, bp 95–114° (18 mm), in 76% yield. Vapor phase chromatography on a 5 ft × 0.25 in. column packed with 20% Carbowax 20M showed an impurity (5%) with the same retention time as 2-methyl-1,2-butanediol. The nmr spectrum of the pure *threo*-2-methyl-1,3-butanediol showed peaks at τ 8.82, 8.92, 9.13, and 9.25 attributed to the two methyl groups. Mixtures of the *erythro*- and *threo*-diols show eight peaks in the region τ 8.8–9.3.

Anal. Calcd for $C_5H_{12}O_2$: C, 57.76; H, 11.54. Found: C, 57.68; H, 11.83.

The cyclopentanone ketal of *threo*-2-methyl-1,3-butanediol was prepared as described for the *erythro* isomer. The nmr spectrum showed a doublet (3 H) at τ 8.93, J = 7 cps, and a doublet (3 H) at τ 9.02, J = 7 cps, ascribed to the two methyl groups. The cyclopentane protons appeared as a multiplet at τ 8.3.

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.65; H, 10.67. Found: C, 70.59; H, 10.65.

(24) J. Pascual and J. Vinas, *Bull. Soc. Chim. Fr.*, 1430 (1960).

(25) J. Pascual and F. Lacasa, *An. Real. Soc. Espan. Fis. Quim., Ser. B*, **51**, 551 (1955).

(26) A. S. Dreiding and J. A. Hartman, *J. Amer. Chem. Soc.*, **75**, 939 (1953).

(27) M. Jorgenson, *Tetrahedron Lett.*, 559 (1962).

(28) A. Lauchenauer and H. Sching, *Helv. Chim Acta*, **34**, 1514 (1951).

(29) H. C. Brown and K. A. Kelbys, *J. Amer. Chem. Soc.*, **86**, 1791 (1964).

Tiglyl Benzyl Ether.—To a stirred mixture of 16 g of sodium hydride and 590 ml of dry N,N-dimethylformamide was added 52.5 g of tiglic alcohol. Benzyl chloride (130 g) was slowly added to the resulting suspension and the mixture was stirred for 36 hr. The mixture was hydrolyzed with water and the crude product was isolated by extraction with hexane. Fractional distillation afforded 46 g of pure tiglyl benzyl ether, bp 126–128° (21 mm).

Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.20; H, 9.23.

(−)-*threo*-2-Methyl-3-hydroxybutyl Benzyl Ether.—Tiglyl benzyl ether (46 g) was subjected to hydroboration–oxidation as described for the preparation of (−)-*trans*-2-hydroxymethylcyclohexanol. The crude product was fractionally distilled to yield a forerun of terpene material and the following fractions: fraction 1, 7.5 g, bp 100–105° (3 mm); fraction 2, 19 g, bp 105–114° (3 mm); fraction 3, 24 g, bp 114–140° (1.5 mm). The first two fractions were separated by preparative glpc on a 10 ft × 3/8 in. column packed with 5% Carbowax 20M on Chromosorb G. A total of 11 g (22%) of (−)-*threo*-3-hydroxy-2-methylbutyl benzyl ether, $[\alpha]_{578}$ 5.16 (*c* 3.94, CCl_4), was obtained along with 5 g (10%) of 2-hydroxy-2-methylbutyl benzyl ether. The nmr spectrum of the *threo*-3-hydroxy-2-methylbutyl benzyl ether showed normal absorption for the benzyloxy group and four sharp signals (6 H) at τ 9.23, 9.12, 8.98, and 8.89 ascribed to the two methyl groups.

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.29; H, 9.35. Found: C, 74.16; H, 9.13.

The nmr spectrum of the 2-hydroxy-2-methyl-1-butyl benzyl ether showed normal benzyloxy absorption, a triplet (3 H) at τ 9.15 (J = 7 cps), and a singlet (3 H) at τ 8.92 ascribed to the two methyl groups.

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.29; H, 9.35. Found: C, 74.13; H, 9.18.

2-Methyl-1,2-butanediol.—A mixture of 1.2 g of the 2-hydroxy-2-methyl-1-butyl benzyl ether and 0.4 g of 30% palladium on carbon in 40 ml of ethanol was hydrogenated at room temperature. The theoretical amount of hydrogen was absorbed overnight to furnish a quantitative yield of the diol which was purified by vapor phase chromatography using a 5 ft × 0.25 in. column pcked with 20% Carbowax 20M on firebrick. The nmr spectrum showed a singlet at τ 8.92 (3 H) and a triplet τ 9.10 (J = 7 cps) (3 H), attributed to the two methyl groups. The bis(*p*-nitrobenzoate) derivative melted at 106–107° (lit.[30] mp 107–109°).

The β-naphthalenesulfonate of *threo*-2-methyl-3-hydroxybutyl benzyl ether was obtained from the corresponding alcohol by the action of β-naphthalenesulfonyl chloride in pyridine. The arensulfonate was obtained in 49% yield as plates, mp 36.5–38.5°, on crystallization from ether–hexane. The crystalline material showed only very slight optical activity.

Anal. Calcd for $C_{22}H_{24}SO_4$: C, 68.72; H, 6.29. Found: C, 68.78; H, 6.48.

***threo*-1-Hydroxy-2-methyl-3-butyl β-Naphthalenesulfonate.**—A mixture of 5.5 g of the β-naphthalenesulfonate of *threo*-2-methyl-3-hydroxybutyl benzyl ether, 15 drops of 2% palladium chloride in 2 *N* hydrochloric acid, and 0.74 g of 30% palladium on carbon in ethyl acetate (70 ml) was hydrogenated at room temperature. After 5 hr the theoretical amount of hydrogen had been absorbed. The spectra of the crude product indicated that some of the material had been acetylated after hydrogenolysis and the entire crude product was subjected to methanolysis as previously described.[5] The product from the methanolysis reaction showed the anticipated spectra properties but it was not obtained in crystalline form.

2-Methyl-2-hydroxymethylpropyl Tosylate.—A solution of 2,2-dimethyl-1,3-propanediol in 3 ml of pyridine was cooled to 0° and a solution of 1.22 g of *p*-toluenesulfonyl chloride in pyridine (4 ml) was added with stirring. The mixture was stored at room temperature for 1.75 hr and processed in the usual manner. The crude product was chromatographed over silica gel with chloroform to give 400 mg (16%) of the ditosylate, mp 117–118° (lit.[31] mp 116–120°) after crystallization from chloroform–petroleum ether (bp 30–60°). Continued elution with chloroform afforded the monotosylate, 810 mg (50%), which could not be crystallized.

Anal. Calcd for $C_{12}H_{18}O_4S$: C, 55.81; H, 6.97. Found: C, 55.74; H, 7.00.

Solvolysis of (−)-*trans*-2-Hydroxymethylcyclohexyl Brosylate.—A solution of 4.0 g of the hydroxy brosylate, 80 ml of acetone, and 100 ml of 1.26 *M* phosphate buffer (pH 6.8) was heated under reflux for 30 hr and processed as previously described.[5] The product mixture contained 60% 3-hydroxymethylcyclohexene, 30% *cis*- and *trans*-2-hydroxymethyl cyclohexanols, 8% 1-hydroxymethylcyclohexanol identified by comparison with an authentic sample prepared previously,[16] and 2% unidentified products. The mixture of *cis*- and *trans*-2-hydroxymethylcyclohexanols (0.163 g, 11%) was collected and converted into the corresponding acetonides which were separated as previously described.[16] Because the rotation of the optically active acetonides are much smaller and opposite in sigh to those of the corresponding diols, the acetonide was hydrolyzed *in situ* using 80% ethanol–water 0.2 *M* in *p*-toluenesulfonic acid. This solvent caused rapid and complete hydrolysis of the acetonide. The rotation of the diol was measured at five wavelengths: $[\alpha]^{22}_{578}$ −6.85°, $[\alpha]^{22}_{546}$ −7.77°, $[\alpha]^{22}_{436}$ −12.6°, $[\alpha]^{22}_{365}$ −19.2° (*c* 2.51).

Sodium Amalgam Cleavage of (−)-*trans*-2-Hydroxymethylcyclohexyl Brosylate.—A solution of 0.45 g of the hydroxy brosylate in 30 ml of dry methanol was stirred overnight with 13 g of 4% sodium amalgam.[32] The resulting mixture was made slightly acidic with anhydrous hydrogen chloride and then basified to pH with anhydrous potassium carbonate. The mixture was filtered and the solid was extracted with hot ether and combined with the filtrate. Evaporation of the organic extracts and vapor phase chromatography afforded 0.083 g (50%) of (−)-*trans*-2-hydroxymethylcyclohexanol which was converted into the acetonide. The rotation of the diol resulting from the *in situ* hydrolysis of the acetonide was measured at four wavelengths: $[\alpha]^{22}_{578}$ −6.89°, $[\alpha]^{22}_{546}$ −7.84°, $[\alpha]^{22}_{436}$ −13.2°, $[\alpha]^{22}_{365}$ −20.1° (*c* 4.61).

Solvolysis of *threo*-1-Hydroxy-2-methyl-3-butyl β-Naphthalenesulfonate.—A solution of 2.0 g of the arenesulfonate, 60 ml of acetone, 66 ml of 1.26 *M* phosphate buffer (pH 6.8), and 50 ml of water was refluxed for 60 hr. The acetone was distilled under a fractionating column and the aqueous residue was continuously extracted with ether. Vapor phase chromatography of the product on 10 ft × 0.25 in. column packed with 5% cyanoethylsucrose on Chromosorb G showed six products. The following products were isolated and identified (the yields correspond to the percentage of the peak area): tiglic–angelic alcohol mixture (26%), 2-methyl-2-hydroxybutanol (17%), 2-methyl-3-hydroxybutanol. The 1,3-diol mixture (119 mg) isolated by glpc was dissolved in benzene and cyclopentanone after which some of the benzene was distilled to yield the cyclopentanone ketal. The ketal was subjected to glpc on a 20 ft × 0.25 in. column packed with 10% silicone XF 1150 on Chromosorb P and found to contain 95% of ketal derived from the *erythro*-diol and 5% of its diastereomer. A sample of the arenesulfonate was cleaved with sodium amalgam and the diol obtained was converted into the cyclopentanone ketal which was found to contain 97% ketal derived from the *threo*-diol and 3% isomeric ketal.

Solvolysis of *trans*-2-Hydroxymethylcyclopentyl β-Naphthalenesulfonate.—A solution of 4 g of the arenesulfonate, 100 ml of acetone, 120 ml of 1.26 *M* phosphate buffer (pH 6.8), and 60 ml of water was heated under reflux for 55 hr. The reaction mixture was processed as described for the solvolysis of *trans*-2-hydroxymethylcyclohexyl brosylate. Vapor phase chromatography on a 5 ft × 0.25 in. column packed with 20% Carbowax 20M on firebrick at 200° indicated the presence of ten components, but the mixture did not contain any *trans*-2-hydroxymethylcyclopentanol. *cis*-2-Hydroxymethylcyclopentanol compressed 33% of the material and three other components were tentatively identified. The first eluted component (30%) appeared to be 2- or 3-hydroxymethylcyclopentene: nmr, multiplet at τ 4.35 (2 H), vinyl protons; doublet at τ 6.60 (2 H), J = 6 cps, carbinyl protons. The second component (20%) appeared to be 1-hydroxymethylcyclopentene: nmr, multiplet at τ 4.48 (1 H), vinyl proton; singlet at τ 5.95 (2 H), carbinyl protons. The third component (8%) appeared to be 1-hydroxymethylcyclopentanol: nmr, singlet at τ 6.49 (2 H) carbinyl protons; broad singlet at τ 8.34 (8 H).

(30) R. E. Bowman, A. Campbell, and W. R. N. Williamson, *J. Chem. Soc.*, 3864 (1964).

(31) R. F. Brown and N. van Gulick *J. Amer. Chem. Soc.*, **77**, 1089 (1955).

(32) W. B. Renfrow, Jr., and C. R. Hauser, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p 609.

Solvolysis of *cis*-2-Hydroxycyclohexylcarbinyl Brosylate.—A solution of 3.52 g of the hydroxy brosylate, prepared as previously described, 100 ml of acetone, 83 ml of 1.26 *M* phosphate buffer (pH 6.8), and 60 ml of water was refluxed for 151 hr. The reaction mixture was processed in the usual manner and glpc on a 5 ft × 0.25 in. column packed with 20% Carbowax 20M on firebrick gave three products (in order of elution): 2-methylcyclohexanone (17%) identified by comparison with an authentic sample, *cis*-2-hydroxymethyl cyclohexanol (76%), and *trans*-2-hydroxy-1-methylcyclohexanol (7%) identified by comparison with an authentic sample, mp 78–80° (lit.[33] mp 85°), prepared as previously described.[33] A component of shorter retention time than 2-methylcyclohexanone was found to be formed from acetone when exposed to the reaction solvent in the absence of the hydroxy brosylate.

Solvolysis of 2-Methyl-2-hydroxymethylpropyl Tosylate.—A mixture of 1.95 g of the tosylate and 50 ml of 0.4 *M* acetate buffer (pH 4) was heated in a sealed tube at 115° for 72 hr. The mixture was continuously extracted with ether and the ether was distilled under a factionating column. The residue was found to contain 95% 2-methylbutanal and 5% 2,2-dimethyl-1,3-propanediol by glpc using a 5 ft × 0.25 in. column packed with 5% SE 30 on Chromosorb W at 120°. An alliquot of the reaction mixture was treated with 2,4-dinitrophenylhydrazine solution to afford 2-methylbutanal 2,4-dinitrophenylhydrazone, mp 125–126° (lit.[34] mp 120°). The yield corresponded to 32% based on starting arenesulfonate. Another experiment afforded 2-methylbutanal 2,4-dinitrophenylhydrazone in 36% yield. A weighed sample of pure 2-methylbutanal gave the 2,3-dinitrophenylhydrazone in 36% yield.

(33) S. Nametkin and A. Jarzeff, *Ber.*, **56**, 1803 (1923).

Registry No.—(−)-*trans*-2-hydroxymethylcyclohexyl brosylate, 16897-79-3; *cis*-2-hydroxymethylcyclopentanol, 1883-85-8; *trans*-2-carbomethoxycyclopentyl β-naphthalenesulfonate, 16897-81-7; *trans*-2-acetoxymethylcyclopentyl β-naphthalenesulfonate, 16897-82-8; *erythro*-2-methyl-1,3-butanediol, 16897-83-9; cyclopentanone ketal of *erythro*-2-methyl-1,3-butanediol, 16897-84-0; *threo*-2-methyl-1,3-butanediol, 16897-85-1; cyclopentanone ketal of *threo*-2-methyl-1,3-butanediol, 16897-86-2; tiglyl benzyl ether, 16897-87-3; (−)-*threo*-methyl-3-hydroxybutyl benzyl ether, 16897-88-4; 2-hydroxy-2-methyl-1-butyl benzyl ether, 16897-89-5; β-naphthalenesulfonate of *threo*-2-methyl-3-hydroxybutyl benzyl ether, 16897-90-8.

(34) 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., p 320.

Synthesis of γ- and δ-Chloroalkanesulfonamides *via* the Photorearrangement of N-Chlorosulfonamides

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The photorearrangement of N-*t*-butyl- and N-methyl-N-chloroalkanesulfonamide in benzene and in acid solution was studied with the object of preparing γ- and δ-chloroalkanesulfonamides, intermediates for sultam synthesis. In benzene, γ- and δ-chloroalkanesulfonamides were formed almost exclusively from N-*t*-butyl derivatives, while, in the reaction of N-methyl-N-chlorobutanesulfonamide, β-chlorobutanesulfonamide was apparently formed in addition to γ- and δ-chlorobutanesulfonamides. In acid solution (H_2SO_4–AcOH), on the other hand, the rate of formation of γ-chloro derivatives increased and that of β-chloro derivatives decreased owing to the relatively higher reactivity of the protonated sulfonamide radical for intramolecular hydrogen abstraction. The isolation of each rearranged product from the reactions was undertaken and N-*t*-butyl-γ-chlorobutanesulfonamide N-*t*-butyl-δ-chloropentanesulfonamide, and N-*t*-butyl-γ-chloropentanesulfonamide were obtained pure.

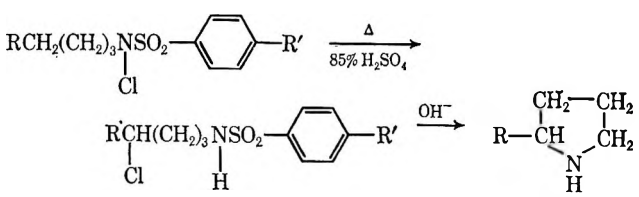
In studies on the free-radical rearrangement of N-halo compounds, the synthesis of pyrrolidine derivatives from N-haloamines (Hofmann–Löffler reaction[1]) and γ-lactone formation from N-haloamides[2–5] and N-haloimides[6] have been reported.

Although N-alkyl-N-chloroarylsulfonamides are reported to rearrange to N-δ-chloroalkyl derivatives[7] under similar reaction conditions as the Hofmann–Löffler reaction (Scheme I), the analogous rearrangement of N-alkyl-N-chloroalkanesulfonamides has not yet been reported.

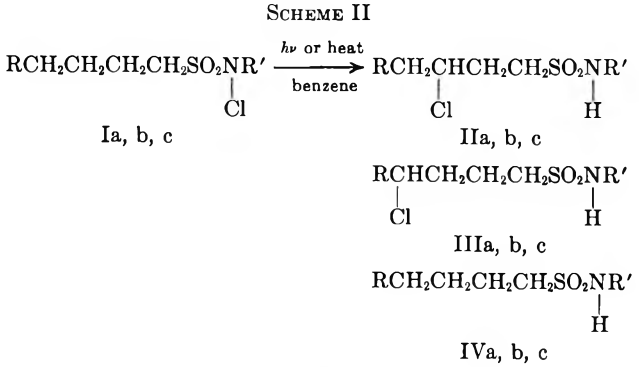
In a previous paper,[8] the authors reported that N-alkyl-N-chloroalkanesulfonamides readily rearrange to the corresponding chloroalkanesulfonamides under the influence of photoirradiation or heat (Scheme II).

The purpose of the present study was to investigate

SCHEME I



SCHEME II



a, R = H; R′ = *t*-C_4H_9
b, R = H; R′ = CH_3
c, R = CH_3; R′ = *t*-C_4H_9

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(4) A. L. J. Beckwith and J. E. Goodrich, *Aust. J. Chem.*, **18**, 747 (1965).
(5) R. S. Neale, N. L. Marcus, and R. G. Schepers, *J. Amer. Chem. Soc.*, **88**, 3051 (1966).
(6) R. C. Petterson and A. Wambsgans, *ibid.*, **86**, 1648 (1964).
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TABLE I

PROPERTIES AND ANALYSES OF N-CHLOROSULFONAMIDES

Cl | RSO_2NR'	Bp, °C (mm)	$n^{20}D$	Ir absorptions, cm^{-1}	Uv absorptions[a] max, mμ (ε)	Cl, %[b,c]
R = n-C_4H_9; R′ = t-C_4H_9	86–87 (0.2)	1.4718	2960, 1360, 1155, 625, 587	274 (150)	15.3 (15.56)
R = n-C_4H_9; R′ = CH_3	99–100 (4)	1.4690	2960, 1350, 1150, 615, 570	265 (106)	18.9 (19.09)
R = n-C_5H_{11}; R′ = t-C_4H_9	110 (2)	1.4727	2960, 1345, 1150, 620, 570	275 (182)	14.4 (14.24)

[a] In ethanol. [b] Positive chlorine. [c] Values in parentheses are calculated values.

TABLE II

PHOTOREARRANGEMENT OF N-CHLOROSULFONAMIDES IN BENZENE[a]

Cl | RSO_2NR'	Concn, mol/l.	Reaction time, min	Recovery rate,[b] %	Reaction product: Cl, %	Original sulfonamide,[c] %	γ-Chloroalkanesulfonamide,[c] %	δ-Chloroalkanesulfonamide,[c] %
R = n-C_4H_9; R′ = t-C_4H_9	0.20	25	90	12.3	24.0	60.2	14.0
R = n-C_4H_9; R′ = t-C_4H_9	0.26	30	91	12.1	26.0	60.9	12.1
R = n-C_4H_9; R′ = t-C_4H_9	0.52	30	90	13.0	19.7	61.9	15.1
R = n-C_4H_9; R′ = t-C_4H_9	1.03	25	93	14.0	14.6	67.1	17.2
R = n-C_4H_9; R′ = t-C_4H_9	1.94	25	91	14.1	17.7	62.0	15.9
R = n-C_4H_9; R′ = t-C_4H_9	2.58	25	92	13.6	18.6	60.5	15.5
R = n-C_4H_9; R′ = t-C_4H_9	Neat	30	91	14.0	20.1	50.8	14.1
R = n-C_4H_9; R′ = CH_3[d–f]	0.27	35	85	8.8	48.6	20.3	0.5
R = n-C_5H_{11}; R′ = t-C_4H_9	0.85	20	93	13.1	19.9	42.1	38.0
R = n-C_5H_{11}; R′ = t-C_4H_9[g]	0.85	120	92	11.8	23.0	40.3	37.1

[a] Irradiation with a 150-W high pressure mercury lamp, 10–15°, under nitrogen unless specified otherwise. [b] The weight of the product obtained/the weight of N-chlorosulfonamides × 100. [c] Weight percent based on recovered reaction product, average values. [d] A compound (13.2%) thought to be β-chloro derivative was present in the reaction mixture in addition to those listed. [e] Very small amount of crystal identified as chlorinated benzene was isolated from the reaction mixture. [f] Average molecular weight of the reaction mixture, 192. [g] Irradiation with a 30-W low pressure mercury lamp, 10–13°, under nitrogen.

more fully the synthetic aspects of this new rearrangement.

Results and Discussion

The starting materials, N-t-butyl- and N-methyl-N-chloro-n-butanesulfonamide and N-t-butyl-N-chloro-n-pentanesulfonamide, were prepared by chlorinating the corresponding sulfonamides by the procedures previously described.[8]

These N-chlorosulfonamides are stable and can be purified by distillation at reduced pressure; their properties and chlorine content are shown in Table I.

The N-chlorosulfonamides were irradiated in benzene or acid solution at 10–15° under nitrogen with a high or low pressure mercury arc lamp equipped with a quartz filter until the positive chlorine content of the solution was negligible. Positive chlorine disappeared within 35 min in benzene solution, whereas in acid solution the reaction needed a longer time. The reaction product from benzene solution was recovered almost quantitatively after the removal of the solvent; it was analyzed by glpc.

Glpc analysis of the products generally showed three major peaks. One peak was identified as the original sulfonamide (IVa, b) and, from N-t-butyl- or N-methyl-N-chloro-n-butanesulfonamide, two other peaks were identified as N-alkyl-γ-chlorobutanesulfonamide (IIa, b) and N-alkyl-δ-chlorobutanesulfonamide (IIIa, b), respectively, by means of a comparison of their retention times with those of the authentic compounds.

However, in the gas chromatogram of the product from N-chloro-N-methyl-n-butanesulfonamide, the peak of δ-chlorobutanesulfonamide was very small, and another peak was observed preceding the peak of IIb. This peak was supposed to correspond to N-methyl-β-chlorobutanesulfonamide (VIII) by comparing the gas chromatogram with that of the photochlorination product of N-methyl-n-butanesulfonamide.[9]

In the case of N-t-butyl-N-chloro-n-pentanesulfonamide, two peaks in the gas chromatogram were also identified as N-t-butyl-γ- and -δ-chloropentanesulfonamide, respectively, by nmr analysis of the isolated products, and the peaks corresponding to the other isomers, that is β- or ε-chloropentanesulfonamide, were not observed. Quantitative analysis of the rearranged products was also done by glpc. Results of the reaction in benzene are shown in Table II.

In the reaction of N-t-butyl-N-chloro-n-butanesulfonamide, not much difference was observed in the composition of the products over the concentration range 0.20–2.58 mol/l.

Formation of products of higher molecular weight was suggested in the irradiation of N-chloro-N-methyl-n-butanesulfonamide because the total amount of each compound, determined by glpc, was rather low (about 83%) and the average molecular weight of the reaction mixture was slightly higher than the calculated value. Intramolecular dehydrochlorination is presumed to occur competitively in this case, where hydrogens are present on the carbon atom adjacent to nitrogen, as observed by Neale[5] in the rearrangement of N-halo-N-methylamides.

When the reaction was carried out in acid solution (H_2O–H_2SO_4–AcOH), the recovery rate of the product decreased slightly, and the amount of unsubstituted

(9) Although this compound could not be isolated in the pure state, it was ascertained to contain one bound chlorine atom in the molecule. Also, in photochlorination of many aliphatic compounds,[10–12] it is known that the retention times of the position isomers increase in order of the increase of the position number of chlorine, that is, 1 < 2 < 3 . . . .

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(11) H. Singh and J. M. Tedder, *J. Chem. Soc., Sect. B*, 608 (1966).

(12) M. Okahara, S. Yanagida, and S. Komori, *Tech. Rept. Osaka Univ.*, **17**, 205 (1967).

TABLE III

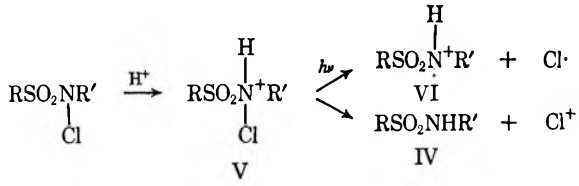
PHOTOREARRANGEMENT OF N-CHLOROSULFONAMIDE IN H_2O–H_2SO_4–AcOH

Cl | RSO_2NR'	Reaction time, min	Recovery rate, %	Reaction product: Cl, %	Unsubstituted sulfonamide, wt %[a]	γ-Chloroalkanesulfonamide, wt %[a]	δ-Chloroalkanesulfonamide, wt %[a]
R = *n*-C_4H_9; R′ = CH_3[b-d]	240	70	9.6	47.9	36.8	0.5
R = *n*-C_5H_{11}; R′ = *t*-C_4H_9[b,e]	90	75	10.1	32.4	43.6	24.0
R = *n*-C_5H_{11}; R′ = *t*-C_4H_9[f,e]	50	78	10.8	28.9	43.1	27.6
R = *n*-C_5H_{11}; R′ = *t*-C_4H_9[f,g]	45	82	10.3	32.1	40.6	27.1

[a] Weight percent based on recovered reaction products, average value. [b] Irradiation with a low pressure mercury arc lamp (30 W) inside the reaction vessel. [c] Ten grams of sample dissolved in 140 g of acid solution (a mixture of 11.2 g of H_2SO_4, 50.6 g of H_2O, and 78.2 g of AcOH). [d] A compound (7.0%) thought to be N-methyl-N-β-chlorobutanesulfonamide was found in the reaction product in addition to the compounds listed. [e] The sample (2.3 g) dissolved in 40 g of acid solution (H_2SO_4, 4.8 g; AcOH, 13.5 g; H_2O, 21.7 g). [f] Irradiation with a high pressure mercury arc lamp (150 W) inside the reaction vessel. [g] Ten grams of sample dissolved in 264 g of acid solution (H_2SO_4, 30.6 g; AcOH, 139.6 g; H_2O, 93.8 g).

original sulfonamides increased, but the formation of γ-chloroalkanesulfonamide was greatly raised as shown in Table III.

The higher ratio of formation of γ- to δ-chloroalkanesulfonamide in acid solution is assumed to be due to the relatively higher reactivity of intramolecular hydrogen abstraction by the protonated sulfonamide radical (VI) in the competition between intra- and intermolecular hydrogen abstraction. However, the decomposition of the intermediate conjugate acid (V) to unsubstituted sulfonamides (IV), as reported by Buckles,[13] and Derbyshire[14] with N-bromoamides and N-bromosuccinimides, would occur to a certain extent.



At the step of hydrogen abstraction, three processes are supposed to occur competitively, *i.e.*, the intramolecular hydrogen abstraction by sulfonamide radical (process 1), the intermolecular hydrogen abstraction by sulfonamide radical (process 2), and the hydrogen abstraction by chlorine atom (process 3).

In the decomposition of N-*t*-butyl-N-chloro-*n*-alkanesulfonamides in benzene, process 1 is the main process but process 2 would participate competitively to an appreciable extent in the reaction. On the other hand, in the decomposition of N-chloro-N-methyl-*n*-butanesulfonamide in benzene, process 3 is supposed to be the main process because the distribution of products is similar to that obtained in the photochlorination of N-methyl-*n*-butanesulfonamide in benzene.

In the decomposition of N-*t*-butyl-N-chloro-*n*-pentanesulfonamide in acid solution, the higher formation ratio of γ- to δ-chloro derivative strongly suggests that process 1 is the main process and process 2 is retarded owing to the solvation and the electrostatic repulsion between the positively charged species.[15]

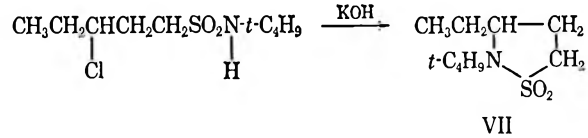
Furthermore in the decomposition of N-chloro-N-methyl-*n*-butanesulfonamide in acid solution, perhaps the three processes competitively occur. However, processes 2 and 3 are supposed to be suppressed to some extent because the formation of a compound thought to be β-chloro derivative was found to be small.

Isolation of the rearranged products from the reaction mixture was also undertaken. Unsubstituted sulfonamides could be separated by distillation under reduced pressure. N-*t*-butyl-γ-chlorobutanesulfonamide (IIa) was isolated as a white crystalline solid from the reaction product of N-*t*-butyl-N-chloro-*n*-butanesulfonamide (Ia) by adding petroleum ether, but isolation of N-*t*-butyl-δ-chlorobutanesulfonamide (IIIa) in the pure state was unsuccessful because its content was generally small.

On the other hand, analogous treatment of the reaction product from N-*t*-butyl-N-chloro-*n*-pentanesulfonamide (Ic) afforded a pure compound as a white crystalline solid, corresponding to the peak having a longer retention time in the gas chromatogram. This compound was confirmed to be N-*t*-butyl-δ-chloropentanesulfonamide (IIIc) because the nmr signal of the terminal methyl protons (τ 8.50) was a doublet.

From the filtrate obtained after removing N-*t*-butyl-δ-chloropentanesulfonamide, a white crystal was isolated by column chromatography on active alumina. This compound was confirmed to be N-*t*-butyl-γ-chloropentanesulfonamide (IIc) because, in its nmr spectrum, the terminal methyl protons (τ 8.93) was a triplet and the methylene protons (τ 6.72) adjacent to N-*t*-butylsulfonamide group was a triplet.

Furthermore a five-membered-ring sultam, N-*t*-butyl-3-ethylpropane sultam (VII), was isolated from the reaction mixture obtained by the alkali treatment of the irradiation product of N-*t*-butyl-N-chloro-*n*-pentanesulfonamide.



VII

The structure of this five-membered-ring sultam was confirmed by its nmr spectrum in which the absorption (τ 9.10) of the terminal methyl protons in the side-chain ethyl group was found to be split into a triplet.

(13) R. E. Buckles, *J. Amer. Chem. Soc.*, **71**, 1157 (1944).

(14) C. Derbyshire and W. A. Waters, *J. Chem. Soc.*, 573 (1950).

(15) Also, a referee has pointed out that a six-membered transition state is stereochemically more favorable for the protonated N radical than for the neutral radical.

Experimental Section[16]

N-*t*-Butyl-*n*-butanesulfonamide.—*n*-Butanesulfonyl chloride (78.4 g, 0.5 mol), prepared as described by Douglass and Johnson,[17] was added to an ether solution (200 ml) of *t*-butylamine (95.2 g, 1.3 mol) with stirring at 5° over 1 hr. After removal of precipitated *t*-butylamine hydrochloride, the ether solution was washed with water and dried over anhydrous sodium sulfate. The residue, obtained by evaporation, was distilled under reduced pressure to yield N-*t*-butyl-*n*-butanesulfonamide [72.4 g (75%)]: bp 155–156° (6 mm); n^{20}D 1.4530. Characteristic infrared bands appeared at 3280, 2960, 1320, 1140, and 1000 cm^{-1}.

Anal. Calcd for $C_8H_{19}NO_2S$: C, 49.69; H, 9.93; N, 7.25. Found: C, 49.68; H, 9.95; N, 7.12.

N-Methyl-*n*-butanesulfonamide.—As described above, *n*-butanesulfonyl chloride (78.4 g, 0.5 mol) was allowed to react with a 30% aqueous solution of methylamine (130 g) yielding N-methyl-*n*-butanesulfonamide (60.4 g, 80%): bp 147–148° (4 mm); n^{20}D 1.4528. Characteristic infrared bands appeared at 3300, 2960, 1320, and 1140 cm^{-1}.

Anal. Calcd for $C_5H_{13}NO_2S$: C, 39.70; H, 8.68; N, 9.26. Found: C, 39.65; H, 8.50; N, 9.35.

N-*t*-Butyl-*n*-pentanesulfonamide.—Reaction of *n*-pentanesulfonyl chloride (50 g) with *t*-butylamine (48.2 g) in ether (200 ml) afforded N-*t*-butyl-*n*-pentanesulfonamide (49.7 g, 83%): bp 125–126 (2 mm); n^{20}D 1.4531. Characteristic infrared bands appeared at 3280, 2960, 1450, 1320, and 1130 cm^{-1}.

Anal. Calcd for $C_9H_{21}NO_2S$: C, 52.15; H, 10.21; N, 6.76. Found: C, 52.02; H, 10.23; N, 6.56.

N-Chlorination of N-Alkylalkanesulfonamides.—N-Alkyl-*n*-alkanesulfonamide (0.1 mol) was suspended in water (150 ml) in the presence of sodium hydroxide (4 g). Chlorine gas was passed into the stirred suspension at 5–10° until the yellow color of chlorine persisted. The insoluble yellow oil that separated as a lower layer was washed with water and dried over anhydrous sodium sulfate. The colorless liquid obtained in quantitative yield was almost pure and could be further purified by distillation at reduced pressure. The properties of N-chloro-N-alkyl-*n*-alkanesulfonamides are described in Table I.

The Photorearrangement of N-*t*-Butyl-N-chloro-*n*-butanesulfonamide in Benzene.—N-*t*-Butyl-N-chloro-*n*-butanesulfonamide (10 g) in anhydrous benzene (85 ml) was irradiated at 10–15° under nitrogen with a high pressure mercury arc lamp inside the reaction flask until the active chlorine content of the solution was negligible. After evaporation of the solvent, a pale yellow viscous liquid (9.3 g) was obtained. This product contained three main compounds, as shown by glpc analysis on a column of 10% Apiezon L grease or silicone grease DC 200 on Diasolid L (60–80 mesh, 1 m, column temperature 210°, hydrogen carrier gas, 150 cc/min). Components were identified as IVa, IIa, and IIIa, in order of increasing retention time, by comparison of their retention times with those of the pure compounds. Quantitative analysis was done by glpc using N-methyl-*n*-propanesulfonamide as an internal standard. Results of the reaction at various concentrations are shown in Table II.

The Photorearrangement of N-*t*-Butyl-N-chloro-*n*-pentanesulfonamide in Benzene.—Irradiation of N-*t*-butyl-N-chloro-*n*-pentanesulfonamide (35 g) in anhydrous benzene (180 ml) with a high pressure mercury arc lamp produced a yellow viscous liquid (32.6 g) which was found to contain only three compounds, identified as IVc (19.9%), IIc (42.1%), and IIIc (38.0%). The similar result was obtained in the decomposition reaction using a low pressure mercury arc lamp (Table II). Glpc was on a column of Triton X-305 10% on Diasolid L (60–80 mesh, 1 m, column temperature, 170°, hydrogen carrier gas, 150 cc/min).

The Photorearrangement of N-Chloro-N-methyl-*n*-butanesulfonamide in Benzene.—Irradiation of N-chloro-N-methyl-*n*-butanesulfonamide (10 g) in anhydrous benzene (200 ml) produced a pale yellow liquid (8.5 g; Cl, 8.8%). This was analyzed by glpc on a column of Triton X-305 10% on Diasolid L (60–80 mesh, 1 m, column temperature, 174°, hydrogen carrier gas, 115 cc/min). It contained IVb (48.6%), IIb (20.3%), VIII (13.2%), and IIIb (0.5%).

A small amount (about 70 mg) of white crystals (mp 153°) also separated from the reaction products. By ir and elemental analysis, it was identified as chlorinated benzene.

Anal. Calcd for $C_6H_6Cl_6$: C, 24.78; H, 2.08. Found: C, 25.02; H, 2.49.

The Photochlorination of N-Methyl-*n*-butanesulfonamide.—N-methyl-*n*-butanesulfonamide (6 g) was dissolved in benzene (120 ml), and chlorine gas was passed into the solution at 10–13° under irradiation with a high pressure mercury arc lamp. The yellow viscous liquid obtained after removing benzene (Cl, 3.8%) was analyzed by glpc and found to contain IVb (78.3%), IIb (8.8%), IIIb (trace), a compound assumed to be N-methyl-β-chlorobutanesulfonamide (VIII) (6.2%), and the chlorinated benzene.

Photorearrangement of N-Chloro-N-methyl-*n*-butanesulfonamide and N-*t*-Butyl-N-chloro-*n*-pentanesulfonamide in Acid Solution.—N-Chloro-N-methyl-*n*-butanesulfonamide (10.0 g) in acid solution (11.2 g of H_2SO_4, 50.6 g of H_2O, 78.2 g of AcOH) was irradiated with a low pressure mercury arc lamp (30 W) at 10–15° under nitrogen until the active chlorine was negligible. The reaction mixture was poured onto ice, and the organic layer was extracted with ether. The pale yellow liquid obtained (7.0 g; Cl, 9.6%) was analyzed by glpc and found to contain IVb (47.9%), IIb (36.8%), VIII (7.0%), and a trace amount of IIIb. N-*t*-Butyl-N-chloro-*n*-pentanesulfonamide (2.3 g) was also irradiated in an analogous manner in acid solution (4.8 g of H_2SO_4, 13.5 g of AcOH, and 21.7 g of H_2O). The yellow liquid obtained (1.7 g; Cl, 10.1%) was found to contain IVc (32.4%), IIc (43.6%), and IIIc (24.0%) by glpc using a Triton-X column. Similar results were obtained in the decomposition using a high pressure, mercury arc lamp (Table III).

Preparation of Authentic Compounds. N-*t*-Butyl-δ-chlorobutanesulfonamide.—4-Chlorobutanesulfonyl chloride [57 g, 0.3 mol; bp 108° (0.8 mm), lit.[18] bp 110–112° (1–1.5 mm)] was prepared from 4-chlorobutyl acetate as described by Helfreich.[18] It was added with stirring to an ethereal solution of *t*-butylamine (44 g, 0.6 mol) at 5°. After removing *t*-butylamine hydrochloride, the ether was evaporated, leaving white crystalline N-*t*-butyl-δ-chlorobutanesulfonamide. This was recrystallized from a small amount of ether: yield, 47.7 g (70%); mp 39.5°; nmr (in $CDCl_3$), τ 5.58 (singlet, 1 H), 6.45 (triplet, 2 H), 6.95 (triplet, 2 H), 8.05 (quintet, 4 H), and 8.61 (singlet, 9 H).

Anal. Calcd for $C_8H_{18}ClNO_2S$: C, 42.18; H, 7.98; N, 6.15; Cl, 15.56. Found: C, 42.05; H, 8.01; N, 6.30; Cl, 15.3.

N-*t*-Butyl-γ-chlorobutanesulfonamide.—3-Chlorobutanesulfonyl chloride was prepared by passing chlorine in the presence of water into α-acetyl-γ-chlorobutyl mercaptan (16.6 g), which was prepared by the addition of thiolacetic acid to 3-chloro-1-butene [bp 64–66° (760 mm), lit.[19] bp 63° (748 mm)], with rapid stirring at 5° until the aqueous layer became yellow. The yellow oil that separated was extracted with ether, washed with water, and dried over anhydrous sodium sulfate. Distillation of the residue obtained by evaporation of the ether afforded 3-chlorobutanesulfonyl chloride: yield, 11.2 g (62%); bp 95–97° (6 mm). 3-Chlorobutanesulfonyl chloride (19.1 g, 0.1 mol) was added to an ether solution (100 ml) of *t*-butylamine (14.6 g, 0.2 mol) with stirring at 5° over 1 hr. After removing *t*-butylamine hydrochloride and ether, white crystals were obtained. The product was recrystallized from a small amount of ether: yield, 15.9 g (70%); mp 63.0°; nmr (in $CDCl_3$), τ 5.30 (singlet, 1 H), 5.90 (multiplet, 1 H), 6.75 (triplet, 2 H), 7.80 (multiplet, 2 H), 8.42 (doublet, 3 H), 8.60 (singlet, 9 H).

Anal. Calcd for $C_8H_{18}ClNO_2S$: C, 42.18; H, 7.98; N, 6.15; Cl, 15.56. Found: C, 42.30; H, 8.18; N, 6.30; Cl, 15.7.

N-Methyl-δ-chlorobutanesulfonamide.—4-Chlorobutanesulfonyl chloride (19 g) was added with stirring to an aqueous solution (23 g) of methylamine at 5°. The yellow oil that separated was extracted with dichloromethane, washed with water, and dried over anhydrous sodium sulfate. Distillation of the residue obtained by evaporation of the solvent afforded N-methyl-δ-chlorobutanesulfonamide (12.9 g): bp 140–142° (0.2 mm); nmr in $CDCl_3$ τ 5.40 (1 H), 6.45 (triplet, 2 H), 6.93 (triplet, 2 H), 7.20 (doublet, 3 H), 8.08 (quintet, 4 H).

(16) Infrared spectra (KBr disks or liquid films) were recorded on a Nihon Bunko instrument; nmr spectra were obtained in CCl_4 or $CDCl_3$ solution. Glpc analyses were conducted using Apiezon L grease 10%, silicone DC 200 10%, or Triton X-305 10% on Diasolid L, 60–80 mesh, 4.5 mm × 1 m column. Titrations for positive chlorine were conducted by sodium thiosulfate assay of iodine liberated from 10% aqueous KI acidified with 0.1 *N* hydrochloric acid. Petroleum ether had bp 40–60°. The commercial, pure grade of benzene was dried over sodium wire and used as the reaction solvent.

(17) I. B. Douglass and J. B. Johnson, *J. Amer. Chem. Soc.*, **60**, 1486 (1938).

(18) B. Helfreich and K. G. Kleb, *Chem. Ber.*, **93**, 91 (1960).

(19) A. L. Henne, H. Chanan, and A. Turk, *J. Amer. Chem. Soc.*, **63**, 3474 (1941).

Anal. Calcd for $C_5H_{12}ClNO_2S$: C, 32.35; H, 6.52; Cl, 19.09. Found: C, 32.30; H, 6.31; Cl, 19.3.

N-Methyl-γ-chlorobutanesulfonamide.—3-Chlorobutanesulfonyl chloride (19.1 g, 0.1 mol) was added with stirring to a 30% aqueous solution of methylamine (24 g) at 5°. The yellow oil that separated was treated as described for N-methyl-δ-chlorobutanesulfonamide. Distillation of the residue obtained by evaporation of the solvent afforded N-methyl-γ-chlorobutanesulfonamide (11.1 g): bp 134–135° (0.1 mm); nmr in $CDCl_3$ τ 5.45 (singlet, 1 H), 5.85 (multiplet, 1 H), 6.80 (triplet, 2 H), 7.20 (doublet, 3 H), 7.80 (multiplet, 2 H), 8.43 (doublet, 3 H).

Anal. Calcd for $C_5H_{12}ClNO_2S$: C, 32.35; H, 6.52; Cl, 19.09. Found: C, 32.15; H, 6.41; Cl, 18.8.

Isolation of the Rearranged Products from the Reaction Mixture. Isolation of N-*t*-Butyl-*n*-butanesulfonamide.—The viscous liquid obtained in the photorearrangement was distilled under reduced pressure and a fraction of bp 120–122° (2 mm) was obtained. The ir and nmr spectra of this fraction were the same as those of known N-*t*-butyl-*n*-butanesulfonamide.

Isolation of N-*t*-Butyl-γ-chlorobutanesulfonamide.—A white precipitate was obtained when petroleum ether was added to the viscous liquid (9.0 g) obtained in the photorearrangement. The precipitate was collected by filtration and washed with cold light petroleum ether and then recrystallized from petroleum ether solution (yield 3.8 g), mp 63.0°, not depressed by mixture with the authentic compound. The ir and nmr spectra of this compound were the same as those of authentic N-*t*-butyl-γ-chlorobutanesulfonamide.

Isolation of pure N-*t*-butyl-δ-chlorobutanesulfonamide was unsuccessful because of its low initial content and the small difference in solubility in petroleum ether between γ- and δ-chlorobutanesulfonamides.

Isolation of N-*t*-Butyl-δ-chloropentanesulfonamide.—By adding petroleum ether to the reaction product (32.6 g; Cl ,13.1%) obtained from N-*t*-butyl-N-chloro-*n*-pentanesulfonamide (35.0 g), a white precipitate was obtained. This precipitate was collected by filtration, washed with cold petroleum ether, and recrystallized from petroleum ether. The white crystals (11 g), mp 59°, were identified as N-*t*-butyl-δ-chloropentanesulfonamide (IIIc) by the infrared and nmr spectra and elemental analysis. Characteristic infrared bands appeared at 3380, 2960, 1320, 1140, and 1020 cm^{-1}; nmr (in CCl_4) bands were at τ 4.70 (1 H), 6.00 (multiplet 1 H), 6.90 (triplet, 2 H), 8.15 (multiplet, 4 H), 8.50 (doublet, 3 H), and 8.60 (singlet, 9 H).

Anal. Calcd for $C_9H_{20}ClNO_2S$: C, 44.71; H, 8.34; Cl, 14.24. Found: C, 44.36; H, 8.36; Cl, 14.5.

Isolation of N-*t*-Butyl-γ-chloropentanesulfonamide.—The filtrate (10.0 g) obtained by the treatment described above was passed through an active alumina column and eluted with carbon tetrachloride. N-*t*-Butyl-γ-chloropentanesulfonamide (3.0 g) was isolated as a white crystal and purified by recrystallization from the petroleum ether solution, mp 42°. Characteristic infrared bands appeared at 3380, 2960, 1320, and 1140 cm^{-1}; nmr (in $CDCl_3$) bands were at τ 5.70 (1 H), 6.00 (multiplet, 1 H), 6.72 (triplet, 2 H), 7.83 (multiplet, 2 H), 8.30 (multiplet, 2 H), 8.60 (singlet, 9 H), 8.93 (triplet, 3 H).

Anal. Calcd for $C_9H_{20}ClNO_2S$: C, 44.71; H, 8.34; N, 5.79; Cl, 14.24. Found: C, 44.52; H, 8.51; N, 5.68; Cl, 14.3.

Isolation of N-*t*-Butyl-3-ethylpropanesultam.—The viscous liquid (24 g) obtained in the photoirradiation of N-chloro-N-*t*-butyl-*n*-pentanesulfonamide was dissolved in ethanol. Potassium hydroxide (6 g) was added, and the solution was refluxed for 3 hr. The salt that formed was filtered off, and the ethanol was evaporated. The residue (19 g) was dissolved in ether (50 ml), and the ether solution was extracted with water (50 ml). After evaporation of water, a yellow liquid (2 g) was obtained from the aqueous layer. This product was found to be almost pure by glpc, but it was further refined on a silica gel column. Characteristic infrared bands appeared at 2960, 1300, 1220, and 1135 cm^{-1}; nmr (in $CDCl_3$) bands were at τ 6.60 (multiplet, 1 H), 6.90 (triplet, 2 H), 7.80 (multiplet, 2 H), 8.40 (multiplet, 2 H), 8.60 (singlet, 9 H), and 9.10 (triplet, 3 H).

Anal. Calcd for $C_9H_{19}NO_2S$: C, 52.66; H, 9.33. Found: C, 53.06; H, 9.63.

Registry No.—Ia, 16339-81-4; Ib, 16867-16-6; Ic, 16867-17-7; IIa, 16339-82-5; IIb, 16867-19-9; IIc, 16867-20-2; IIIa, 16339-83-6; IIIb, 16867-22-4; IIIc, 16867-23-5; IVa, 16867-24-6; IVb, 16867-25-7; IVc, 16867-26-8; VII, 16867-27-9.

Acknowledgment.—The authors wish to thank Professor D. Swern, Temple University, for advice and helpful discussion.

Steric Enhancement of Resonance. IV. Absorption Spectra of N-Alkyl- and N,N-Dialkylpicramides

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Spectral displacements on N-alkylation and N,N-dialkylation of picramide are discussed in terms of inductive and steric effects. The phenomenon, *steric enhancement of resonance*, is considered to operate in this series.

In earlier papers of this series, it was proposed that an effect, characterized as *steric enhancement of resonance*, might explain progressive bathochromic displacements of ultraviolet maxima and longer wavelength band edges with increasing bulk of the substituent group in the 1-alkyl-2,4-dinitrobenzenes,[1] 1-alkyl-2,4,6-trinitrobenzenes,[2] and N,N-dialkyl-2,4-dinitroanilines.[3] We wish now to suggest that the same phenomenon accounts for spectral shifts in the N-alkyl- and N,N-dialkylpicramides, and discuss some aspects of conformation which may be deduced from the spectra.

The ultraviolet spectrum of picramide (1) in methanol shows two N→V bands above 250 mμ (Table I and Figure 1). From comparison with 2-nitro-, 4-nitro-, 2,4-dinitro- and 2,6-dinitroaniline spectra,[3] the max-

TABLE I

SPECTRA OF PICRAMIDE DERIVATIVES IN METHANOL[a]

		$(R_2{}^+N{=}C_1{\rightarrow}C_6{=}NO_2{}^-)$ transition			$(R_2{}^+N{=}C_1{\rightarrow}C_2{=}NO_2{}^-)$ transition		
	Picramide	λ_{max}, mμ	ν_{max}, cm^{-1}	ϵ_{max}	λ_{max}, mμ	ν_{max}, cm^{-1}	ϵ_{max}
1.	Unsubstituted	318	31,450	12,000	407	24,570	7,900
2.	N-Methyl-	337	29,670	14,700	408	24,510	6,290
3.	N-Ethyl-	338	29,590	14,960	410	24,390	6,120
4.	N-Isopropyl-	337.5	29,630	14,330	410	24,390	5,610
5.	N,N-Dimethyl-	(335)	(29,850)	(9,400)			
		371	26,950	11,670			
6.	N,N-Diethyl-	(335)	(29,850)	(6,750)			
		384	26,040	10,200			

[a] Values in parentheses are for shoulders or inflections.

(1) H. G. Adolph, B. Johnson, and M. J. Kamlet, *J. Org. Chem.*, **30**, 2864 (1965).

(2) M. J. Kamlet, J. C. Hoffsommer, and H. G. Adolph, *J. Amer. Chem. Soc.*, **84**, 3925 (1962).

(3) M. J. Kamlet, H. G. Adolph, and J. C. Hoffsommer, *ibid.*, **86**, 4018 (1964).

imum at 318 mμ (ε 12,000) has been attributed to the ($H_2{}^+N{=}C_1{\rightarrow}C_4{=}NO_2{}^-$) electronic transition, and that at 407 mμ (ε 7900) has been attributed to the two mutually equivalent ($H_2{}^+N{=}C_1{\rightarrow}C_2{=}NO_2{}^-$) transitions. This band assignment has received confirmation in a novel manner.[4] Spectra of **1** and 2,3,4,6-tetranitroaniline in dioxane were compared and, based on the above assignments, the angles of twist from planarity, θ, of the 4-nitro substituent in the latter compound was estimated from Braude's relationship[5] (eq 1) and

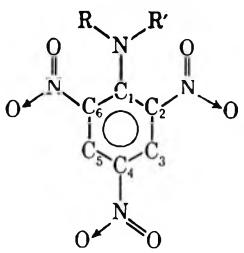
$$\cos^2\theta = \epsilon/\epsilon_0 \quad (1)$$

the angle of twist of the 2-nitro substituent from a modification of the expression in eq 1 (eq 2). These angles

$$\cos^2\theta = (\epsilon - {}^1/_2\epsilon_0)/{}^1/_2\epsilon_0 \quad (2)$$

of twist estimated from the spectra corresponded closely to values of θ observed in a total crystal structure determination.[4,6]

On N-alkylation of **1** [N-methyl- (**2**), N-ethyl- (**3**) and N-isopropylpicramide (**4**)], two effects are observed in the spectra: (a) progressive reductions in intensity of the ($RH^+N{=}C_1{\rightarrow}C_2{=}NO_2{}^-$) band with increasing bulk of R, but with no appreciable displacement in position, and (b) bathochromic–hyperchromic shifts of the ($RH^+N{=}C_1{\rightarrow}C_4{=}NO_2{}^-$) band from 318 to 337–338 mμ.



1, R = R′ = H
2, R = CH_3; R′ = H
3, R = C_2H_5; R′ = H
4, R = $(CH_3)_2CH$; R′ = H
5, R = R′ = CH_3
6, R = R′ = C_2H_5

The first of these effects is readily rationalized in terms of classical steric inhibition of resonance. Maximum resonance stabilization in **2**–**4** is achieved in the conformer wherein the alkylamino group remains coplanar with the ring. The resulting molecular crowding imposes a twist from planarity on one of the *o*-nitro groups, with consequent diminished absorption intensity in the electronic transition involving this substituent.

It is possible to arrive at some rough estimates of the values of θ for these twisted *o*-nitro groups. The 408–410-mμ bands of **2**–**4** are superimposed on the tails of the 337–338-mμ bands. Assuming that the latter resemble the spectral envelopes for the corresponding N-alkyl-4-nitroanilines (*i.e.*, the same ratio of ϵ/ϵ_{max} at the same $\Delta\nu$), these tails would in each case contribute

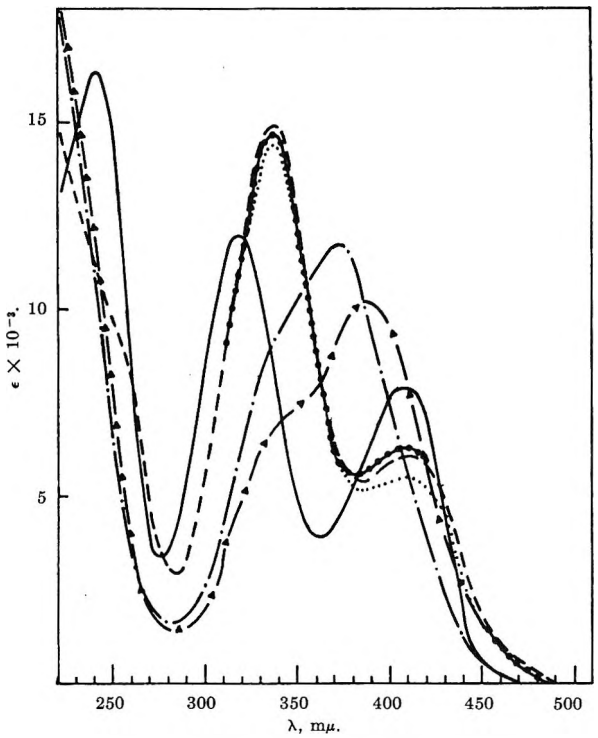


Figure 1.—Spectra of picramide derivatives in methanol: picramide, ———; N-methyl, -•-•-•-; N-ethyl, — — — —; N-isopropyl, ...; N,N-dimethyl, —·—·—; N,N-diethyl, —▲—▲—.

~1700 to ϵ_{409} of **2**–**4**.[7] The residual molar extinction coefficients due to the ($RH^+N{=}C_1{\rightarrow}C_2{=}NO_2{}^-$) transitions would therefore be ~4590 for **2**, ~4420 for **3**, and ~3910 for **4**. Assuming that the unhindered *o*-nitro groups in **2**–**4** remain totally coplanar, and that their full contributions to ϵ_{max} of the 408–410-mμ bands are realized, the angles of twist of the displaced nitro groups may be calculated from eq 2.[7] These estimated values of θ are 66° for **2**, 70° for **3**, and 90° for **4**.

The influence of substituents on the 318-mμ band of **1** requires more detailed analysis. N-Alkylation has a bathochromic–hyperchromic effect on the spectra of most aniline derivatives.[3,8] This is attributed to inductive electron release by alkyl which results in increased ground-state electron density on nitrogen and consequently lower energy requirements in the ($RH^+N{=}C_1{\rightarrow}C_4{=}X^-$) electronic transition. Whereas such must account, in part, for the 19–20-mμ spectral displacements in **2**–**4** relative to **1**, the further effect, *sterec enhancement of resonance*, may also come into play.

As the *o*-nitro groups are twisted from planarity in **2**–**4**, they exert only fractional electron withdrawal (inductive but not mesomeric). Ground-state electron densities on the amine nitrogens are therefore higher than in hypothetical totally coplanar **2**–**4** and the ($RH^+N{=}C_1{\rightarrow}C_4{=}NO_2{}^-$) electronic transition energies are lowered further. In effect ($RHN{-}C_1{=}C_4{-}NO_2 \leftrightarrow RH^+N{=}C_1{\rightarrow}C_4{=}NO_2{}^-$) resonance is enhanced in consequence of the steric interactions between N-alkyl and *o*-nitro which inhibit ($RHN{-}C_1{=}C_2{-}NO_2 \leftrightarrow RH^+N{=}C_1{\rightarrow}C_2{=}NO_2{}^-$) resonance.

(4) C. Dickinson, J. R. Holden, and M. J. Kamlet, *Proc. Chem. Soc.*, 232 (1964).

(5) E. A. Braude in "Determination of Organic Structures by Physical Methods," E. A. Braude and F. C. Nachod, Ed., Academic Press, New York, N. Y., 1955, p 172.

(6) C. Dickinson, J. M. Stewart, and J. R. Holden, *Acta Crystallogr.*, **21**, 663 (1966).

(7) Band overlap in **1** is appreciably less than in **2**–**4** (Figure 1). From similar reasoning, the contribution of the tail of the 318-mμ band to absorption at 407 mμ is almost nil. The full value of 7900 is therefore taken for ε in the calculations.

(8) M. J. Kamlet, *Israel J. Chem.*, **1**, 428 (1963).

We may evaluate the relative magnitudes of inductive and steric effects by comparing spectral displacements on N-alkylation ($\Delta\nu_{max}$, Table II) in the picramide series with those in the 4-nitro- and 2,4-dinitroanilines,[9] where the inductive but not the steric effect is observed.[10] In the latter two series, the spectral shifts in the N-methyl- and N-ethyl- relative to the unsubstituted derivatives are about the same, $\Delta\nu_{max}$ -1020 to -1050 cm^{-1}.[3] In **2** relative to **1**, however, $\Delta\nu_{max}$ -1780 cm^{-1}, and in **3** relative to **1**, Δ_{max} -1860 cm^{-1}. We attribute these increased displacements ($\Delta\Delta\nu_{max}$ -730 and -810 cm^{-1}) to the *steric enhancement of resonance* phenomenon.

TABLE II

SPECTRAL DISPLACEMENTS ON N-ALKYLATION, ($R_2^+N{=}C_1{\rightarrow}C_4{=}NO_2^-$) BAND

	$\Delta\nu_{max}(\nu_{max} - \nu_{max}^{X=NH_2})$, cm^{-1}			Contribution of steric enhancement, $\Delta\Delta\nu_{max}$, cm^{-1}
X	4-$NO_2C_6H_4X$	2,4-$(NO_2)_2$-C_6H_3X	2,4,6-$(NO_2)_3$-C_6H_2X	
CH_3NH–	-1050	-1020	-1780	-730
C_2H_5NH–	-1050	-1020	-1860	-810
$(CH_3)_2N$–	-1310	-2590[a]	-4500	-3190
$(C_2H_5)_2N$–	-1540	-3090[a]	-5410	-3870[b]

[a] These shifts also show the effects of steric enhancement of resonance.[3] [b] Includes contribution of ring deformation; see text.

The spectral effects of *steric enhancement of resonance* are more pronounced, albeit with some complications, in N,N-dimethyl- (**5**) and N,N-diethylpicramide (**6**), which show single maxima at 371 mμ (ϵ 11,670) and 384 mμ (ϵ 10,200), respectively. The complications arise from the lowered absorption intensities in **5** and **6** relative to **2** and **3**,[11] and from a minor shoulder at ~335 mμ in **5** which becomes more strongly evident in **6** (Figure 1).

Possible ($R_2^+N{=}C_1{\rightarrow}C_2{=}NO_2^-$) bands in the dialkylpicramides may be disposed of summarily. Both the 2- and the 6-nitro groups appear to be sufficiently twisted from planarity in all stable conformers that any absorptions at 400–425 mμ due to such *ortho* interactions[12] are of sufficiently low intensities that not even inflections may be discerned on the longer wavelength band edges to mark their contributions to the spectral envelopes of **5** or **6**.

Substituent effects on the ($R_2^+N{=}C_1{\rightarrow}C_4{=}NO_2^-$) electronic transition may be rationalized on the assumption that **5** and **6** exist, in each case, as mixtures of two comparably stable rotational conformers, A and B: rotomers **5A** and **6A** in which the two *o*-nitro groups are twisted and the dialkylamino groups are essentially coplanar with the rings [possibly the C_1—C_2—$N(O_2)$ and the C_1—C_6—$N(O_2)$ bond angles are expanded from 120° and the C_1—C_2 and C_1—C_6 bond distances are increased from normal values to allow this coplanarity]; rotomers **5B** and **6B** in which the nitro groups are twisted as before, but increasing steric requirements also impose a twist (or possibly a folding back from planarity) on the dialkylamino groups.[13]

From *a priori* considerations, it would be expected that the A rotomers would become decreasingly stable relative to the B rotomers and that the population of the latter would increase with increasing bulk of the alkyl substituents. On this basis the weakening 371- and 384-mμ maxima are attributed to the ($R_2^+N{=}C_1{\rightarrow}C_4{=}NO_2^-$) electronic transitions in rotomers **5A** and **6A**; the strengthening 335-mμ inflections are attributed to the same electronic transitions, but in rotomers **5B** and **6B**.

It is convenient to examine the phenomena which come into play on N,N-dialkylation of picramide by considering first the effects on the A rotomers of **5** and **6** relative to **1**–**4**, then on the B rotomers, and finally on the summations as reflected in the total spectral envelopes.

In **5A** and **6A** the maxima are displaced by -4500 and -5410 cm^{-1}, respectively, relative to **1** ($\Delta\nu_{max}$, Table II). These compare with shifts of -1310 and -1540 cm^{-1}, respectively, for N,N-dimethyl- and N,N-diethyl-4-nitroaniline relative to 4-nitroaniline, which reflect the inductive influence of two alkyl groups. The increased spectral displacements ($\Delta\Delta\nu_{max}$) we attribute, as before, to *steric enhancement of resonance*. The 2- and 6-nitro substituents exert only fractional electron withdrawal compared with hypothetical totally coplanar **5** and **6**. The electron densities on amine nitrogens are consequently higher, and the ($R_2^+N{=}C_1{\rightarrow}C_4{=}NO_2^-$) electronic transition energies are consequently lower.

With **5B** and **6B** two offsetting phenomena influence the band positions and intensities. Noncoplanarity of the 2- and 6-nitro groups introduces steric enhancement; noncoplanarity of the dialkylamino group introduces steric inhibition of ($R_2N{-}C_1{=}C_4{-}NO_2 \leftrightarrow R_2^+N{=}C_1{\rightarrow}C_4{=}NO_2^-$) resonance. The former effect is strongly bathochromic and weakly hyperchromic; the latter is weakly hypsochromic and strongly hypochromic (lowers ϵ). In combination, these phenomena lead to positions of the shoulders in **5** and **6** which do not differ markedly from those of the maxima for the monoalkyl derivatives **2**–**4**. The dominant result is in a strongly reduced absorption intensity (steric inhibition in the B rotomer).

Summations for the mixtures of rotomers, *i.e.*, total spectral envelopes attributable to ($R_2^+N{=}C_1{\rightarrow}C_4{=}NO_2^-$) transitions, show appreciable band broadening in **5** and **6** relative to **2**–**4** (compare band widths at half-heights) and decreasing integrated absorption intensities as the population of the B rotomer increases.

One further question deserves discussion. If, as the spectrum seems to show, the angles of twist of the 2- and 6-nitro groups already approach 90° in the A rotomer of **5**, why is there an increased $\Delta\Delta\nu_{max}$ in going from **5A** to **6A**? It has been mentioned that, to ac-

(9) No steric effect is observed in the monoalkyl-2,4-dinitroanilines which can easily assume the *s-trans* conformation, but steric enhancement is observed in this series on dialkylation.[3]

(10) A further minor complication due to the effects of changing hydrogen bonding on the spectra is discussed in ref 8, but has been ignored here. If the influence of changing hydrogen bonding is taken into account in all three series, the spectral displacements ascribed to steric enhancement become slightly greater.

(11) The normal effect of N-alkylation is hyperchromic as was observed in **2** and **3** relative to **1**. In the 4-nitroaniline series the order of extinction coefficients is $Et_2N > Me_2N = EtNH > MeNH > H_2N$; in the 2,4-dinitroaniline series the order is $Et_2N = Me_2N > EtNH = MeNH > H_2N$.[3]

(12) Positions of the ($R_2^+N{=}C_1{\rightarrow}C_2{=}NO_2^-$) bands in 2-nitroanilines are displaced relatively little from 400 to 410 mμ by a wide variety of N and ring substituents.[3]

(13) A contrary viewpoint has been taken by Gould, who suggests that a 4.8 unit increase in pK relative to **1** derives from a preferred conformation in **5** wherein the 2- and 6-nitro groups remain coplanar and the dialkylamino group is twisted from planarity: E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart and Winston, New York, N. Y., 1959, p 237. While the latter conformation is inconsistent with the spectra, the conformations suggested here are completely consistent with the pK values.

commodate coplanar dialkylamino groups, the C_1—C_2—$N(O_2)$ and C_1—C_6—$N(O_2)$ angles in A rotomers might be expanded from 120° and C_1—C_2 and C_1—C_6 bond distances could also increase from normal values. Internal ring angles might also change, and even bending or folding of the benzene ring is not out of the question.[14] Increased molecular distortions of these types with increasing substituent bulk in compounds closely related to **5** and **6** may be observed in a comparison of total crystal structures of N-nitro-N-methylpicramide (tetryl)[15] and N-nitro-N-trifluoroethylpicramide.[16]

Ingraham has commented on a slight bathochromic effect of molecular distortion in benzene derivatives.[17] Additional effects of these types, which would be expected to increase from dimethyl to diethyl, might account for the increased $\Delta\Delta\nu_{max}$.

It deserves comment that, had we considered the spectrum of **6** *ab initio*, an analysis such as the above would have been all but impossible. Only by examining trends, first on monoalkylation, then on dialkylation, and by observing the progressive growth of one band and concommitant shrinking of another with increasing alkyl bulk, were we able to arrive at the above assignments.

(14) In the crystal, the ring of 2,3,4,6-tetranitroaniline shows a slight boat shape in the C_1—C_4 axis. Bond distances and internal and external bond angles also differ appreciably from normal values.[6]

(15) H. Cady, *Acta Crystallogr.*, **23**, 601 (1967).

(16) J. R. Holden and C. Dickinson, to be published.

(17) L. L. Ingraham in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p 500.

Experimental Section

All materials were commercially available or prepared by literature methods from picryl chloride and the appropriate mono- or dialkylamine. They were purified by standard means to meet conventional spectrophotometric criteria of purity. Absorption spectra were determined in methanolic solution using a Cary Model 14 recording spectrophotometer with matched 1-cm silica cells. Concentrations were 3–5 × 10^{-5} *M*. Previously described precautions[18] were taken to guard against photochemical transformations.

Registry No.—**1**, 489-98-5; **2**, 1022-07-7; **3**, 7449-27-6; **4**, 16876-54-3; **5**, 2493-31-4; **6**, 13029-07-7.

Acknowledgments.—Helpful discussions with Drs. J. C. Dacons and L. A. Kaplan and Messers. C. Dickinson and D. J. Glover are gratefully acknowledged. The work was done under Foundational Research Task FR-44 of the U. S. Naval Ordnance Laboratory.

(18) M. J. Kamlet and L. A. Kaplan, *J. Org. Chem.*, **22**, 576 (1957).

Fluoronitroaliphatics. II. Fluorodinitromethyl Compounds. Synthetic Approaches and General Properties[1]

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Preparative procedures are described for a new class of compounds containing the $FC(NO_2)_2$– moiety. Three general synthesis methods are most useful in this series: (1) fluorination of 1,1-dinitro carbanion salts with perchloryl fluoride; (2) aqueous fluorination of 1,1-dinitro carbanions (the Grakauskas reaction); (3) reactions of fluorotrinitromethane with a variety of nucleophiles.

In the course of studies concerning the chemistry of polynitroaliphatic compounds, a program was initiated at this laboratory with the aim of developing synthesis methods for fluorodinitromethyl analogs, then undescribed, of known trinitromethyl and other halodinitromethyl compounds.[2-5] In this and the following papers, we wish to report some of the results of this work and, in addition, describe a number of novel fluorodinitromethyl derivatives for which the corresponding $C(NO_2)_3$– or $RC(NO_2)_2$– analogs are as yet unknown.

Pathways for the synthesis of fluorodinitromethyl compounds considered at the outset and during the course of this investigation included (a) introduction of a second nitro group into compounds already containing the fluoronitromethyl function; (b) introduction of two nitro groups into simple or activated monofluorohydrocarbons; (c) introduction of fluorine into 1,1-dinitro compounds. Since 1,1-dinitroalkanes had previously been reported in considerable number and were fairly readily available,[2] we have directed our attention primarily to pathway c.

An analogy for the introduction of fluorine existed in the ease with which 1,1-dinitro carbanions reacted with chlorinating and brominating agents to form the corresponding chloro- and bromodinitromethyl compounds.[2]

$$RC(NO_2)_2^- + Cl_2 \longrightarrow RC(NO_2)_2Cl + Cl^-$$

Accordingly, the problem was one of finding suitable fluorinating agents which would selectively attack the dinitromethyl anion in a manner similar to the reaction with chlorine, while leaving intact as wide as

(1) Part I: H. G. Adolph and M. J. Kamlet, *J. Amer. Chem. Soc.*, **88**, 4761 (1966). See also 1-fluoro-1,1-dinitroalkanes [M. J. Kamlet, U. S. Patent 3,366,697 (Jan 30, 1968)] and 4-fluoro-4,4-dinitrobutyric acid [M. J. Kamlet, U. S. Patent 3,356,714 (Dec. 5, 1967)].

(2) P. Noble, F. G. Borgardt, and W. L. Reed [*Chem. Rev.*, **61**, 19 (1964)] provide a comprehensive review of the polynitroaliphatic chemistry field through 1963.

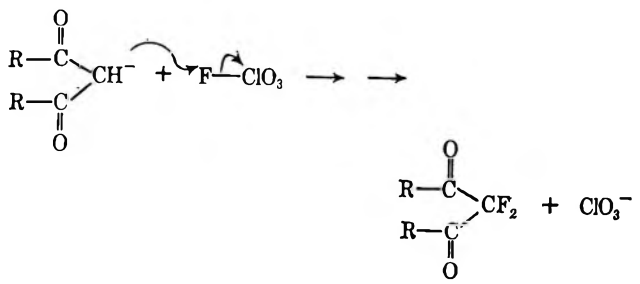
(3) Occasional reports on fluorodinitromethyl compounds have appeared in the literature during the past year, but these generally make reference to earlier work by us or Grakauskas and Baum (see following paper[4]) in the form of private communications. These include fluorodinitroalkyl esters of monocarboxylic acids [O. S. Schaeffler, U. S. Patent 3,316,292 (April 25, 1967)], fluorodinitroalkane preparation [M. Graff, W. E. McQuistion, and J. W. Sterling, U. S. Patent 3,274,264 (Sept 20, 1966)], and heat of formation and properties of fluorotrinitromethane [M. F. Zimmer, R. A. Robb, E. E. Baroody, and G. A. Carpenter, *J. Chem. Eng. Data*, **11**, 577 (1966)]. While the present paper was in process of revision, a report appeared describing solid phase fluorinations of potassium nitroform and dipotassium 1,1,2,2-tetranitroethane to yield, *inter alia*, some of the products reported here. A fluorine–nitrogen mixture was passed over these salts in a matrix of potassium fluoride and granulated copper.[5]

(4) V. Grakauskas and K. Baum, *J. Org. Chem.*, **33**, 3080 (1968).

(5) L. T. Eremenko, F. Ya. Natsibullin, and I. P. Borovinskaya, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 429, 431 (1968).

possible a variety of other type functionality in the molecule.

Fluorination with Perchloryl Fluoride.—Although no such agents were known to us when this study was undertaken,[6] the first reports on perchloryl fluoride as a selective fluorinating agent were published soon thereafter by Inman, Oesterling, and Tyczkowski,[7] who described the reactions of the sodium salts of such active methylene compounds as acetoacetic ester, malonic ester, and 2,4-pentanedione with perchloryl fluoride to yield primarily the difluoro derivatives at the active methylene sites.



These reactions presumably involved attack of the carbanion on fluorine with displacement of chlorate ion and seemed to parallel the desired fluorination of 1,1-dinitroalkane ions mechanistically. The question remained to be answered, however, as to whether the less basic dinitro carbanions would be sufficiently reactive and whether their ambident nature[2] would lead to a multiplicity of products deriving from C and O fluorination.[8]

In four instances the reactions of the potassium salts of the 1,1-dinitro compounds with perchloryl fluoride in methanol or aqueous methanol at 25–40° proved to be relatively straightforward. From potassium dinitromethylbenzene we obtained in 95% yield fluorodinitromethylbenzene (I) which on nitration with HNO_3–FSO_3H was converted into a mononitro derivative, presumably α-fluoro-α,α,3-trinitrotoluene (II). Potassium 1,1-dinitroethane and potassium 1,1-dinitropropane yielded 54% pure 1-fluoro-1,1-dinitroethane (III) and 59% 1-fluoro-1,1-dinitropropane (IV), respectively. Potassium methyl 4,4-dinitrobutyrate gave 93% methyl 4-fluoro-4,4-dinitrobutyrate (V), characterized as the corresponding butyric acid (VI), into which it was converted in practically quantitative yield by refluxing with concentrated hydrochloric acid.

$$RC(NO_2)_2^-K^+ + FClO_3 \longrightarrow RC(NO_2)_2F + KClO_3$$

I, R = C_6H_5–
III, R = CH_3–
IV, R = C_2H_5–
V, R = $MeOOCCH_2CH_2$–

$$I \xrightarrow{HNO_3,\ FSO_3H} 3\text{-}NO_2C_6H_4C(NO_2)_2F$$
II

$$V \xrightarrow{\text{concd HCl}} CF(NO_2)_2CH_2CH_2COOH$$
VI

With potassium or sodium 2,2-dinitroethanol the fluorination reaction was very much more complex. Under a variety of conditions the best yields of 2-fluoro-2,2-dinitroethanol (VII) ranged from 20 to 25%. Of

$$HOCH_2C(NO_2)_2^-M^+ + FClO_3 \longrightarrow HOCH_2C(NO_2)_2F + MClO_3$$
VII

the solvents tried in this case, only in aqueous methanol and in DMF, in which the salts are somewhat soluble,[9] did reaction take place at a reasonable rate. In such solvents the dinitroethanol anion participates in a series of formylation–deformylation equilibria involving 2,2-dinitro-1,3-propanediol together with smaller amounts of dinitromethane, 2,2,4,4-tetranitro-1-butanol (from dinitroethanol and dinitroethylene), and 2,2,4,4-tetranitro-1,5-pentanediol.[10] Certain of these species would also be expected to react with perchloryl fluoride and, by contrast with the previous examples, the products obtained from the fluorinations of the dinitroethanol salts were complex mixtures. Only by repeated fractional distillation was a reasonably pure sample of VII obtained.

Unsuccessful attempts to fluorinate 1,1-dinitroalkane salts with perchloryl fluoride involved 2,2-dinitroethylamine zwitterion[11] in a methanol–water–ether mixture and potassium nitroform in a variety of solvents. The failure of the latter to react was not unexpected in view of the lower basicity (pK of nitroform = *ca.* 0)[12] and nucleophilicity of the trinitromethide anion compared with those of the dinitro carbanions (pK values of parent dinitro compounds range from 3.5 to 6.5).[12]

Fluorination with Elemental Fluorine.—Soon after our initial work on the perchloryl fluoride fluorination of dinitro carbanions, it was shown by Grakauskas that many types of fluorination reactions could be carried out by the surprisingly simple expedient of passing a stream of a nitrogen–fluorine mixture into an aqueous solution of the appropriate substrate.[13] Among the reactions carried out by Grakauskas to demonstrate the versatility of this most useful technique were aqueous fluorinations of the potassium salts of 1,1-dinitroethane and 2,2-dinitroethanol. The products, 1-fluoro-1,1-dinitroethane and 2-fluoro-2,2-dinitroethanol, were the same as we had obtained by the perchloryl fluoride method, but the yields as well as the purity of the product in the fluorodinitroethanol preparation were vastly improved.

(6) Our original intent was to investigate nitryl fluoride as a fluorinating agent. We had earlier found that, depending on the solvent and substrate, nitryl chloride reacted with 1,1-dinitro carbanion salts to yield either the trinitro or the chlorodinitro derivative: unpublished information.

(7) C. E. Inman, R. E. Oesterling, and E. A. Tyczkowski, *J. Amer. Chem. Soc.*, **80**, 6533 (1958); H. Gershon, *et al.*, *J. Org. Chem.*, **31**, 916 (1966).

(8) While this work was in progress, H. Shechter and A. B. Roberson, Jr. [*J. Org. Chem.*, **25**, 175 (1960)] reported that C fluorination occurred in the reaction of a number of mononitro carbanions with PF in methanol, but that oxidation (presumably arising from O fluorination) was a major side reaction.

(9) See Experimental Section for a discussion of factors governing choice of solvents in perchloryl fluoride fluorinations.

(10) Summary Report No. 461, Aerojet Engineering Corp., Azusa, Calif., July 20, 1950 (available through the Defense Documentation Center, Cameron Station, Alexandria, Va.); K. Klager, J. P. Kispersky, and E. Hamel, *J. Org. Chem.*, **26**, 4368 (1961).

(11) M. J. Kamlet and J. C. Dacons, *ibid.*, **26**, 3005 (1961).

(12) (a) V. I. Slovetskii, S. A. Shevelev, V. I. Erashko, L. I. Biryukova, A. A. Fainzil'berg, and S. S. Novikov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 655 (1966). (b) M. E. Sitzmann, H. G. Adolph, and M. J. Kamlet, *J. Amer. Chem. Soc.*, **90**, 2815 (1968).

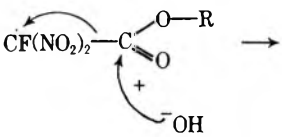
(13) Because of the novelty, extreme versatility, and utility of this procedure, we have taken the liberty of naming it the Grakauskas reaction. Very little of Grakauskas' work has yet appeared in print (what has, indeed, is reported by other later workers) and we wish to thank Dr. Grakauskas for making much of this information available to us in a series of private communications. See following paper.[4]

We have extended the aqueous fluorination of dinitro carbanions to compounds containing a variety of additional functional groups to explore the scope of the Grakauskas reaction.

$$RC(NO_2)_2^-K^+ \xrightarrow{F_2/N_2} RC(NO_2)_2F$$

V, R = $MeOOCCH_2CH_2-$ (88%)
VIII, R = $EtOOC-$ (61%)
IX, R = CH_3OCH_2- (76%)

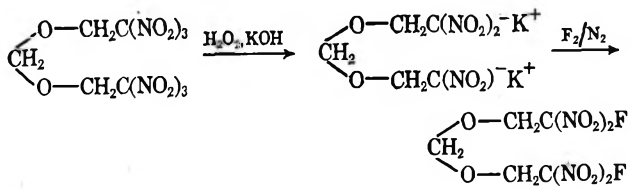
Since attack of fluorine occurs on the carbanion, and since partially ionized 1,1-dinitroalkanes tend to undergo various types of self-condensation,[14] the reaction mixture is preferably maintained at a pH which ensures essentially complete ionization of the substrate. Most aqueous fluorinations of 1,1-dinitro compounds were therefore carried out in a pH range of 8–10. In the fluorination of potassium ethyl dinitroacetate, the presence of base led to the formation of *ca.* 20% fluorodinitromethane (X) as a by-product, probably as a result of hydroxide attack on the ethyl fluorodinitroacetate.[15]



$$[FC(NO_2)_2^- + CO_2 + ROH] \xrightarrow{H^+} FC(NO_2)_2H$$

X

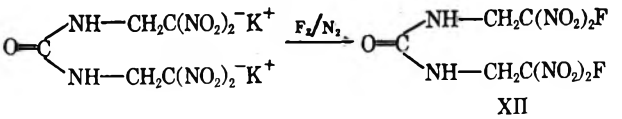
The aqueous fluorination of dipotassium bis(2,2-dinitroethyl)formal, obtained by the alkaline hydroperoxide reduction of bis(2,2,2-trinitroethyl)formal, proceeded smoothly at both ends of the chain, affording bis(2-fluoro-2,2-dinitroethyl)formal (XI)[16] in 55% over-all yield.



XI

This illustrates a general method whereby a trinitro compound may be reduced to the dinitro carbanion salt with alkaline hydroperoxide[17] or potassium iodide[18] and thence converted into the corresponding fluorodinitro derivative.

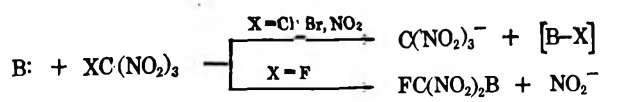
Under the conditions of the aqueous fluorination, fluorine also attacks amides, amines, and urethans on nitrogen.[19] The fluorination of dipotassium N,N′-bis(2,2-dinitroethyl)urea, which in addition to the carbanion sites can also undergo reaction at the urea nitrogens, therefore provided an opportunity to obtain qualitative information about the relative reactivity of the two nucleophilic centers. Although both reactions proceeded at not markedly dissimilar rates, C fluorination was somewhat more rapid, permitting the isolation of N,N′-bis(2-fluoro-2,2-dinitroethyl)urea (XII) in moderate yield; in addition, N-fluorinated but otherwise unidentified by-products were formed.



XII

In isolated instances, perchloryl fluoride may be the more advantageous for the fluorination of 1,1-dinitro salts. Thus, it has been shown that carbon–carbon double bonds are attacked by fluorine under conditions of aqueous fluorination, while the use of perchloryl fluoride in the fluorination of 4,4-dinitro-1-butene salts left the unsaturation in the molecule intact.[20] It is also possible that, with compounds containing an amide function in addition to the dinitromethyl group, perchloryl fluoride will give better results because of its relative inertness toward amide nitrogen. In general, however, the Grakauskas method with elemental fluorine is to be preferred. It is safer,[21] gives at least as good or better yields in most cases where both procedures have been tried, and, except for the initial setup of the fluorination apparatus, is more convenient to carry out because of a generally much simpler work-up of the reaction mixture.

Preparation of Fluorodinitromethyl Compounds from Fluorotrinitromethane.—Although perchloryl fluoride and aqueous fluorination allow the preparation of a wide variety of substituted fluorodinitromethanes, a third method, which is indirectly based on the Grakauskas reaction, permits the synthesis of a variety of materials for which the corresponding 1,1-dinitro carbanion salts are not accessible. We have found that fluorotrinitromethane, obtained by the aqueous fluorination of nitroform salts,[22] reacts with certain nucleophiles with formal substitution of one of the nitro groups. This is in marked contrast to tetranitromethane and chloro- and bromotrinitromethane, whose reactions with a variety of bases and reducing agents generally lead to nitroform anion.[23]



Thus, the reactions of fluorotrinitromethane with sodium ethoxide and sodium trifluoroethoxide, using

(14) For example, an autocondensation product is formed wherever 1,1-dinitroethane coexists in appreciable concentrations with its carbanion: J. S. Belew, C. E. Grabiel, and L. B. Clapp, *J. Amer. Chem. Soc.*, **77**, 1110 (1955).

(15) A similar cleavage of negatively substituted esters which does not proceed through the corresponding carboxylic acid has been reported by, among others, E. Bergman, *J. Org. Chem.*, **23**, 476 (1958).

(16) This material was first prepared by the condensation of VII with formaldehyde in strong sulfuric acid by Dr. F. E. Martin of the Aerojet-General Corp., whose priority in this regard we herewith acknowledge. A single trial at perchloryl fluoride fluorination of dipotassium bis(2,2-dinitroethyl)formal yielded *ca.* 3% XI.

(17) D. J. Glover, *Tetrahedron, Suppl. 1*, **19**, 219 (1963), and references cited therein.

(18) D. J. Glover and M. J. Kamlet, *J. Org. Chem.*, **26**, 4734 (1961).

(19) V. Grakauskas, "Direct Fluorination of Alkyl Carbamates in Solution," Third International Symposium on Fluorine Chemistry, Munich, 1965.

(20) Private communication, Dr. M. B. Frankel, Roeketdyne Corp., Canoga Park, Calif.

(21) See Experimental Section for a discussion of some hazards in perchloryl fluoride fluorinations. We know of at least one very serious accident resulting from the use of this material: private communication, Professor E. D. Bergmann, The Hebrew University, Jerusalem.

(22) K. Baum and V. Grakauskas, private communication. Later workers (Zimmer, *et al.*[3]) have acknowledged us as the authors of a private communication regarding the synthesis of this material, while in fact we were only transmitting information first obtained from Baum and Grakauskas. See following paper.[4]

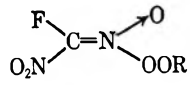
(23) (a) A. Hantzsch, *Chem. Ber.*, **39**, 2479 (1906); Chattaway and Harrison, *J. Chem. Soc.*, **109**, 173 (1916). (b) A. K. Macbeth and D. D. Pratt, *ibid.*, **119**, 333 (1921); K. Klager, *Anal. Chem.*, **23**, 534 (1951).

the parent alcohols as solvents, gave the corresponding fluorodinitromethyl ethers in moderate to good yields.

$$CF(NO_2)_3 + RO^-Na^+ \longrightarrow CF(NO_2)_2OR + NaNO_2$$

XIII, R = C_2H_5– (74%)
XIV, R = CF_3CH_2– (55%)

The structures of these ethers were assigned on the basis of analytical results which confirmed the presence of nitro and ethoxy groups in XIII in the ratio of 2:1 (see Experimental Section). A peroxide or O-ether structure of the type



was ruled out primarily on the basis of the ultraviolet spectrum which showed λ_{max}^{MeOH} 285 mμ (ε *ca.* 95). Low intensity absorption near 280 mμ is characteristic of unconjugated nitro- and polynitroaliphatics[24] (ε 25 to 35 per nitro group),[25] and is in marked contrast with the spectral behavior of 1,1-dinitroalkane *aci*-ethers which typically show high intensity absorption at 315–320 mμ (ε 6000–9000).[26]

The analogous reaction of fluorotrinitromethane with sodium azide in dimethylformamide afforded fluorodinitromethyl azide in approximately 35% yield.

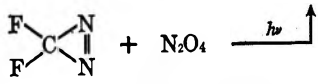
$$CF(NO_2)_3 + N_3^- \longrightarrow FC(NO_2)_2N_3 + NO_2^-$$

XV

With potassium fluoride in sulfolane, the corresponding reaction provided difluorodinitromethane (XVI), which has also been reported to result from photochemical addition of N_2O_4 or NO_2Cl to difluorodiaziridine.[27]

$$CF(NO_2)_3 + F^- \longrightarrow CF_2(NO_2)_2 + NO_2^-$$

XVI



Although no unequivocal evidence is available at this time, it is likely that these reactions involve simple nucleophilic substitutions of a nitro group with the nucleophile attacking on carbon rather than on nitrogen or oxygen as is more frequently observed in polynitroaliphatic chemistry,[17,18] or on halogen, as must be the case with the other halotrinitromethanes. Two factors may contribute to the different pathways taken in the reactions of B: with X–$C(NO_2)_3$ or R–$C(NO_2)_3$. The carbon atom is, of course, sterically most accessible where X = F, leading to an increased rate of nucleophilic attack on carbon; the decreased stability of the fluorodinitromethide leaving group relative to trinitromethide or other dinitro carbanions [evidenced by the following p*K*'s: $C(NO_2)_3H$, 0.17; $ClC(NO_2)_2H$, 3.53; $BrC(NO_2)_2H$, 3.6; $CH_3C(NO_2)_2H$, 5.21; $FC(NO_2)_2H$, 7.70][1,28] may contribute to a lowered rate of nucleophilic attack on oxygen or nitrogen.

A possibly related reaction of fluorotrinitromethane, which constitutes a useful synthesis of 2-fluoro-2,2-dinitroethanol (VII), was found in its reduction by alkaline hydrogen peroxide in the presence of formaldehyde.

$$CF(NO_2)_3 + {}^-OOH \longrightarrow [FC(NO_2)_2OOH + NO_2^-]$$

$$\downarrow$$

$$[FC(NO_2)_2H + O_2] \xrightarrow{CH_2O} FC(NO_2)_2CH_2OH$$

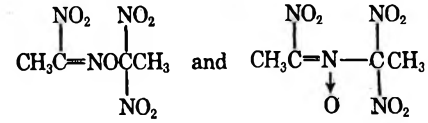
VII

In this case, however, the over-all result of the reaction can also be explained in terms of attack by hydroperoxide ion on oxygen or nitrogen of one of the nitro groups with displacement of fluorodinitromethide ion.[29]

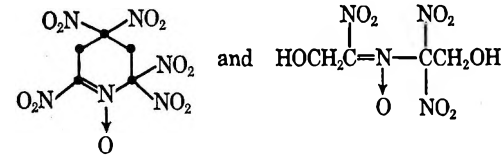
$$CF(NO_2)_3 + {}^-OOH \longrightarrow FC(NO_2)_2^- + [O{=}NOOOH \text{ or } O_2NOOH]$$

When this reaction is carried out in the absence of formaldehyde, fluorodinitromethane is obtained, but only in moderate yield because of the instability of this material under the reaction conditions.[30]

Referring to the ethers XIII and XIV, it should be mentioned that references to compounds containing the –O–$C(NO_2)_2$– moiety are few. Belew, Grabiel, and Clapp[14] have suggested

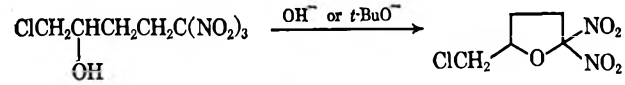


as possible structures for the autocondensation product of 1,1-dinitroethane. Although the available information did not allow an unequivocal choice, they expressed a preference for the –C=NOC$(NO_2)_2$– structure and, more recently, spectra of this material and its derivatives were reported to provide confirmatory evidence in this regard.[31] It is worth comment, however, that compounds closely analogous to the alternative nitrone structure, *i.e.*



are likely intermediates in the reported[32] self-condensation of potassium 2,2-dinitroethanol in dilute sulfuric acid to form 2,4,6-trinitropyridine 1-oxide.

More closely akin to XIII and XIV, both in structure and in proposed mode of formation, is 5-chloromethyl-2,2-dinitrotetrahydrofuran, which is reported[33] to arise from the oxy anion of 1-chloro-5,5,5-trinitro-2-pentanol



(24) V. I. Slovetskii, *et al.*, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1709 (1960); 330 (1961).

(25) The slightly higher extinction coefficient for XIII causes us no concern since this absorption is superimposed on the tail of a high-intensity shorter wavelength band whose maximum is below 200 mμ. This latter band seems to be displaced bathochromically (as best one can judge from its tail) relative to the corresponding band for other nitroaliphatics.

(26) A. I. Ivanov, I. E. Chlenov, V. A. Tartakovskii, V. I. Slovetskii, and S. S. Novikov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1491 (1965).

(27) R. A. Mitsch, *J. Heterocycl. Chem.*, **1**, 233 (1964).

(28) A. I. Ivanov, V. I. Slovetskii, S. A. Shevelev, V. I. Erashko, A. A. Fainzil'berg and S. S. Novikov, *Zh. Fiz. Khim.*, **40**, 2298 (1966).

(29) J. C. Hoffsommer has shown that in the analogous reaction of tetranitromethane with *t*-butyl hydroperoxide the nucleophile attacked on oxygen of one of the nitro groups: Ph.D. Dissertation, George Washington University, Washington, D. C., 1965.

(30) The chemistry and properties of fluorodinitromethane will be described in a subsequent paper in this series.

(31) A. I. Ivanov, L. A. Ustynyuk, V. I. Slovetskii, A. A. Fainzil'berg, and S. S. Novikov, *Zh. Organ. Khim.*, **2**, 763 (1966).

(32) K. D. Gundermann and H. U. Alles, *Angew. Chem.*, **78**, 906 (1966).

(33) E. Steininger, *ibid.*, **77**, 427 (1965).

TABLE I

PREPARATION AND PHYSICAL PROPERTIES OF FLUORODINITROMETHYL COMPOUNDS

Compound No.	Compound Z- = $FC(NO_2)_2$-	Method of preparation[a]	Yield, %	Mp, °C	Bp, °C (mm)
X	Z-H	Hydrolysis of VIII	[b]		65 (80)
		Reduction of $FC(NO_2)_3$	~40		125 (760)
III	Z-CH_3	PF fluorination	54		41 (20)
		Aqueous fluorination	65		57 (44)
IV	Z-CH_2CH_3	PF fluorination	59		145 (760)
VII	Z-CH_2OH	PF fluorination	25	12	55 (0.5)
		$FC(NO_2)_3$ reduction + CH_2O	90		
IX	Z-CH_2OCH_3	Aqueous fluorination	76		48 (4.0)
XI	$[Z\text{-}CH_2O]_2CH_2$	PF fluorination	~3	0[h]	
		Aqueous fluorination	55	11–12	
XII	$[Z\text{-}CH_2NH]_2C{=}O$	Aqueous fluorination	30	218–219[i]	
V	Z-$CH_2CH_2COOCH_3$	PF fluorination	(93)[c]	(2–3)[c]	
		Aqueous fluorination	(88)[c]		
VI	Z-CH_2CH_2COOH	Hydrolysis of V	77[d]	38–39	
I	Z-C_6H_5	PF fluorination	(95)[e]		
II	Z-C_6H_4-NO_2-m	Nitration of I	73[f]	31–32	
VIII	Z-$COOC_2H_5$	Aqueous fluorination	61[g]		
XIII	Z-OCH_2CH_3	$FC(NO_2)_3$ + ethoxide	74		61 (20)
XIV	Z-OCH_2CF_3	$FC(NO_2)_3$ + $CF_3CH_2O^-$	55		45 (15)
XV	Z-N_3	$FC(NO_2)_3$ + azide	34		45 (60)
XVI	Z-F	$FC(NO_2)_3$ + fluoride	59		

[a] PF = perchloryl fluoride. [b] Obtained in *ca.* 20% yield in aqueous fluorination leading to VIII. [c] Values in parentheses are for crude products; material was not purified, but was characterized by conversion into VI. [d] Over-all yield for two steps (aqueous or PF fluorination and hydrolysis) based on potassium methyl 4,4-dinitrobutyrate. [e] Yield is for crude material. Characterized by conversion into II. [f] Yield based on crude I. [g] X (*ca.* 20%) obtained as a by-product. [h] Metastable polymorph. [i] A metastable polymorph has been found, mp 185–186°.

through an apparently analogous displacement of a nitro group by an alkoxy group with the assistance of ring formation.

Physical and Spectral Properties of Fluorodinitro Compounds.—A summary of the physical properties of the new fluorodinitromethyl compounds prepared in this study is given in Table I. Table I also allows a facile comparison of yields where several preparative methods have been used.

As already mentioned, the $FC(NO_2)_2$- group exhibits no distinct absorption in the uv spectrum other than the low-intensity band near 280 mμ characteristic of the unconjugated nitro groups.[24] Similarly, the frequencies of the symmetrical and asymmetrical nitro stretching vibrations in the infrared are only minimally displaced from their positions in the spectra of other negatively substituted nitroaliphatics,[34] and were found in the ranges 1290–1330 and 1600–1630 cm^{-1} for all compounds studied. A set of two bands at *ca.* 800 and 850 cm^{-1}, with the rather constant relative ratios 2:1, was found in all $FC(NO_2)_2$- compounds investigated except X (750, 830 cm^{-1}) and III (770, 850 cm^{-1}). These maxima, which are also found in some trinitromethyl compounds, are probably associated with the C–N bonds and are therefore not necessarily indicative of the fluorodinitromethyl group. Except in one case, specific C–F absorption could not be identified with certainty in these compounds owing to the presence of several bands in the 1000–1100-cm^{-1} region. Important features in the infrared spectra of some of the materials discussed here are summarized in Table II.

The pmr spectra of the $FC(NO_2)_2CH_2$- group in various of the compounds reported here exhibited a doublet (J_{HF} = 16–19 cps) at δ 4.5 to 5 (relative to TMS) in CCl_4 or $CDCl_3$ solutions.

TABLE II

PRINCIPAL INFRARED BANDS OF SOME FLUORODINITROMETHYL COMPOUNDS

Compd	NO_2 assym	NO_2 sym	C–F	750–900 region	Miscellaneous
VII	1600	1320		802, 852	
VIII	1605	1308		795, 845	1780, —COOR
III	1600	1330		770, 850	
IX	1605	1320		800, 850	
V	1600	1322		802, 845	1740, —COOR
XI	1605	1320		798, 850	
X	1610	1325		750, 830	
XVI	1630	1330		805, 860	
$FC(NO_2)_3$	1625	1290	1018	805, 855	
XIII	1610	?		805, 840	
XIV	1608	1310		800, 850	1185, C—O?

Experimental Section

General (Caution!).—Most of the starting materials and products described in this paper are explosives of moderate to considerable sensitivity to initiation by impact, shock, friction, or other means. They should therefore be *handled with care*. Furthermore, many fluorodinitro compounds show varying degrees of toxicity; fluorodinitromethane and particularly fluorodinitroethanol may cause painful burns when brought into contact with the skin.

Microanalyses and molecular weight determinations were by Professor Mary H. Aldridge, American University, Washington, D. C., and Mr. D. J. Glover of this laboratory. Methodic difficulties were encountered in obtaining reproducible analytical results on a number of the fluorodinitro compounds reported here and somewhat larger than usual deviations from calculated values were therefore occasionally judged acceptable. Melting and boiling points are uncorrected.

Fluorination with Perchloryl Fluoride (Caution!).—Many of the procedures described below involve filtrations of potassium chlorate from mixtures containing both combustible solvents

(34) J. F. Brown, Jr., *J. Amer. Chem. Soc.*, **77**, 6341 (1955); V. I. Slovetskii, A. A. Fainzil'berg, V. I. Gulevskaya, and S. S. Novikov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 683 (1961); see also ref 24.

and explosive organic materials and it should be recognized that during these filtrations one goes through a stage where the chlorate–fuel–explosive ratio may represent a potentially hazardous situation. For this reason the filtration operations are well shielded and the filter cakes are exhaustively washed with additional solvent before being allowed to air dry.

Perchloryl fluoride was purchased from the Pennsalt Chemicals Corp. and was used without further purification.[35] Reactions of potassium or sodium dinitro compounds with perchloryl fluoride were carried out by bubbling the gas into a well-stirred suspension of the salt. Apparatus generally involved a gas inlet tube and stirrer in a three-necked, round-bottomed flask surmounted by a reflux condenser and with bubble counters fore and aft. After introducing the salt and solvent, most of the air was purged from the system by blowing through a rapid stream of perchloryl fluoride which was vented to the hood. The rate of input was then cut back until there was a partial vacuum in the system as shown by the liquid level rising in the bubble counter aft, this partial vacuum being due to uptake of the perchloryl fluoride by the solvent in forming a saturated solution. Reaction with the salt of the dinitro compound was then evidenced by a rapid gas input with the partial vacuum being maintained. Generally, where reaction took place, the rate was determined by the speed of solution of the gas. Increasing the stirring rate increased the perchloryl fluoride uptake; decreasing it had the converse effect.

Where reaction took place it was also evidenced by the gradual solution of the yellow dinitro salt and precipitation of white potassium chlorate. Preferred solvents were those in which perchloryl fluoride and the dinitro salt had mutually maximal solubilities. Thus, reactions were extremely slow in ether in which the dinitro salt was insoluble and in water in which the perchloryl fluoride was relatively insoluble. Methanol was a more rapid solvent, aqueous methanol was faster, and dimethylformamide the most rapid solvent tried.

Temperatures were chosen between 0 and 50° to give the most convenient rates and, except in one case, temperature control was easy. The reactions appeared to be slightly exothermic and could be held at the desired temperature by varying the perchloryl fluoride input rate and by moderate cooling. A self-sustaining exothermal decomposition (*fume-off!*) took place with potassium methyl 4,4-dinitrobutyrate in DMF, but in the slower solvent, methanol, the reaction was easily controlled.

Fluorodinitromethylbenzene (I).—A suspension of 9.7 g of potassium dinitromethylbenzene in 200 ml of methanol was maintained at 25° while perchloryl fluoride was slowly bubbled in. After the yellow-orange salt had been replaced by a white precipitate and the color of the solution had changed to pale chartreuse (*ca.* 1.5 hr), 120 ml of ether was added to the reaction mixture, and 5.1 g of potassium chlorate was filtered off. Stripping off the solvent, adding ether, filtering off an additional 0.2 g of potassium chlorate (total 98%), and again stripping off the ether *in vacuo* gave 8.30 g (95%) of crude I as a yellow oil. This material was not purified further, but was converted into and analyzed as its *m*-nitro derivative (see below).

α-Fluoro-α,α,3-trinitrotoluene (II).—Portionwise addition of 3.3 g of crude fluorodinitromethylbenzene at 0–5° to a stirred mixture of 10 ml of 96% nitric acid and 10 ml of fluorosulfonic acid caused vigorous bubbling, evolution of brown fumes, and the eventual formation of a homogeneous pale yellow solution. Pouring the mixture over crushed ice gave a yellow oil which slowly solidified on standing. The solid was collected, triturated with a small amount of cold methanol, and filtered to give 3.0 g (73%) of crude II, mp 29–30°. Recrystallization from ether–hexane or methanol–water raised the melting point to 31–32°.

Anal. Calcd for $C_7H_4FN_3O_6$: C, 34.29; H, 1.63; N, 17.15. Found: C, 34.20; H, 1.85; N, 17.06.

1-Fluoro-1,1-dinitroethane (III).—A satisfactory rate of reaction was achieved by bubbling perchloryl fluoride into a suspension of 90 g of potassium 1,1-dinitroethane in 750 ml of methanol plus 200 ml of water at 40°, about 7 hr being required for the complete replacement of the yellow starting material by potassium chlorate. After filtering off the latter material, the solution was diluted with 500 ml of water and extracted with 500 ml of ether. The ether phase was washed several times with water and dried over calcium chloride, and the ether was evaporated off *in vacuo*. Fractionation of the residue yielded 42.5 g (54%) of pure III, bp 40.5–41.5° (20 mm). About 10 g of a higher boiling oil remained as a pot residue.

Anal. Calcd for $C_2H_3FN_2O_4$: C, 17.38; H, 2.17; N, 20.25. Found: C, 17.58; H, 2.18; N, 19.81.

1-Fluoro-1,1-dinitropropane (IV).—The perchloryl fluoride fluorination of 100 g of potassium 1,1-dinitropropane in a mixture of 750 ml of methanol and 100 ml of water at 35–40° required *ca.* 3.5 hr. Approximately 1 l. of water was added to dissolve most of the potassium chlorate and the product was extracted into chloroform. The extracts were washed with 250 ml of water, 250 ml of 2% sodium carbonate solution, and again with 250 ml of water, and dried over magnesium sulfate, and the chloroform was stripped off *in vacuo*. Fractionation of the residue under reduced pressure gave 51.6 g of IV (59%): bp 45–47° (15 mm), 144.5° (760 mm).

Anal. Calcd for $C_3H_5FN_2O_4$: C, 23.68; H, 3.29; N, 18.41. Found: C, 23.93; H, 3.29; N, 18.05.

Methyl 4-Fluoro-4,4-dinitrobutyrate (V).—At 37° uptake of perchloryl fluoride by a suspension of 73 g of potassium methyl 4,4-dinitrobutyrate in 750 ml of methanol was substantially complete in 5 hr. After cooling the mixture to −10°, 37.5 g of potassium chlorate was filtered off, most of the methanol was stripped off *in vacuo*, an additional 0.8 g of potassium chlorate was filtered off (98.5% total), and the remaining methanol was removed to leave 62 g of crude V as a pale yellow oil which solidified on standing in the freezer, mp *ca.* 2–3°. For analysis, this ester was converted into the corresponding acid (see below).

4-Fluoro-4,4-dinitrobutyric Acid (VI).—A 52-g sample of crude V (see above) was refluxed for 2–3 hr with 500 ml of constant-boiling hydrochloric acid. The almost clear solution which resulted was filtered hot through a layer of Celite on a sintered-glass funnel and chilled, and the precipitate was filtered off. Concentration of the mother liquor afforded an additional two crops, leading to a total of 35.9 g (77%) of crude VI, mp 35–38°. Recrystallization from chloroform–carbon tetrachloride afforded pure VI as long white needles, mp 37–38°.

Anal. Calcd for $C_4H_5FN_2O_6$: C, 24.48; H, 2.55; N, 14.28; F, 9.69. Found: C, 24.73; H, 2.88; N, 13.87; F, 9.46.

2-Fluoro-2,2-dinitroethanol (VII).—To a cooled, stirred solution of 53.0 g of 85% potassium hydroxide in 140 ml of water and 500 ml of methanol was added portionwise 132.8 g of 2,2-dinitro-1,3-propanediol in 240 ml of methanol; the temperature was kept below 12°. The precipitated potassium 2,2-dinitroethanol was separated from the solvent through the use of a filter stick and washed twice with 250-ml portions of methanol and once with 350 ml of ether, 500 ml of dimethylformamide was then added, the mixture was cooled to 15°, and perchloryl fluoride was bubbled in at this temperature. The uptake was relatively rapid, with the mixture slowly discoloring until, by the time the perchloryl fluoride uptake was complete, the solution was dark brown. The insoluble material was filtered off and washed with ether. Addition of 2 ml of concentrated sulfuric acid to the dark brown mother liquor caused a color change to bright orange. Most of the solvent was then distilled off below 30° (1.5 mm). The residue was taken up in 250 ml of ether and washed with three 100-ml portions of water, the combined aqueous washes were reextracted with 250 ml of ether, and the combined ether phases were washed with 100 ml of 3% hydrochloric acid.[36] The ether was stripped off and the residual orange oil was fractionated *in vacuo* to yield 30.7 g of VII (25% of theory), bp 55–57° (1.5 mm). A second fractionation gave the analytical sample which was still relatively impure, but whose infrared spectrum and retention volume were essentially identical with those of a purer sample obtained by fluorotrinitromethane reduction (see below).

Anal. Calcd for $C_2H_3FN_2O_5$: N, 18.20. Found: N, 17.28, 16.99.

Fluorination with Elemental Fluorine (The Grakauskas Reaction).—All experiments with elemental fluorine were carried out in a well-shielded and vented area. Fluorine–nitrogen mixtures in ratios of approximately 1:1 to 1:3 were generally used and were delivered through an apparatus constructed essentially according to the recommendations given by the Gen-

(35) Properties and methods of handling this material are described in Pennsalt Chemicals Corp. New Products Booklet DC-1819, "Perchloryl Fluoride," 1957.

(36) In earlier trials where this cumbersome separation procedure was not used, fume-offs occurred during the fractionation step, probably owing to 2,2-dinitro-1,3-propanediol in the pot residue. At the time the work was done it was not known that VII is a moderately stable to weak alkali, which would have simplified the separation appreciably. Also, if we were to repeat the work, we would run the fluorination in the presence of excess weak base.

eral Chemical Division, Allied Chemical Corp.[37] The setup was modified by incorporating a surge tank of about 500-ml capacity between the back pressure control valve and the back pressure indicator in order to minimize bouncing of the rotometer float. Metal to glass connections were of Teflon tubing. The fluorinations were carried out in ordinary glass equipment consisting of a four-neck flask fitted with stirrer, thermometer, gas inlet tube, and condenser; the stirrer was well lubricated with water. Little etching of the apparatus was observed, even after extensive use. Occasionally, where methanol-wet dinitroalkane salts were used as starting materials, small "flashes of blue fire" were observed in the gas inlet tube, accompanied by slight popping sounds, but these were never sufficient to rupture the apparatus and could be avoided easily.

Methyl 4-Fluoro-4,4-dinitrobutyrate (V).—A mixture of 51.5 g of potassium methyl 4,4-dinitrobutyrate, 10 g of sodium bicarbonate, and 300 ml of water in a 1-l. standard fluorination apparatus was stirred vigorously and held at 20–25° as a 2:1 nitrogen–fluorine mixture was introduced. The reaction mixture changed in color from yellow to red-orange as the starting material gradually dissolved; after about 45 min a sharp, milky white end point was observed. The system was purged of fluorine with pure nitrogen, the reaction mixture was extracted with ether, and the extracts were washed with water, dried, and concentrated. There remained 41.4 g of crude V (88%) as a yellow oil.

Methyl 2-Fluoro-2,2-dinitroethyl Ether (IX).—At 0–5° a 2:1 nitrogen–fluorine mixture was bubbled through a solution of 2.5 g of potassium 2,2-dinitroethyl methyl ether in 100 ml of water until the yellow color disappeared. The reaction mixture was purged with nitrogen and extracted with methylene chloride, and the extract was dried and distilled. Thus was obtained 1.7 g of IX (76%), bp 47–48° (4.0 mm).

Anal. Calcd for $C_3H_5FN_2O_5$: N, 16.66; F, 11.30. Found: N, 16.85, F, 10.93.

Bis-(2-fluoro-2,2-dinitroethyl)formal (XI).—Dipotassium bis-(2,2-dinitroethyl)formal was prepared by the hydroperoxide reduction[17] of bis(2,2,2-trinitroethyl)formal as follows. To 30.0 g of bis(2,2,2-trinitroethyl)formal in 225 ml of methanol at 0° was added 45 ml of cold 30% hydrogen peroxide; then, dropwise with stirring and continued cooling over a period of 30 min, 36 g of 85% potassium hydroxide in 210 ml of methanol was also added, the temperature being kept below 10°. The mixture was stirred a further 20 min and filtered. The precipitate was washed with three 100-ml portions of methanol, the methanol-wet salt was suspended in a solution of 10 g of sodium carbonate in 500 ml of water, and the mixture was concentrated[38] to a total volume of 400 ml at a temperature not above 50°. The solution was then rapidly cooled to 22° with vigorous stirring to impart small particle size to the reprecipitating salt.

The resulting mixture was fluorinated in the standard fluorination apparatus at 20–25° with a nitrogen–fluorine ratio of 3:1. A milky white end point was reached in about 2 hr, after which time the reaction mixture was purged with nitrogen and the product was extracted into chloroform. The extracts were washed with four 100-ml portions of 5% sodium hydroxide and once with water. After drying, the solvent was stripped off; the last traces were removed by holding the temperature at 70° (1 mm) for several hours. There remained 14.1 g (55%) of very pale yellow XI.

The analytical sample was obtained by thoroughly washing a methylene chloride solution of XI with concentrated sulfuric acid, then with water, dilute sodium hydroxide, again with water, drying, removing the solvent, and recrystallizing the residual oil from methylene chloride–hexane, mp[39] 11–12.

Anal. Calcd for $C_5H_6F_2N_4O_{10}$: C, 18.76; H, 1.89; F, 11.88. Found: C, 19.05; H, 2.02; F, 11.32.

Ethyl 2-Fluoro-2,2-dinitroacetate (VIII) and Fluorodinitromethane (X).—A fluorine–nitrogen mixture (3:1) was introduced at 0° with stirring into a solution of 21.6 g of potassium ethyl 2,2-dinitroacetate in 200 ml of water containing 18 g of sodium bicarbonate. The exit gases were passed through a trap held at −70°. The system was purged with nitrogen, the reaction mixture was extracted with methylene chloride, and the trap contents were combined with the extracts. Removal of the solvent yielded 16.5 g of a pale yellow oil which was shown by glpc (column: 10% May-Baker silicon oil on Haloport F) to be a mixture of two products. By fractional distillation at 40 mm (bath temperature not above 100°), the lower boiling component could be removed almost completely. The remaining oil was distilled in a molecular still at 80° (0.01 mm) to yield 12.0 g of VIII (61.2%) of an estimated purity of 98% (glpc).

Anal. Calcd for $C_4H_5FN_2O_6$: N, 14.29; F, 9.69. Found: N, 14.10; F, 9.42.

The lower boiling fraction was refractionated at 80 mm to give 2.5 g of fluorodinitromethane (20.3%) as a colorless oil of pungent odor, bp 64–65° (80 mm) and 125° (760 mm).

Anal. Calcd for $CHFN_2O_4$: N, 22.58; F, 15.31; neut equiv, 124. Found: N, 22.58; F, 14.92; neut equiv, 121.

Bis(2-fluoro-2,2-dinitroethyl)urea (XII).—N,N′-Bis(2,2,2-trinitroethyl)urea (39 g) was added gradually to a stirred mixture of 66 g of potassium iodide in 500 ml of methanol;[18] the mixture was stirred 24 hr at room temperature, cooled in an ice bath, and filtered. The solid was washed with a small amount of methanol and liberally with ether to give 24 g (64.2%) of crude dipotassium N,N′-bis(2,2-dinitroethyl)urea.

The crude salt was dissolved in 400 ml of water containing 10 g of sodium bicarbonate and was fluorinated in the standard apparatus at 0° until the mixture became slightly acidic. The pale yellow, gummy solid was filtered off, dissolved in methylene chloride–ether (1:1), and filtered through a 1 × 15 in. column of silica (G. F. Smith, Columbus, Ohio). The colorless portion of the eluate was collected and concentrated until precipitation started. Addition of methylene chloride and chilling afforded 6.4 g of crude XII (29.8% based on dipotassium salt). After recrystallization from toluene–ethyl acetate, the product melted at 185–186° dec. In later experiments a second polymorph, mp 218–219° dec, was obtained and we can no longer make the metastable 186° form in this laboratory.

Anal. Calcd for $C_5H_6F_2N_6O_9$: N, 25.31; F, 11.42; mol wt, 332. Found: N, 25.29; F, 11.61; mol wt (MEK), 325.

Reactions with Fluorotrinitromethane.—Fluorotrinitromethane was prepared by the aqueous fluorination of nitroform salts with slight modifications on a procedure first reported by Grakauskas and Baum[22] and was used without further purification.

Fluorotrinitromethane.—A solution of 114 g of nitroform in 1000 ml of 5% sodium carbonate solution was fluorinated at 0–5° in the standard apparatus until the mixture was bleached to a milky white suspension of pH 6. The product, a heavy colorless oil, was separated, washed with 5% sodium bicarbonate solution and with water, and dried over magnesium sulfate to give 115 g (90%) of fluorotrinitromethane of 98 mol % purity (glpc).

Ethyl Fluorodinitromethyl Ether (XIII).—At −10 to −15° and over a period of 15 min, a solution of sodium ethoxide prepared by dissolving 4.6 g of sodium in 70 ml of ethanol was added to 16.9 g of fluorotrinitromethane in 70 ml of methylene chloride; the mixture was stirred another 10 min below 10°. The mixture was then poured into ice-cold dilute sulfuric acid, the phases were separated, the aqueous phase was extracted with methylene chloride, and the combined extracts were washed with water, dried, and distilled to yield 12.45 g of crude XIII (74%). Refractionation gave 11.2 g of pure material, bp 60–62° (20 mm), λ_{max}^{MeOH} 285 mμ (ε *ca.* 95).[40]

Anal. Calcd for $C_3H_5FN_2O_5$: C, 21.44; H, 3.00; F, 11.30; N, 16.66; ethoxyl, 26.8; NO_2, 54.7. Found: C, 21.55; H, 2.92; F, 10.61; N, 16.12; ethoxyl, 25.3; NO_2, 50.1.[41]

2,2,2-Trifluoroethyl Fluorodinitromethyl Ether (XIV).—A solution of sodium trifluoroethoxide was prepared by dissolving 6.9 g of sodium in 100 ml of hot trifluoroethanol and cooled to *ca.* 5° with the gradual addition of 25 ml of dimethyl sulfoxide to keep the mixture stirrable. Fluorotrinitromethane (34 g) was added with stirring. The mixture was stirred 5 hr at 20–25° and filtered through a sintered-glass funnel (11 g of sodium nitrite was obtained), and the filtrate was poured into cold dilute sul-

(37) Product Data Sheet PD-TA-85413A, 9-15-1958, Product Development Department, General Chemical Division, Allied Chemical Corp., New York, N. Y.

(38) The purpose of this concentration step was to remove most of the methanol carried in with the starting material (methanol wet for desensitizing purposes), which otherwise caused the "flashes of blue fire" mentioned above.

(39) A lower melting polymorph of mp *ca.* 0° exists. If seed crystals are not available, the initial crystallization may require cooling to −70° and extensive scratching.

(40) The material decomposed in methanol at a measurable rate with the appearance of characteristic nitrous acid (or methyl nitrite) "fingerprint" absorption centering around 350 mμ.

(41) Determined as nitrite by its absorption at 354 mμ by D. J. Glover of this laboratory; the accuracy of the method has not been established.

furic acid. This was extracted with methylene chloride, the extract was dried and freed from solvent, and the residue was washed twice with water and dried over magnesium sulfate. Distillation of the oil afforded 25 g of XIV (55.3%), bp 44–45° (15 mm).

Anal. Calcd for $C_3H_2F_4N_2O_5$: N, 12.62; F, 34.22. Found: N, 12.34; F, 33.84.

Fluorodinitromethyl Azide (XV).—To a solution of 85 g of fluorotrinitromethane in 175 ml of dimethylformamide was added, at −15 to −20° and over a period of 10–15 min, 40 g of sodium azide. The mixture was stirred 2 hr at −15 to −20° (*Caution! at higher temperatures the reaction may get out of hand*) and then poured into ice–water (strong gassing). The product was extracted into methylene chloride, the solvent was removed at a temperature below 65°, and the residue was washed with water, dried, and fractionated at 40 mm of pressure. At *ca.* 40°, 31.5 g of crude XV containing *ca.* 10% starting material distilled over (yield *ca.* 34%). Refractionation at 60 mm (bp 45°) gave a material which appeared to be pure by glpc (silicon oil on Teflon column), but which exhibited a weak band in the 1700-cm^{-1} region of the infrared spectrum which suggested the presence of an impurity. The spectrum also showed a strong azide band at 2200 cm^{-1} in addition to the usual nitro bands at 1325 and 1610 cm^{-1}.

Fluorodinitromethyl azide decomposes slowly at room temperature and should be handled with care. Further characterization and reactions of this material will be described in a subsequent paper.

Difluorodinitromethane (XVI).—A 500-ml, four-necked flask was fitted with a stirrer, thermometer, and a vented addition funnel whose stem extended almost to the bottom of the vessel. The fourth neck was connected to a cold trap held at −70° during the experiment. The system was purged with a slow stream of dry nitrogen through the vent of the addition funnel, the flask was charged with 35 g of anhydrous potassium fluoride and 250 ml of sulfolane, and the mixture was heated to 150° for 15 min and allowed to cool to 95°. At this temperature, 50.7 g of fluorotrinitromethane was added over a period of 1.5 hr; the mixture was stirred an additional 0.5 hr at 100° and allowed to cool. The trap contents were dried over magnesium sulfate and were shown by glpc and by comparison of the infrared spectrum with that of a sample prepared by the method of Mitsch[27] to be essentially pure XVI, yield 25 g (58.7%).

2-Fluoro-2,2-dinitroethanol (VII) by FTM Reduction.—Methanol (90 ml) and 42 ml of 30% aqueous hydrogen peroxide were mixed at 0° in a 500-ml, three-neck flask fitted with stirrer, thermometer, and vented addition funnel. A solution of 14.5 g of sodium hydroxide in 70 ml of water was prepared and 1 ml of this was added at −5 to −10°. At the same temperature, 30 ml of 36–37% aqueous formaldehyde solution was added gradually (exotherm) followed by 50 g of fluorotrinitromethane. With the temperature kept at −5 to −10°, the remainder of the sodium hydroxide solution was added over a 30-min period; the yellow solution was then stirred an additional 15 min while the temperature was allowed to rise to 0°.

Dilute sulfuric acid (equivalent to 5 ml of concentrated H_2SO_4) was added dropwise to the reaction mixture with the temperature maintained at 0° until, toward the end of the addition, a strong exotherm raised it to 10–15°. After saturation of the reaction mixture with sodium chloride, it was extracted with one 100-ml and two 50-ml portions of methylene chloride and the extracts were dried and freed from solvent. Vacuum fractionation of the residual oil gave 41.3 g VII (90.6%) of excellent purity (glpc), bp 55° (0.5 mm).

Anal. Calcd for $C_2H_3FN_2O_5$: N, 18.20; F, 12.33. Found: N, 18.51; F, 12.01.

Fluorodinitromethane (X) by FTM Reduction.—To a solution of 5 g of fluorotrinitromethane in 10 ml of methanol was added dropwise at −10° a mixture of 6.7 g of 30% hydrogen peroxide and 3.3 g of potassium hydroxide in 15 ml of methanol. A thick yellow precipitate formed (efficient stirrer necessary). The mixture was poured into ice-cold dilute sulfuric acid, the resulting clear solution extracted with methylene chloride, the extracts dried, and the solvent distilled off through a Vigreaux column. The residue on fractionation gave 1.5 g (41%) of crude X. The product was identical with, although less pure than, the material obtained as a by-product in the aqueous fluorination of potassium ethyl dinitroacetate.

Registry No.—I, 17003-70-2; II, 17003-71-3; III, 13214-58-9; IV, 17003-25-7; V, 15895-14-4; VI, 15895-15-5; VII, 17003-75-7; VIII, 17003-76-8; IX, 17003-77-9; X, 7182-87-8; XI, 17003-79-1; XII, 17003-80-4; XIII, 17021-83-9; XIV, 17003-81-5; XV, 17003-82-6; XVI, 1185-11-1; $FC(NO_2)_3$, 1840-42-2.

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Aqueous Fluorination of Nitronate Salts[1]

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The fluorination of aqueous solutions of nitronate salts gave *gem*-fluoronitro compounds. The following compounds were synthesized by this reaction: fluorotrinitromethane, 1-fluoro-1,1-dinitroethane, 1-fluoro-1,1-dinitropropane, 2-fluoro-2,2-dinitroethanol, 1-fluoro-1-nitroethane, and 1-fluoro-1-nitropropane.

Although many examples of the direct chlorination and bromination of nitronate salts to give α-halonitro compounds are known,[2] only indirect methods have been reported for fluorination. Perchloryl fluoride has been used to convert *gem*-nitronitronate salts[3] and simple secondary nitronate salts[4] into the corresponding fluorine derivatives, but attempts to apply this reaction to simple primary nitronate salts were unsuccessful. Perfluoropiperidine has also been used as a fluorinating agent to prepare 2-fluoro-2-nitropropane.[5]

The present investigation concerns the preparation of fluoronitro compounds by the direct fluorination of aqueous solutions of nitronate salts, under conditions similar to those generally used for chlorination and bromination of nitronate salts. Although the fluorination of sodium hydroxide in aqueous solution is the standard

(1) This work was supported by the Office of Naval Research.

(2) P. Noble, Jr., F. G. Borgardt, and W. L. Reed, *Chem. Rev.*, **61**, 19 (1964).

(3) M. J. Kamlet and H. G. Adolph, *J. Org. Chem.*, **33**, 3073 (1963).

(4) H. Shechter and E. R. Robinson, Jr., *ibid.*, **25**, 175 (1960).

(5) R. E. Banks and O. E. Williamson, *Chem. Ind.* (London), 1864 (1964).

method of preparing oxygen difluoride,[6] this technique has only recently been shown to be applicable to organic substituents with the fluorination of urea,[7] and, subsequently, other nitrogenous compounds such as alkyl carbamates,[8] sulfamides,[9] and cyanamide.[10]

The fluorinations were conducted simply by bubbling fluorine diluted with nitrogen into aqueous solutions of the nitronate salts. Salts of terminal *gem*-dinitro compounds and of nitroform gave high yields of the corresponding fluoronitro compounds. Thus, the sodium salt of nitroform gave a 92.3% yield of fluorotrinitromethane, bp 81–82°. Similarly, the salts of 1,1-dinitroethane and 1,1-dinitropropane gave 1-fluoro-1,1-dinitroethane and 1-fluoro-1,1-dinitropropane in yields of 82 and 70%, respectively. The fluorination of the salt of 2,2-dinitroethanol[11] gave 2-fluoro-2,2-dinitroethanol in 84% yield. The same yield was obtained when this salt was prepared *in situ* by the addition of sodium hydroxide to a solution of 2,2-dinitro-1,3-propanediol; the liberated formaldehyde did not interfere with the fluorination. 1-Fluoro-1,1-dinitro-

$$HOCH_2C(NO_2)_2CH_2OH \xrightarrow{OH^-} HOCH_2C(NO_2)_2^- + CH_2O$$

$$\downarrow F_2$$

$$HOCH_2C(NO_2)_2F$$

ethane, 1-fluoro-1,1-dinitropropane, and 2-fluoro-2,2-dinitroethanol were prepared previously using perchloryl fluoride as the fluorinating agent.[3]

The aqueous fluorination technique was less satisfactory as a preparative method when salts of simple mononitroalkanes were used as starting materials. The sodium salts of nitroethane and 1-nitropropane gave 1-fluoro-1-nitroethane and 1-fluoro-1-nitropropane in yields of 5.5 and 14%, respectively. The products were contaminated by large amounts of the unsubstituted nitroalkanes and were isolated by gas chromatography. The yields were much more sensitive to reaction conditions than those for the fluorination of *gem*-nitronitronate salts. For example, when the rate at which fluorine was introduced into a solution of the sodium salt of 1-nitropropane was increased threefold, only 1-nitropropane was isolated, although the fluorine was still consumed smoothly. The yields can, no doubt be improved if the reaction parameters are varied systematically. Simple 1-fluoro-1-nitroalkanes have not been reported previously.

The acid-forming side reaction that results in low yields of fluorinated mononitro compounds appears to be the fluorination of hydroxide ion; the pK_a values of mononitro compounds exceed those of the corresponding terminal *gem*-dinitro compound by about 3 units.[2]

The nmr spectral data for the fluoronitro compounds are shown in Table I. The ^{19}F septet observed for fluorotrinitromethane indicates coupling to three nitrogens. The fact that the nitrogen quadruple effect does not obscure the coupling indicates that the electric fields surrounding the nitrogen nucleus are highly symmetrical.[12] Coupling to nitrogen is also evident in the ^{19}F spectra of 1-fluoro-1,1-dinitroethane and 1-fluoro-1,1-dinitropropane, but not in that of 2-fluoro-2,2-dinitroethanol. The hydroxyl of the latter thus distorts the field around the nitrogens enough to prevent observable coupling.

Infrared spectra are described in the Experimental Section.

TABLE I

NMR DATA[a]

Compd	Proton	Fluorine
$FC(NO_2)_3$	...	φ 86.3 septet
		J_{F-N} = 9.8 cps
$FC(NO_2)_2CH_3$	δ 2.47 d	φ 97.6 m
	J_{HF} = 17.7 cps	(>7 lines)
$FC(NO_2)_2CH_2CH_3$	δ 1.17 t (CH_3)	φ 106.3 m
	J_{HH} = 7.3 cps	(>9 lines)
	δ 2.83 d, q (CH_2)	
	J_{HH} = 7.3 cps	
	J_{HF} = 19.7 cps	
$FC(NO_2)_2CH_2OH$	δ 3.97 t (OH)	φ 111.3 t
	J_{HH} = 7.0 cps	J_{HF} = 15 cps
	δ 5.80 d, d (CH_2)	
	J_{HH} = 7.0 cps	
	J_{HF} = 15.9 cps	
$FCH(NO_2)CH_3$	δ 1.88 d, d (CH_3)	φ 144.2 d, q
	J_{HF} = 21 cps	$J_{HF_{gem}}$ = 51 cps
	J_{HH} = 6.3 cps	$J_{HF_{vic}}$ = 21 cps
	δ 5.84 d,q (C—H)	
	J_{HF} = 51 cps	
	J_{HH} = 6.3 cps	
$FCH(NO_2)CH_2CH_3$	δ 5.75 d,t (CH)	φ 149.3 d, t
	J_{HF} = 51 cps,	$J_{HF_{gem}}$ = 54 cps
	J_{HH} = 5 cps	$J_{HF_{vic}}$ = 23 cps
	δ 2.20 d,d,q (CH_2)	
	J_{HF} = 22 cps	
	δ 1.09 t (CH_3)	
	J_{HH} = 7.5 cps	

[a] Abbreviations used are d = doublet, t = triplet, q = quartet, m = symmetrical multiplet.

Experimental Section

General.—Fluorinations were conducted in a glass, standard taper, three-necked flask fitted with a mechanical stirrer, a glass tube extending below the liquid level used as a gas inlet, and a standard taper thermometer well with an opening for gas exit. Standard fluorine-handling hardware[13] was used and the fluorine was diluted threefold with nitrogen. Exit gases were vented through an aqueous potassium iodide trap. Safety shielding is strongly recommended because of the potentially explosive nature of the products. Particular care should be exercised in handling 2-fluoro-2,2-dinitroethanol to prevent contact with the skin; painful inflamation can result.

Fluorotrinitromethane.—A solution prepared from 78.5 g (0.50 mol) of nitroform and 20.0 g (0.50 mol) of sodium hydroxide in 700 ml of water was fluorinated at 0–5°; 0.50 mol of fluorine was absorbed over a 1.5-hr period. The mixture was saturated with sodium chloride. The lower layer was separated, dried over sodium sulfate, and distilled to give 78 g (92.3% yield) of colorless liquid: bp 81–82°; $n^{25}D$ 1.3930.

Anal. Calcd for CFN_3O_6: C, 7.1; H, 0.0; F, 11.2, N, 24.9. Found: C, 7.0; H, 0.1; F, 11.0, N, 24.6.

The infrared spectrum consisted of the following peaks (μ): 3.36(w), 3.45(w), 3.78(w), 3.88(w), 6.19(vs), 7.38(w), 7.72(vs), 8.20(w), 9.90(w), 11.20(w), 12.55(vs).

(6) D. M. Yost, "Inorganic Synthesis," Vol. I, H. S. Booth, Ed., McGraw-Hill Book Co., Inc., New York, N. Y., 1939, p 109.

(7) V. Grakauskas, Abstracts, the 140th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1961, p 23 M.

(8) V. Grakauskas, Third International Fluorine Symposium, Munich, Sept 1965; R. E. Banks, R. N. Haszeldine, and J. P. Lalu, *J. Chem. Soc., Sect.* C, 1514 (1966).

(9) R. A. Wiesboeck and J. K. Ruff, *Inorg. Chem.*, **5**, 1629 (1966).

(10) M. D. Meyers and S. Frank, *ibid.*, **5**, 1455 (1966).

(11) H. Feuer, G. B. Backman, and J. P. Kispersky, *J. Amer. Chem. Soc.*, **73**, 1360 (1951).

(12) L. M. Jackman, "Applications of Nuclear Magnetic Resonance in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, p 73.

(13) Allied Chemical Corp., Data Sheet PD-TA-85413A.

1-Fluoro-1,1-dinitroethane.—A solution of 20.0 g (0.50 mol) of sodium hydroxide and 60.0 g (0.50 mol) of 1,1-dinitroethane in 300 ml of water was fluorinated at 0–5° with 0.5 mol of fluorine over a 2-hr period. The product was extracted with two 75-ml portions of methylene chloride and the solution was dried over sodium sulfate and distilled to give 57 g (82% yield) of colorless liquid: bp 42–43° (30 mm); $n^{25}D$ 1.3960.

Anal. Calcd for $C_2H_3FN_2O_4$: C, 17.4; H, 2.2; F, 13.8, N, 20.3. Found: C, 17.2, H, 2.1; F, 13.5; N, 20.1.

The infrared spectrum consisted of the following peaks (μ): 3.3(w), 3.4(w), 3.45(w), 6.25(vs), 6.98(m), 7.2(s), 7.37(w), 7.55(s), 7.83(s), 8.60(s), 8.90(s), 10.35(w), 11.4(w), 11.75(s), 13.05(s).

1-Fluoro-1,1-dinitropropane.—A solution of 13.6 g (0.10 mol) of 1,1-dinitropropane and 4.0 g (0.10 mol) of sodium hydroxide in 300 ml of water was fluorinated at 0–5°, using 0.1 mol of fluorine in 45 min. The product was extracted with three 30-ml portions of methylene chloride, dried, and distilled to give 9.5 g (70% conversion) of colorless liquid: bp 43–44° (25 mm); $n^{25}D$ 1.4050.

Anal. Calcd for $C_3H_5FN_2O_4$: C, 23.7; H, 3.3; F, 12.5; N, 18.4. Found: C, 23.6; H, 3.3; F, 12.1; N, 17.8.

Unreacted 1,1-dinitropropane, 1.4 g, was recovered from the distillation residue.

The infrared spectrum showed the following bands (μ): 3.3(w), 3.37(w), 3.44(w), 6.26(vs), 6.82(w), 6.98(w), 7.17(w), 7.30(w), 7.53(m), 7.64(m), 8.00(w), 8.73(w), 9.18(m), 9.75(m), 10.21(w), 11.82(s), 12.39(s), 12.90(m).

2-Fluoro-2,2-dinitroethanol.—A solution of 20 g (0.5 mol) of sodium hydroxide in 100 ml of water was added dropwise at 0–5° to a solution of 83 g (0.5 mol) of 2,2-dinitro-1,3-propanediol in 400 ml of water. The solution was fluorinated at 0–5° with 0.5 mol of fluorine over a 2.5-hr period. The solution was then saturated with sodium chloride and was extracted with four 100-ml portions of methylene chloride. The methylene chloride solution was dried over sodium sulfate and distilled to give 65 g (84% yield) of colorless liquid: bp 38–39° (0.1 mm); $n^{25}D$ 1.4430.

Anal. Calcd for $C_2H_3FN_2O_5$: C, 15.6; H, 1.9; F, 13.0; N, 18.2. Found: C, 15.5; H, 2.0, F, 13.0, N, 18.1.

The infrared spectrum showed the following peaks (μ): 2.8 (s); 2.9(s), 3.4(w), 3.43(w), 6.25(vs), 6.93(m), 7.4(w), 7.6(s), 7.95(w), 8.2(w), 9.3(vs), 10.0(m), 10.95(w), 11.45(w), 11.79(s), 12.55(vs), 13.20(w).

1-Fluoro-1-nitroethane.—Nitroethane (41.2 g, 0.55 mol) was dissolved in a solution of 22 g (0.55 mol) of sodium hydroxide in 70 ml of water. The solution was diluted to 650 ml and was reacted with 0.55 mol of fluorine over a 5-hr period at 0–5°. The product was extracted with three 50-ml portions of methylene chloride, dried, and distilled to give 14 g of colorless liquid, bp 22–23° (25 mm). Analysis by gas chromatography (4 ft × 3/16 in. column of 5% diethylene glycol adipate on Chromosorb P, 60°, He flow 50 cc/min) showed the distillate was an 80:20 mixture of nitroethane and 1-fluoro-1-nitroethane (5.5% yield). An analytical sample was isolated by gas chromatography.

Anal. Calcd for $C_2H_4FNO_2$: C, 25.8; H, 4.3; N, 15.0, F, 20.4. Found: C, 25.4; H, 4.4; N, 14.5; F, 20.0.

The infrared spectrum showed the following bands (μ): 3.40(w), 6.34(vs), 6.91(m), 7.18(m), 7.32(m), 7.42(m), 7.63(w), 8.63(s), 8.82(m), 9.47(m), 10.94(w), 11.60(w).

1-Fluoro-1-nitropropane.—The above procedure starting with 49 g (0.55 mol) of 1-nitropropane gave 32 g of distillate, bp 33–35° (25 mm), which was found by gas chromatography to consist of 75% 1-nitropropane and 24% of 1-fluoro-1-nitropropane (14% yield).

Anal. Calcd for $C_3H_6FNO_2$: C, 33.6; H, 5.6; N, 13.1; F, 17.7. Found: C, 33.2; H, 5.8; N, 12.7; F, 17.4.

Registry No.—Fluorotrinitromethane, 1840-42-2; 1-fluoro-1,1-dinitroethane, 13214-58-9; 1-fluoro-1,1-dinitropropane, 17003-25-7; 2-fluoro-2,2-dinitroethanol, 17003-75-7; 1-fluoro-1-nitroethane, 17003-27-9; 1-fluoro-1-nitropropane, 17003-28-0.

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Reactions of Phosphorus Compounds. XVII. Reactions of Cyclopropylmethyl and Certain C_4-Triphenylphosphonium Salts

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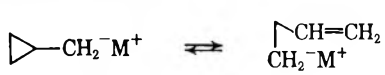
Certain reactions of cyclopropylmethyltriphenylphosphonium bromide were examined. No products derived from ring opening were found. It was shown that no equilibration exists between the ylide **4** and an acyclic isomer, **5**. No cyclopropane derivatives were detected in the reactions of crotyl- or 3-butenyltriphenylphosphonium halides under basic conditions. No products attributable to ring opening were observed in the reactions of cyclobutyltriphenylphosphonium bromide. Preparations are described for *o*-hydroxybenzylidenecyclobutane, benzylidenecyclobutane, and 1-cyclopropyl-2-phenylethylene. Also prepared were cyclobutyl-, 3-butenyl-, crotyl-, and cyclopropylmethyldiphenylphosphine oxides. The lithium aluminum hydride reduction of cyclopropylmethyltriphenylphosphonium bromide (**3**) gave triphenylphosphine.

It has been shown[2-4] that the cyclopropylcarbinyl anion (**1**) may exist in reversible equilibrium with the acyclic carbanion **2**. The stability of the acyclic isomer compared with that of the cyclic form is profoundly affected both by the nature of the cation (M^+) and by the polarity of the solvent.[5,6]



1 **2**

In view of Maercker's recent communication[7] we wish to report our work involving cyclopropylmethyltriphenylphosphonium bromide (**3**) and certain other C_4-triphenylphosphonium halides.

The reactions of salt **3** were examined with the thought that the equilibration of the ylide **4** with **5** followed by proton migration to the crotyl ylide **6a–b** was a distinct possibility (Scheme I). Reaction of **4** with benzaldehyde in dimethylformamide (DMF) gave only *cis–trans* mixtures of 1-cyclopropyl-2-phenylethylene (**7a**). Even under conditions expected[4,6] to favor ring opening to the acyclic ylide **5**, the reaction of **4** with benzaldehyde (eq 1)

(1) Taken in part from the M.S. Thesis of T. A. U. in partial fulfillment of the M.S. Degree, June 1967.

(2) J. D. Roberts and R. H. Mazur, *J. Amer. Chem. Soc.*, **73**, 2509 (1951).

(3) M. S. Silver, P. R. Shafer, J. E. Nordlander, C. Ruchardt, and J. D. Roberts, *ibid.*, **82**, 2646 (1960).

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(6) A. Maereker and J. D. Roberts, *ibid.*, **88**, 1742 (1966).

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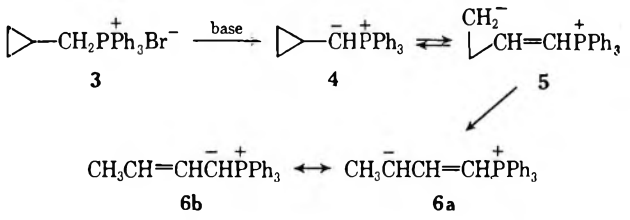
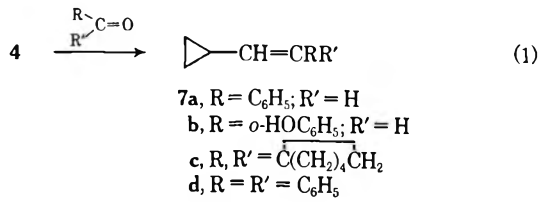
SCHEME I



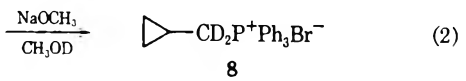
in benzene solvent gave only **7a**, although in lower yield. Similarly, reaction of cyclopropylmethylenetriphenylphosphorane (**4**) and the sodium salt of salicylaldehyde (eq 1) gave only *cis*- and *trans*-1-cyclopropyl-2-(*o*-hydroxyphenyl)ethylene (**7b**). Cyclohexanone and **4** gave cyclohexylidenecyclopropylmethane (**7c**), whereas benzophenone and **4** yielded diphenylmethylenecyclopropylmethane (**7d**) (eq 1). These products attested to the stability of the cyclopropane moiety in these reactions; at no time were products observed which could be attributed to the acyclic zwitterion **5**.



(1)

7a, R = C_6H_5; R′ = H
b, R = *o*-HOC_6H_5; R′ = H
c, R, R′ = $C(CH_2)_4CH_2$
d, R = R′ = C_6H_5

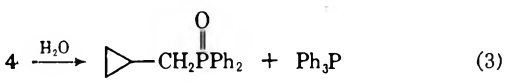
A different approach to the detection of equilibration of **4** and **5** was the refluxing of salt **3** with base followed by quenching of the ylide with anhydrous HBr; however, the reaction of salt **3** with (a) benzyltrimethylammonium hydroxide, (b) NaH, or (c) phenyllithium followed by neutralization with HBr gave only recovered starting material **3**. No signals in the nmr spectra were seen which could be attributed to any ring-opened product. Salt **3** was refluxed for 48 hr in CH_3OD solvent with an equivalent of $NaOCH_3$. No exchange of deuterium for ring protons was detected by nmr although the α protons were 98% exchanged to yield salt **8** (eq 2).



(2)

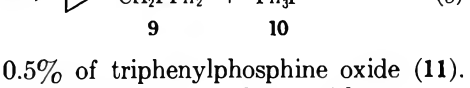
There was no evidence for any acyclic structure in the nmr spectrum.

Decomposition with water of ylide **4** derived from salt **3** gave 99% cyclopropylmethyldiphenylphosphine oxide (**9**) (eq 3). The analytical technique used (vpc) would

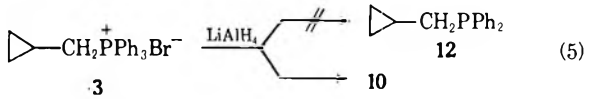


(3)

have detected 0.5% of triphenylphosphine oxide (**11**). Hydrolysis of the phosphonium salt **3**, with aqueous NaOH directly, gave **9** in 97% yield (eq 4). Interestingly, the reduction of the cyclopropylmethyltriphenylphosphonium salt **3** with $LiAlH_4$ gave only triphenylphosphine (**10**) and no cyclopropylmethyldiphenylphosphine (**12**) (eq 5). In view of the fact that the cyclopropylcarbinyl group is not eliminated in the alkaline



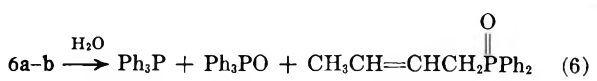
(4)



(5)

hydrolysis of **3**, its preferential elimination by hydride reduction seems anomalous. The explanation probably lies in the nature of the reaction. Hydrolysis of primary phosphonium salts occurs by attack of hydroxyl at the phosphorus moiety[8] resulting in the expulsion of the most stable carbanion,[8,9] whereas the $LiAlH_4$ reduction probably occurs by S$_N$ attack of the hydride ion at the α-carbon atom.[10]

It seemed pertinent to investigate the stability of the cyclopropane moiety by examining the possible cyclic–acyclic equilibrium (**4** to **5**) by approaching the system from the direction of the open-chain isomer. An approach to the cyclic ylide **4** from acyclic precursors might be conceived as coming *via* the initial conversion of ylide **6** into **5**. In an attempt to see if any crossover was possible between the crotyl ylide **6** and the 1-butenyl zwitterion **5**, crotyltriphenylphosphonium chloride (**13**) was refluxed with sodium methylate and O-deuteriomethanol in tetrahydrofuran (THF) solvent. No exchange of the methyl protons for deuterium was detectable by nmr spectroscopy, although the α protons were 26% exchanged after 18 hr. Base-catalyzed conversion of the crotyl salt **13** into the 1-butenyl isomer **14** with benzyltrimethylammonium hydroxide according to the procedure of Keough and Grayson[11] was not successful. Refluxing the crotyl ylide **6** in THF for 18 hr followed by hydrolysis gave a mixture of products (eq 6). No alkyl-

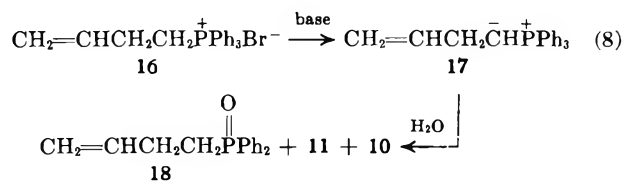


(6)

substituted cyclopropane derivatives were detectable by nmr as indicated by the absence of characteristic[12] nmr signals upfield from 0.85 ppm. The mixture contained four components: 91% triphenylphosphine oxide **11**, 3% triphenylphosphine (**10**), 2% crotyldiphenylphosphine oxide (**15**), and less than 1% an unknown which was shown (by vpc) not to be cyclopropylmethyldiphenylphosphine oxide (**9**). By way of comparison, direct hydrolysis of salt **13** with 20% aqueous solution of NaOH gave 94% **11** and 2% of **10** (eq 7).

(7)

Similarly, the reaction of 3-butenyltriphenylphosphonium bromide (**16**) with base (eq 8) generated the



(8)

(8) C. A. VanderWerf, W. E. McEwen, and M. Zanger, *J. Amer. Chem. Soc.*, **81**, 3806 (1959).
(9) S. T. D. Gough and S. Trippett, *J. Chem. Soc.*, 4263 (1961).
(10) W. J. Bailey and S. A. Buckler, *J. Amer. Chem. Soc.*, **79**, 3567 (1957).
(11) P. T. Keough and M. Grayson, *J. Org. Chem.*, **29**, 631 (1964).
(12) (a) H. M. Hutton and T. Schaeffer, *Can. J. Chem.*, **41**, 2429 (1963); (b) D. S. Patel, M. E. H. Howden, and J. D. Roberts, *J. Amer. Chem. Soc.*, **85**, 3218 (1963); (c) A. Abrahams, S. E. Wiberley, and F. C. Nachod, *Appl. Spectrosc.*, **18**, 13 (1964).

phosphorane **17**. Hydrolysis of **17** after 48 hr of refluxing in THF gave a 72% yield of triphenylphosphine (**10**), 8% **11**, and 3.9% 3-butenyldiphenylphosphine oxide (**18**). However, hydrolysis of salt **16** with aqueous alkali gave a 91% yield of **18**, 3% **11**, and only traces of **10**.

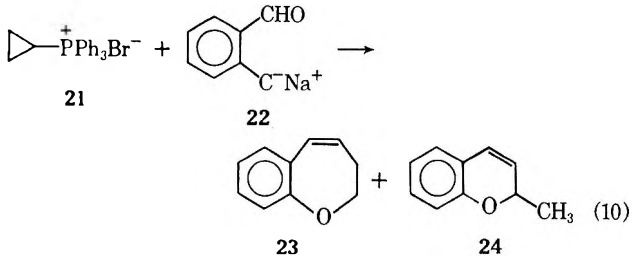
Obviously, aqueous hydrolysis of the heat-treated phosphorane **17** proceeds by a different path from that of the alkaline hydrolysis of salt **16**. A possible explanation is that **17** may equilibrate with the allylic betaine **19** *via* a proton transfer; the betaine **19** in turn may undergo extensive β elimination[13] to **10** and butadiene (**20**) prior to the addition of water (eq 9).

$$\underset{\mathbf{17}}{CH_2{=}CHCH_2\overset{-}{C}H\overset{+}{P}Ph_3} \rightleftharpoons \underset{\mathbf{19}}{CH_2{=}\overset{-}{C}HCH\overset{+}{C}H_2PPh_3} \longrightarrow \mathbf{10} + \underset{\mathbf{20}}{CH_2{=}CHCH{=}CH_2} \quad (9)$$

The reactions of the phosphoranes derived from salts **13** and **16** with carbonyl reagents were also examined. 3-Butenylidenetriphenylphosphorane (**17**) and benzaldehyde gave a mixture of five isomers, presumably geometric isomers of both 1-phenyl-1,4-pentadienes and 1-phenyl-1,3-pentadienes.[14] This was indicated by the hydrogenation of the mixture to a single product, *n*-pentylbenzene. Neither the isomeric mixture nor the hydrogenation product showed any alkylcyclopropane resonance signals[12] in the nmr spectrum. Reaction of phosphorane **6** with benzaldehyde gave a similar isomeric mixture, but it consisted of only three components. This mixture also was shown, by nmr spectroscopy, to contain no cyclopropane derivatives. Hydrogenation yielded one product, *n*-pentylbenzene. The lower number of isomers in the latter reaction was expected since a pair of *cis–trans* isomers with a terminal double bond could be obtained from the ylide **17**; if **17** then rearranges irreversibly to the ylide **6** two less isomers are possible from the ylide **6**.

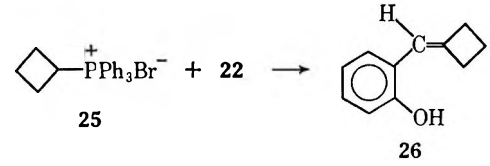
In the reactions examined, the cyclopropane moiety of **3** and **4** shows pronounced resistance to cleavage; efforts to effect cyclization to the ylide **4** from open-chain phosphorane precursors have been unsuccessful to date.

Recently, we disclosed[15] the preparation of 2,3-dihydro-1-benzoxepin (**23**) and 2-methyl-2H-1-benzopyran (**24**) from the reaction of cyclopropyltriphenylphosphonium bromide (**21**) with the sodium salt of salicylaldehyde (**22**) (see eq 10).



(10)

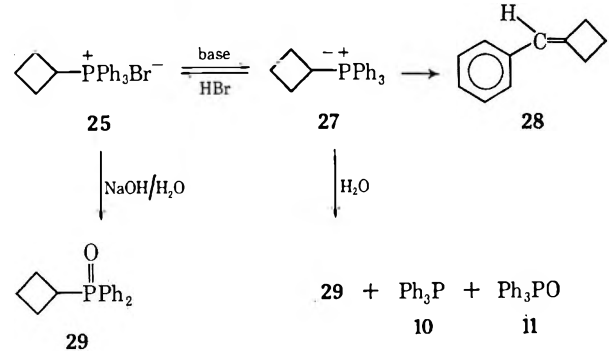
It was deemed of interest to examine certain reactions of the higher homolog of salt **21**, cyclobutyltriphenylphosphonium bromide (**25**). The reaction of salt **25** with **22** gave a 47% yield of *o*-hydroxybenzylidenecyclobutane (**26**), together with some salicylaldehyde (eq 11). No indications of ring-opened products were found.



(11)

In other reactions, also, the cyclobutyl salt **25** gave only unrearranged derivatives. When treated with base, salt **25** gave ylide **27**, which reacted with benzaldehyde to give benzylidenecyclobutane (**28**) (previously prepared by an amine oxide degradation[16]) in 64% yield (Scheme II). Quenching ylide **27** with anhydrous HBr yielded only recovered starting material (pure by tlc). Hydrolysis of salt **25** with excess 20% aqueous NaOH gave only cyclobutyldiphenylphosphine oxide (**29**) in 95% yield, whereas alkaline hydrolysis of salt **25** with 1 equiv of base yielded 79% unreacted starting material, **25**, and the phosphine oxide **29**. However, hydrolysis of ylide **27**, formed from the reaction of **25** with sodium hydride, gave not only **29**, but small amounts of triphenylphosphine (**10**) and triphenylphosphine oxide (**11**) (Scheme II). At no time were rearranged or ring-opened products observed.

SCHEME II



Experimental Section

General.—Infrared (ir) spectra were obtained on a Perkin-Elmer Model 137 spectrophotometer and nuclear magnetic resonance (nmr) spectra on a Varian A60-A spectrometer using tetramethylsilane (TMS) as an internal reference. The chemical shift in parts per million was followed by the splitting pattern (m = multiplet, t = triplet, d = doublet, s = singlet), the number of protons found by integration, the coupling constant (J), and the assignment of the resonance signal when known.

Vapor phase chromatography (vpc) was performed on a Wilkins Aerograph Model A-90P instrument using a 20% Ucon Polar on firebrick (60–80 mesh, 10 ft × 0.25 in.) column, a 15% Carbowax 20M on Chromosorb W (60–80 mesh, 10 ft × 0.25 in.) column, or, more generally, 10% UC-W98 (silicone) on Chromosorb W (DMCS, AW; 60–80 mesh, 10 ft × 0.25 in.) column. The internal standard procedure was used in yield determinations. Ascending thin layer chromatography (tlc) was effected using 2 in. × 8 in. glass plates coated with silica gel G (Brinkmann); the coating's thickness was 0.25 mm for analytical use and 1.0 mm for preparative applications. The solvent systems used in tlc were 20% methanol in chloroform (for phosphonium salts), ethyl acetate (for phosphine oxides), and hexane (for phosphines). In ethyl acetate and hexane the phosphonium salts are immobile, and in hexane both phosphonium salts and the phosphine oxides are immobile. An iodine chamber was used to visualize the spots. The limits of detection by vpc of the

(13) (a) G. Wittig, H. Eggers, and P. Duffner, *Ann.*, **619**, 10 (1958); (b) J. A. Ford and C. V. Wilson, *J. Org. Chem.*, **26**, 1433 (1961).

(14) K. Alder and M. Schumacher, *Ann.*, **571**, 122 (1951), and references cited therein.

(15) E. E. Schweizer, C. J. Berninger, and J. G. Thompson, *J. Org. Chem.*, **33**, 336 (1968).

(16) S. H. Graham and A. J. S. Williams, *J. Chem. Soc., Sect. C*, 655 (1966).

following solid compounds is listed: triphenylphosphine oxide (≥0.25%), other listed phosphine oxides (≥0.05%), and phosphines (≥0.01%). By tlc the limits of detection were phosphonium salts (≥0.01%), phosphines (≥0.01%), and phosphine oxides (≥0.1%).

Unless otherwise indicated, anhydrous conditions were employed in the following procedures; the glassware was oven dried for a minimum of 2 hr. at 120°; and a dry nitrogen atmosphere was used in all anhydrous preparations, with exception of those procedures in which it is specified that a calcium chloride ($CaCl_2$) drying tube was used on top of the reflux condenser. Tetrahydrofuran was distilled from lithium aluminum hydride (and, occasionally, sodium hydride) directly into the previously dried reaction flask. The sodium hydride (50 and 52.6% dispersions in mineral oil), and phenyllithium (2.0 *M* in 75:25 benzene–ether) were obtained from Alpha Inorganics, Inc. Melting points were determined on a Fisher-Johns melting point apparatus and are corrected. Boiling points are uncorrected. Analyses were performed by Micro-Analysis, Inc., Wilmington, Del.

Cyclopropylmethyltriphenylphosphonium Bromide (3).—In a 500-ml, three-necked flask fitted with a sealed stirrer and reflux condenser (topped with a $CaCl_2$ tube) were placed 35 g (0.13 mol) of triphenylphosphine (**10**), 18 g (0.13 mol) of cyclopropylmethyl bromide,[17] and 250 ml of ethyl acetate as solvent. The stirred mixture was refluxed for 5 days, then cooled, and filtered with suction. The white crystalline product **3** (dried overnight in a vacuum oven at 85°) weighed 44 g (83%), mp 183° (lit.[7] mp 175–177°).

Attempted Base-Catalyzed Isomerization of Cyclopropylmethyltriphenylphosphonium Bromide (3).—Into a 100-ml flask fitted with reflux condenser and magnetic stirrer was distilled 50 ml of THF. To the flask were added 4.0 g (0.01 mol) of salt **3** and 0.49 g (0.011 mol) of sodium hydride dispersion. The reaction mixture was refluxed for 48 hr (nitrogen atmosphere). The red suspension was then cooled and quenched by passing gaseous hydrogen bromide through the mixture until it was decolorized to a white suspension. Dissolution of the reaction mixture in 200 ml of hot water and extraction of the resulting solution with two 100-ml portions of chloroform gave a solution which was shown by tlc to contain only one phosphonium salt. Concentration of the extract to 25 ml, drying ($CaCl_2$), and pouring into boiling ethyl acetate (250 ml) with rapid stirring gave 3.8 g (95%) of recovered cyclopropylmethyltriphenylphosphonium bromide (**3**): mp 187–189° (lit.[7] mp 175–177°); nmr and ir spectra were identical with those of an authentic sample. Similar isomerization attempts employing benzyltrimethylammonium hydroxide or phenyllithium yielded only recovered starting material (salt **3**).

Preparation of α,α-Dideuteriocyclopropylmethyltriphenylphosphonium Bromide (8).—In a 50-ml flask fitted with magnetic stirrer and reflux condenser were placed 5 ml of d_1-methanol and 0.23 g (0.01 g-atom) of metallic sodium. After the sodium completely reacted, 4 g (0.01 mol) of salt **3** was added to the solution and the mixture was refluxed for 48 hr, then poured into 100 ml of water which was extracted with three 25-ml portions of chloroform. The organic extract was dried ($CaCl_2$), concentrated to 10 ml, and poured with rapid stirring into 100 ml of boiling EtOAc. After the suspension was cooled, filtration gave 3.85 g (97%) of (α,α-dideuterio)cyclopropylmethyltriphenylphosphonium bromide (**8**), mp 180–182°; nmr showed only the α protons to be exchanged; integration of nmr signals showed exchange to be 98% complete at the α carbon. Thin layer chromatography and nmr spectroscopy showed that only one phosphonium salt was present.

***cis*- and *trans*-1-Cyclopropyl-2-phenylethylene (7a). A.**—Into a three-necked, 500-ml flask fitted with a sealed stirrer and reflux condenser were placed 200 ml of THF, 80 g (0.2 mol) of **3**, and 10 g (0.021 mol) of sodium hydride dispersion. The stirred mixture was refluxed for 48 hr. To the red-orange suspension was then added, slowly, 16 g (0.15 mol) of freshly distilled benzaldehyde. (Addition was made only to the point at which the red ylide color disappeared.) After refluxing for 0.5 hr, the mixture was poured into 300 ml of water, then extracted with three 100-ml portions of ether. The combined organic extracts were dried ($CaCl_2$) and distilled to remove solvents. Short-path distillation, under vacuum, of the high-boiling residue, at a bath temperature of 150° (0.1 mm), gave 16.2 g (75%) of a liquid which was shown (vpc) to contain two products only. A sample of each component was isolated by preparative vpc and shown to be *cis*- and *trans*-1-cyclopropyl-2-phenylethylene (**7a**) in the relative amounts of 66 and 34%, respectively. Triphenylphosphine oxide (**11**) (21 g, 88%) was isolated from the distillation residue.

B.—In a similar reaction (0.05 mol scale), using benzene as solvent, a mixture of *cis*- and *trans*-1-cyclopropyl-2-phenylethylene (2.15 g, 30%) was obtained; the relative amounts of the *cis* and *trans* isomers was 69 and 31%, respectively. The yield of triphenylphosphine oxide was 4.6 g (37%). Identification of all components was effected by comparison of ir and nmr spectra with those of authentic samples (see procedure C).

C.—In an analogous manner of reaction and work-up, 19.9 g (0.05 mol) of salt **3** and 2.28 g (0.05 mol) of sodium hydride dispersion in 175 ml of DMF were mixed with 5.31 g (0.05 mol) of benzaldehyde. After 48 hr, dilution with water, neutralization with HBr, and distillation of the ether extract gave 7.17 g (84%) of a 61:39 mixture of *cis* and *trans* olefin, 1-cyclopropyl-2-phenylethylene (**7a**). Analytically pure samples of each were obtained by preparative vpc. ***trans*-1-Cyclopropyl-2-phenylethylene** had the following properties: bp 60° (0.4 mm); ir (neat), 3050, 1660, 1092, 1015, 955 cm^{-1}; nmr ($DCCl_3$), δ 0.41–0.99 (m, 4, cyclopropyl CH_2's), 1.22–1.86 (m, 1, cyclopropyl-C–H), 5.71 (q, 1, $J_{vinyl\ HH}$ = 9.0 Hz, $J_{vinyl\ H-vinyl\ H}$ = 15.6 Hz, vinylic H), 6.46 (d, 1, $J_{vinyl\ H-vinyl\ H}$ = 15.6 Hz, vinylic H), 7.06–7.40 ppm (m, 5, C_6H_5's). ***cis*-1-Cyclopropyl-2-phenylethylene** had the following properties: bp 58° (0.4 mm); ir (neat), 3060, 1655, 1620, 1075, 1020, 940, 696 cm^{-1}; nmr ($DCCl_3$), δ 0.32–1.01 (m, 4, cyclopropyl CH_2's), 1.58–2.18 (m, 1, cyclopropyl-C–H), 5.05 (q, 1, $J_{vinyl\ H-H}$ = 9.8 Hz, $J_{vinyl\ H-vinyl\ H}$ = 11.3 Hz, vinylic H), 6.35 (d, 1, $J_{vinyl\ H-vinyl\ H}$ = 11.3 Hz, vinylic H), 7.12–7.60 ppm (m, 5, C_6H_5's).

Anal. Calcd for $C_{11}H_{12}$: C, 91.61; H, 8.39. Found (*cis* **20a**): C, 91.44; H, 8.22. Found (*trans* **20a**): C, 91.48; H, 8.22.

1-Cyclopropyl-2-(*o*-hydroxyphenyl)ethylene (7b).—The reaction of 9.94 g (0.025 mol) of **3** with 1.14 g (0.025 mol) of NaH dispersion and 3.60 (0.025 mol) of the sodium salt of salicylaldehyde (in 175 ml of dimethylformamide for 2 days at 80°) gave 2.44 g (36%) of **7b** (91.4% *cis* **7b** and 7.8% *trans* **7b**), bp 76–80° (0.4 mm). *cis* **7b** was isolated by preparative vpc (99% pure): bp 80° (0.4 mm); ir (neat), 3500, 3020, 1650, 1017, 935 cm^{-1}; nmr (neat), δ (−) 0.05–0.49 (m, 4, cyclopropyl CH_2's), 0.87–1.53 (m, 1, cyclopropyl-C–H), 4.66 (q, 1, $J_{H-vinyl\ H}$ = 10 Hz, $J_{vinyl\ H-vinyl\ H}$ = 11 Hz, vinylic H), 5.68 (S, 1, –O–H), 5.97 (d, 1, *J* = 11 Hz, vinylic H), 6.29–7.12 ppm (m, 4, C_6H_4's). *trans* **7b**, collected by preparative vpc, showed ir absorptions (neat) at 3500, 3020, 1660, 1017, and 960 cm^{-1}.

Anal. Calcd for $C_{11}H_{12}O$: C, 82.46; H, 7.55; O, 9.99. Found for **7b** (*cis*–*trans* mixture): C, 82.36; H, 7.77; O, 9.85.

Cyclohexylidenecyclopropylmethane (7c).—The reaction of 4.56 g (0.1 mol) of NaH dispersion; 39.7 g (0.1 mol) of salt **3**, and 9.8 g (0.1 mol) of cyclohexanone (under conditions analogous to those employed in the preparation of **7b** gave 4.6 g (32%) of cyclohexylidenecyclopropylmethane (**7c**): bp 187° (760 mm); $n^{20}D$ 1.4954; ir (neat), 3030 s, 2980 s, 2900 s, 1445 s, 1235 m, 992 s, 805 s cm^{-1}; nmr ($DCCl_3$), δ 0.01–0.78 (m, 4, cyclopropyl CH_2), 1.07–1.4 (m, partially obscured by cyclohexyl CH_2's, cyclopropyl-C–H), 1.4–1.68 (m, 6, cyclohexyl CH_2's), 1.82–2.41 (m, cyclohexyl α-CH_2's), 4.5 (d, 1, *J* = 8.3 Hz, vinylic H).

Anal. Calcd for $C_{10}H_{16}$: C, 88.16; H, 11.84. Found: C, 88.33; H, 11.89.

2-Cyclopropyl-1,1-diphenylethylene (7d).—In a procedure directly analogous to that used in the preparation of **7b**, 13.9 g (0.035 mol) of salt **3**, 1.59 g (0.035 mol) of NaH dispersion, and 6.37 g (0.035 mol) of benzophenone yielded 7.61 g (75%) of 1,1-diphenyl-2-cyclopropylmethylene (**7d**): bp 124–125° (1.0 mm) [lit.[7] bp 95° (0.01 mm)]; $n^{20}D$ 1.6034; ir (neat), 3050 m, 3030 m, 1647 m, 1603 m, 1445 s, 1050 m, 1032 m, 1022 m, 958 s cm^{-1}; nmr ($DCCl_3$), δ 0.37–0.82 (m, 4, cyclopropyl CH_2's), 1.18–1.82 (m, 1, cyclopropyl C–H), 5.33 (d, 1, *J* = 10 Hz, vinylic H), 7.06–7.48 ppm (m, 10, C_6H_5's).

Anal. Calcd for $C_{17}H_{16}$: C, 92.68; H, 7.32. Found: C, 92.50; H, 7.62.

Cyclopropylmethyldiphenylphosphine Oxide (9). A.—A mixture of 50 ml of a 20% aqueous solution of sodium hydroxide and 1 g (0.0025 mol) of cyclopropylmethyltriphenylphosphonium bromide (**3**) was heated to boiling, then cooled, and extracted with three 5-ml portions of $CHCl_3$. The extracts were dried ($CaCl_2$) and concentrated to 5 ml. Dilution with 25 ml of heptane followed by concentration to 10 ml and cooling in a Dry Ice–acetone bath gave 0.62 g (97%) of cyclopropylmethyldiphenylphosphine oxide (**9**) only, mp 131–133° (lit.[7] mp 134–136°).

(17) J. S. Meek and J. W. Rowe, *J. Amer. Chem. Soc.*, **77**, 6675 (1955).

B.—In a dry atmosphere, 2.0 g (0.005 mol) of salt **3** and 0.24 g (0.005 mol) of NaH dispersion were refluxed for 16 hr in 25 ml of THF. Two aliquots (5 ml) were removed. One aliquot was quickly quenched by addition to 25 ml of water; the other was hydrolyzed by the slow addition of water (25 ml) to the ylide. Each aqueous mixture was extracted with 5 ml of $CHCl_3$ and the organic extracts were concentrated to 1 ml. Examination of the contents by vpc (silicone rubber) in each case established the presence of two components of low volatility. Comparison of vpc retention times with those of authentic compounds indicated the components in the mixture to be 99% cyclopropylmethyldiphenylphosphine oxide (**9**) and 1% triphenylphosphine (**10**). Triphenylphosphine oxide (**11**) was not detected; if any was present, it was less than 0.5%. To confirm the identity of the product, half of the remaining ylide solution was hydrolyzed, giving 0.23 g of cyclopropylmethyldiphenylphosphine oxide (**9**) mp and mmp 133–134° (lit.[7] 134–136°). Vpc examination of this hydrolysis mixture showed the same product composition as found in the two previous small-scale hydrolyses.

Base-Catalyzed Deuterium Exchange Experiment with Crotyltriphenylphosphonium Chloride (13).—Into a 100-ml flask fitted with a reflux condenser and magnetic stirrer were placed 50 ml of THF, 3.5 g (0.01 mol) of crotyltriphenylphosphonium chloride (**13**),[13b] 3.1 g (0.1 mol) of d_1-methanol, and 0.54 g (0.01 mol) of sodium methylate, generated *in situ* by reaction of 0.23 g (0.01 mol) of metallic sodium with the deuteriomethanol. The mixture was refluxed (under nitrogen) for 18 hr, then cooled in an ice bath, and filtered. The filtration residue was dried overnight in a vacuum oven at 85°. The yield of product **13**, mp 232–233°, was 3.15 g (90%). Integration of the nmr signals, relative to the phenyl protons, showed that deuterium exchange at the α-methylene carbon atom was 26%. No methyl protons were exchanged (as shown by nmr spectroscopy).

Alkaline Hydrolysis of Crotyltriphenylphosphonium Chloride (13).—Into a 250-ml beaker were placed 20 g (0.057 mol) of salt **13** and 160 ml of a 20% aqueous NaOH solution. The mixture was brought to a boil, cooled, and extracted with two 100-ml portions of chloroform. After the extract was dried ($CaCl_2$), it was evaporated to dryness, yielding a gummy residue which tlc showed to contain three components, one of which was present in trace amounts only. Repeated fractional crystallization (hexane) gave 14.0 g (94%) of triphenylphosphine oxide (**11**) and 0.25 g (2%) of triphenylphosphine (**10**) both of which were identified by ir comparison with authentic compounds.

Examination (vpc) of the concentrated mother liquors showed no cyclopropylmethyldiphenylphosphine oxide (**9**).

Hydrolysis of Crotyltriphenylphosphorane (6a–b). Preparation of Crotyldiphenylphosphine Oxide (15).—Into 125 ml of THF in a 250-ml flask fitted with a reflux condenser and sealed stirrer were placed 17.6 g (0.05 mol) of salt **13** and 2.5 g (0.05 mol) of NaH dispersion. The mixture was refluxed for 18 hr (under nitrogen); then the red ylide was decomposed by the slow addition of 500 ml of water. The aqueous mixture was extracted with two 100-ml portions of chloroform; the extracts were dried ($CaCl_2$) and concentrated to 15 ml. Crystallization by addition of ethyl acetate–hexane gave an amorphous solid, which was shown, by tlc, to contain at least three components. Examination by vpc (silicone rubber column) showed four components. Separation of these by column chromatography (alumina) was not successful. Separation and collection (in the case of the three larger components) of the compounds by preparative vpc in combination with fractional crystallization (hexane) gave 12.6 g (91%) of triphenylphosphine oxide (**11**) (identified by comparison of ir spectrum with that of authentic sample), 0.45 g (3%) of triphenylphosphine (**10**) (identity established by ir), and an unknown component (1%) which was not **9**, **18**, nor cyclobutyldiphenylphosphine oxide (**29**) as shown by different vpc retention times. Crotyldiphenylphosphine oxide (**15**) (0.18 g, 2%) was also found and had the following properties: mp 84–86°; ir (KBr), 3005 w, 2920 w, 1640 w, 1435 s, 1180 s, 1115 s, 995 m, 996 m, 832 m, 743 s, 715 s, 690 s cm.$^{-1}$.

Anal. Calcd for $C_{16}H_{17}OP$: C, 74.98; H, 6.69. Found: C, 74.80; H, 6.43.

Reduction of Cyclopropylmethyltriphenylphosphonium Bromide (3) with Lithium Aluminum Hydride.—Into 100 ml of THF in a three-necked, 250-ml flask fitted with a magnetic stirrer and reflux condenser (topped with $CaCl_2$ tube) were placed 4 g (0.01 mol) of cyclopropylmethyltriphenylphosphonium bromide (**3**) and 0.38 g (0.01 mol) of lithium aluminum hydride. The mixture was stirred at room temperature for 1 day. (A reddish color appeared after 1 hr and persisted for about 12 hr.) The excess hydride was destroyed by slow addition of ethyl acetate to the reaction flask, and the resulting suspension was filtered with suction; the filtrate was stripped of solvent under reduced pressure. The residue was extracted with 100 ml of boiling heptane; the extract was concentrated to 5 ml and cooled in a Dry Ice bath. Filtration yielded 1.33 g (51%) of triphenylphosphine (**10**), mp 79–80°; mixture melting point and ir comparison with an authentic sample confirmed the identity.

3-Butenyltriphenylphosphonium Bromide (16). A.—Into 100 ml of warm water were placed 4.8 g (0.01 mol) of 4-bromobutyltriphenylphosphonium bromide,[18] 1.16 g (0.005 mol) of silver oxide, and a few drops of 1% phenolphthalein alcoholic solution. To the stirred mixture was added slowly 1 *N* acetic acid at such a rate that the color of the indicator was colorless to faint pink. After a half hour no further reaction was observed as indicated by the unchanging color; the warm suspension was filtered with suction. The residue was extracted with two 100-ml portions of hot water. The combined filtrates were extracted with three 100-ml portions of methylene chloride; the extracts were dried ($CaCl_2$) and concentrated to 25 ml; dilution with 200 ml of ethyl acetate gave a precipitate which upon filtration and drying gave 1.2 g (30%) of **16**, mp 228–229° (lit.[19] mp 226–228°).

B.—In a 1-l., three-necked flask fitted with a sealed stirrer and reflux condenser (topped with $CaCl_2$ tube) were placed 600 ml of ethyl acetate, 68 g (0.5 mol) of freshly distilled 4-bromo-1-butene (Aldrich Chemical Co., Milwaukee, Wis.), and 132 g (0.5 mol) of triphenylphosphine. The stirred mixture was refluxed for 48 hr, then cooled, and filtered. The filtration residue was washed with two 100-ml portions of ethyl acetate, then dried in a vacuum oven at 85° overnight. The product **16**, melting at 224–227°, weighed 131.5 g (66%). A recrystallized sample of the salt (from EtOAc–CH_2Cl_2) melted at 227–228° (lit.[19] mp 226–228°): ir (KBr), 1747 m, 1598 m, 1441 s, 1112 s, 994 m cm^{-1}; nmr ($DCCl_3$), δ 2.13–2.78 (m, 2, allylic CH_2), 3.58–4.16 (m, 2, α-CH_2), 4.72–5.28 (m, 2, vinylic C–H), 5.68–5.77 (m, 2, vinylic CH_2), 7.03–8.16 ppm (m, 15, C_6H_5's).

Anal. Calcd for $C_{22}H_{22}BrP$: C, 66.50; H, 5.58; P, 7.77. Found: C, 66.21; H, 5.33; P, 7.58.

Attempted Base-Catalyzed Isomerization of Crotyl- (13) to 1-Butenyltriphenylphosphonium Chloride (14).—Reaction of 3.52 g (0.01 mol) of salt **13** and 1 ml of a 35% methanolic solution of benzyltrimethylammonium hydroxide (Aldrich Chemical Co., Milwaukee, Wis.), in 25 ml of refluxing acetonitrile for 48 hr, according to the method of Keough and Grayson,[11] gave 3.33 g (96%) of recovered starting material **13** (from methylene chloride–ethyl acetate). Identity of the product (only one component by tlc) was confirmed by comparison of its ir spectrum with that of authentic compound.

3-Butenyldiphenylphosphine Oxide (18). A.—Into 100 ml of 20% aqueous solution of sodium hydroxide was placed 4.0 g (0.001 mol) of 3-butenyltriphenylphosphonium bromide (**16**). The mixture was heated to boiling, allowed to cool, and then extracted with three 50-ml portions of chloroform. The organic extracts were dried ($CaCl_2$) and concentrated to 10 ml. Crystallization from ethyl acetate–hexane gave a trace of triphenylphosphine (**10**) (as indicated by tlc) and 0.1 g (3%) of triphenylphosphine oxide (**11**) (mp 156–158°) whose ir spectrum was identical with that of an authentic sample. Also 3-butenyldiphenylphosphine oxide **18** (2.3 g, 91%) was obtained: mp 102–103°; ir (KBr), 1645 w, 1441 m, 1188 m, 1130 m cm^{-1}; nmr ($DCCl_3$), δ 2.08–2.65 (m, 4, $-CH_2-CH_2-$), 4.80–5.22 (m, 2, $-CH=CH_2$), 5.54–6.71 (m, 1, $-CH=CH_2$), 7.30–8.02 ppm (m, 10, C_6H_5's).

Anal. Calcd for $C_{16}H_{17}OP$: C, 74.98; H, 6.69; P, 12.09. Found: C, 74.81; H, 6.57; P, 12.06.

B.—Into a 1-l., three-necked flask fitted with sealed stirrer and a reflux condenser were placed 500 ml of THF, 2.4 g (0.05 mol) of sodium hydride dispersion, and 20 g (0.05 mol) of salt **16**. The mixture was refluxed for 48 hr; then the red-orange mixture was quenched by pouring onto crushed ice (250 g). Extraction of the resulting mixture with six 250-ml portions of ether gave a solution which, by tlc, contained three components. Concentration of the solution to dryness and chromatography over alumina gave 9.5 g (72%) of **10** (mp 78–80°, ir spectrum identical with that of an authentic sample), 1.5 g (8%) of **11** (mp 154–156°), and 0.5 g (3.9%) of **18** (mp 103–105°) identified by comparison of ir

(18) D. W. Dicker and M. C. Whiting, *J. Chem. Soc.*, 1994 (1958).
(19) S. E. Anderson, M.S. Thesis, University of Delaware, 1966.

spectrum with that obtained from the product of the preceding hydrolysis (procedure A).

1-Phenylpentadienes. A.—Into a 500-ml, three-necked flask, fitted with sealed stirrer and reflux condenser, were placed 250 ml of THF, 70.5 g (0.2 mol) of **13**, and 10.10 g (0.21 mol) of sodium hydride dispersion. After refluxing the mixture for 54 hr, 18 g (0.17 mol) of freshly distilled benzaldehyde was added slowly to the red-orange suspension; addition was made to the point at which the red color just faded to creamy white. After the reaction mixture refluxed for an additional 0.5 hr, it was stirred into 300 ml of water, and barely acidified by addition of 48% hydrobromic acid. The organic phase was separated and the aqueous phase was extracted with two 100-ml portions of ether. The combined organic phases were washed with four 150-ml portions of water, dried ($CaCl_2$, $MgSO_4$), and then distilled. The distillate collected between 116° (47 mm) and 108° (18 mm) contained three products by vpc; the over-all yield of the three presumed isomers was 13.5 g (55%). Triphenylphosphine oxide was recovered from the distillation residue, 39 g (82%). A solvent-free sample of the mixture of presumed isomers was obtained by preparative vpc. That the mixture contained no alkyl cyclopropane derivatives was shown by nmr spectroscopy, which showed no absorptions in the cyclopropane[11] region: nmr ($CDCl_3$), δ 1.58–1.83 (m, 3, CH_3), 5.24–6.93 (m, 4, vinyl), 7.00–7.58 (m, 5, aromatic).

Anal. Calcd for $C_{11}H_{12}$: C, 91.67; H, 8.33. Found: C, 91.55; H, 8.39.

B.—In a procedure directly analogous to the preceding one, the reaction of 20 g (0.05 mol) of salt **16**, 25 ml (0.05 mol) of 2.0 *M* phenyllithium, and 4.1 g (0.038 mol) of benzaldehyde gave a mixture of five presumed isomers in a yield of 3.2 g (48%), bp 114° (31 mm) to 85° (4.8 mm). Also isolated was 8 g (76%) of triphenylphosphine oxide (identified by ir spectroscopy). That this mixture also contained no cyclopropane derivatives was shown by the nmr spectrum of a solvent-free sample of the mixture collected by preparative vpc: nmr ($CDCl_3$), δ 1.50–1.81 (m, 3, $-CH_3$), 2.61–2.96 (m, 4, $-CH_2-$), 4.83–6.71 (m, 12, vinyl), 6.95–7.54 ppm (m, 15, aromatic).

Anal. Calcd for $C_{11}H_{12}$: C, 91.67; H, 8.33. Found: C, 91.45; H, 8.33.

***n*-Pentylbenzene. A.**—Low-pressure hydrogenation in methanol (5% Rh on charcoal) of a sample (1.50 g) of the mixture of three isomers obtained from the reaction of salt **13**, sodium hydride, and benzaldehyde gave only one product by vpc. This compound, *n*-pentylbenzene, was obtained in a yield of 1.48 g (97%): nmr (neat), δ 0.70–1.02 (m, 3, CH_3), 1.03–1.72 (m, 6, CH_2's), 2.32–2.68 (m, 2, Ph–CH_2-), 6.88–7.19 ppm (m, 5, C_6H_5's). Identification was confirmed by comparison of its ir spectrum with that of an authentic sample (Sadtler Spectrum No. 23608).

B.—Likewise, hydrogenation of a sample (1.0 g) of the mixture of five isomers obtained for the reaction of salt **16**, phenyllithium, and benzaldehyde gave 0.93 g (89%) of a single compound (according to vpc) which was identified as *n*-pentylbenzene by its ir and nmr spectra; its ir spectrum was identical with that of an authentic sample (Sadtler Spectrum No. 23608).

Cyclobutyltriphenylphosphonium Bromide (25).—The preparation of **25** from 4-bromobutyltriphenylphosphonium bromide[20] and NaH in THF–dimethylformamide (25:1) gave a 67% yield: mp 280–281° (lit.[21] mp 278.5–279.5°); nmr ($DCCl_3$), δ 1.38–3.29 (broad m, 6, CH_2's), 5.26–5.83 (m, 1, –C–H), 7.23–8.25 ppm (m, 15, C_6H_5's).

***o*-Hydroxybenzylidenecyclobutane (26).**—Into a one-necked, 250-ml flask fitted with a short-path distillation head was placed an intimately ground mixture of 20 g (0.05 mol) of salt **25** and 10.8 g (0.075 mol) of salt **22**. The flask was connected to a receiver cooled in Dry Ice and the system was evacuated slowly to 0.5 mm and immersed in a silicone oil bath at 150°. No reaction was observed until the bath was heated to 220°, when yellowish distillate was observed. After 15 min of stirring under vacuum, the melt in the reaction flask evolved no more product. The residue was green-blue, and was found to contain 4.2 g (20%) of unreacted starting material **25** (identified by nmr). Examination of the volatile fraction by vpc showed only salicylaldehyde and one other component. Chromatography (hexane) of the mixture over alumina gave 3.54 g (26%) of salicylaldehyde (identity confirmed by ir spectroscopy), 0.5 g (9%) of triphenylphosphine oxide (**11**) (mp 156–157°, identity confirmed by ir spectroscopy), and 3.0 g (38%) of *o*-hydroxybenzylidenecyclobutane (**26**) (47% yield based on recovered starting material): mp 57–58°; ir (KBr), 3268 s, 2912 m, 1658 w, 1580 m, 1445 s, 1365 m, 1341 m, 1233 s, 936 w, 871 m, 850 m, 749 s cm^{-1}; nmr ($DCCl_3$), δ 1.72–2.24 (m, cyclobutyl CH_2-), 2.53–3.12 (m, 4, cyclobutyl CH_2-'s), 5.49–5.70 (s, 1, –OH), 6.08–6.35 (m, 1, vinyl H), 6.54–7.28 ppm (m, 4, C_6H_5's).

Anal. Calcd for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.39; H, 7.41.

Benzylidenecyclobutane (28).—Into a three-necked, 500-ml flask fitted with a sealed stirrer and reflux condenser were placed 250 ml of THF, 15.8 g (0.04 mol) of salt **25**, and 20 ml (0.04 mol) of phenyllithium solution. The mixture was refluxed for 12 hr, then 4.2 g (0.04 mol) of freshly distilled benzaldehyde was added dropwise. After refluxing for 15 min, the mixture was poured into 250 ml of water. The organic phase was separated and the aqueous phase was extracted with two 100-ml portions of $CHCl_3$. The combined organic phases were washed with two 100-ml portions of water, dried ($CaCl_2$), and distilled at atmospheric pressure to remove the solvent. The concentrate was vacuum distilled through a narrow diameter, 8-in. Vigreaux column at an oil-bath temperature of 150° (0.1 mm). The pot residue was crystallized from EtOAc–CH_2Cl_2 giving 7.0 g (81%) of triphenylphosphine oxide (**11**) (identity established by ir spectroscopy). The yield of the product **28** (95% pure by vpc) was 3.2 g (64%), bp 112–113° (15 mm). A pure sample of benzylidenecyclobutane (**28**) was collected by preparative gas chromatography: $n^{26}D$ 1.5766 [lit.[16] b.p. 114° (15 mm)]; ir (neat), 2930 s, 1668 w, 1475 w, 908 m, 855 m, 760 s, 685 s cm^{-1}; nmr (neat), δ 1.10–1.72 (m, 2, cyclobutyl CH_2), 2.06–2.62 (m, 4, cyclobutyl CH_2's), 5.41–5.62 (m, 1, vinyl H), 6.51–6.82 ppm (m, 4, C_6H_5's).

Anal. Calcd for $C_{11}H_{12}$: C, 91.67; H, 8.33. Found: C, 91.49; H, 8.56.

Attempted Base-Catalyzed Isomerization of Cyclobutyltriphenylphosphonium Bromide (25).—Into a 50-ml flask fitted with magnetic stirrer and reflux condenser were placed 25 ml of THF, 2.0 g (0.005 mol) of salt **25**, and 0.24 g (0.005 mol) of HaH dispersion. The mixture was refluxed for 24 hr; then the red suspension was cooled and quenched by passing gaseous hydrogen bromide into the mixture until it was decolorized to a light tan. The suspension was poured into 150 ml of water acidified with 48% aqueous HBr and extracted with two 100-ml portions of $CHCl_3$. The organic extracts were combined, dried ($CaCl_2$), and evaporated. The gummy residue (containing only one phosphonium salt, by tlc) was crystallized from ethyl acetate–methylene chloride giving 1.85 g (85%) of starting material **25**. The nmr and ir spectra were identical with those of authentic salt **25**.

Cyclobutyldiphenylphosphine Oxide (29). A. Aqueous Alkaline Hydrolysis of Cyclobutyltriphenylphosphonium Bromide (25).—To 50-ml of 20% aqueous solution of sodium hydroxide in a beaker was added 3.4 g (0.0085 mol) of salt **25**. The mixture was heated to boiling and then allowed to cool to room temperature, and the oily globules of product were then recovered by extraction with two 50-ml portions of $CHCl_3$. The extracts were combined, dried ($CaCl_2$), and evaporated to near dryness. Thin layer chromatography showed only one spot. The gummy residue was recrystallized from EtOAc–heptane and dried overnight in a vacuum oven (80°) to give 2.0 g (95% yield) of cyclobutyldiphenylphosphine oxide (**29**) melting at 173–174°: ir (KBr), 3025 m, 2970 m, 1435 m, 1190 s, 1137 s, 918 m, 750 s, 722 s, 750 s cm^{-1}; nmr ($DCCl_3$), 1.68–2.92 (m, 6, CH_2's), 3.00–3.68 (m, 1, C–H), 7.30–7.95 ppm (m, 10, C_6H_5's).

Anal. Calcd for $C_{16}H_{17}OP$: C, 74.98; H, 6.69. Found: C, 74.91; H, 6.62.

Aqueous Hydrolysis of Cyclobutylidenetriphenylphosphorane (27).—In an oven-dried, 100-ml, three-necked flask, fitted with stirrer and reflux condenser, were mixed 3.97 g (0.01 mol) of salt **25**, 0.48 g (0.01 mol) of NaH dispersion, and 50 ml of THF. The stirred mixture was refluxed for 18 hr; then the red-orange suspension was cooled. An aliquot of 5 ml was quenched by slow addition to 20 ml of water. The aqueous mixture was extracted with a 5-ml portion of $CHCl_3$, which was concentrated to 0.5 ml and examined by vpc; vpc showed 94.5% **29**, 4.3% **10**, and 1.2% **11**.

C. Aqueous Hydrolysis of Cyclobutyl Salt 25 with 1 Equiv of NaOH.—From the reaction of 2 g (0.005 mol) of salt **25** with 0.2 g (0.005 mol) of NaOH in 25 ml of water (1 hr, reflux) was ob-

(20) D. W. Dicker and M. C. Whiting, *J. Chem. Soc.*, 1994 (1958).
(21) K. V. Scherer, Jr., and R. S. Lunt, *J. Org. Chem.*, **30**, 3215 (1965).

tained 1.58 g (79%) of recovered salt **25** and cyclobutyldiphenylphosphine oxide (**29**) as the only product (shown by vpc).

Registry No.—**3**, 14799-82-7; **7a** (*cis*), 16958-34-2; **7a** (*trans*), 16958-35-3; **7b** (*cis*), 16958-36-4; **7b** (*trans*), 16958-37-5; **7c**, 16958-38-6; **7d**, 14799-59-8; **8**, 16958-40-0; **9**, 14799-61-2; **10**, 603-35-0; **11**, 791-28-6; **15**, 16540-56-0; **16**, 16958-42-2; **18**, 16958-43-3; **26**, 16958-45-5; **28**, 5244-75-7; **29**, 16958-47-7; **32**, 16958-48-8.

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Reactions of Carbamoyldiphenylphosphine

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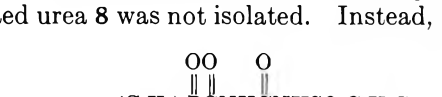
The preparation of carbamoyldiphenylphosphine (**1**) and the derivatives **2**–**7** is described. With *p*-toluenesulfonyl isocyanate a cycloaddition reaction gave the stable oxazetidone **9**.

A recent publication by Papp and Buckler[1] described the preparation of carbamoyldiphenylphosphine (**1**) and its oxide (**2**). We also prepared these compounds as part of a program on the chemistry of isocyanic acid[2-4] and wish to report on several new derivatives.

Isocyanic acid reacted smoothly with diphenylphosphine in degassed benzene to give carbamoyldiphenylphosphine (**1**) in 75% yield. It was necessary to recrystallize the product from degassed benzene under nitrogen, since recrystallization in the presence of air led to phosphine oxide **2**. Attempted sublimation decomposed the product, re-forming diphenylphosphine and presumably isocyanic acid.

Carbamoyldiphenylphosphine underwent a variety of reactions characteristic of tertiary phosphines (Scheme I). Oxidation with hydrogen peroxide produced the phosphine oxide (**2**) in 53% yield. Treatment with sulfur in refluxing benzene gave an 81% yield of the phosphine sulfide (**3**). When 2 equiv of the phosphine were added to nickel carbonyl, carbon monoxide was readily displaced and a 91% yield of dicarbonylbis(carbamoyldiphenylphosphine)nickel (**4**) was obtained. Addition of benzyl iodide to a hot benzene solution of the phosphine resulted in a vigorous reaction and precipitation of the highly insoluble phosphonium iodide (**5**). A similar reaction with benzyl bromide produced the phosphonium bromide (**6**). Treatment of tetrachlorobis(ethylene)diplatinum with excess carbamoyldiphenylphosphine resulted in displacement of ethylene and a 46% yield of dichlorobis(carbamoyldiphenylphosphine)platinum (**7**).

When a benzene solution of the phosphine was treated with 1 equiv of *p*-toluenesulfonyl isocyanate, the expected urea **8** was not isolated. Instead, a 3% yield of



$(C_6H_5)_2PCNHCNHSO_2C_6H_4CH_3$

8

a product tentatively identified as 4-amino-4-diphenylphosphinyl-3-*p*-tolylsulfonyl-1,3-oxazetidone (**9**) was obtained. The cycloadduct **9** was favored over the urea structure **8** by both infrared and mass spectral evidence. A doublet carbonyl band at 1750 and 1780 cm^{-1} is consistent with the four-membered ring in **9**, but not with either of the carbonyl groups in the urea **8**.[5] A major carbon dioxide peak in the mass spectrum of the compound is also easily explained by structure **9**, but not by **8**.

Compounds similar to **9** have been suggested as intermediates in the reaction of isocyanates with disubstituted amides.[6,7] In these cases, loss of carbon dioxide occurred spontaneously and amidines were the sole product. The thermal stability of our product (mp 170° dec) is surprising in view of these results, although stable oxazetidones have recently been prepared from alkyl isocyanates and electronegatively substituted ketones.[8] A doublet carbonyl band was observed in these compounds, but occurred at much higher frequency (1890 and 1935 cm^{-1} for the product of hexafluoroacetone and methyl isocyanate) than that observed for **9**. This increase is probably due to the presence of two electronegative trifluoromethyl groups. The compounds also had an intense CO_2 peak at *m/e* 44 in the mass spectrum, as does **9**.

Experimental Section[9]

Carbamoyldiphenylphosphine (**1**).—A solution of 5.3 g (0.123 mol) of isocyanic acid in 25 ml of degassed benzene was added dropwise to 16.4 g (0.088 mol) of diphenylphosphine. A water bath surrounding the reaction flask kept the temperature below 30°. After the addition was complete, the solution was allowed to stand at room temperature for 2 hr. The precipitated solid (12.0 g., 60% yield) was filtered under nitrogen and recrystallized from degassed benzene under nitrogen. After drying, the sample had mp 118–120° (lit.[1] mp 115–116°).

Anal. Calcd for $C_{13}H_{12}NOP$: C, 68.11; H, 5.28; N, 6.11; P, 13.52. Found: C, 68.12; H, 5.47; N, 6.04; P, 13.79.

The nmr spectrum (acetone-d_6) of the compound showed a series of complex peaks from 7.1 to 7.7 ppm. After addition of deuterium oxide, a DOH peak appeared at 4.0 ppm. The ratio of the aromatic signals to this signal was approximately 5:1.

A second preparation under similar conditions furnished 75% yield of product.

Attempted sublimation of the product resulted in its decomposition. The liquid that formed on the cold finger had an infrared spectrum identical with that of diphenylphosphine.

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(2) F. W. Hoover, H. B. Stevenson, and H. S. Rothrock, *ibid.*, **28**, 1825 (1963).
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(5) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1958, p 214.
(6) H. Ulrich, *Chem. Rev.*, **65**, 369 (1965).
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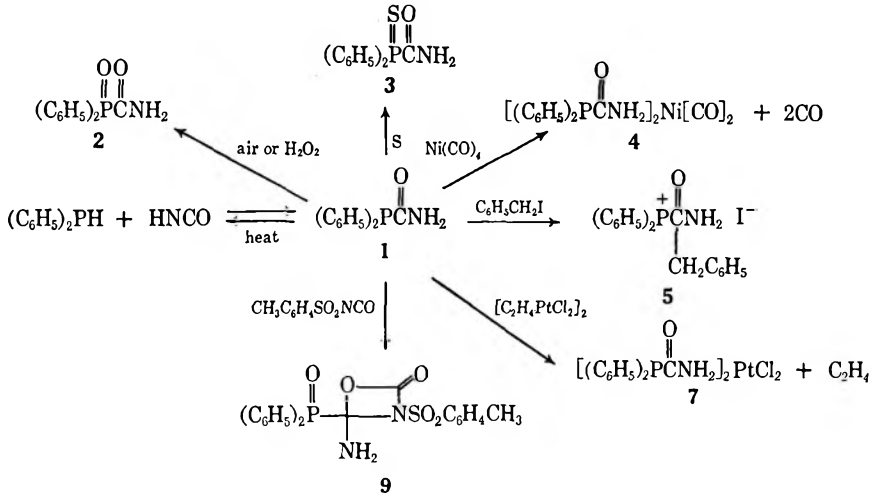
(8) R. J. Shozda, *ibid.*, **32**, 2960 (1967).
(9) All melting points (Fisher-Johns apparatus) are uncorrected. Proton nmr spectra were obtained with Varian A-60 spectrometer.

SCHEME I



Diphenylcarbamoylphosphine Oxide (2).—When an attempt was made to recrystallize carbamoyldiphenylphosphine from benzene in the presence of air, the phospine oxide slowly precipitated, mp 197–200° dec (lit.[1] mp 190–191°). This compound had a strong P=O infrared band at 1180 cm^{-1} which was absent in the spectrum of the parent phosphine.

Anal. Calcd for $C_{13}H_{12}NO_2P$: C, 63.67; H, 4.94; N, 5.71; P, 12.63. Found: C, 64.04; H, 4.93; N, 5.77; P, 12.73.

In the nmr spectrum (DMSO-d_6) of this compound the amide protons appeared as three broad bands at 8.50, 8.75, and 8.93 ppm. The aromatic protons appeared as a series of complex signals between 7.4 and 8.1 ppm. The intensities of these signals were in the expected ratio of 1:5. The amide signals disappeared completely when the sample was shaken with deuterium oxide.

The oxide was prepared more conveniently by addition of 30% hydrogen peroxide (0.6 g of H_2O_2, 17.6 mmol) to a solution of 3.2 g (14 mmol) of carbamoyldiphenylphosphine in 40 ml of acetone. The solution refluxed vigorously for 30 sec and a solid immediately precipitated. After recrystallization from toluene, 2.4 g of product was obtained (53% yield, mp 197° dec) This product had an infrared spectrum identical with that of a sample previously prepared by air oxidation of the phosphine.

Carbamoyldiphenylphosphine Sulfide (3).—To a solution of 5.0 g (21.8 mmol) of carbamoyldiphenylphosphine in 25 ml of benzene was added 2.0 g (62.5 mmol) of sulfur. After the mixture was refluxed for 4 hr, the benzene was removed under vacuum. The residue was washed with 10 ml of carbon disulfide and recrystallized from benzene, furnishing 4.0 g of product, mp 143°. The mother liquor was chromatographed on Florisil to obtain an additional 0.6 g. The total yield of product was 4.6 g (81% yield).

Anal. Calcd for $C_{13}H_{12}NOPS$: C, 59.76; H, 4.63; N, 5.36; P. 11.86; S, 12.27. Found: C, 60.02; H, 4.97; N, 5.31; P, 12.38; S, 12.01.

In the nmr spectrum ($CDCl_3$), the amide protons appeared as a broad band between 7.2 and 7.5 ppm. The aromatic protons appeared as complex signals between 7.6 and 8.1 ppm. On addition of deuterium oxide the amide signal slowly disappeared.

Dicarbonylbis(carbamoyldiphenylphosphine)nickel (4).—To a solution of 1.5 g (6.5 mmol) of carbamoyldiphenylphosphine in 40 ml of benzene was added 0.555 g (3.25 mmol) of nickel carbonyl. As the mixture was heated the phosphine dissolved and a solid began to precipitate as the benzene started to reflux. The heat was then removed, and the solution was stirred for 1 hr while cooling to room temperature. Filtration gave 1.7 g of product (91% yield), mp 171–172° dec.

Anal. Calcd for $C_{28}H_{24}N_2NiO_4P_2$: C, 58.67; H, 4.22; N, 4.90; Ni, 10.24. Found: C, 58.78; H, 4.12; N, 5.03; Ni, 10.23.

The compound could be recrystallized from nitromethane, but developed a pale green color (probably due to Ni^{2+}) when heated in this solvent.

Benzylcarbamoyldiphenylphosphonium Iodide (5).—To a solution of 3.0 g (13.1 mmol) of carbamoyldiphenylphosphine in 70 ml of hot degassed benzene was added 5.2 g (24 mmol) of benzyl iodide. An exothermic reaction caused the benzene solution to reflux for 5 min. The mixture was stirred at room temperature overnight, then filtered to give 4.0 g of the phosphonium salt. The filtrate was refluxed for 2 hr and furnished an additional 1.5 g of the salt. Total yield of product was 5.5 g (94% yield), mp 222° dec.

Anal. Calcd for $C_{20}H_{19}INOP$: C, 53.71; H, 4.28; N, 3.13. Found: C, 53.84; H, 4.67; N, 1.95.

This salt was insoluble in all common organic solvents.

Benzylcarbamoyldiphenylphosphonium Bromide (6).—A procedure similar to that used for the corresponding iodide was followed. From 2.0 g (8.75 mmol) of carbamoyldiphenylphosphine and 5 ml of benzyl bromide, 2.6 g (74% yield) of product was obtained, mp 202° dec.

Anal. Calcd for $C_{20}H_{19}BrNOP$: C, 60.01; H, 4.78; N, 3.50. Found: C, 60.20; H, 4.83; N, 2.61.

Dichlorobis(carbamoyldiphenylphosphine)platinum (7).—A slurry of 0.61 g (1.035 mmol) of tetrachlorobis(ethylene)diplatinum and 1.2 g (5.24 mmol) of carbamoyldiphenylphosphine in 20 ml of benzene was refluxed for 10 min, then stirred at room temperature overnight. The precipitated solid was filtered and recrystallized from a mixture of ethyl acetate and methanol. The product had mp 252–254° dec; a yield of 0.7 g (46.5%) was obtained.

Anal. Calcd for $C_{28}H_{24}Cl_2N_2O_2P_2Pt$: C, 43.10; H, 3.34; N, 3.86; Pt, 26.94. Found: C, 44.00; H, 3.75; N, 2.15; Pt, 27.54.

4-Amino-4-diphenylphosphinyl-3-*p*-tolylsulfonyl-1,3-oxazetidone (9).—To a solution of 3.0 g (13.0 mmol) of carbamoyldiphenylphosphine in 50 ml of benzene was added a solution of 3.84 g (19.5 mmol) of *p*-toluenesulfonyl isocyanate in 20 ml of benzene. No temperature rise was observed during the addition, but the phosphine partially dissolved. The solution was heated to 78° for 5 min and allowed to cool. The benzene was removed under vacuum, and the oily residue was dissolved in absolute ethanol, treated with charcoal, and filtered. On cooling, a solid formed (175 mg, 3% yield) which, after two recrystallizations from ethanol, had mp 170° dec.

Anal. Calcd for $C_{21}H_{19}N_2O_5PS$: C, 57.01; H, 4.33; N, 6.33; P, 7.00. Found: C, 56.92; H, 4.28; N, 6.39; P, 6.81.

The nmr spectrum of this product (pyridine-d_5) had peaks at 9.0 (broad singlet), 6.0–8.8 (complex multiplets), and 2.12 ppm (sharp singlet) in an approximate ratio of 2:14:3. On addition of D_2O the peak at 9.0 ppm exchanged completely.

Registry No.—**1**, 3659-43-6; **2**, 3659-45-8; **3**, 16790-96-8; **4**, 16799-84-1; **5**, 16790-97-9; **6**, 16790-98-0; **7**, 16799-83-0; **9**, 16790-99-1.

α-Aminoarylmethylphosphonic Acids and Diethyl α-Aminoarylmethylphosphonate Hydrochlorides. Aluminum–Amalgam Reduction of Oximes of Diethyl Aroylphosphonates[1]

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A new general procedure has been developed for the synthesis of α-aminoarylmethylphosphonate hydrochlorides and the corresponding acids. Dialkyl aroylphosphonates form oximes (65–100%) when treated with hydroxylamine hydrochloride. Reduction of the oximes in water–ethanol by Al–Hg gave excellent yields (up to 85%) of α-aminoarylmethylphosphonates which were converted into hydrochlorides for purification. Acid hydrolysis of the hydrochlorides gave the corresponding α-aminoarylmethylphosphonic acids (73–88%). Spectral assignments (nmr and infrared) are recorded for the first time for the oximes, α-aminoarylmethylphosphonates, and the α-aminoarylmethylphosphonic acids. Analysis of the data indicates intramolecular hydrogen bonding between the P→O group and the proton on the OH group and NH_2 group in the oximes and α-aminoarylmethylphosphonates, respectively.

Certain α-aminoalkylphosphonic acids may be considered to be phosphorus analogs of aminocarboxylic acids. Although none of the α-aminoalkylphosphonic acids has yet been found in living organisms, they have been found to possess biological activity.[3] Quin[4,5] has found 2-aminoethylphosphonic acid in protozoa, in certain coelenterata, in some fresh-water mollusks, in bovine brain, and in caprine liver.

Present general methods for the preparation of α-aminoarylmethylphosphonic acids and dialkyl α-aminoarylmethylphosphonate hydrochlorides have certain intrinsic limitations. The most recent synthetic route[6] utilizes the Curtius degradation of substituted diethyl phosphonoacetylhydrazides; it is long and depends upon the availability of suitable phosphonoacetic esters. Chambers and Isbell prepared three α-aminoalkylphosphonic acids *via* this route and reported over-all yields from the α-halocarboxylate of 21% for aminomethylphosphonic acids, 66% for 2-aminoethylphosphonic acid, and less than 56% for 1-amino-2-phenylethylphosphonic acid.

This method apparently cannot be used to prepare esters of α-aminoalkylphosphonic acids inasmuch as the reaction sequence calls for boiling the urethan derivative of the dialkyl α-aminoalkylphosphonates in concentrated hydrochloric acid for 2 days which would remove the alkyl groups of the phosphorus esters.

Kabachnik and Medved[7–9] have obtained α-aminoalkylphosphonic acids from both aldehydes and ketones, ammonia, and dialkyl hydrogenphosphonates. Yields were low (8–43%) and the dialkyl α-aminoalkylphosphonates could not be easily separated from the dialkyl α-hydroxyalkylphosphonates which occurred as by-products. Kosolapoff[10] reduced the *p*-nitrophenylhydrazone of diethyl benzoylphosphonate with 2% palladium–charcoal catalyst but was unable to separate the α-aminobenzylphosphonic acid from traces of the aniline salt. Dialkyl α-aminoalkylphosphonates remain difficult substances to prepare to date and α-aminoalkylphosphonic acids have not been realized in high yields.

Results and Discussion

This paper reports the synthesis of a new family of compounds, the oximes **3** of dialkyl aroylphosphonates **2**. Also new methods are given for the syntheses of α-aminoarylmethylphosphonic acids **7** and diethyl α-aminoarylmethylphosphonate hydrochlorides **5** in good yields by aluminum–amalgam reduction of oximes **3** of dialkyl aroylphosphonates **2**. The infrared and nmr spectra of diethyl aroylphosphonate oximes **3**, diethyl α-aminoarylmethylphosphonate hydrochlorides **5**, and α-aminoarylmethylphosphonic acids **7** are reported for the first time. Unique intramolecularly hydrogen-bonded structures, as indicated by the infrared spectra, were found to exist in the oximes **3** of diethyl aroylphosphonates **2** and the diethyl α-aminoarylmethylphosphonate hydrochlorides **5**. The nmr analysis of diethyl α-aminoarylmethylphosphonate hydrochlorides **5** indicated the existence of magnetically nonequivalent alkoxy groups as expected from the presence of an asymmetric center. See Scheme I.

This present synthetic route begins with readily available acid halides and leads to diethyl aroylphosphonates **2**, diethyl aroylphosphonate oximes **3**, diethyl α-aminoarylmethylphosphonates **4**, diethyl α-aminoarylmethylphosphonate hydrochlorides **5**, α-aminoarylmethylphosphonic acid hydrochlorides **6**, and α-aminoarylmethylphosphonic acids **7**. Several members of families **2**, **3**, **5**, and **7** were isolated and characterized. Starting from the diethyl aroylphosphonates **2**, the free α-aminoarylmethylphosphonic acids can be prepared in reasonable yields [29, 45, and 71% (Table I) of pure material was obtained for **7b**, **7d**, and **7h**, respectively] when one isolates the inter-

(1) We very gratefully acknowledge support by the Public Health Service, Grant GM 10367-06. Presented in part at the 155th National Meeting of the American Chemical Society, San Francisco, Calif., April 1968.

(2) Predoctoral candidate 1964–1967; National Science Foundation Trainee, Summer, 1966. This work is abstracted from the thesis (R. T. C.) submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy to the Oklahoma State University.

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(10) G. M. Kosolapoff, *J. Amer. Chem. Soc.*, **69**, 2112 (1947).

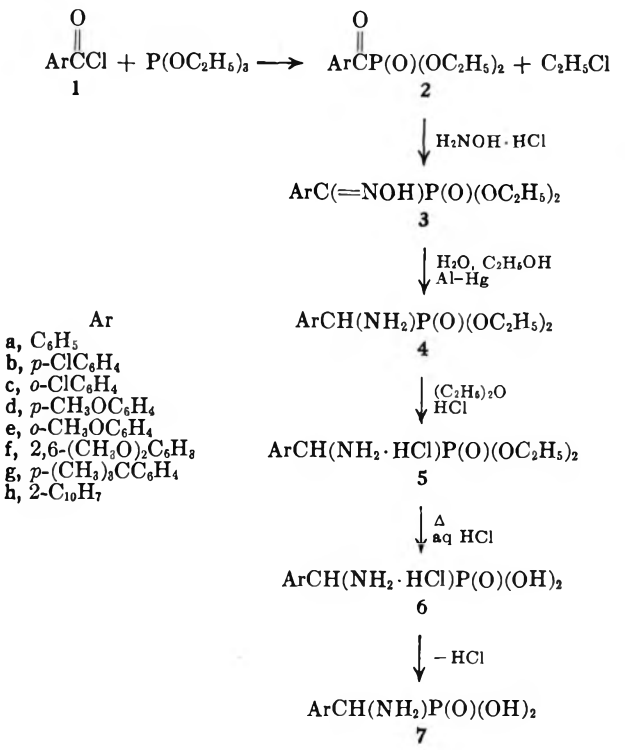
TABLE I

α-AMINOARYLMETHYLPHOSPHONIC ACIDS, $ArCH(NH_2)P(O)(OH)_2$

Acid[a]	Moles of 5 × 10³	Mp, °C of acid	Yield % of acid	Anal, % N Calcd	N Found	P Calcd	P Found
7b	5.79 (5b)	291.3–292.5	72.7	6.32	6.39	13.98	14.16
7d	5.92 (5d)	277.8–278.3	87.5	5.98[b]	5.91	...	...
7h	3.06 (5h)	307.3–308.4	75.9	5.90	5.01	13.06	13.28

[a] Recrystallized from water. [b] The analysis is for the monohydrate.

SCHEME I

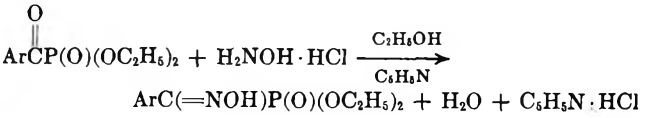


mediates. However, in one case if one does not isolate the intermediate materials, the yield improved. For example, in a study beginning with **2b**, an over-all yield of 66.5% **7b** was achieved.

Yields of 66% (quantitative) were realized in the preparation of the oximes of diethyl aroylphosphonates. The reduction of the oximes to diethyl α-aminoarylmethylphosphonates **4** and subsequent formation of the hydrochlorides **5** were accomplished with yields ranging from 38 to 85%. The hydrolysis of the diethyl α-aminoarylmethylphosphonate hydrochlorides **5** to the free acids gave 73–88% yields of products.

Diethyl Aroylphosphonates 2.—The diethyl aroylphosphonates **2** were prepared from triethyl phosphite and aroyl chlorides **1** utilizing the classical Michaelis–Arbuzov rearrangement as described previously.[11–13] The Experimental Section contains a list of the diethyl aroylphosphonates **2** along with some of their physical properties. The nmr and infrared spectra for some members of **2** have been adequately discussed elsewhere[11–13] and further elaboration will not be included herein.

Diethyl Aroylphosphonate Oximes 3.—White, crystalline oximes **3** can generally be formed from the diethyl aroylphosphonates **2** through reaction with hydroxylamine hydrochloride in pyridine and ethanol (if dialkyl esters other than those from ethanol are desired, the alcohol containing the same alkyl group as the dialkyl



aroylphosphonate employed must be used to prevent transesterification). Yields for the crude oximes **3** are generally near quantitative, and the crude oximes can be used directly in the aluminum–amalgam reduction. The Experimental Section contains a list of the oximes along with some of their physical properties. The proton of the oxime moiety of the diethyl aroylphosphonate oximes is probably slightly acidic.[14]

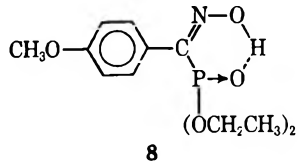
Infrared and nmr spectral data were recorded for the oximes **3**. Inasmuch as **3** is a new family of compounds, no infrared or nmr data have been previously reported. The infrared spectra showed phosphoryl absorptions of 1214–1252 cm^{-1} for **3**. It is widely believed that phosphoryl absorptions between 1200 and 1250 cm^{-1} indicate hydrogen-bonded phosphoryl groups, whereas P→O frequencies from 1250 to 1300 cm^{-1} represent free phosphoryl functions.[11,15–19] In all cases the phosphoryl absorptions in the oximes **3** occurred at longer wavelengths than did the phosphoryl absorptions in the corresponding diethyl aroylphosphonates **2**. The differences for cognomers of the two families varied from 11 to 40 cm^{-1}. No correlation of the shifts of the phosphoryl absorptions with the structures of the compounds was obvious.

Simple oximes in general absorb broadly at 3150–3300 cm^{-1} owing to bonded O–H stretching and near 930 cm^{-1} owing to the stretching of the N–O linkage.[15] The diethyl aroylphosphonate oximes **3** exhibited O–H stretching frequencies of 3104–3208 cm^{-1}, N–O stretching frequencies of 927–933 cm^{-1}, and P–O–CH_2–CH_3 absorptions (CH_3 rocking)[15] at 1163–1171 cm^{-1}.

The infrared spectrum of diethyl *p*-methoxybenzoylphosphonate oxime (**3d**) was obtained both in a KBr pellet and in chloroform solution in order to determine whether the oxime was inter- or intramolecularly hydrogen bonded. By the aid of dilution studies of **3d** in chloroform it was found that the hydroxyl group was

(11) K. D. Berlin and H. A. Taylor, *J. Amer. Chem. Soc.*, **86**, 3862 (1964).
(12) K. D. Berlin, D. M. Hellwege, and M. Nagabhsushanam, *J. Org. Chem.*, **30**, 1265 (1965).
(13) K. D. Berlin and D. H. Burpo, *ibid.*, **31**, 1304 (1966).
(14) Sodium hydroxide titrations (aqueous solutions) of diethyl acetylphosphonate oxime (prepared in the same manner as were the diethyl aroylphosphonate oximes) gave data from which a pK_a of 9.33 was calculated.
(15) N. B. Colthrup, L. H. Daly, and S. E. Wiberley, "Introduction to Infrared and Raman Spectroscopy," Academic Press, New York, N. Y., 1964.
(16) E. M. Popov, M. I. Kabachnik, and L. S. Mayants, *Usp. Khim.*, **30**, 846 (1961); *Russ. Chem. Rev.* (Eng. Transl.), **30**, 362 (1961).
(17) J. P. Phillips, "Spectra-Structure Correlation," Academic Press, New York, N. Y., 1964, p 134 ff.
(18) L. W. Daasch and D. C. Smith, *Anal. Chem.*, **23**, 853 (1951).
(19) D. E. C. Corbridge, *J. Appl. Chem.*, **6**, 456 (1956).

shifted only slightly in position although the intensity was reduced. This suggests the hydrogen bonding is intramolecular as shown by **8**. The variations are



8

within the limits (± 199 cm^{-1}) found for various other related examples of phosphorus compounds in the literature.[20] Miller and coworkers have studied the infrared spectra of dialkyl α-hydroxyalkylphosphonates both in crystalline (mineral oil mull) and in carbon disulfide solution and reported shifts as high as 64 cm^{-1} for P→O and shifts up to 45 cm^{-1} for O–H.[20] These workers concluded that the dialkyl α-hydroxyalkylphosphonates were intramolecularly hydrogen-bonded structures.

The nmr spectra for the oximes **3** are quite similar to those for the diethyl aroylphosphonates **2**. In addition to the aromatic proton absorptions the ethyl groups exhibit a triplet at δ 1.17–1.30 (J = 7 cps, CH_3) and an imperfect quintet (due to H–H and P–H splitting patterns which overlap) at δ 8–4.6 (J = *ca.* 7 cps, CH_2). A broad multiplet (integration showed that this peak represented one proton) is observed in the region of δ 10.1–14.6 for the proton of the oxime moiety.

The chemical shifts of the hydroxyl proton of oximes have recently been studied.[21] This reference[21] lists signals of δ 8.6–13.3 for the hydroxyl proton in various oximes. Two peaks were observed in the spectra of those oximes possessing nonequivalent or *syn* and *anti* oxime groupings. Our observation of a single, broad absorption for the hydroxyl proton in diethyl aroylphosphonate oximes **3** correlates well with the nmr data just mentioned[21] and lends support to the presence of a single intramolecularly hydrogen-bonded structure, **8**, and precludes *syn*- and *anti*-oxime formation.

Aluminum–Amalgam Reduction of Diethyl Aroylphosphonate Oximes 3 to Diethyl α-Aminoarylmethylphosphonates 4. Subsequent Formation of the Hydrochloride Salts 5.—An aluminum–amalgam–ethanol–water mixture easily reduces the oximes **3** of diethyl aroylphosponates under very mild conditions without hydrolyzing the ester function to any noticeable extent. The diethyl α-aminoarylmethylphosphonates **4** can be isolated as the hydrochlorides **5** in yields of 38–85% based on the oximes.

$$\mathrm{ArC(=NOH)P(O)(OC_2H_5)_2 + Al(Hg) + H_2O \xrightarrow{C_2H_5OH} ArCH(NH_2)P(O)(OC_2H_5)_2}$$

Although a few dialkyl α-aminoalkylphosphonates and their salts have been reported previously, no infrared or nmr data have been given. The infrared spectra exhibited a phosphoryl absorption between 1221 and 1258 cm^{-1} which indicated hydrogen bonding. In all cases the phosphoryl absorptions from **5** were lower than that of the corresponding diethyl aroylphosphonate cognomers. Inasmuch as the phosphoryl frequency is influenced both by hydrogen bonding and by the total electronegativity of the substituents on the phosphorus atom, the lowering of the phosphoryl absorption cannot easily be correlated with hydrogen-bonding effects alone.

The hydrochlorides **5** exhibit a peak in the region of 1947–2062 cm^{-1} which is assigned to the $-{}^+NH_3$ moiety. Amino carboxylic acids show an absorption[15] between 2000 and 2200 cm^{-1} which is assigned as a combination band of $-{}^+NH_3$ asymmetric deformation and $-{}^+NH_3$ hindered rotation. Primary amine salts also exhibit a band near 2000 cm^{-1} which is believed to be a combination band of $-{}^+NH_3$ torsional oscillation and asymmetric deformation.[15] The $-{}^+NH_3$ frequency near 2000 cm^{-1} in **5** is believed to be a combination band for this group.

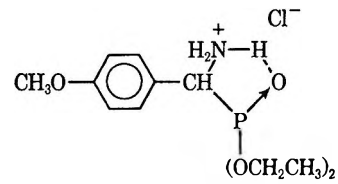
That the diethyl α-aminoarylmethylphosphonate hydrochlorides **5** are intramolecularly hydrogen-bonded structures can be shown by comparison of infrared spectral data of a KBr pellet of the compounds with that of a solution of the same. This study of infrared spectra was done with diethyl α-amino-*p*-methoxybenzylphosphonate (**5d**) and showed only insignificant changes in the $-{}^+NH_3$ and P→O absorptions. Table II gives the infrared spectral data for chloroform solutions of **5d**.

TABLE II

INFRARED ANALYSIS OF CHLOROFORM SOLUTIONS OF **3d** AND **5d** (cm^{-1})

Compd	Concn. of solution, %	N–H	O–H	P→O
3d	5.4	...	3236	1260
3d	1.8	...	3236	1260
3d	0.48	...	3234	1260
5d	1.3	2950	...	1250
5d	0.93	2965	...	1244

The shift of 15 cm^{-1} by the N–H band and the shift of 6 cm^{-1} by P→O are within the variation ± 199 cm^{-1} mentioned previously.[20] The structure for **5d** showing intramolecular hydrogen bonding is illustrated.

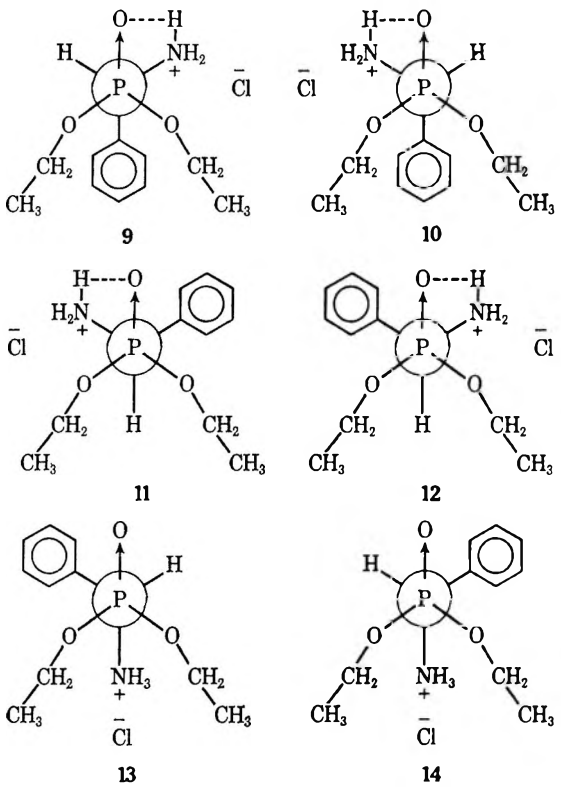


5d

The diethyl α-aminoarylmethylphosphonate hydrochlorides **5** are, consequently, believed to exist as the intramolecularly hydrogen-bonded structures represented by Newman projections **11** [(*R*)-diethyl α-aminobenzylphosphonate hydrochloride (**5a**)] and **12** [(*S*)-diethyl α-aminobenzylphosphonate hydrochloride (**5a**)]. Conformations **9**, **10**, **13**, and **14** are probably higher energy forms which may not be present in high population. In **11** and **12** the aromatic ring lies between the oxygen of the phosphoryl group and an ethoxy group (the least hindered position for the bulkier aromatic function) and the ammonium group lies between an ethoxy group and the oxygen of the phosphoryl group to which it is intramolecularly hydrogen

(20) C. D. Miller, R. C. Miller, and W. R. Rogers, *J. Amer. Chem. Soc.*, **80**, 1562 (1958).

(21) G. C. Kleinspehn, J. A. Jung, and S. A. Studniarz, *J. Org. Chem.*, **32**, 460 (1967).



bonded. Although structures **9** and **10** allow for intramolecular hydrogen bonding, they force the aromatic moiety to a position between two ethoxy groups, and these are expected to be high energy conformations. In structures **13** and **14**, although the aromatic ring lies between the phosphoryl oxygen and an ethoxy group, intramolecular hydrogen bonding between the P→O and $-^{+}NH_3$ groups is not possible.

The nmr spectra for **5** are not so simple as those for families **2** and **3** and exhibit several interesting features. The benzyl proton in **5** occurs as a doublet and is seen at δ 4.7–5.6. The P–C–H splitting pattern generally results in a doublet with a coupling constant of 18 cps [a value of 17 cps is observed for diethyl α-amino-*p*-methoxyphosphonate hydrochloride (**5d**)]. The nmr spectra of dialkyl α-hydroxybenzylphosphonates exhibit a coupling constant of J_{P-C-H} = 13.5 cps for diethyl and dimethyl α-hydroxybenzylphosphonates[22] which are known also to exist as intramolecularly hydrogen-bonded structures.[20] Geminal P–C–H coupling reportedly is related to the electron densities in both the P–C and C–H bonds (and thus dependent upon the substituents on both phosphorus and carbon)[23] and the P–C–H angle.[24] Unfortunately, very little bond-angle data are available for compounds similar to those being studied. It also seems reasonable that the P–C–H coupling constant may vary with the strength of the hydrogen bond that forms in both **5** and the corresponding dialkyl α-hydroxybenzylphosphonates.

The nmr spectra of diethyl α-aminoarylmethylphosphonate hydrochlorides **5** exhibit magnetically nonequivalent ethyl groups. The methylene group (of the alcoholic portion of the molecule) exhibits a multiplet in the region δ 3.5–4.6 in **5** in contrast to the better defined "imperfect" quintet patterns observed for **2** and **3**. The methyl groups of the ethoxy functions give rise to two triplets. These two triplets may give the appearance of a quartet (as in the cases of **5a**, **5e**, and **5f**) when their centers are separated by 7 cps, a sextet (as in the case of **5h**) when their centers are separated by 3.5 cps, or as a multiplet when separations other than 3.5 or 7 cps are realized. These methyl signals show chemical shifts of δ 0.8–1.4.

The intramolecularly hydrogen-bonded structures shown by the Newman projections for (*RS*)-diethyl α-aminobenzylphosphonate hydrochloride (**5a**) conformations (shown previously by **11** and **12**) are the least hindered conformations which also allow for hydrogen bonding. In conformers **11** and **12** one of the ethoxy groups lies nearer the magnetically anisotropic benzene ring than the second ethoxy group. Thus the two ethoxy moieties in **5** experience different magnetic environments and consequently exhibit two triplets. This magnetic nonequivalence found in **5** is likely not a result of "long-range" P–O–C–C–H splitting since this type of splitting generally does not exceed 1.1 cps. Also "long-range" P–O–C–C–H splitting is not observed in the nmr spectra of the similar **2** and **3**.

Magnetically nonequivalent alkoxy groups in phosphorus esters have been reported previously.[25,26] Magnetically nonequivalent alkoxy groups have also been observed in the nmr spectra of racemic dialkyl α-hydroxybenzylphosphonates.[22]

α-Aminoarylmethylphosphonic Acids 7.—The acid salts **6** were obtained through acid hydrolysis of the diethyl α-aminoarylmethoxyphosphonate hydrochlorides **5**. The solution was evaporated to dryness, and the resulting solid was dissolved in a minimum of cold water and boiled until the free white acid began to

$$RCH(NH_2\cdot HCl)P(O)(OC_2H_5)_2 + H_2O \xrightarrow[\Delta]{HCl} RCH(NH_2\cdot HCl)P(O)(OH)_2 \xrightarrow{-HCl} RCH(NH_2)P(O)(OH)_2$$

crystallize. High yields (73–88%) of the free acids were realized (based on **5**). The new α-aminoarylmethylphosphonic acids along with some of their physical properties are listed in Table I.

Infrared spectral data for three acids **7b**, **7d**, and **7h** are characterized by broad diffuse bands from 1800 to 3650 cm^{-1} making it difficult to make definitive assignments in this region. These broad diffuse bands are anticipated in light of data reported for similar compounds.[15–19] Inasmuch as aminomethylphosphonic acid has been shown to exist as a zwitterion,[27] other α-aminoalkylphosphonic acids are expected to exist also as zwitterions. Whether or not this is the case, α-aminoarylmethylphosphonic acids **7** would be expected to show extensive hydrogen bonding which would contribute heavily to the broadness of the absorptions of **7** in the 1800–3650-cm^{-1} region.

Bands in the areas of 1077–1085 and 1193–1270 cm^{-1} also occur in the spectra of **7**. Phosphonic and phosphinic acids generally show a strong absorption at 910–

(22) D. M. Hellwege, Ph.D. Thesis, Oklahoma State University, 1966.
(23) 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, Chapter 8.
(24) M. Gordon, Ph.D. Thesis, University of Pittsburgh, 1965.
(25) T. H. Siddall, III, *J. Phys. Chem.*, **70**, 2249 (1966).
(26) K. D. Berlin, D. H. Burpo, R. U. Pagilagan, and D. Bude, *Chem. Commun.*, **20**, 1060 (1967).
(27) V. Chavane, *Bull. Soc. Chim. Fr.*, **27**, 774 (1948).

1040 cm^{-1} which probably involves the stretching of the P–O bond of the P–O–H linkage.[15] Salts of $R_2P(O)(O^-)$ and $R(H)P(O^-)$ display two strong bands at 1100–1190 and 1000–1075 cm^{-1} which are reported to be a result of symmetric and asymmetric stretch of O←P–O^-.[15] The phosphoryl group in **7** also gives rise to an absorption in the 1200–1300-cm^{-1} region but cannot be definitely assigned since other vibrations occur in the same area. The hydrogen-bonding capabilities of **7** could cause the peaks in the 970–1300-cm^{-1} region to be diffuse creating even greater difficulty in assigning frequencies.

The nmr spectra of the free acids **7** exhibit a multiplet in the region δ 7.2 and 8.4 and is assigned to the ammonium group. Suitable solvents for **7** are lacking and trifluoroacetic acid was used to obtain these nmr spectra. This solvent would protonate a free NH_2 group if $Ar–CH(NH_2)–P(O)(OH)_2$ is the prevailing structure for **7** or would protonate the oxide ion if $Ar–CH(^+NH_3)–P–(O)(O^-)(OH)$ is the actual form. In any case, a signal for the ammonium group would result in the nmr spectra of **7** and would integrate for three protons. Thus the multiplet at δ 7.2 to 8.4 in the nmr spectra cannot be taken as evidence for the existence of **7** as zwitterions even though integration shows three protons for this band. The benzyl proton in **7** occurs as a broad doublet near δ 5.0, and the coupling constant is estimated to be about 16 ± 2 cps.

Nmr spectral investigations of α-aminoalkylphosphonic acids have not been previously reported. The nmr of 2-aminoethylphosphonic acid has been determined in D_2O but exchange with the ammonium protons and POH protons prevented information for these protons.[28] Berlin and Nagabhushanam have investigated the nmr of several organophosphorus acids (no α-aminoalkylphosphonic acids were included).[29] These workers observed a geminal P–C–H coupling constant of 17 cps for the CH_2 group in phenylbenzylphosphinic acid (P–O–H exhibited a peak at δ 10.28). Ferraro and Peppard have also studied the nmr spectra of acidic organophosphorous compounds.[30]

Some preliminary studies on inhibition of growth of certain microorganisms by esters **5a**, **5b**, and **5d** appear in Table III. In all cases where inhibition was observed a fivefold lower concentration of the compound failed to inhibit growth. The concentrations listed are the highest tested. Growth after prolonged incubation was probably due to mutation to resistance rather than to inactivation of the inhibition compound since this varied with the organism for any specific compound.

TABLE III
RESULTS OF GROWTH STUDIES

	Compound					
	5a		5b		5d	
Organism	μg/ml	% I	μg/ml	% I	μg/ml	% I
Micrococcus roseus	850	79	850	100	850	100
Pseudomonas aeruginosa					850	0
Escherichia coli					850	9
Bacillus megaterium					850	19[a]
Alcaligenes species	850	0	850	100[a]	850	14
Arthrobacter species	850	100[a]	850	100[a]	850	77[a]
Sarcina hansenii	850	100	850	86	850	92
Staphylococcus aureua	850	0	850	29	850	18

[a] Inhibition was overcome after prolonged incubation.

Experimental Section

Procedures.—All melting points were corrected and determined with a Thomas–Hoover capillary melting point apparatus. Boiling points were uncorrected. Elemental analyses were performed by the Galbraith Laboratories, Inc., Knoxville, Tenn. Nuclear magnetic resonance spectra were obtained from a Varian Associates Model A-60 spectrophotometer using tetramethylsilane (TMS) as an internal reference.

The infrared spectra were obtained using a Beckman IR-5A recording spectrometer (as films on sodium chloride cells for liquid samples or as potassium bromide pellets where the compounds were solids). Infrared spectra of chloroform solutions of diethyl *p*-methoxybenzoylphosphonate oxime (**3d**) and diethyl α-amino-*p*-methoxybenzylphosphonate hydrochloride (**5d**) were obtained using a rock salt cell having a film thickness of 0.01 mm. The chloroform peaks were eliminated in the spectra by adjustment of a variable wedge rock salt cell until a flat response was obtained. Copies of infrared and nmr data can be obtained from the senior author.

Preparation of Diethyl Aroylphosphonates 2.—The general procedure employed is described. A slight excess of triethyl phosphite [bp 62–64° (24 mm)] was added dropwise to an aroyl chloride (commercially available materials or synthesized from commercially available acids using standard methods) under deoxygenated, anhydrous nitrogen[31] and at such a rate so that the temperature of the reaction mixture did not exceed 40°. When necessary, an ice–water bath was provided to control the temperature of the exothermic reaction. The solutions became yellow while being stirred for 4 hr. Chloroethane was evolved during the course of the reaction. The products were purified by vacuum distillation. Elemental analyses and spectral data were used to confirm the structure of new diethyl aroylphosphonates **2**. In examples where the diethyl aroylphosphonates were known, the comparison of spectral and physical properties with those of authentic samples established identity.

Deviations from the above general procedure were employed with 2-naphthoyl chloride (**1h**) and 2,6-dimethoxybenzoyl chloride (**1f**), both of which were solids. These aroyl chlorides were heated (48° for 2-naphthoyl chloride and 66° for 2,6-dimethoxybenzoyl chloride, *i.e.*, to temperatures just above their melting points) prior to the addition of triethyl phosphite.

Preparation of Diethyl Aroylphosphonate Oximes 3.—A diethyl aroylphosphonate **2** (0.100 mol)[32] was slowly added (dropwise at such a rate so as to maintain the temperature of the slightly exothermic reaction below 30°) to a mixture of 200 ml[32] of absolute ethanol, 9.25 g (0.133 mol[32]—33% excess) of hydroxylamine hydrochloride and 11.85 g (0.150 mol[32]—50% excess) of pyridine. The yellow color of the diethyl aroylphosphonates **2** slowly disappeared [except in the case of diethyl 2,6-dimethoxybenzoylphosphonate (**2f**)] in the course of oxime formation. The mixtures were stirred at room temperature for 72 hr. Evaporation of the ethanol *in vacuo* gave a syrup which was mixed with 75 ml of distilled water. This aqueous mixture was extracted with three 75-ml portions of methylene chloride. The organic layers were combined and dried ($MgSO_4$). The solvent was removed, and the syrup was vacuum dried (1–5 mm, room temperature) for 1–3 hr. Infrared spectra and nmr spectra were also recorded.

Deviations from the above general procedure are as follows. Efforts to purify crude diethyl benzolphosphonate oxime (**3a**) through crystallization from a variety of solvents and mixtures of solvents failed. Attempted distillation of **3a** resulted in a violent decomposition as the temperature at the head of the distillation column approached 60° (0.7 mm). The vacuum-dried diethyl benzoylphosphonate oxime (**3a**) was, therefore, used

(28) J. S. Kittredge and R. R. Hughes, *Biochemistry*, **3**, 991 (1964). See also, M. Horiguchi and M. Kandatsu, *Nature*, **184**, 901 (1959), and *Bull. Agr. Chem. Soc. Jap.*, **24**, 565 (1960); and J. S. Kittredge, E. Roberts, and D. G. Simonsen, *Biochemistry*, **1**, 624 (1962).

(29) K. D. Berlin and M. Nagabhushanam, *Proc. Okla. Acad. Sci.*, **45**, 111 (1965).

(30) J. R. Ferraro and P. F. Peppard, *J. Phys. Chem.*, **67**, 2639 (1963).

(31) P. Arthur, *Anal. Chem.*, **36**, 701 (1964).

(32) In all cases 200 ml of ethanol was used. The quantity of aroylphosphonate varied from 0.05 to 0.2 mol, and the quantities of hydroxylamine hydrochloride and pyridine varied so as to maintain the 0.100:0.133:0.150 molar ratio of reagents.

without further purification. In addition to stirring at room temperature (70 hr), the reaction mixture in the preparation of diethyl 2,6-dimethoxybenzoylphosphonate oxime (**3f**) was boiled an additional 2 hr at the end of the stirring period.

Preparation of Aluminum–Amalgam.—This procedure is a modification of that used by Hartman and Phillips.[33] Approximately 100 ml of aqueous 5% mercuric chloride solution was added to 10.0 g (3.70 g-atoms) of aluminum foil (6 × 6 × 0.001 in.) which had been cut into approximately 2-cm squares. The foil remained in contact with the mercuric chloride solution for 5–10 min to effect amalgamation. Three 1-l. portions of distilled water were used to wash the coated aluminum which was used immediately since it rapidly reacts with moisture.

Aluminum–Amalgam Reduction of Diethyl Aroylphosphonate Oximes 3 and Subsequent Salt Formation.—Reduction of either the pure or crude oximes of diethyl aroylphosphonates could be effected by aluminum–amalgam in ethanol–water.

To a fresh aluminum–amalgam prepared in a 2-l. flask was added 500 ml of ethanol (absolute). The oxime (0.01–0.05 mol) dissolved in 200 ml of ethanol (absolute) was added to the aluminum–amalgam mixture. Distilled water (200 ml) was added, and the mixture was stirred for 24 hr. The solids obtained were filtered and thoroughly washed with two 100-ml portions of ethanol (absolute). All washings were combined with the mother liquor. The solvents were stripped from the crude diethyl α-aminoarylmethylphosphonates **4** which was then dissolved in approximately 100 ml of anhydrous ether. Dry hydrogen chloride was slowly bubbled through the ether solution for 5 min. The insoluble hydrochloride salts **5** separated either as oils or white, crystalline solids. The oily materials were crystallized using various solvents. Infrared and nmr spectra data were recorded.

Hydrolysis of the Hydrochloride Salts 5 of Diethyl α-Aminoarylmethylphosphonates 4 to α-Aminoarylmethylphosphonic Acids 7.—The free α-aminoarylmethylphosphonic acids **7** were obtained by boiling the hydrochloride salts **5** in 9 *M* hydrochloric acid for 4 hr. Water was removed by evaporation to give the hydrochloride salts **6** of the α-aminoarylmethylphosphonic acids. These salts were dissolved in a minimum of cold water and heated to boiling. The less soluble free acids **7** precipitated as white crystalline solids and were collected after cooling. A listing of acids **7** along with some of their physical properties are found in Table I. Nmr spectral data for **7** were also recorded.

The Direct Preparation of α-Amino-*p*-chlorobenzylphosphonic Acid (7b) from Diethyl *p*-Chlorobenzoylphosphonate (2b).—A total of 23.12 g (0.0761 mol) [bp 164–166° (0.4–0.6 mm)] of diethyl *p*-chlorobenzoylphosphonate (**2b**) was added dropwise to a mixture of 7.05 g (0.101 mol) of hydroxylamine hydrochloride, 13.11 g (0.166 mol) of pyridine, and 100 ml of ethanol (absolute) at such a rate that the temperature of the mixture did not exceed 30°. The mixture was stirred for 72 hr. The solvent was removed *in vacuo* and 100 ml of water was added to the syrup. Four 100-ml portions of CH_2Cl_2 were used to extract the aqueous mixture. The CH_2Cl_2 layers were dried ($MgSO_4$); the solvent was removed *in vacuo*. The crude diethyl *p*-chlorobenzylphosphonate oxime (**3b**) was dissolved in 100 ml of ethanol and the resulting solution added to a mixture of aluminum–amalgam (prepared as described previously from 20 g of aluminum foil, 1 l. of absolute ethanol, and 400 ml of water). These materials were stirred for 40 hr. The solids were filtered off and washed with ethanol. The washings and filtrate were combined and the solvents were removed *in vacuo*. The resultant syrup was boiled in a solution of 130 ml of concentrated HCl and 100 ml of water for 14 hr. Removal of the volatile components *in vacuo* left an amber syrup. This syrup was mixed with a solution of 30 ml of water and 40 ml of concentrated HCl and decolorized. After the solution was filtered, the solvent was removed *in vacuo*. A syrup resulted which was mixed with 30 ml of water; crystals formed upon standing. The solid was filtered off and dissolved in a minimum of cold water and boiled. The less soluble free acid **7b** precipitated as a white crystalline solid which was collected after cooling. The yield of α-amino-*p*-chlorobenzylphosphonic acid (**7b**) was 11.16 g [66.5% based on diethyl *p*-chlorobenzoylphosphonate (**2b**)]. The infrared and nmr spectra of the free acid were identical with those for a sample prepared and characterized as described previously. A melting point of 288.5–289.2° (mmp 290.4–291.8) was observed.

Dilution Studies by Infrared Analysis of Diethyl *p*-Methoxybenzoylphosphonate Oxime (3d) and Diethyl α-Amino-*p*-methoxybenzylphosphonate Hydrochloride (5d).—The infrared spectra of **3d** and **5d** in chloroform solution were determined using the cells previously described. After balancing the cells until a flat base line was obtained for the chloroform, solutions of **3d** and **5d** at several concentrations were analyzed. See Table II.

Growth Studies. Materials and Methods.—The compounds were tested at concentrations ranging from 20 to 2500 μg/ml. The medium used for testing was nutrient broth (Difco) and incubation was in 18-mm tubes on a reciprocal shaker at 30°. Compounds were dissolved in nutrient broth, filter sterilized, and diluted with broth to the desired final concentration before inoculation. Growth was measured as optical density at 540 mμ using a Coleman Model 6-D spectrophotometer. The bacteria were grown overnight on nutrient agar, and a small amount of growth was transferred with a sterile loop to control tubes (broth only) and those containing the compound to be tested. Initial optical density at 540 mμ was approximately 0.1. Measurements of optical density were made at frequent intervals and the per cent inhibition was calculated at the point of maximum growth in the control cultures. Incubation was continued for an additional 24–48 hr for cultures showing significant inhibition. The results are found in Table III.

Data on Compounds.—**Diethyl aroylphosphonates ArC(O)P(O)$(OC_2H_5)_2$** obtained yielded the following data: **2a**, bp 136–137° (1.4–1.5 mm),[34] yield 84.0%; **2b**, bp 192–197° (0.4–0.6 mm), 33.6% [Calcd (found): C, 47.76 (47.81), H, 5.10 (5.17); P, 11.20 (11.10)]; **2c**, bp 158–160 (2.3 mm), 80.4% [Calcd (found): C, 47.76 (47.71); H, 5.10 (5.25)]; **2d**, bp 175–179° (1.5 mm),[35] 75.9%; **2e**, bp 170–171 (2.2 mm), 89.7% [Calcd (found): C, 52.94 (52.16); H, 6.29 (6.31)]; **2f**, bp 186–189° (0.6–0.8 mm), 69.6% [Calcd (found): C, 51.66 (52.22); H, 6.34 (6.48)]; **2g**, bp 153–155° (3.0 mm), 88.4% [Calcd (found): C, 60.39 (60.20); H, 7.77 (7.83); P, 10.38 (10.52)]; **2h**, bp 188–191° (1.2 mm), 70.2% [Calcd (found): C, 61.64 (61.88); H, 5.86 (5.87); P, 10.60 (10.00)].

Oximes obtained yielded the following data: **3a**;[36] **3b**, bp 93–95°, 82.6% [Calcd (found): N, 4.80 (5.01); P, 10.62 (10.75)]; **3c**, mp 123.3–123.8°, 66.7% [Calcd (found): N, 4.80 (4.82); P, 10.62 (10.77)]; **3d**, mp 83.6–84.9°, 99.0% [Calcd (found): N, 4.88 (5.08); P, 10.78 (11.00)]; **3e**, mp 113.4–114.6°, 89.5% [Calcd (found): N, 4.88 (5.12); P, 10.78 (10.82)]; **3f**, mp 137.5–138.7°, 64.8%;[37] **3g**, mp 117.9–119.1°, 76.3% [Calcd (found): N, 4.47 (4.61); P, 9.88 (9.77)]; **3h**.[37]

Diethyl α-aminoarylmethylphosphonates, ArCH(NH_2·HCl)P(O)$(OC_2H_5)_2$, obtained yielded the following data: **5a**, mp 162.2–163.4°, 74.5% [Calcd (found): P, 11.07 (11.30)]; **5b**, mp 173.3–173.8°, 48.5% [Calcd (found): P, 9.86 (9.83)]; **5d**, mp 169.3–169.7°, 82% [Calcd (found): P, 10.00 (9.79)]; **5e**, mp 126.7–127.1°, 37.9% [Calcd (found): P, 10.00 (10.45)]; **5f**, mp 143.7–144.2°, 85.2% [Calcd (found): P, 9.12 (9.39)]; **5g**, mp 168.5–169.7°, 77.9% [Calcd (found): C, 53.65 (53.78)], H, 8.10 (8.13); **5h**, mp 181.3–183.1°, 58.7% [Calcd (found): P, 8.96 (9.17)].

Registry No.—**2a**, 3277-27-8; **2b**, 10570-46-4; **2c**, 16656-42-1; **2d**, 16703-95-0; **2e**, 16656-43-2; **2f**, 16656-44-3; **2g**, 10570-47-5; **2h**, 16656-46-5; **3b**, 16656-47-6; **3c**, 16656-48-7; **3d**, 16703-96-1; **3e**, 16703-97-2; **3f**, 16703-98-3; **3g**, 16656-49-8; **5a**, 16656-50-1; **5b**, 16656-51-2; **5d**, 16656-52-3; **5e**, 16656-53-4; **5f**, 16656-54-5; **5g**, 16656-56-7; **5h**, 16656-58-9; **7b**, 16656-60-3; **7d**, 16656-61-4; **7h**, 16703-99-4.

(33) W. W. Hartman and R. Phillips, "Organic Syntheses," Coll. Vol. II, A. H. Blatt, Ed., John Wiley and Sons, Inc., New York, N. Y., 1943, p 232.

(34) M. I. Kabachnik and P. A. Rossiiskaya [*Bull. Acad. Sci. SSSR, Classe Sci. Chim.*, 364 (1945); *Chem. Abstr.*, **40**, 4688 (1948)] found bp 141° (2.5 mm).

(35) K. D. Berlin and H. A. Taylor, *J. Amer. Chem. Soc.*, **86**, 3862 (1964): bp 158 (0.4 mm).

(36) Liquid sample; **3a** could not be crystallized using a variety of solvents and violently decomposed upon attempted distillation.

(37) This material was reduced directly since it also tended to decompose on heating.

Dihydrotazettine Methine, an Unusual Noncoplanar Phenylcyclohexene

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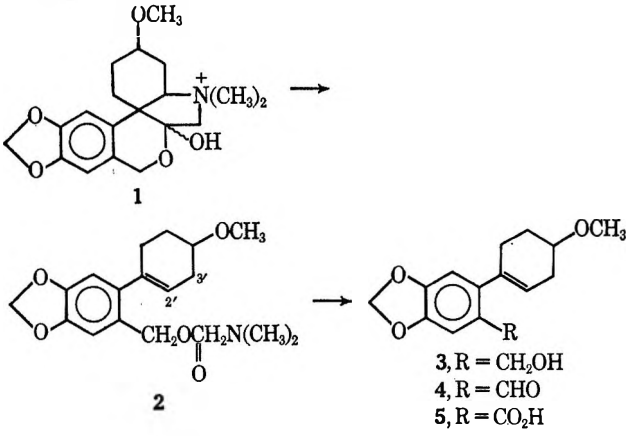
The structure of dihydrotazettine methine must be corrected to **2**, in which steric crowding prevents a planar conformation and conjugation. The derivative alcohol **3** displays a strong hydrogen bond forming a ten-membered ring. Acid treatment converts **2** into the tetrahydrofluorene **11**, and the aldehyde **4** into the dihydroisofluorene **12**. Performic acid converts the acid **5** into the lactones **15** and **16**. In the mass spectra of these compounds, some fragmentation routes apparently correspond to these cyclizations.

During the brief period in which the chemistry of dihydrotazettine methine was critical to the structural studies on tazettine, attention centered upon the position of the double bond.[1,2] This paper describes an investigation which unexpectedly revealed that the position generally accepted for this double bond (2′,3′ in **2**) is erroneous.



In the context of the chemistry of tazettine, the main features of the product of the Hofmann decomposition of the methiodide of dihydrotazettine (**1**) are quite clear. The 6-(4′-methoxycyclohexenyl)piperonyl system is present and has been demonstrated by reduction of the methine to a derivative of haemanthamine.[3] The presence of the ester function is inferred from the infrared absorption and analogy to the formation of an ester in the Hofmann decomposition of tazettine.[4] These characteristics have been further substantiated by the observations recorded below. Evidence on the position of the double bond was limited to the ultraviolet spectrum (Figure 1), which resembles that of safrole, rather than that of the styrene system of isosafrole, and the nonconjugated position (2′,3′) has been generally accepted.[1,2,5]

In the course of the earlier work it was observed that acid treatment converts the methine into a neutral material. To allow further investigation of this product, a fresh quantity of the methine was prepared, which was now examined by nmr spectrometry. This spectrum displays the characteristics anticipated of a compound known to possess the gross features enumerated above, but, surprisingly, shows a peak corresponding to a single olefinic hydrogen atom and requires that the double bond be in the 1′,2′ position (**2**). Although the alicyclic protons could not be well resolved in deuteriochloroform, in perdeuterioacetic acid[6] the spectrum showed resonance at δ 2.0 (m, ~2, C-5′), at 2.2 (m, ~4, C-3′ and C-6′), and a broad peak centered at 3.6 ppm (1, C-4′). Were the double bond in the 2′,3′ position, the spectrum should show a peak near 2.0 ppm (4, C-5′, 6′), peaks for *two* olefinic protons, and peaks for the C-1′ proton substantially downfield from those observed at 2.2 ppm.

Basic hydrolysis of the methine proceeded smoothly to provide a neutral alcohol, **3**. The nmr spectrum resembles that of the relevant portion of **2**, again with a single olefinic proton; the ultraviolet spectrum again resembles that of safrole. Stirring a chloroform solution of this material with manganese dioxide for 10 hr provided the aldehyde **4**, again showing a single olefinic proton in the nmr, and with an ultraviolet absorption resembling that of piperonal. Alkaline hydrogen peroxide converted the aldehyde into an acid **5**, with similar spectral features.

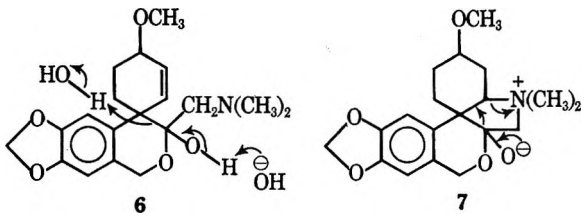
Although evidence cited to this point comprises two conflicting sets of spectral observations, the more circumstantial nature of the nmr spectra greatly favors the formally conjugated structure **2**. Oxidation to β-methoxyadipic acid, discussed elsewhere in connection with the absolute configuration of the parent alkaloid,[7] settled the conflict unambiguously. The studies described below provide further evidence in support of this conclusion.

Although it is somewhat surprising that the ultraviolet spectra of these compounds fail to show the double bond conjugated with the aromatic system, evidently the bulk of the group *ortho* to the cyclohexenyl system in each is sufficient to force the double bond out of a position coplanar with the aromatic group. Reference to the spectra of the tolyl cyclohexenes removes all doubt: 1-*p*-tolylcyclohexene shows a styrene chromophore [λ_{max} 249 mμ (ε 12,800)], while 1-*o*-tolylcyclohexene does not [λ_{max} 271 (ε 350)].[8]

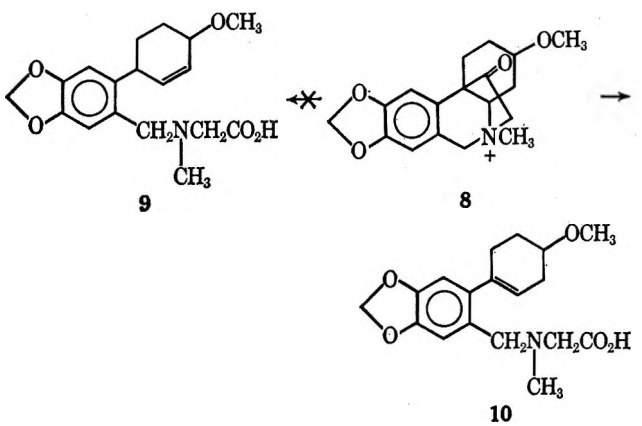
Reassigning the position of the double bond in dihydrotazettine methine requires that the mechanism of the Hofmann decomposition be reconsidered. It is quite clear that the hydroxyl group of the hemiacetal is involved, for the Hofmann decomposition of O,N-

(1) R. J. Highet and W. C. Wildman, *Chem. Ind.* (London), 1159 (1955).
(2) T. Ikeda, W. I. Taylor, Y. Sude, S. Uyeo, and H. Yajima, *J. Chem. Soc.*, 4749 (1956).
(3) H. M. Fales and W. C. Wildman, *J. Amer. Chem. Soc.*, **82**, 197 (1960).
(4) W. I. Taylor, S. Uyeo, and H. Yajima, *J. Chem. Soc.*, 2962 (1955).
(5) *Cf.* W. C. Wildman in "The Alkaloids," Vol. VI, R. H. F. Manske, Ed., Academic Press Inc., New York, N. Y., 1960, p 289; H.-G. Boit, "Ergebnisse der Alkaloid-Chemie bis 1960," Academie-Verlag, Berlin, 1961, p 410.
(6) *Cf.* J. C. N. Ma and E. W. Warnhoff, *Can. J. Chem.*, **43**, 1849 (1965).
(7) R. J. Highet and P. F. Highet, *J. Org. Chem.*, **33**, 3105 (1968).
(8) *o*-Tolylcyclohexene shows a rising end absorption which, however, has ε 1700 at 249 mμ. The nmr spectra of these compounds similarly reflect these effects: 1-*o*-tolylcyclohexene, δ 7.13 (4 H, aromatic), 5.57 (1 H olefinic); 1-*p*-tolylcyclohexene, 7.30, 7.08 (2 H each, aromatic), 6.05 ppm (1 H, olefinic). On the basis of these chemical shifts, the dihedral angle of the olefinic bond and the aromatic ring of *o*-tolylcyclohexene has been estimated as 69 or 100°; *cf.* E. W. Garbisch, *J. Amer. Chem. Soc.*, **85**, 927 (1963).

dimethyltazettine takes quite a different course.[2] The fact that the dimethylaminomethylene moiety is retained requires that the benzylic ether bond remain in the product ester and that the decomposition occur on the intact hemiacetal. The earlier belief that the double bond occupies the nonconjugated position required that the formation of the methine be rationalized by a mechanism involving a normal Hofmann decomposition to **6**, followed by the cleavage indicated. This mechanism is clearly precluded by the conjugated position of the double bond, and a concerted mechanism **7** is now more attractive.[1,9,10]



The formation of a product similar to dihydrotazettine methine has been reported from the Hofmann degradation of dihydrooxohaemanthamine methiodide, **8**.[3] Assigning the position of the double bond again depended on the ultraviolet absorption which favored the 2′,3′ position **9**. Through the courtesy of Dr. H. M. Fales, of this laboratory, it has been possible to examine the nmr spectrum of this methine which reveals a single olefinic proton (δ 5.55 ppm, m). It is evident that **10** is the correct structure and that the ultraviolet absorption is also misleading in this case.



Because the double bond of the methine is crowded by the hydroxymethyl, it was anticipated that the alcohol might show hydrogen bonding to it. The infrared spectrum of the alcohol reveals intramolecular hydrogen bonding by two peaks in the OH-stretching region, at 3620 and 3500 cm^{-1}, the latter with a width at half-intensity of 80 cm^{-1}, unchanged on dilution to 0.004 *M* in carbon tetrachloride.[11] However, it is unlikely that the absorption at 3500 cm^{-1} results from interaction of the hydroxyl with the double bond, for hydroxyl groups so bonded seldom absorb below 3550

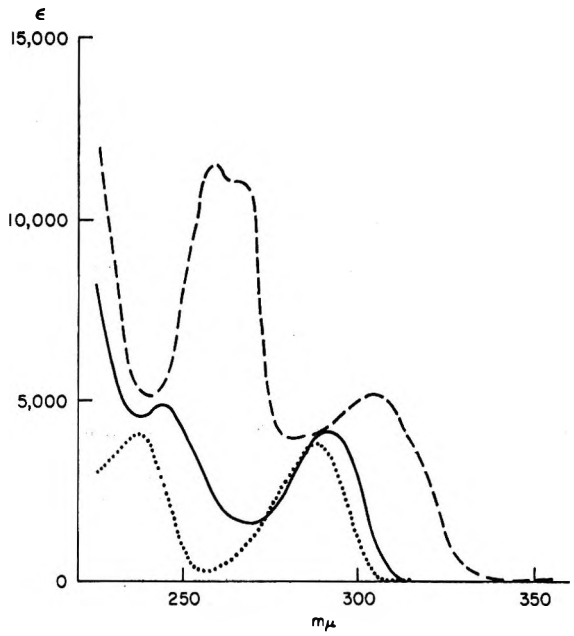
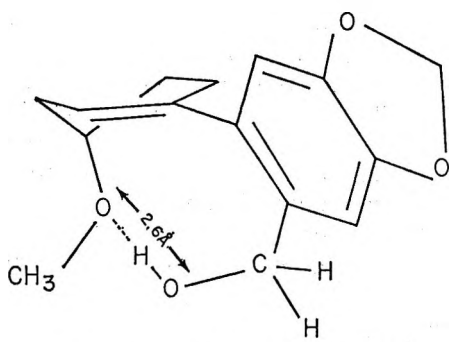


Figure 1.—Ultraviolet spectra: ———, dihydrotazettine methine; – – – –, isosafrole; · · · ·, safrole.

cm^{-1}.[12] Dreiding models of the molecule reveal the probable nature of this bond, for the hydroxyl can approach within 1.6 Å of the methoxyl oxygen, with a linear conformation and O···O distance of 2.6 Å.



dihydrotazettine methine alcohol

This unusual hydrogen bond adds rigidity to the molecular conformation, which is revealed in the nmr spectrum of the benzylic methylene group. This appears as an AB quartet, which coalesces to a singlet at approximately 68° (see Figure 2). Because the outer limbs of the quartet are sometimes lost in the instrumental noise, the signal sometimes appears as a doublet, such as might result from coupling of the methylene protons with the hydroxyl proton. However, the hydroxyl signal is a singlet, and exchanging the proton for a deuterium atom does not alter the absorption of the benzylic methylene group.

It is clear that the nonequivalence of the methylene protons results from the hydrogen bond, for the parent ester **2** does not show this phenomenon, and addition of a polar material [here $(CD_3)_2SO$] to a dilute carbon

(9) K. Wiesner and Z. Valenta, *Chem. Ind.* (London), R36 (1956).

(10) It is ironic to note that such a four-center elimination was first suggested to lead to the methine when it was supposed to have a nonconjugated double bond and led to an erroneous structure for tazettine.[1] Had the conjugated nature of the methine been recognized, this mechanism would have led to the correct structure for tazettine.

(11) A preliminary description of the phenomena associated with this hydrogen bond has appeared; *cf.* R. J. Highet, J. C. N. Ma, and P. F. Highet, *Tetrahedron Lett.*, 1049 (1966).

(12) *Cf.* (a) H. M. Fales and W. C. Wildman, *J. Amer. Chem. Soc.*, **85**, 784 (1963); (b) P. von R. Schleyer, D. S. Trifan, and R. Backsai, *ibid.*, **80**, 6691 (1958); (c) P. von R. Schleyer, C. Wintner, D. S. Trifan, and R. Backsai, *Tetrahedron Lett.*, 1 (1959). (d) It is further unlikely that the olefin is involved in the hydrogen bond because 2-hydroxymethylbiphenyls fail to show bonding of the hydroxyl to the adjacent aromatic ring; *cf.* W. F. Baitinger, P. von R. Schleyer, and K. Mislow, *J. Amer. Chem. Soc.*, **87**, 3168 (1965).

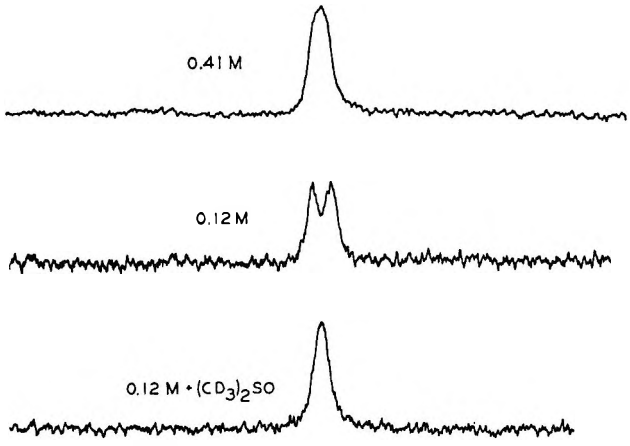


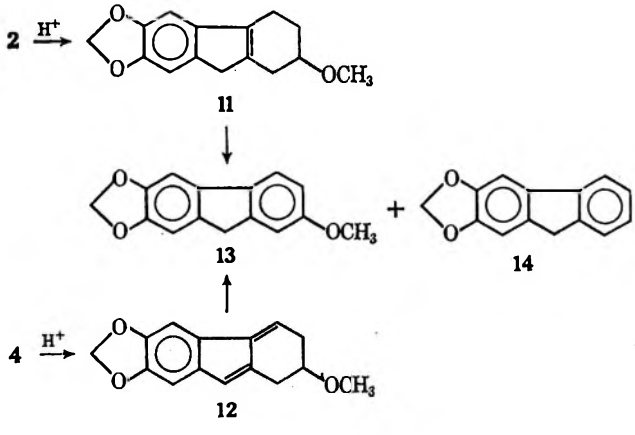
Figure 2.—Nmr spectra of dihydrotazettine methine alcohol in carbon tetrachloride solution at δ 4.7 ppm.

tetrachloride solution of the alcohol disrupts the bond, converting the quartet into a singlet.

The cage structure resulting from this hydrogen bond places the aromatic system in an asymmetric environment, which can be detected in the optical rotatory properties of the molecule. The ORD curve (Figure 3) of a dilute hexane solution of the alcohol shows a Cotton effect which is not present in the parent ester. A methanolic solution of the alcohol reveals only a plain curve to 250 mμ.

Such a hydrogen bond made possible across many atoms by an unusual conformation is not unique to this molecule, but such bonds are unusual in simple systems.[13] Although the methoxyl group must occupy the energetically less favored axial position, the energy difference of the axial and equatorial conformations is evidently comparable with that of the hydrogen bond.

Acid Transformation Products.—The methine **2** turns cloudy on warming in acid, producing a neutral material of the composition $C_{15}H_{16}O_3$. The ultraviolet



spectrum of this product showed a double bond conjugated with the aromatic system, while the infrared and nmr spectra showed the environment of the aromatic system, the alicyclic protons and the methoxyl group to be otherwise unchanged; there were no olefinic peaks, and one broad singlet of two protons remained unassigned, δ 3.08 ppm. As the nmr spectrum and empirical formula show the benzylic substituent to have been eliminated, the product may be supposed to be that of cyclization, **11**.[14] The chemical shift of the unassigned peak corresponds reasonably to that of indene, 3.33.[15]

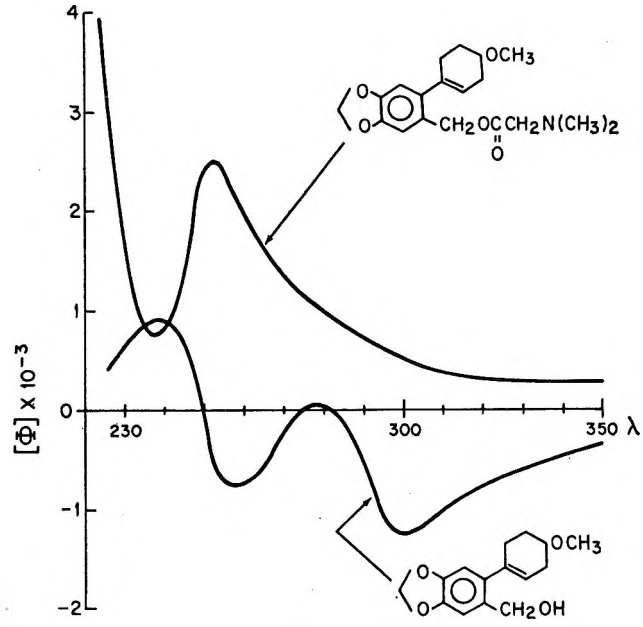
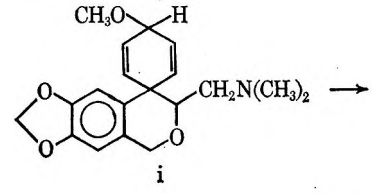
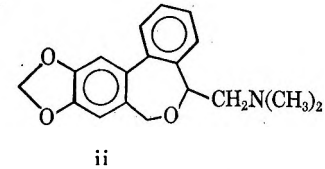


Figure 3.—ORD of dihydrotazettine methine and its alcohol in hexane solution.

The aldehyde **4** also proved to be sensitive to acid, brief warming forming a handsome golden precipitate with the composition $C_{15}H_{14}O_3$. The nmr spectrum of this product shows two olefinic protons, one as a singlet broadened only by allylic coupling, and the other as a triplet corresponding to coupling with an adjacent methylene group. These may reasonably be assigned to C-9 and C-4 of **12**. Although the spectra of **12** do not eliminate the C-1 position for the methoxyl, dehydrogenation produces a mixture of the methylenedioxyfluorene **14** and its methoxy derivative **13**, with the characteristic nmr spectrum of a 1,2,4-substituted aromatic ring. The same materials are produced by dehydrogenation of the tetrahydrofluorene **11**.



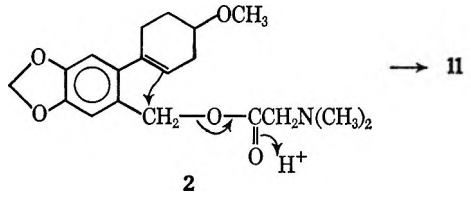


(13) A remarkable case is that of dehydropristimerin II: K. Nakanishi, Y. Takahashi, and H. Budzikiewicz, *J. Org. Chem.*, **30**, 1729 (1965).

(14) The sensitivity of the methine to acid parallels that of deoxytazettine methine (i), which is converted under similar conditions into the optically active neomethine ii and piperonyl alcohol. (*Cf.* E. W. Warnhoff in "Molecular Rearrangements," Vol. 2, P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, p 851. As this material has been previously reported optically inactive[2] and experimental details supporting the optical activity have not been reported elsewhere, these have kindly been supplied by Dr. Warnhoff and are included in the Experimental Section.)

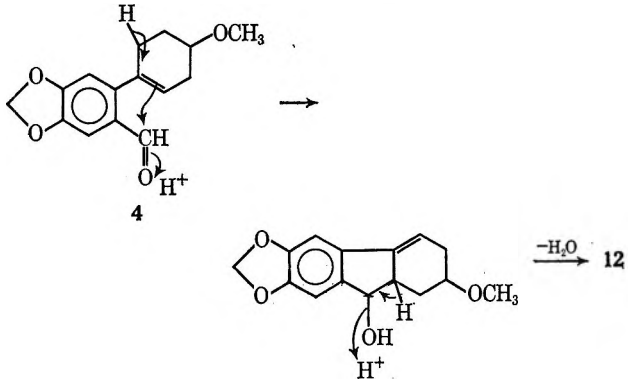
(15) N. B. Bhacca, L. F. Johnson, and J. N. Shoolery, "Nmr Spectra Catalog," Varian Associates, Palo Alto, Calif., 1962, No. 227.

The cyclization of the methine **2** may be represented by the path



2

The reaction cannot proceed by a mechanism initiated by protonation of the double bond to form a benzylic carbonium ion, for a symmetrical intermediate would be formed, and the product could not possess the optical activity observed. As anticipated from this mechanism, the same product is obtained from acid treatment of the alcohol **3**, but only under prolonged heating. A similar route is proposed for the formation of **12**. Not only is the product optically active, but when



4

the cyclization is performed on the dideuterioaldehyde (**4**, D at 5′ and 6′) one-quarter of the deuterium content is lost in the formation of **12**.[7]

The double bond of the alcohol **3** is quite resistant to oxidation. The acetate of **3**, formed by the action of acetic anhydride in pyridine, was not attacked by treatment with potassium permanganate solution for 2 hr. However, peroxide oxidation of the aldehyde **4** provided the acid **5**, which, with performic acid,[16] produced a series of neutral materials which could be separated by tlc. The two major components, A, mp 182–185°, and B, mp 178–181°, were shown by mass spectrometry to possess the composition $C_{15}H_{16}O_6$. Infrared spectra of these materials show carbonyl peaks near 1750 cm^{-1}, corresponding to five-membered lactones (*cf.* methyl piperonylate, 1719 cm^{-1}). The hydroxyl-stretching frequencies reveal the stereochemistry of the compounds. In dilute carbon tetrachloride solution, A shows a free hydroxyl group, 3632 cm^{-1}, while B shows a hydroxyl group with a strong hydrogen bond, 3490 cm^{-1}. Neither of these corresponds to a *cis*-cyclohexanediol nor a *trans*-equatorial cyclohexanediol derivative, either of which should produce a weakly bonded hydroxyl of *ca.* 3550 cm^{-1}.[17] The two materials are therefore to be represented by **15**, A, with the free hydroxyl and **16**, B, with the

(16) G. Berti, F. Bottari, B. Macchia, and F. Macchia, *Tetrahedron*, **21**, 3277 (1965).

(17) E. Galantay, *ibid.*, **19**, 319 (1963); E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, Inc., New York, N. Y., 1965, p 110.

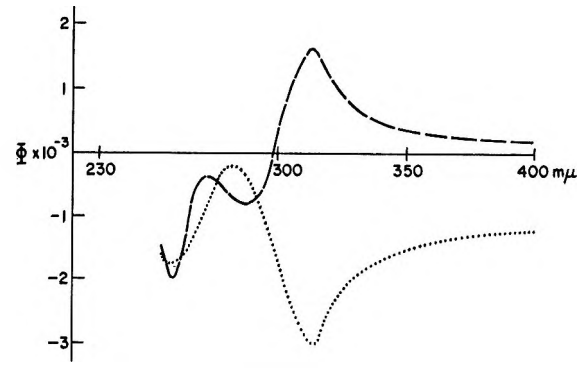
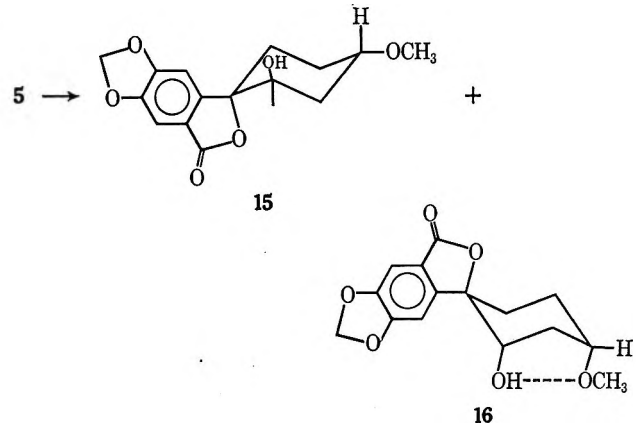


Figure 4.—ORD of lactones A (————) and B (.....) in ethanol.



15 **16**

hydroxyl strongly bonded to the *cis*-methoxyl in a 1,3-diaxial relation.

The properties conform quite well to the products anticipated from the reaction, for the cyclohexenyl ring of the acid **5**, with the methoxyl in the equatorial conformation, should be equally hindered on either side; the two intermediate epoxides are evidently formed in similar amounts and suffer *trans*-diaxial opening to the lactones observed.[16]

Although the two lactones have one asymmetric center in common, that bearing the methoxyl group, the two asymmetric centers nearest the chromophoric group possess opposite absolute configurations. The optical rotatory dispersion curves reflect this fact and show Cotton effects of opposite character, centered at 305 mμ (see Figure 4).

Mass Spectral Observations.—The mass spectra of the compounds discussed here (Experimental Section and Figure 5) comprise ions evidently formed largely by the elimination of small and simple moieties, as summarized in Table I. The processes postulated conform to the composition of the ions determined by accurate mass measurement (Table II) and to the corresponding peaks of the deuterated materials available from the study of the absolute configuration of alkaloids related to tazettine.[7] They are perhaps best discussed in order of the increasing complexity of the compounds.

(Table III lists the mass spectra of **11**–**16**.)

The sequential elimination of the elements of formaldehyde and carbon monoxide from the methylenedioxyaromatic system form the dominant ions of the dehydrogenation products **13** and **14**, and the terminating sequences of the fragmentations of the more complex molecules of the series. The elimination of the elements of methanol from the dihydroisofluorene **12**

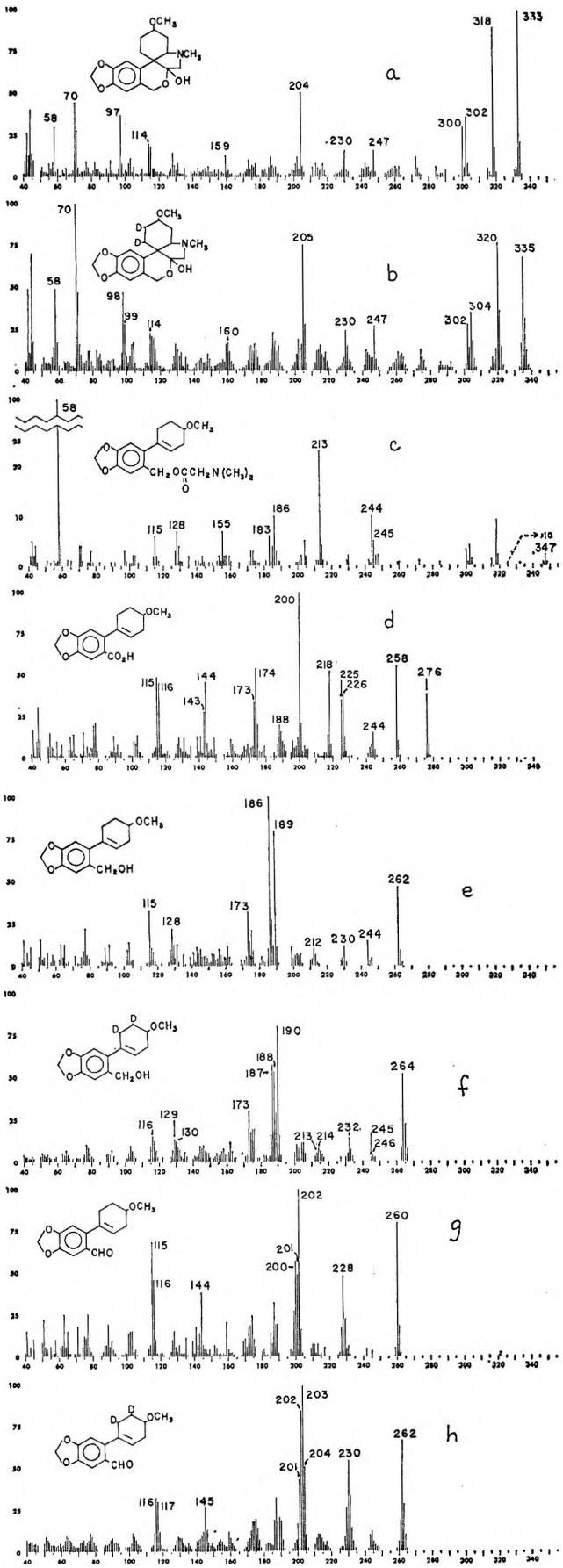
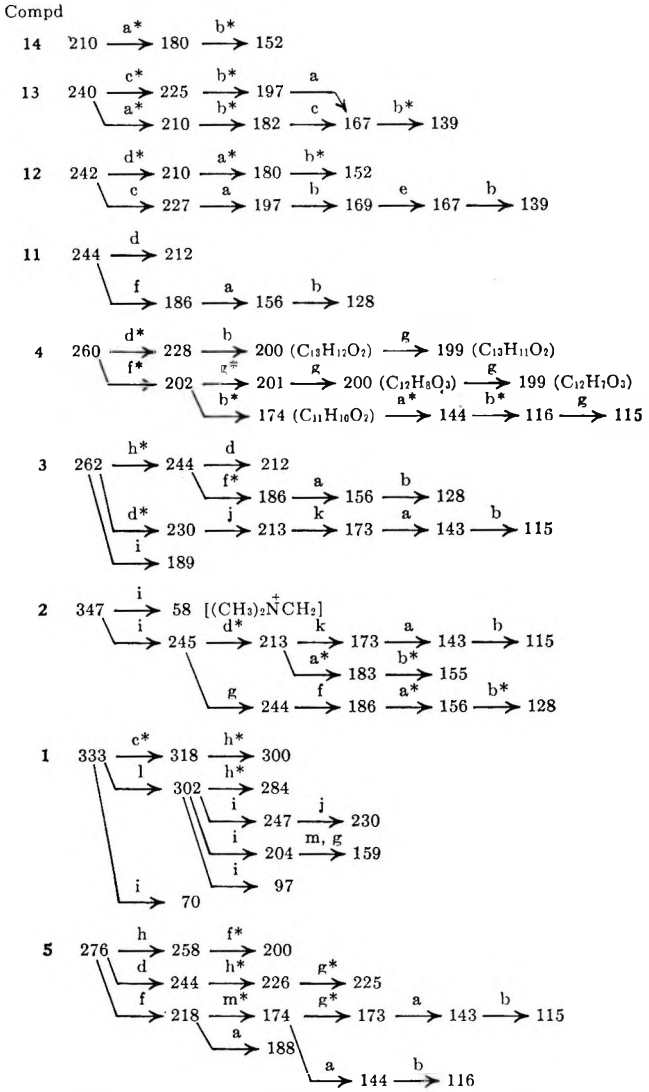


Figure 5.—Mass spectra of dihydrotazettine methine and derivatives. Registry no.: a, 16831-29-1; b, 16831-30-4; f, 16831-31-5; h, 16831-32-6.

TABLE I

FRAGMENTATION UNDER ELECTRON BOMBARDMENT[a]



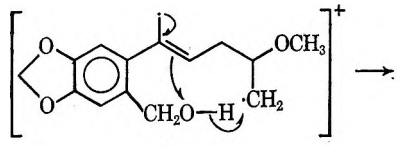
[a] An asterisk indicates that spectra show metastable ions corresponding to these transitions: a, CH_2O; b, CO; c, CH_3; d, CH_3OH; e, H_2; f, $CH_3OCH{=}CH_2$; g, H; h, H_2O; i, see text; j, OH; k, C_3H_4; l, CH_3O; m, CO_2.

evidently produces an ion very similar to the parent ion of **14**, for the characteristic ions from the fragmentation of that parent appear, along with those of the competing sequence originated by the elimination of methyl from the methoxyl group.

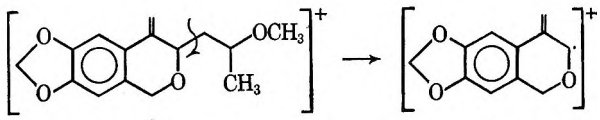
The spectrum of the tetrahydrofluorene **11** is dominated by the reverse Diels–Alder elimination, the process which also produces the base peak of the aldehyde **4** (Figure 5g and h) and of the acid **5** (Figure 5d). However, in the fragmentation of these latter compounds, alternative routes compete to produce spectra of greater complexity.

The striking feature of the spectrum of **3** (Figure 5e and f) is that the reverse Diels–Alder process forming the base peak does not occur from the parent ion, but from the product of dehydration, *m/e* 244, which can evidently be assigned the structure of the tetrahydrofluorene **11**, for the characteristic peaks of this latter compound can be seen at lower masses. The dehydration process evidently is preceded by an isomerization of the double bond, for the dideuterated material shows dehydration products as mono- and dideuterated

doublets (244 shifts to 245 and 246; 186 to 187 and 188). The appearance of a strong peak at *m/e* 189 (190 in the deuterated compound) is rationalized as cleavage of an allylic bond to form **a**, cyclization and proton transfer in one or two steps to form **b**, which cleaves to the observed ion of *m/e* 189, **c**. The sequence

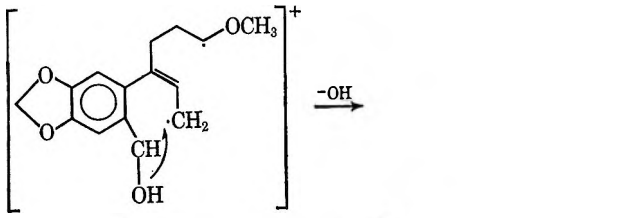


a

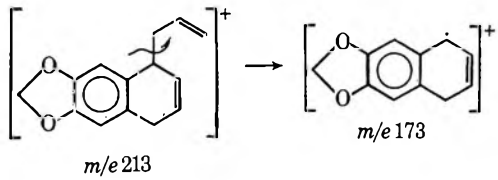


b **c**

leading to the ion of *m/e* 173, unchanged in the spectrum of the deuterated material, is represented as the product of the alternative allylic cleavage and cyclization.



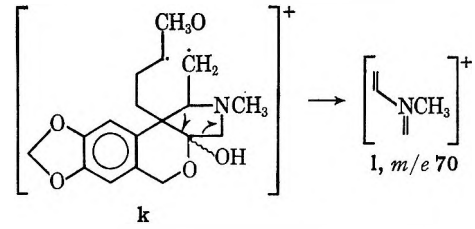
m/e 245



m/e 213 *m/e* 173

The mass spectrum of the methine **2** is dominated by the facile departure of the dimethylaminomethylene moiety, *m/e* 58, which provides the base peak. The same cleavage forms the ion of *m/e* 245, which fragments by processes common to the alcohol and tetrahydrofluorene described above. The ions of *m/e* 333, 318, 302, 300, 204, 97, 71, and 70 evidently arise from dihydrotazettine contaminating the difficultly purified methine.

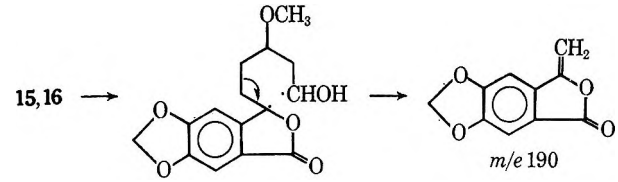
The stability of the polycyclic system of dihydrotazettine **1** is reflected in the appearance of the parent ion as the base peak. The familiar losses of methyl, hydroxyl, and methoxyl are observed, the last leading to the intermediate **d**, *m/e* 302 (Chart I), regarded as the starting point for fragmentations of the alicyclic ring. Elimination of C-1 to C-4 *via* the process **e** produces the ion of *m/e* 247, **f**, and, with loss of hydroxyl, *m/e* 230, both of which incorporate no deuterium. Cleavage next to the hemiketal position with hydrogen transfer allows the elimination of C-2 to C-4 (**g**), and the formation of **h**, *m/e* 204. A similar cleavage without hydrogen transfer, **i**, produces a charge-bearing moiety of small weight, **j**, *m/e* 97. Cleavage of the parent ion at the methoxyl site to produce **k** allows the elimination of the ion of *m/e* 70, **l**. The peaks of *m/e*



k **l**, *m/e* 70

114, 71, and 58 can evidently be similarly explained.

The base peaks of the very simple spectra of the lactones **15** and **16** evidently arise from elimination following the facile glycol cleavage.



15,16 *m/e* 190

Experimental Section[18]

Dihydrotazettine Methine (2).[1,2]—A solution of 440 mg of dihydrotazettine in 10 ml of acetone was treated with 5 ml of methyl iodide at room temperature for 30 min and then evaporated to dryness. The residue was dissolved in 5 ml of methanol and stirred 2 hr with silver oxide, freshly prepared from 280 mg of silver nitrate and dilute sodium hydroxide. The suspension was filtered, the filtrate was evaporated to dryness, and the residue was heated at 130° under reduced pressure for 30 min. The residue was dissolved in ether, and the solution was washed with brine and evaporated to dryness, providing 404 mg of the methine as an oil which was unstable to distillation, but could be shown by tlc and glpc to be essentially one material, $[\alpha]^{25}_{589}$ +29.5°. The methine formed a picrate which crystallized from ethanol, mp 136.5–137.5° (lit.[1] mp 136–137°).

Anal. Calcd for $C_{25}H_{28}N_4O_{12}$: C, 52.08; H, 4.89; N, 9.72. Found: C, 52.35; H, 4.89; N, 9.57.

Regeneration of the free base provided material with the following spectral properties: λ_{max} 243 mμ (ε 4900) and 290 (4100) [safrole shows λ_{max} 237 (4120) and 287 (3900); isosafrole shows 259 (11,650), 266.5 (11,150), and 305 (5180)]; ν_{max} 1740, 1040, and 935 cm^{-1}.

Anal. Calcd for $C_{19}H_{25}NO_5$: *m/e*, 347.173. Found: *m/e*, 347.174.

6-(4′-Methoxycyclohexenyl)piperonyl Alcohol (3).—A solution of 90 mg of the above ester in 4 ml of ethanol was treated with 2 ml of 1 *M* sodium carbonate and refluxed 1 hr. The solution was diluted with water and extracted with ether, and the ethereal layer was washed with brine, filtered, and evaporated to dryness to provide 70 mg of an oil. Crystalline material was obtained after sublimation (75°, 0.001 mm) or preparative tlc (ether–chloroform, 1:1): mp 63–64°; $[\alpha]_{589}$ −3.2° (*c* 0.34); λ_{max} 240 mμ (ε 5100), and 290 (3900); ν_{max} (dil CCl_4) 3630 and 3500 cm^{-1}; nmr 6.93 (C-2, s, 1), 6.64 (C-5, s, 1), 5.95 (OCH_2O, s,

(18) Melting points were observed on a Kofler microscope hot stage and are corrected. Rotations were measured in chloroform with a Rudolph photoelectric spectropolarimeter using 2-dm tubes; the optical rotatory dispersions of Figures 3 and 4 were determined on a Cary 60 recording spectropolarimeter in 1-cm cells; ultraviolet spectra were obtained in absolute ethanol solution on a Cary Model 11 MS recording spectrophotometer; infrared spectra were recorded on either a Perkin-Elmer Model 21 or a Beckman IR-7 double-beam spectrophotometer in chloroform solution; nmr measurements were obtained on a Varian A-60 spectrometer in deuteriochloroform solution, using tetramethylsilane (δ 0.0) as an internal standard. Exceptions to the specified solvents are noted in the text. Mass spectra were determined with an Associated Electrical Industries MS-9 double-focusing mass spectrometer at 70 eV; accurate mass measurements were obtained by comparing the weights of unknown ions with those of ions of heptacosafluorotributylamine of slightly lower weight. Tlc was performed on silicic acid plates.

TABLE II

ACCURATE MASSES OF IONS

Compd	Obsd	Formula	Required
14	210.067	$C_{14}H_{10}O_2$	210.068
	180.056	$C_{13}H_8O$	180.058
	152.062	$C_{12}H_8$	152.063
13	240.077	$C_{15}H_{12}O_3$	240.079
	225.054	$C_{14}H_9O_3$	225.055
	210.065	$C_{14}H_{10}O_2$	210.068
	197.058	$C_{13}H_9O_2$	197.060
	182.070	$C_{13}H_{10}O$	182.073
	167.050	$C_{12}H_7O$	167.050
	139.056	$C_{11}H_7$	139.055
12	242.093	$C_{15}H_{14}O_3$	242.094
	227.072	$C_{14}H_{11}O_3$	227.071
	210.070	$C_{14}H_{10}O_2$	210.068
	197.060	$C_{13}H_9O_2$	197.060
	180.058	$C_{13}H_8O$	180.056
	169.065	$C_{12}H_9O$	169.065
	167.051	$C_{12}H_7O$	167.050
	152.063	$C_{12}H_8$	152.063
	139.057	$C_{11}H_7$	139.055
11	244.108	$C_{15}H_{16}O_3$	244.110
	212.083	$C_{14}H_{12}O_2$	212.084
	186.063	$C_{12}H_{10}O_2$	186.068
	156.055	$C_{11}H_8O$	156.058
	128.062	$C_{10}H_8$	128.063
4	260.101	$C_{16}H_{16}O_4$	260.105
	244.111	$C_{15}H_{16}O_3$	244.110
	242.097	$C_{15}H_{14}O_3$	242.094
	228.078	$C_{14}H_{12}O_3$	228.079
	202.060	$C_{12}H_{10}O_3$	202.063
	201.052	$C_{12}H_9O_3$	201.055
	200.082	$C_{13}H_{12}O_2$	200.084
	200.045	$C_{12}H_8O_3$	200.048
	199.074	$C_{13}H_{11}O_2$	199.076
	199.038	$C_{12}H_7O_3$	199.040
	187.073	$C_{12}H_{11}O_2$	187.076
	174.068	$C_{11}H_{10}O_2$	174.068
	174.034	$C_{10}H_6O_3$	174.032
	159.044	$C_{10}H_7O_2$	159.045
	144.056	$C_{10}H_8O$	144.058
	116.064	C_9H_8	116.063
	115.054	C_9H_7	115.055
3	262.118	$C_{15}H_{18}O_4$	262.121
	244.111	$C_{15}H_{16}O_3$	244.110
	230.094	$C_{14}H_{14}O_3$	230.094
	213.090	$C_{14}H_{13}O_2$	213.092
	212.081	$C_{14}H_{12}O_2$	212.083
	199.076	$C_{13}H_{11}O_2$	199.076
	189.054	$C_{11}H_9O_3$	189.055
	186.066	$C_{12}H_{10}O_2$	186.068
	175.074	$C_{11}H_{11}O_2$	175.076
	175.040	$C_{10}H_7O_3$	175.039
	173.064	$C_{11}H_9O_2$	173.061
	156.057	$C_{11}H_8O$	156.058
	143.047	$C_{10}H_7O$	143.050
	128.062	$C_{10}H_8$	128.063
	115.056	C_9H_7	115.055
2	347.172	$C_{19}H_{25}NO_5$	347.173
	245.115	$C_{15}H_{17}O_3$	245.118
	244.112	$C_{15}H_{16}O_3$	244.110
	230.088	$C_{14}H_{14}O_3$	230.094
	213.091	$C_{14}H_{13}O_2$	213.095
	186.067	$C_{12}H_{10}O_2$	186.068
	183.081	$C_{13}H_{11}O$	183.081
	155.084	$C_{12}H_{11}$	155.086
	155.050	$C_{11}H_7O$	155.050
	155.016	$C_{10}H_3O_2$	155.013
	143.048	$C_{10}H_7O$	143.050
	128.063	$C_{10}H_8$	128.063
	115.055	C_9H_7	115.055
	586.048	C_8H_8N	58.0657
1	333.157	$C_{18}H_{23}NO_5$	333.158
	318.131	$C_{17}H_{20}NO_5$	318.134
	302.138	$C_{17}H_{20}NO_4$	302.139
	300.124	$C_{17}H_{18}NO_4$	300.124
	290.116	$C_{17}H_{18}O_5$	290.115
	284.129	$C_{17}H_{18}NO_3$	284.129
	272.127	$C_{16}H_{18}NO_3$	272.129
	272.105	$C_{16}H_{16}O_4$	272.105
	247.084	$C_{13}H_{13}NO_4$	247.084
	230.082	$C_{13}H_{12}NO_3$	230.082
	204.040	$C_{11}H_8O_4$	204.042
	186.065	$C_{12}H_{10}O_2$	186.068
	173.120	$C_9H_{17}O_3$	173.118
	173.060	$C_{11}H_9O_2$	173.060
	159.043	$C_{10}H_7O_2$	159.045
	128.062	$C_{10}H_8$	128.063
	115.055	C_9H_7	115.055
	114.092	$C_6H_{12}NO$	114.092
	97.088	$C_6H_{11}N$	97.089
	71.0726	C_4H_9N	71.0735
	71.0492	C_4H_7O	71.0497
	70.067	C_4H_8N	70.066
	58.067	C_3H_8N	58.066
15	292.094	$C_{15}H_{16}O_6$	292.095
	190.026	$C_{10}H_6O_4$	190.026
16	292.094	$C_{15}H_{16}O_6$	292.095
	190.026	$C_{10}H_6O_4$	190.026
5	276.101	$C_{15}H_{16}O_5$	276.100
	258.089	$C_{15}H_{14}O_4$	258.089
	244.073	$C_{14}H_{12}O_4$	244.074
	226.061	$C_{14}H_{10}O_3$	226.063
	225.056	$C_{14}H_9O_3$	225.055
	218.057	$C_{12}H_{10}O_4$	218.058
	200.047	$C_{12}H_8O_3$	200.047
	188.046	$C_{11}H_8O_3$	188.047
	174.065	$C_{11}H_{10}O_2$	174.068
	173.058	$C_{11}H_9O_2$	173.060
	144.057	$C_{10}H_8O$	144.058
	143.048	$C_{10}H_7O$	143.050
	116.062	C_9H_8	116.063
	115.055	C_9H_7	115.055

2), 4.56 (α-C, s or q, 2), 5.50 (C-2′, br, 1) 3.42 (OCH_3, s, 3), *ca.* 3.7 (C-4′, m, 1), *ca.* 2.3 (C-3′, C-6′, and OH, demonstrated by exchange with D_2O,[19] br, 5), *ca.* 1.93 (C-5′, m, 2).

Anal. Calcd for $C_{15}H_{18}O_4$: *m/e*, 262.120. Found: *m/e*, 262.123.

(19) H. M. Fales and A. V. Robertson, *Tetrahedron Lett.*, No. 3, 111 (1962).

6-(4′-Methoxycyclohexenyl)piperonyl Acetate.—The alcohol **3**, 40 mg, in 1 ml of pyridine was mixed with 0.2 ml of acetic anhydride. After standing overnight at 5°, the solution was evaporated to dryness under reduced pressure. The residue was dissolved in ether, washed with water, and dried with sodium sulfate to give 42 mg of 90% purity as shown by glpc: $[\alpha]_{589}$ +10.4° (*c* 0.23); ν_{max} 1725 cm^{-1}; nmr 6.87 (C-2, s, 1), 6.64 (C-5, s, 1), 5.94 (OCH_2O, s, 2), 5.46 (C-2′, br, 1), 5.01 (α-C, s,

CHART I

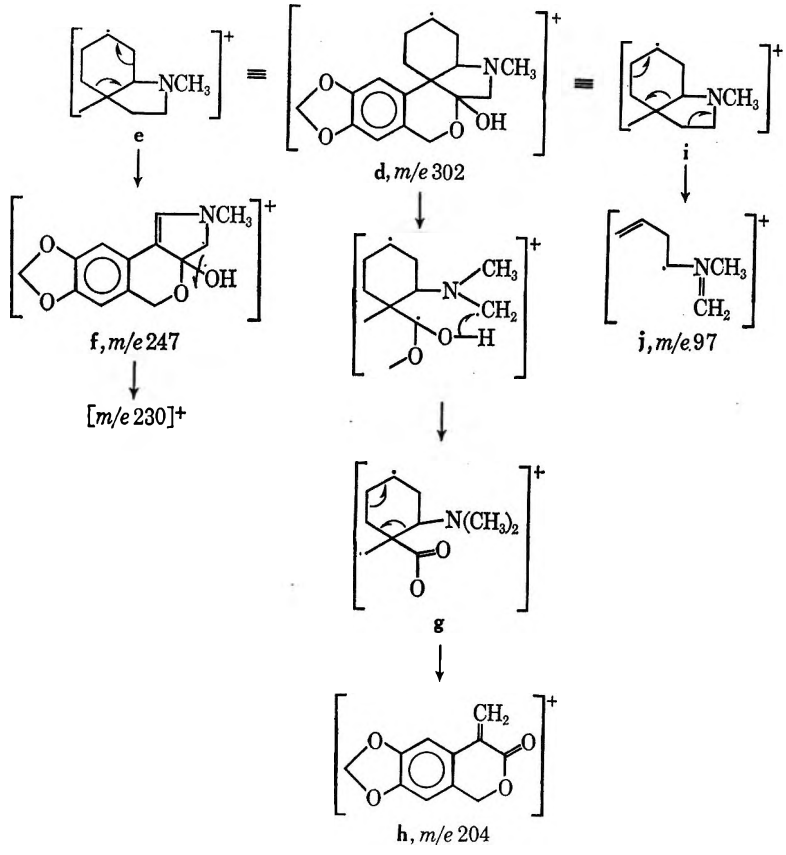


TABLE III

MASS SPECTRA OF FLUORENE DERIVATIVES AND LACTONES

Compd	m/e (relative intensity)
11	245 (9), 244 (26), 213 (5), 212 (17), 210 (5), 187 (23), 186 (100), 185 (15), 156 (8), 152 (5), 128 (25), 115 (7), 77 (5), 76 (8), 71 (7), 63 (5), 55 (5), 45 (6), 44 (8), 43 (6), 41 (5)
11, 1,2-d_2	247 (12), 246 (29), 245 (9), 214 (11), 188 (22), 187 (100), 186 (38), 185 (7), 157 (8), 156 (5), 154 (5), 130 (6), 129 (19), 128 (10), 116 (6), 77 (5), 44 (12)
12	243 (21), 242 (100), 227 (7), 212 (8), 211 (19), 210 (41), 209 (6), 199 (6), 198 (9), 197 (34), 181 (13), 180 (19), 169 (10), 168 (5), 167 (7), 153 (15), 152 (29), 151 (8), 141 (10), 140 (9), 139 (23), 128 (5), 126 (5), 115 (9), 76 (9), 69 (5), 44 (5)
12, 2-d and 12, 1,2-d_2	246 (14), 245 (44), 244 (100), 243 (96), 242 (13), 229 (8), 228 (8), 214 (13), 213 (35), 212 (62), 211 (48), 210 (15), 200 (19), 199 (39), 198 (38), 183 (23), 182 (40), 181 (28), 171 (14), 170 (17), 169 (14), 155 (29), 154 (52), 153 (48), 152 (22), 143 (18), 142 (25), 141 (40), 140 (34), 139 (11), 116 (14), 77 (15), 76.5 (11), 44 (28)
13	241 (16), 240 (100), 226 (9), 225 (50), 210 (4), 197 (2), 182 (4), 167 (6), 139 (20), 120 (11)
14	211 (18), 210 (100), 209 (9), 181 (10), 180 (46), 153 (19), 152 (90), 151 (28), 150 (16), 126 (7), 105 (6), 104 (6), 76 (28), 75.5 (5), 75 (10), 74 (6), 63 (10), 51 (6), 44 (29)
15	292 (11), 204 (5), 192 (5), 191 (19), 190 (100), 189 (5), 149 (9), 148 (6), 134 (8), 120 (6), 89 (10), 71 (21), 59 (6), 44 (7), 41 (5)
16	292 (15), 216 (5), 204 (7), 191 (18), 190 (100), 189 (7), 188 (6), 149 (10), 148 (8), 134 (9), 120 (10), 119 (5), 89 (10), 77 (5), 71 (22), 65 (7), 63 (7), 62 (7), 59 (5), 57 (5), 55 (6), 51 (5), 44 (6), 43 (6), 41 (12)

2), 3.40 (OCH_3, s, 3), *ca.* 3.5 (C-4′, m, 1), *ca.* 2.3 (C-3′ and C-6′, m, 4), *ca.* 2.0 (C-5′, m, 2).

Anal. Calcd for $C_{17}H_{20}O_5$: *m/e*, 304.131. Found: *m/e*, 304.126.

6-(4′-Methoxycyclohexenyl)piperonal (4).—A solution of 300 mg of the above alcohol in 30 ml of chloroform was stirred for 6 hr at room temperature with 3 g of manganese dioxide;[20] the suspension was filtered and the filtrate concentrated to dryness under reduced pressure to leave a residue of 292 mg, mp 70°. Recrystallization from methanol provided rectangular plates of mp 73–74°; $[\alpha]_{589}$ +28.7° (c 0.54); λ_{max} 238 mμ (ε 22,100), 278 (6800), and 321 (6800) [*cf.* piperonal: λ_{max} 275 mμ (6300) and 315 (10,000)]; ν_{max} 1667, 1610, 1036, and 935 cm^{-1}; nmr 10.07 (α-C, s, 1), 7.38 (C-2, s, 1), 6.75 (C-5, s, 1), 6.04 (OCH_2O, s, 2), 5.55 (C-2′, m, 1), 3.65 (C-4′, br, 1), 3.41 (OCH_3, s, 3), *ca.* 2.4 (C-3′ and C-6′, br), *ca.* 1.95 (C-5′, br).

Anal. Calcd for $C_{15}H_{16}O_4$: C, 69.21; H, 6.20; *m/e*, 260.105. Found: C, 68.98; H, 6.31; *m/e*, 260.108.

2-Methoxy-6,7-methylenedioxy-1,2,3,4-tetrahydrofluorene (11) (7-Methoxy-5,6,7,8-tetrahydro[9H]fluoreno[2,3-*d*]-1,3-dioxole).—A 150-mg sample of dihydrotazettine methine was dissolved in 4 ml of 1 *N* hydrochloric acid and heated on a steam bath 30 min. The suspension was diluted with brine and extracted with ether; the ethereal solution was washed with water and dried over sodium sulfate. The suspension was filtered and concentrated to dryness under reduced pressure to provide 102 mg of the tetrahydrofluorene; examination of the crude material by glpc and tlc (15% ether in benzene) showed it to be essentially pure. Crystallization from methanol provided material with mp 96–98°; $[\alpha]_{436}$ +91.6°, $[\alpha]_{589}$ +42.9° (*c* 1.01); λ_{max} 278 mμ (ε 6700), 307.5 (5800), and 320 sh (4350); ν_{max} 1635, 1605, 1035, 938 cm^{-1}; nmr 6.88 (C-8, s, 1), 6.67 (C-5, s, 1), 5.90 (OCH_2O, s, 2), *ca.* 3.6 (C-2, m, 1), 3.40 (OCH_3, s, 3), *ca.* 3.1 (C-9, br, 2), *ca.* 2.4 (C-1 and C-4, m, 4), *ca.* 2.0 (C-3, m, 2).

Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60; *m/e*, 244.110. Found: C, 73.60; H, 6.59; *m/e*, 244.109.

2-Methoxy-6,7-methylenedioxy-1,2-dihydro[3H]isofluorene (12) (7-Methoxy-7,8-dihydro[6H]fluoreno[2,3-*d*]-1,3-dioxole).—A suspension of 42 mg of the aldehyde 4 in 5 ml of 1 *N* hydrochloric acid was heated on a steam bath for 1 hr; yellow crystals formed

(20) J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jensen, and T. Walker, *J. Chem. Soc.*, 1094 (1952).

promptly during the heating. The suspension was distilled to dryness under reduced pressure; the residue was dissolved in ether; the ethereal solution was washed with sodium bicarbonate solution and brine and dried over sodium sulfate. Distillation of the ether left a residue of 40 mg which was shown by gas chromatography to be essentially pure. In an alternative preparation, 75 mg of the aldehyde was dissolved in 1 ml of 6 *N* hydrochloric acid. The solution was warmed on a steam bath for 10 min, then allowed to cool. The yellow precipitate was separated by centrifugation, washed with water and ethanol, and dried under reduced pressure, yielding 41 mg of material, mp 140°. Recrystallization from methanol provided golden prisms: mp 142–143°; $[\alpha]_{589}$ +38.4° (*c* 0.08); λ_{max} 272 mμ (ε 19,800), 277 (18,800), 282 (19,100), 320 (6300), and 389 (400); ν_{max} (CS_2) 1037, 940, 855, and 811 cm^{-1}; nmr 7.00 (C-8, s, 1), 6.72 (C-5, s, 1), 6.66 (C-4, t, br, 1), 6.34 (C-9, s, br, 1), 5.93 (OCH_2O, s, 2), *ca.* 3.65 (C-2, m, 1), 3.40 (OCH_3, s, 3), *ca.* 2.8 (C-1 and C-3, br, 4).

Anal. Calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.83; *m/e*, 242.094. Found: C, 74.36; H, 5.93; *m/e*, 242.096.

Dehydrogenation Experiments.—A 25-mg sample of the tetrahydrofluorene **11** was mixed with 100 mg of palladized charcoal (5%) and heated under nitrogen for 20 min in an oil bath maintained at 200°. The residue was dissolved in chloroform, the suspension was filtered through Celite, and the filtrate was evaporated to dryness to provide 15 mg of a mixture which was shown by glpc (190°) to be approximately 17% the fluorene **14** (retention time, 3.7 min) and 83% the methoxyfluorene **13** (8.5 min). Separation by preparative tlc (benzene–petroleum ether, 3:2) provided small samples of 2,3-methylenedioxyfluorene **14**, R_f 0.41, mp 111.5–113° after being sublimed at 80°, 0.001 mm and recrystallized from methanol, and 7-methoxy-2,3-methylenedioxyfluorene **13**, R_f 0.22, mp 158–159.5° after being sublimed and recrystallized from ethyl acetate.

The fluorene **14** showed these spectral properties: λ_{max} 270 mμ sh (ε 9000), 275 (10,000), 291 (6000), 315 sh (9500), 322 (11,000), and 327 (10,500); ν_{max} (CS_2) 1036, 941, 840, 761, and 724 cm^{-1}; nmr *ca.* 7.2 (aromatic, br, 6), 5.92 (OCH_2O, s, 2), 3.67 (C-9, s, 2).

Anal. Calcd for $C_{14}H_{10}O_2$: *m/e*, 210.068. Found: *m/e*, 210.071.

The 7-methoxy-2,3-methylenedioxyfluorene **13** showed the following spectral properties: λ_{max} 235 mμ (ε 9000), 280 (13,000), 298 (9000), 323 sh (9000), and 333 (10,000); ν_{max} (CS_2) 1033, 941, 840, 833, 816, 803, 754, and 740 cm^{-1}; nmr *ca.* 7.2 (aromatic, br, 5), 5.97 (OCH_2O, s, 2), 3.85 (OCH_3, s, 3), 3.72 (C-9, br, 2).

Anal. Calcd for $C_{15}H_{12}O_3$: *m/e*, 240.079. Found: *m/e*, 240.077.

In a similar manner, a 23-mg sample of 2-methoxy-6,7-methylenedioxy-1,2-dihydro[3H]isofluorene (**12**) was heated under nitrogen with 100 mg of 5% palladized charcoal at 200° to provide 10 mg of a similar mixture, which was again separated by preparative thin layer chromatography to give 2,3-methylenedioxyfluorene and 7-methoxy-2,3-methylenedioxyfluorene. The two products were identical in all respects with the fluorene **14** and the methoxyfluorene **13**.

6-(4′-Methoxycyclohexenyl)piperonylic Acid (5).—A solution of 590 mg of the aldehyde in 6 ml of 50% sodium hydroxide and 15 ml of ethanol diluted to 30 ml with water was heated on a steam bath and treated with approximately 30 ml of 30% hydrogen peroxide in 1-ml portions. Addition and heating were at rates sufficient to maintain foaming; total addition time was 90 min. Most of the ethanol was then boiled off, and the mixture was diluted with water and extracted three times with chloroform. The chloroform was washed with water and brine and evaporated under reduced pressure to give 29 mg of neutral material.

The aqueous solution was acidified with hydrochloric acid and extracted repeatedly with chloroform and 4:1 chloroform–ethanol; the organic layers, when washed with water and brine and concentrated under reduced pressure, provided 477 mg of material of mp 145–175° after trituration with acetone. This was recrystallized twice from acetone to yield 186 mg of colorless needles: mp 170–173°; $[\alpha]_{589}$ +40°, $[\alpha]_{436}$ +84°, $[\alpha]_{380}$ +125.5° (*c* 1.20); λ_{max} 252 mμ (ε 7850) and 294 (5060); ν_{max} 2620 (OH, br), 1685 (C=O), 1612 (aromatic), 1035, 932 (OCH_2O); nmr, *ca.* 10.1 (COOH, br, 1), 7.43 (C-2, s, 1), 6.63 (C-5, s, 1), 6.00 (OCH_2O, s, 2), *ca.* 5.42 (C-2′, br, 1), *ca.* 3.6 (C-4′, br, 1), 3.40 (OCH_3, s, 3), 2.5–2.1 (C-3′ and C-6′, br, *ca.* 4), 2.1–1.8 (C-5, br, *ca.* 2).

Anal. Calcd for $C_{15}H_{16}O_5$: *m/e*, 276.100. Found: *m/e*, 276.101.

Performic Acid Treatment of 6-(4′-Methoxycyclohexenyl)-piperonylic Acid.—A solution of 150 mg of the acid **5**, mp 170–173°, in 20 ml of ether was stirred with 210 mg of sodium acetate trihydrate, 1.5 ml of 88% formic acid, and 2 ml of 30% hydrogen peroxide for 18 hr at room temperature. The mixture was diluted with water, made basic with potassium bicarbonate, and extracted three times with ether, which was then washed twice with water and twice with brine, and concentrated to dryness under reduced pressure to provide 169 mg of a crystalline residue. Tlc (benzene–dioxane–acetic acid, 90:25:4) showed three products: a minor component with blue fluorescence under λ 254 mμ, R_f 0.42, imperfectly separated from A; A, R_f 0.45; and B, R_f 0.64. Glpc showed 10% the minor component, 30% A, and 60% B. Fractional crystallization from ethyl acetate provided 65 mg of slightly impure B and, on concentration, 34 mg of A. Chromatography on silicic acid (above solvents) and repeated recrystallization provided analytical samples of A and B.

A, mp 182–185°, was recrystallized from benzene: $[\alpha]_{589}$ +32°, $[\alpha]_{436}$ +76°, $[\alpha]_{350}$ +199° (c 0.438); ν_{max} (dil CCl_4) 3632 cm^{-1}; ν_{max} ($CHCl_3$) 1752 (C=O), 1612 (aromatic), 1035, and 935 cm^{-1} (OCH_2O); λ_{max} 223 mμ (ε 27,600), 258 (5600), 301 (7160), unchanged by base; nmr 7.15 (C-2?, s, 1), 7.02 (C-5?, s, 1), 6.00 (OCH_2O, s, 2), 3.83 (C-2′ and C-4′, br, 2), 3.38 (OCH_3, s, 3), 2.53 (OH, eliminated by exchange with D_2O,[19] br, 1), 2.2–1.0 (br).

Anal. Calcd for $C_{15}H_{16}O_6$: *m/e*, 292.095. Found: *m/e*, 292.094.

B, mp 178–181°, was recrystallized from ethyl acetate: $[\alpha]_{589}$ −87°, $[\alpha]_{436}$ −183°, $[\alpha]_{350}$ −399° (c 0.519); ν_{max} (dil CCl_4) 3490 cm^{-1}; ν_{max} ($CHCl_3$) 1748 (C=O), 1612 (aromatic), 940 (OCH_2O); λ_{max} 223 mμ (ε 27,300), 258 (5340), 301 (700), unchanged with base; nmr 7.12 (C-2, C-5, s, 2), 6.08 (OCH_2O, s, 2), 4.33 (OH, eliminated by exchange with D_2O, d, J = 10, 1), 3.75 (C-2′, t, br, 1), 3.55 (C-4′, br, 1), 2.5–1.3 (br); mmp 148–171° with A.

Anal. Calcd for $C_{15}H_{16}O_6$: *m/e*, 292.095. Found: *m/e*, 292.093.

Attempted Oxidation of the Acetate.—To a solution of 30 mg (0.1 mmol) of the acetate of **3** in 2 ml of purified acetone was added 0.0158 g (0.1 mmol) of potassium permanganate in 0.5 ml of water. No change in color was seen after 20 min. The precipitate which formed after 2 hr of stirring was removed by filtration. The filtrate was evaporated to dryness, washed with sodium thiosulfate solution, and extracted with chloroform to give almost complete recovery of unreacted acetate as shown in the nmr spectrum.

Oxodihydrohaemanthamine Methine (10).—The low solubility of the perchlorate in D_2O made it impossible to determine the chemical shifts of broadened peaks accurately. The singlets observed were at 7.03 (C-5), 6.70 (C-2), 6.02 (OCH_2O), 4.38 (α), 3.93 (α′), 3.43 (OCH_3), and 2.85 ($N\text{-}CH_3$). The salt was more soluble in NaOD solution: nmr 7.05 (C-5, s, 1), 6.45 (C-2, s, 1), 5.90 (OCH_2O, s, 2), 5.30 (C-2′, m, 1), 3.50 (α and C-4′, br, 3), 3.40 (OCH_3, s, 3), 3.04 (α′, s, 2), 2.16 ($N\text{-}CH_3$, s, 3); the remaining alicyclic protons formed a broad peak between 1.6 and 2.5.

Tazettadiol.[14]—A solution of 1.535 g (4.61 mmol) of tazettine in 50 ml of dry tetrahydrofuran was heated to reflux whereupon 0.6 g of lithium aluminum hydride was added in small portions. After a 43-hr reflux period the reaction was worked up as usual to yield 1.502 g (97.5%) of a colorless glass that crystallized on trituration with ether–water–ethanol. Recrystallization from ethanol–ether containing a few drops of water gave the hydrate in two crops which were dried at 80° (0.01 mm) to give 1.123 g (73%) of anhydrous tazettadiol.[2]

Deoxytazettine.[14]—To 1.075 g of anhydrous tazettadiol was added 15 ml of 3% aqueous sulfuric acid. A slight cloudiness developed. The solution was heated on a steam bath for 1.5 hr, then diluted with water, washed once with ether, basified with concentrated sodium hydroxide solution, and finally extracted with three portions of ether. The dried combined ethereal solutions were evaporated to leave 919 mg of partially crystalline glass. Recrystallization from ether gave 629 mg (62%) of large colorless prisms, mp 133–138°. A second recrystallization raised the melting point to 136–138° (lit.[2] mp 135–136°).

Deoxytazettine Methiodide.[14]—A solution of 513 mg of deoxytazettine, 7 ml of absolute methanol, and 4 ml of redistilled

methyl iodide was refluxed for 3 hr. The clear solution was evaporated to dryness, and the resulting oil was recrystallized from acetone–methanol to give 632 mg (85%) of stout yellowish prisms in two crops, mp 236–237.5° dec when put on the hot stage at 200° (lit.[2] mp 231–233°).

Deoxytazettine Methine.[14]—A mixture of 250 mg of deoxytazettine methiodide and 8 ml of water was stirred until the methiodide was in solution. Then the freshly prepared silver oxide (neutral) from 0.3 g of silver nitrate was added and the mixture stirred for 15 min more when a test portion showed no iodide ion to be present. The insoluble silver salts were removed by filtration through a layer of Filter-Cel. The colorless clear filtrate was evaporated to dryness *in vacuo*, and the residue was heated at 100° for 30 min under aspirator vacuum. The reaction product was dissolved in benzene and separated from some insoluble material. Evaporation of the benzene left 177 mg (98%) of colorless methine which was chromatographed on 5 g of activity I Merck alumina. Benzene and benzene–ether combinations eluted a total of 145 mg (80%) of methine. A middle fraction had $[\alpha]^{27}_{589}$ −73° (*c* 2.45 in 95% ethanol) (lit.[2] $[\alpha]^{17}_{589}$ −64.2°). The material was a colorless glass that did not crystallize.

Deoxytazettine Neomethine.[14]—Chromatographed deoxytazettine methine (96 mg) was dissolved in 10 ml of 5% hydrochloric acid at room temperature. The solution became cloudy within a few seconds and then deposited crystals. After 1 hr the reaction mixture was washed with two portions of ether. The aqueous layer was basified with concentrated sodium hydroxide solution and extracted with three portions of ether. The ethereal solutions were dried and evaporated to leave 54 mg (62%) of colorless glass, $[\alpha]^{27}_{589}$ −40° (*c* 2.65 in 95% ethanol).

Deoxytazettine Neomethine Methiodide.[14]—(The solution used for the optical rotation was recovered and used.) Deoxytazettine neomethine (52 mg) was dissolved in a mixture of redistilled methyl iodide and acetone (several milliliters) and allowed to stand at room temperature for 20 hr. The acetone and methyl iodide were evaporated to leave 77 mg (99%) of glass which crystallized on trituration with 1 drop of methanol. One recrystallization from acetone–methanol gave 63 mg: mp 254–255.5° dec, $[\alpha]^{27}_{589}$ −5.4° (*c* 1.65, 95% ethanol). A second recrystallization from acetone–methanol raised the melting point to 257–258° dec, $[\alpha]^{27}_{589}$ −5.4° (*c* 1.38, 95% ethanol) {lit. mp 251° dec, $[\alpha]^{18}_{589}$ ±0° (*c* 0.51, ethanol)[2]}.

Registry No.—**1**,[21] 16831-68-8; **2**, 16831-69-9; picrate of **2**, 16831-70-2; **3**, 7111-88-8; acetate of **3**, 16831-72-4; **4**, 16831-73-5; **5**, 16831-74-6; **10**, 16831-75-7; **11**, 16831-76-8; **11**, 1,2-d_2, 16831-21-3; **12**, 16831-22-4; **12**, 2-d, 16831-23-5; **12**, 1,2-d_2, 16831-24-6; **13**, 16831-25-7; **14**, 242-90-0; **15**, 16831-27-9; **16**, 16831-28-0.

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(21) Methiodide.

The Absolute Configuration of Alkaloids Related to Crinine, Tazettine, and Manthine

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Oxidation of dihydrotazettine methine alcohol to (+)-(*R*)-2-methoxyadipic acid establishes unequivocally the stereochemistry of C-3 of tazettine and, hence, of related alkaloids, previously assigned on the basis of Mills' rule. Studies on dideuteriotazettine demonstrate the course of the Hofmann reaction leading to the critical derivative. Compilation of 17 pairs of interrelated epimers shows that Mills' rule may be applied with consistency throughout the group.

One of the results of the extensive investigations of the alkaloids of the *Amaryllidaceae* has been to establish a sizable group, to date comprising some 30 natural materials,[1] of interrelated compounds with the fundamental ring systems of tazettine, crinine, or manthine. The structures and stereochemistry of the three groups have been securely interrelated by studies on two key members, haemanthamine (**1**) and haemanthidine (**3**). Thus hydrogenolysis of diacetyl haemanthidine (**4**) provides dihydrohaemanthamine acetate (**2**) while treatment of haemanthidine with base provides nortazettine (**5**).[2] The interrelation is confirmed by the conversion of tazettine (**6**) by successive treatment with lithium aluminum hydride and with thionyl chloride and pyridine to the methiodide of the C-11 epimer of haemanthamine.[3] Treatment of haemanthamine (**1**) by methanesulfonyl chloride in pyridine and then by methanolic sodium methoxide converts the alkaloid into manthine (**7**).[4] Exhaustive chemical and spectral studies have established the structural and stereochemical relations of the various hydroxyl- and methoxyl-bearing analogs within the groups and the stereochemistry of the ring junctions.[5,6]

The absolute configuration of this series of alkaloids has been assigned on the basis of Mills' rule,[7] which states that a 2-cyclohexenyl derivative of the configuration of **8** will possess a more positive rotation

(1) Review articles list the following related alkaloids: crinine (crinidine), vittatine, (+)-epicrinine, powelline, buphanidrine, buphanisine, undulatine, crinamidine, flexinine, nerbowdine, buphanamine, haemanthamine, haemanthidine, 6-hydroxycrinamine, criwelline, isotazettine, and haemultine. *Cf.* W. C. Wildman in "The Alkaloids," Vol. VI, R. H. F. Manske, Ed., Academic Press Inc., New York, N. Y., 1960, p 289; H.-G. Boit, "Ergebnisse der Alkaloid-Chemie bis 1960," Academie-Verlag, Berlin, 1961, p 410. Later work has assigned the following alkaloids to this group: (a) montanine, coccinine, and manthine: Y. Inubushi, H. M. Fales, E. W. Warnhoff, and W. C. Wildman, *J. Org. Chem.*, **25**, 2153 (1960); (b) crinamine: H. M. Fales and W. C. Wildman, *J. Amer. Chem. Soc.*, **82**, 197 (1960); (c) epihaemanthidine: J. Goosens, P. W. Jeffs, J. Graham, F. L. Warren, and W. G. Wright, *J. Chem. Soc.*, 1088 (1960); (d) epibuphanisine: H. Hauth and D. Stauffacher, *Helv. Chim. Acta*, **45**, 1307 (1962); (e) ambelline: P. Naegeli, E. W. Warnhoff, H. M. Fales, R. E. Lyle, and W. C. Wildman, *J. Org. Chem.*, **28**, 206 (1963); (f) acetylnerbowdine: H. Hauth and D. Stauffacher, *Helv. Chim. Acta*, **46**, 810 (1963); (g) cripaline: W. Doepke, *Arch. Pharm.* (Weinheim), **295**, 868 (1962); (h) squamigerine: S. H. Hung and K. E. Ma, *Yao Hseuh Hsueh Pao*, **11**, 1 (1964); *Chem. Abstr.*, **61**, 3154 (1964); (i) amaryllisine: A. L. Burlingame, H. M. Fales, and R. J. Highet. *J. Amer. Chem. Soc.*, **86**, 4976 (1964); (j) macronine: C. F. Murphy and W. C. Wildman, *Tetrahedron Lett.*, 3857 (1964); (k) tubispacine: W. Doepke, *Arch. Pharm.* (Weinheim), **298**, 704 (1965); (l) pretazettine: W. C. Wildman and D. T. Bailey, *J. Amer. Chem. Soc.*, **89**, 5515 (1967).

(2) H. Irie, Y. Tsuda, and S. Uyeo, *J. Chem. Soc.*, 1446 (1959).

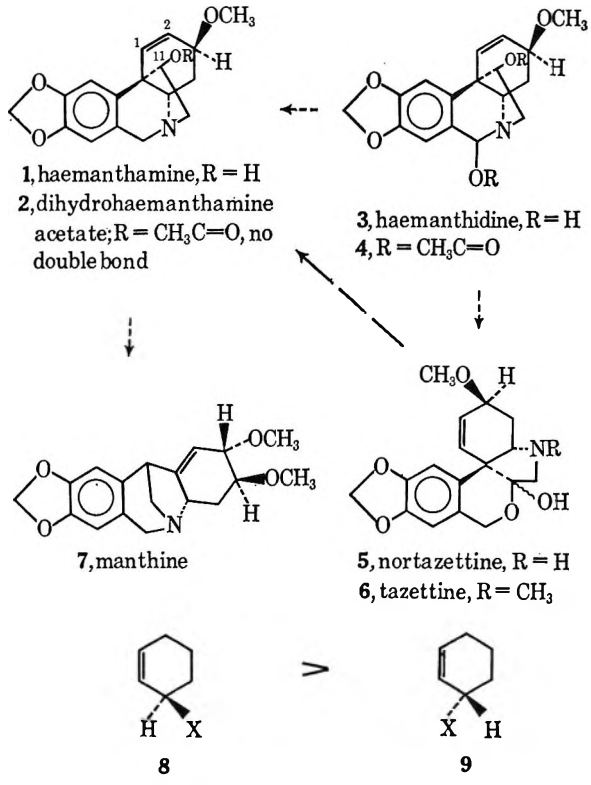
(3) T. Kitagawa, S. Uyeo, and N. Yokayama, *ibid.*, 3749 (1959).

(4) Y. Inubushi, H. M. Fales, E. W. Warnhoff, and W. C. Wildman, *J. Org. Chem.*, **25**, 2153 (1960).

(5) H. M. Fales and W. C. Wildman, *J. Amer. Chem. Soc.*, **85**, 784 (1963).

(6) H. M. Fales and W. C. Wildman, *ibid.*, **82**, 197 and 3368 (1960).

(7) T. Ikeda, W. I. Taylor, Y. Tsuda, S. Uyeo, and H. Yajima, *J. Chem. Soc.*, 4749 (1956).

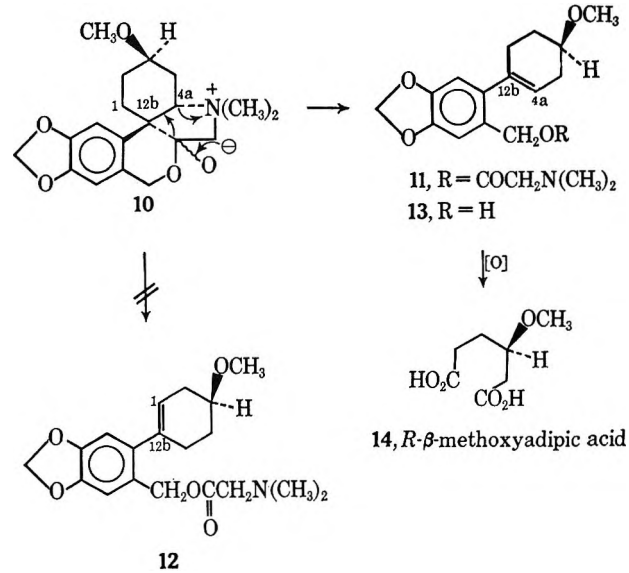


8 **9**

than its epimer, **9**.[8] Early in the work on tazettine it was observed that the rotations of four epimeric pairs of derivatives of tazettine allowed a consistent application of this rule. Tazettine was therefore assigned the configuration of **6**, with the reservation that applying the rule to these alkaloids was uncertain, for it had been derived from studies on steroids.[7] Work to 1960 provided a total of seven pairs, including crinine derivatives, with rotations consistent with the previous assignment.[9] The continuing proliferation of alkaloids and derivatives within the group has now provided at least 17 pairs of epimers, listed in Table I. The series includes a variety of structural types, and the fact that there are no anomalies in rotation strongly suggests that Mills' rule is indeed applicable here. However, there has been no unequivocal evidence on the point, and a recent extensive survey of the optical rotatory dispersion and circular dichroism of structurally related alkaloids has suggested that the assignment must be reversed in the series.[10]

Recently, it has been demonstrated that the product of Hofmann reaction of dihydrotazettine possesses the structure **11**,[11] which retains only one of the asymmetric centers of the parent alkaloid. It appeared likely that this material would provide a basis for relating the series to material of known configuration through its oxidation to β-methoxyadipic acid, the absolute configuration of which has been determined by degradation of calciferol[12] and by synthesis from malic acid.[13] Although the sterically hindered double bond is rather unreactive, exhaustive ozonization and peroxide treatment[14] of recrystallized dihydrotazettine methine alcohol produced a mixture of acids which contained the desired acid in good yield. Preparative gas chromatography of the methyl esters provided a convenient means of isolating this product in sufficient quantity to determine that it was the methyl ester of (+)-(*R*)-β-methoxyadipic acid.

It is now essential to consider the course of the Hofmann decomposition of dihydrotazettine methohydroxide. It has been pointed out[11] that decomposition must occur on the intact hemiacetal, for the ether linkage of the alkaloid appears as the ester linkage of the methine and, furthermore, since the course of the decomposition of O,N-dimethyltazettine proceeds in quite a different manner,[7] that the decomposition in question must involve the hydroxyl group. The course of the reaction is most credibly represented as in process **10** by which the double bond of the methine **11** appears at the atoms C-4a and C-12b of the original alkaloid. However, were the reaction to take an unexpected course with the double bond appearing at the atoms C-12b and C-1 of the parent alkaloid, the product would be the mirror image, **12**. Thus proof of the absolute



configuration of the alkaloid requires that the position of the double bond of dihydrotazettine methine be known in relation to the parent alkaloid. This was shown by running the Hofmann reaction on dideuteriotazettine.

Although catalytic deuteration has been shown to produce extensive isotope exchange at saturated centers in some cases,[15a] the deuteration of tazettine proceeded substantially without exchange. The mass spectrum of the product showed a parent peak at the required *m/e* of 335, with a somewhat enhanced peak at 336. Hofmann decomposition of the methohydroxide and hydrolysis of the methine provided the crystalline alcohol. The vinyl proton appears at δ 5.55 ppm in full strength, and the mass spectrum shows a molecular ion at *m/e* 264, 2 higher than the undeuterated compound, with a negligible peak at 263. If the new double bond were to occur between C-12b and C-1, the product must

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(13) M. Viscontini and P. Miglioretto, *ibid.*, **38**, 930 (1954).
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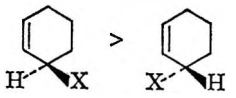
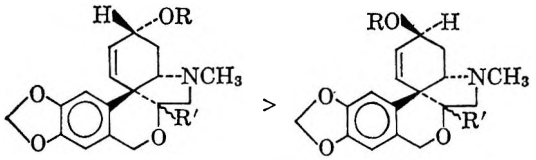
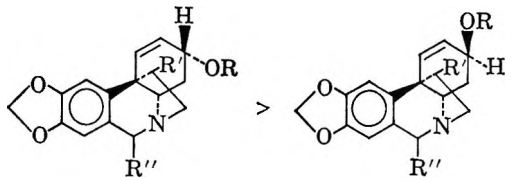
TABLE I

OPTICAL ACTIVITY OF EPIMERIC PAIRS RELATED TO CRININE

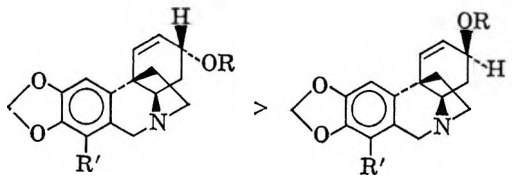




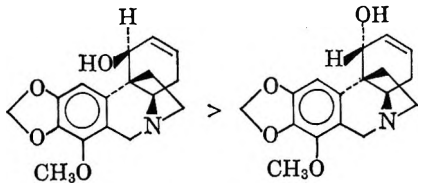
R	R′	R″		MD, deg	Ref		MD	Ref
H	OH		Isotazettinol	+831	*a*	Tazettinol	+377	*a*
H	H		Deoxyisotazettinol	+988	*a*	Deoxytazettinol	+632	*a*
$CH_3C{=}O$	H		Acetyldeoxyisotazettinol	+680	*a*	Acetyldeoxytazettinol	+185	*a*
CH_3	OCH_3		O-Methylisotazettine methiodide	+696	*a*	O-Methyltazettine methiodide	+330	*a*
CH_3	OH		Criwelline	+728	*b*	Tazettine	+536	*c*



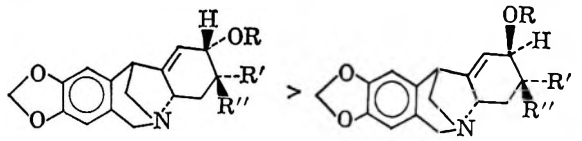
CH_3	OH	H, OH	6-Hydroxycrinamine	+146	*d, e*	Haemanthidine	−130	*f,e*
CH_3	OH	O	6-Oxocrinamine	+91	*g*	Oxohaemanthidine	−130	*h*
CH_3	OH	H_2	Crinamine	+471	*i*	Haemanthamine	+59	*j*
H	H	H_2	(+)-Epicrinine	+368	*k*	Vittatine	+103	*l*



H	H		Crinine	−30	*i*	(−)-Epicrinine	−384	*m*
H	OCH_3		Powelline	0	*n*	Epipowelline	−310	*m*
CH_3	H		Buphanisine	−74	*o*	(−)-Epibuphanisine	−396	*p*



			Epibuphanamine	+69	*q*	Buphanamine	−617	*r*

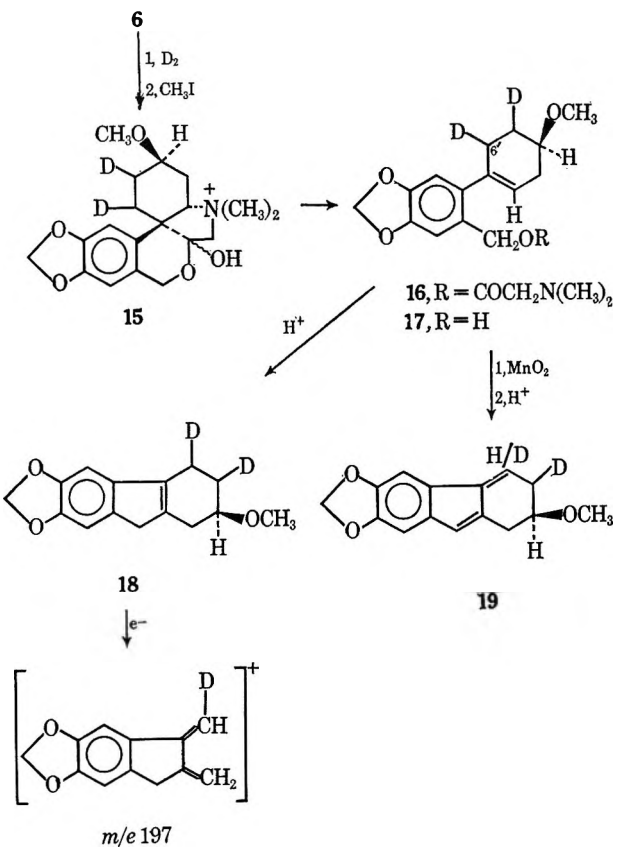


CH_3	H	OH	Montanine	−294	*j*	Coccinine	−569	*j*
			Montanine methiodide	+44.3	*s*	Coccinine methiodide	−268	*j*
H	H	OCH_3	Isohaemanthamine	−219	*s*	Epiisohaemanthamine	−372	*s*
CH_3	H	OCH_3	Manthine	−250	*s*	O-Methylcoccinine	−412	*s*
H	OCH_3	H	β-Isocrinamine	−313	*s*	α-Isocrinamine	−583	*s*

[a] T. Ikeda, W. I. Taylor, Y. Tsuda, S. Uyeo, and H. Yajima, *J. Chem. Soc.*, 4749 (1956). [b] H.-G. Boit and H. Ehmke, *Chem. Ber.*, **89**, 2093 (1956). [c] W. C. Wildman and C. J. Kaufman, *J. Amer. Chem. Soc.*, **76**, 5815 (1954). [d] H. M. Fales, D. H. S. Horn, and W. C. Wildman, *Chem. Ind.* (London), 1415 (1959). [e] It has recently been shown that 6-hydroxycrinamine and haemanthidine exist in solution as mixtures of the C-6 epimers. R. W. King, C. F. Murphy, and W. C. Wildman, *J. Amer. Chem. Soc.*, **87**, 4912 (1965). [f] H.-G. Boit, *Chem. Ber.*, **87**, 1339 (1954). [g] J. Goosen, P. W. Jeffs, J. Graham, F. L. Warren, and W. G. Wright, *J. Chem. Soc.*, 1088 (1960). [h] S. Uyeo, H. M. Fales, R. J. Highet, and W. C. Wildman, *J. Amer. Chem. Soc.*, **89**, 2590 (1958). [i] L. H. Mason, E. R. Puschett, and W. C. Wildman, *ibid.*, **77**, 1253 (1955). [j] W. C. Wildman and C. J. Kaufman, *ibid.*, **77**, 1248 (1955). [k] R. E. Lyle, E. A. Kielar, J. R. Crowder, and W. C. Wildman, *ibid.*, **82**, 2620 (1960). [l] H.-G. Boit, *Chem. Ber.*, **89**, 1129 (1956). [m] W. C. Wildman, *J. Amer. Chem. Soc.*, **80**, 2567 (1958). [n] H.-G. Boit and H. Ehmke, *Chem. Ber.*, **88**, 1590 (1955). [o] H. M. Fales and W. C. Wildman, *J. Amer. Chem. Soc.*, **82**, 3368 (1960). [p] H. Hauth and D. Stauffacher, *Helv. Chim. Acta*, **45**, 1307 (1962). [q] H. M. Fales and W. C. Wildman, *J. Org. Chem.*, **26**, 881 (1961). [r] J. Renz, D. Stauffacher, and E. Seebeck, *Helv. Chim. Acta*, **38**, 1209 (1955). [s] Y. Inubushi, H. M. Fales, E. W. Warnhoff, and W. C. Wildman, *J. Org. Chem.*, **25**, 2153 (1960).

either possess a vinyl deuterium atom or must have lost a deuterium in the course of decomposition; or, in the likely event that either the reduction or decomposition occur without stereospecificity, some combination of these two states must exist.

The location assigned these deuterium atoms was further established by study of known derivatives of the methine. Acid treatment of the methine, **16**, provided the dideuteriodihydrofluorene **18**, with the anticipated nmr spectrum. The mass spectrum of this material is characterized by a base peak resulting from the familiar "reverse Diels–Alder" process;[15b] in this case the methyl vinyl ether fragment lost from the dideuterated parent (*m/e* 246) contained a single deuterium atom. As a result, the base peak at *m/e* 197 is one more than that of undeuterated material and is consistent with the assigned position. Oxidation of the alcohol **17** by manganese dioxide provided the aldehyde, which was



converted by acid treatment into the isofluorene derivative **19**. This cyclization involved the loss of a proton or deuterium from C-6′ of the aldehyde, producing a mixture of dideuterio and monodeuterio material, characterized by a vinyl proton of half strength in the nmr and a mass spectrum with parent peaks of 243 and 244 of equal height.

Thus the study of the derivatives of dideuteriotazettine confirms that the double bond of the methine is situated at C-4a and C-12b of the original alkaloid. The stereochemical relation of the alkaloid, the methine, and the methoxyadipic acid are as depicted in **10**, **11**, and **14**, and the isolation of a dextrorotatory sample of the last compound substantiates the earlier assignment of the absolute configuration.

Experimental Section[16]

Degradation of Dihydrotazettine Methine Alcohol to β-Methoxyadipic Acid.[14]—Ozone was bubbled through a solution of 122 mg of dihydrotazettine methine alcohol[11] in 10 ml of 10:1 chloroform–ethanol for 5 hr, the solvent being replenished as necessary. The solution was allowed to stand overnight, then concentrated to dryness under reduced pressure. The residue was refluxed for 1 hr in a mixture of 2 ml each of formic acid and hydrogen peroxide, again concentrated to dryness under reduced pressure to yield 125 mg of material which was estimated by glpc to contain 49 mg of β-methoxyadipic acid, contaminated with materials of lower molecular weight. The sample was methylated with diazomethane and purified by glpc, using a 12 ft × 4 mm glass column, packed with 100–120 mesh Gas-Chrom P coated with 20% Reoplex 400, at 165°, with argon carrier gas at a pressure of 15 psi. Fractions were collected by condensing the carrier gas with liquid nitrogen. Center cuts of the appropriate peak produced 12 mg of dimethyl β-methoxyadipate, identical with authentic dimethyl *dl*-β-methoxyadipate in ir and mass spectrum and glpc on three columns: retention times on a 12-ft column of 20% Reoplex 400 on 100–120 mesh Gas-Chrom P at 180°, 15 psi, 5.2 min; on a 6-ft column of 1% SE-33 on 80–100 mesh Gas-Chrom P at 120°, 20 psi, 3.5 min; on a 6-ft column of 3% OV-17 on 60–80 mesh Gas-Chrom Q at 120°, 15 psi, 3.9 min; $[\alpha]^{25}_{589}$ +8.50°, $[\alpha]_{436}$ +16.9, $[\alpha]_{350}$ +30.0, $[\alpha]_{300}$ +48.2, $[\alpha]_{260}$ +72.8 (*c* 0.103, $CHCl_3$); ir ($CHCl_3$) 1723 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 204 (0.1), 189 (1), 174 (5), 173 (15), 157 (4), 141 (22), 131 (57), 118 (6), 117 (31), 113 (15), 109 (7), 101 (9), 99 (19), 89 (11), 85 (10), 81 (5), 75 (100), 74 (6), 72 (8), 71 (84), 59 (28), 58 (7), 55 (11), 53 (6), 47 (6), 45 (8), 43 (11), 41 (16).

Synthetic (−)-(*S*)-β-Methoxyadipic Acid and Dimethyl Ester.—Authentic *dl*-β-methoxyadipic acid was prepared by the method of Viscontini and Kohler[17] and resolved by converting material of mp 84.5–87° (lit. mp 85–86°) into the strychnine salt and recrystallizing from water until regenerated portions of the acid showed no further change of rotation. The acid was regenerated by chromatography on Dowex 50 and recrystallized from ether–petroleum ether: mp 71–74.5° (lit.[18] mp 74–75°); $[\alpha]^{25}_{589}$ −14.0°, $[\alpha]_{436}$ −28.2°, $[\alpha]_{350}$ −49.7° (*c* 4.97, $CHCl_3$) (lit.[18] $[\alpha]^{18}_{D}$ −14.5 ± 1.5°, $CHCl_3$).

A 51-mg sample of the (−)-(*S*) acid was treated with diazomethane to provide 61 mg of the methyl ester, which was distilled at 50° (3 μ) to produce material of $[\alpha]^{25}_{589}$ −10.3°, $[\alpha]_{436}$ −20.9, $[\alpha]_{350}$ −35.7, $[\alpha]_{300}$ −56.2, $[\alpha]_{260}$ −85.2 (*c* 0.130, $CHCl_3$).

Dideuteriotazettine was prepared by stirring a solution of 386 mg of tazettine in ethanol-*d* under deuterium in the presence of 167 mg of 10% palladium on charcoal. The product was purified as usual by chromatography on alumina and crystallization from benzene–hexane to yield 251 mg of material of mp 164–167° and 33 mg of less pure material of mp 161–165°. The infrared spectrum differed from that of dihydrotazettine primarily by having a small peak at 2175 cm^{-1}. The nmr differed only in the integrated strength of the broad peaks at *ca.* 2 ppm.

The other deuterated compounds were prepared from this material by previously described methods.[11]

The Hofmann reaction was run on 124 mg and yielded 130 mg (101%) of methine. A 100-mg sample of this was hydrolyzed to 75 mg of the alcohol, which was chromatographed and recrystallized from ether–pentane to give 56 mg (74%) of material of mp 63–64°.

Acid cyclization of 15 mg of the alcohol produced 10 mg (71%) of material, which was crystallized three times from methanol to give 4 mg (29%) of mp 90–92°.

Oxidation of 29 mg of the alcohol with manganese dioxide gave 26 mg of the aldehyde, recrystallized from methanol to 17 mg (59%) of mp 65–68°.

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(16) Melting points were observed on a Kofler microscope hot stage and are corrected. Rotations were measured with a Rudolph photoelectric spectropolarimeter using a 2-dm tube or with a Cary 60 recording spectropolarimeter in 1-cm cells. Infrared spectra were recorded on a Perkin-Elmer Model 21. Nmr measurements were obtained on a Varian A-60 spectrometer in deuteriochloroform solution, using tetramethylsilane (δ 0.0) as an internal standard. Mass spectra were determined with a single-focusing LKB mass spectrometer equipped with a gas chromatographic inlet.

(17) M. Viscontini and H. Köhler, *Helv. Chim. Acta*, **37**, 41 (1954).

(18) A. Lardon and T. Reichstein, *ibid.*, **32**, 1613 (1949).

A 19-mg sample of the aldehyde was cyclized with acid and the product crystallized twice from methanol to yield 9 mg (53%) of yellow crystals, mp 131.5–137.5°. Further recrystallization (four times) produced material of mp 138–142°.

Registry No.—Tazettine, 507-79-9; dihydrotazettine methine alcohol, 16831-67-7; (−)-(*S*)-β-methoxyadipic acid dimethyl ester, 16859-76-0; dieuteriotazettine, 16831-30-4.

The Perchloric Acid Catalyzed Acetic Anhydride Enol Acetylation of Steroidal Δ4-3 Ketones

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Received February 12, 1968

The perchloric acid catalyzed acetic anhydride acylation of 17β-hydroxyandrost-4-en-3-one gave complex mixtures of products in which both O and C acylation occurred. The major constituents of the reaction were 3,17β-diacetoxy-2-acetylandrosta-2,4-diene (6) and 3,17β-diacetoxy-6-acetylandrosta-3,5-diene (3).

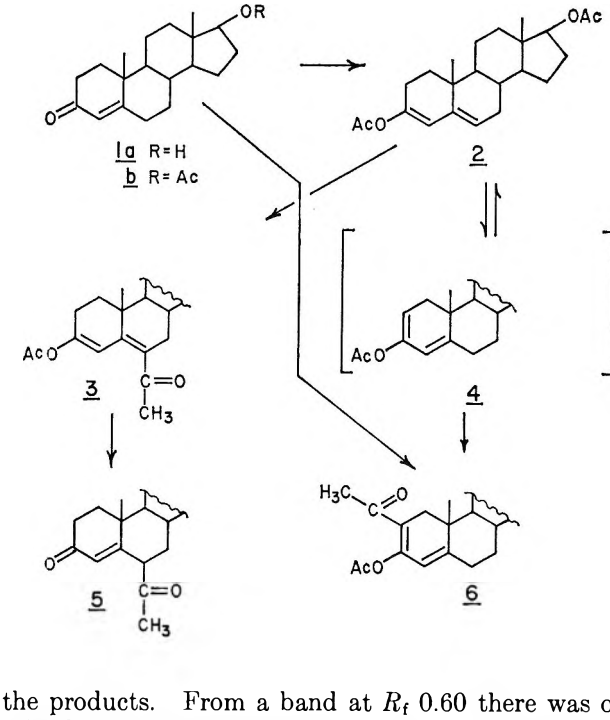
It was previously demonstrated that the C-11β-hydroxyl group of steroids has a pronounced influence on the enolization properties of 3-oxo-5β steroids as measured by the thermodynamically controlled enol acetylation reaction which employs acetic anhydride–perchloric acid mixtures.[2] In order to measure this effect in the biologically active steroids, it became necessary to investigate the perchloric acid–acetic anhydride enol acetylation of Δ4-3 ketones. There are reports[3–6] that this mixture is capable of carrying out O acylations on unsaturated compounds; however, the reagent has not been carefully studied with Δ4-3 ketones.

17β-Hydroxyandrost-4-en-3-one (**1a**) was treated with a solution of perchloric acid in acetic anhydride and the reaction was quenched in 40 min. Gas chromatographic analysis (glpc) of the crude reaction mixture indicated the product to be essentially pure 3,17β-diacetoxyandrosta-3,5-diene (**2**). The compound was isolated in 72% yield and identified by comparison with an authentic sample prepared from the isopropenyl acetate enol acetylation of **1a**.[7,8]

When the reaction time of the perchloric acid catalyzed enol acetylation was extended to 4 hr, eight compounds were detected by glpc in the reaction mixture; five were isolated (Scheme I). The first one eluted by preparative glpc was 3,17β-diacetoxyandrosta-3,5-diene (**2**), identified by comparison with authentic material.[7] A second substance, isolated by preparative glpc, was shown to be 17β-acetoxyandrost-4-en-3-one (**1b**) by comparison with known material. Further attempts to isolate the remaining products by preparative glpc were not successful owing to thermal decomposition of the products during chromatography.

Preparative tlc was used to isolate the remainder of the products. From a band at R_f 0.60 there was obtained pure 3,17β-diacetoxy-6-acetylandrosta-3,5-diene which was assigned structure **3** on the basis of its spectral properties. The infrared spectrum demonstrated enol acetate, ester, and conjugated carbonyl bands. The ultraviolet spectrum exhibited absorptions at λ_{max} 281 mμ (ε 7900) and 220 (8800). The predicted absorption maximum by the Scott modification of the Woodward rules[9a] is at 296 mμ. The observed maximum at 281 mμ and the relatively low intensity of the band suggests an extended chromophore with incomplete conjugation due to the *peri* effect from the C-4 vinylic proton.[10,11] The nmr spectrum of 3,17β-diacetoxy-6-acetylandrosta-3,5-diene (**3**) is recorded in Table I and is consistent with the assigned structure. The locations of the angular methyl group signals in the

SCHEME I



(1) To whom enquiries should be made.

(2) A. J. Liston and M. Howarth, *J. Org. Chem.*, **32**, 1034 (1967).

(3) The use of perchloric acid–acetic anhydride acetylating conditions[4] leads to enol–acetate mixtures which reflect the enolization properties of the cyclic ketone.[5] The enol–acetate ratio has been related to the theoretically calculated stability between isomeric enolic forms.[6]

(4) D. H. R. Barton, R. M. Evans, J. C. Hamlet, P. G. Jones, and T. Walker, *J. Chem. Soc.*, 747 (1954).

(5) J. Champagne, H. Favre, D. Vocelle, and I. Zbikowski, *Can. J. Chem.*, **42**, 212 (1964).

(6) A. J. Liston, *J. Org. Chem.*, **31**, 2105 (1966).

(7) The Δ3,5-dienol acetate was conveniently prepared by the isopropenyl acetate method[8] and compared with known material; *cf.* U. Westphal, *Chem. Ber.*, **70**, 2128 (1937).

(8) W. G. Dauben, R. A. Micheli, and J. F. Eastham, *J. Amer. Chem. Soc.*, **74**, 3852 (1952).

(9) A. I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products," The Macmillan Co., New York, N. Y., 1964: (a) p 50; (b) p 67.

(10) A similar ultraviolet spectrum for 6-acetylcholesta-3,5-diene with uv absorptions at λ_{max} 281 mμ (ε 6150), 221 (9400), was recorded by Elmes, Hartshorn, and Kirk.[11] In both instances the compounds were strongly levorotatory, the 3,17β-diacetoxy-6-acetylandrosta-3,5-diene (**3**) exhibiting an $[\alpha]^{28}D$ −167.8° and 6-acetylcholesta-3,5-diene having $[\alpha]D$ −159°.

(11) B. C. Elmes, M. P. Hartshorn, and D. N. Kirk, *J. Chem. Soc.*, 2285 (1964).

TABLE I

NMR RESONANCE DATA IN PARTS PER MILLION OF THE POLYACETYLATED REACTION PRODUCTS

Compd	C-18 $-CH_3$	C-19 $-CH_3$	C-3 $-OAc$	C-17β $-OAc$	C-2 $-Ac$	C-6 $-Ac$	C-4 $-H$	C-6 $-H$
1b	0.85	1.20	...	2.03	...	...	5.71 s	...
2	0.83	1.01	2.12	2.03	...	...	5.69 d (J = 2 Hz)	5.38 m
3	0.83	1.08	2.12	2.03	...	2.23	6.29 d (J = 2 Hz)	...
6	0.81	1.14	2.15	2.03	1.90	...	5.71 s	...
8	0.87	1.38	...	2.03	...	...	5.81 s	...

spectra of compounds **2** and **3** are identical indicating the $\Delta^{3,5}$-dienic structure. The presence of a single vinylic proton signal at 6.25 ppm in the spectrum of **3** is consistent with the proposed structure since the conjugated C-6 acetyl group places the C-4 vinylic proton in the deshielding zone of the carbonyl group[12] and is responsible for the shift downfield from the position of the vinylic proton signals in the spectra of compounds **1b** and **2**. The C-4 proton signal is split into a doublet with J = 2 Hz which is indicative of long-range coupling. Similar coupling has been observed by Wiechert and Schulz[13] between the C-4 and C-2 protons of 3,17β-diacetoxy-5α-androsta-1,3-diene.

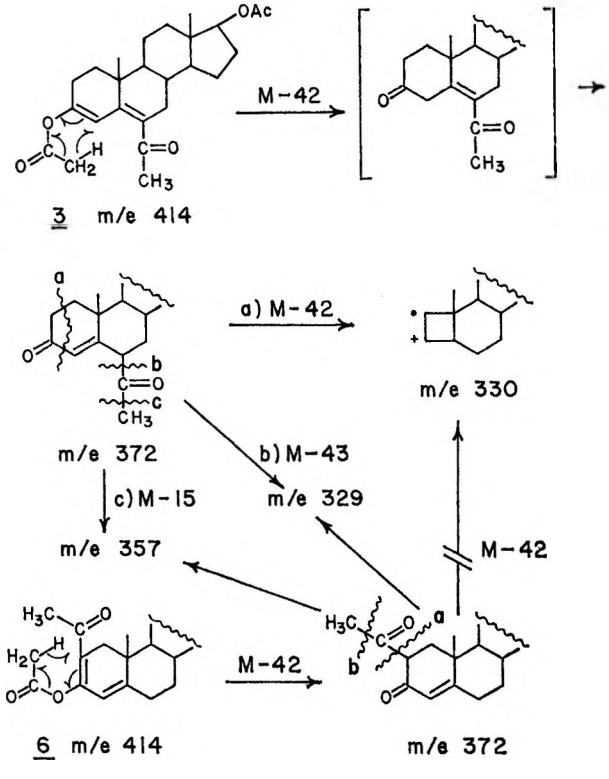
The identity of the compound was further confirmed by treatment with base to saponify the enol acetate function and generate 17β-acetoxy-6β-acetylandrost-4-en-3-one (**5**). The compound was assigned the 6β configuration on the basis of its ultraviolet spectrum, λ_{max} 246 mμ, which is characteristic for the 6β isomer, the epimeric 6α compound has an absorption at λ_{max} 238 mμ.[14] The identity of the saponification product was rigorously established by synthesis of authentic material by the method of Gorodetsky, *et al.*,[14] and comparing the physical properties.[15,16]

The second compound separated from the reaction mixture by preparative tlc was obtained from a band at R_f 0.54. Glpc analysis of the crude material demonstrated two peaks, of which the minor constituent was 17β-acetoxyandrost-4-en-3-one (**1b**) and the major component **6** was the major product of the reaction comprising 45.0% of the total reaction products. Fractional crystallization from acetone–hexane gave pure 3,17β-diacetoxy-2-acetylandrosta-2,4-diene (**6**). The ultraviolet spectrum, λ_{max} 274 (ϵ 9900) and 242 (12,700), is indicative of extended conjugation; however, as with the previous compound **3**, the ultraviolet maximum is lower than the calculated value. This probably reflects the crowding about the C-2 and C-3 positions and the consequent inability to achieve complete conjugation.

The methyl signal of methyl ketones is normally located at δ 2.1 to 2.4 ppm in the nmr spectrum.[17a] However, the C-methyl signal of 3,17β-diacetoxy-2-acetylandrosta-2,4-diene (**6**) is located at δ 1.90 ppm (Table I) which is indicative of a shielding effect by the adjacent O-acetyl group. Examination of molecular models indicates that the crowding about the C-2 and C-3 positions is alleviated by maintaining the C-3 O-acetyl function perpendicular to the plane of the A ring of the steroid. Since the C-2 methyl ketone remains nearly planar because of conjugation it is then situated in the shielding region of the adjacent O-acetyl carbonyl group. The position of the methyl ketone in **6** was verified by saponification of the enol acetate function. The ultraviolet spectrum of the saponification product **7** showed a bathochromic shift in base suggesting a β-diketone structure.

The isomeric dienol diacetates **3** and **6** were subjected to mass spectral analysis and demonstrated similar spectra. Both compounds showed molecular ion peaks at m/e 414. The major fragmentation pattern of 3,17β-diacetoxy-6-acetylandrosta-3,5-diene (**3**) is M^+ 414 → 372 (357, 330, 329). 3,17β-Diacetoxy-2-acetylandrosta-2,4-diene (**6**) gives M^+ 414 → 372 (357, 329). Appropriate metastables were observed in every case. Fragmentation of the enol acetate function in both compounds gives rise to a m/e 372 peak which undergoes fragmentation (*cf.* Scheme II) with loss of either 43 or 15 mass units. The distinguishing feature which supports the C-2 acetyl assignment in **6** is the absence of a sig-

SCHEME II



(12) G. J. Karabatsos, G. C. Sonnichsen, N. Hsi, and D. J. Fenoglio, *J. Amer. Chem. Soc.*, **89**, 5067 (1967).

(13) R. Wiechert and G. Schulz, *Chem. Ber.*, **98**, 3165 (1965).

(14) M. Gorodetsky, E. Levy, R. D. Youssefyeh, and Y. Mazur, *Tetrahedron*, **22**, 2039 (1966).

(15) The hydrolysis product, compound **5**, has the C-6 acetyl group axially oriented, whereas the generally more stable equatorial configuration would be expected. Gorodetsky, *et al.*,[16] have shown that the 17β-acetoxy-6β-acetylandrost-4-en-3-one is more stable than the corresponding 6α epimer. These authors explain this by a possible partial conjugation of the carbonyl group at C-6 with the Δ^4-3-keto group in the 6β-axial compound which is not possible in the 6α-equatorial epimer.

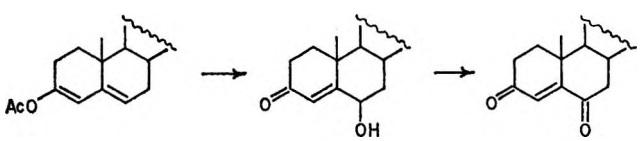
(16) M. Gorodetsky and Y. Mazur, *J. Amer. Chem. Soc.*, **86**, 5213 (1964).

(17) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1966: (a) p 33; (b) p 19.

nificant m/e 330 ion[18] whose genesis in **3** is loss of 42 mass units by the well-established loss of ketene from C-2 and C-3 of Δ4-3 ketones.[19] An unsubstituted C-2 position is required for the latter fragmentation to occur.

A third compound (**8**) separated from the reaction mixture using preparative tlc was isolated in the usual fashion and glpc analysis of the crude material (18 mg) revealed one major product (53%) and four minor constituents. Fractional crystallization yielded pure material which was homogeneous by glpc analysis. The ultraviolet spectrum of the compound demonstrated conjugated carbonyl absorption. Infrared spectroscopy revealed hydroxyl and ester bands and confirmed the presence of a conjugated carbonyl system. The compound was assigned the 17β-acetoxy-6β-hydroxyandrost-4-en-3-one (**8**) structure[20,21] on the basis of its mass spectrum and nmr spectrum. In addition to the signals recorded in Table I there were present two superimposed one-proton multiplets between δ 4.4 and 5.2 ppm. The β configuration of the C-6 hydroxyl group was deduced from additivity constants for the chemical-shift value of the C-19 angular methyl group, which by calculation should be δ 1.39 ppm.[17b] Oxidation of an aliquot of the material with chromium trioxide–pyridine reagent[22] gave a compound whose ultraviolet spectrum was in accordance with the proposed 17β-acetoxyandrost-4-ene-3,6-dione (**9**) structure[9b] (*cf.* Scheme III).

SCHEME III



2 **8** **9**

In previous studies with perchloric acid catalyzed acetic anhydride enol acetylations with saturated keto steroids there was no evidence of C acylation; the O-acylation products were formed almost exclusively.[2,6] Recently Rodig and Zanati[23] investigated the enol acetylation of Δ1-3-oxo-5α steroids and found at equilibrium some 18% C-acylation product, all of which was formed exclusively at the C-4 position. This would indicate a preferential attack by acetylium ion[24] on the enolic double bond of the diene. Attack on the Δ1 double bond does not appear to be favored, presumably because of the lack of participation by the enolic acetate function. Rodig and Zanati have speculated that the C acylation could proceed either (a) by direct attack on the α position of the ketone in the enolic form or enol acetate form, or (b) by the Claisen–Haase type of rearrangement involving intramolecular acetyl group migration. Our studies with Δ4-3 ketones have shown that the first product of the reaction is the Δ3,5-dienol diacetate **2** which is formed almost exclusively using short reaction periods. That compound **2** is the precursor of the C-acylation products was proven by doing parallel experiments with the Δ4-3 ketone **1** and the dienol diacetate **2**. In both cases glpc analysis of the reaction products after 2 hr demonstrated similar product distributions. In the case of the acetylation of **1** there was detected a 10.5% increase in the formation of 3,17β-diacetoxy-6-acetylandrosta-3,5-diene (**3**) which suggests that a portion of the C-6 acylation is probably formed directly with the major portion of the products being formed by a mechanism involving Δ3,5-dienol diacetate. The product distribution obtained in our studies makes it highly improbable that mechanism b contributes to the reaction, since the rearrangement would lead to C-4-acylated product. It has been possible to account for 97% of the reaction products, none of which was acetylated at C-4.

Attack by acetylium ion on the Δ3,5-dienol diacetate **2** occurred at the C-6 position. Similar results were obtained by Gorodetsky, *et al.*,[14] using boron trifluoride–acetic anhydride mixture. Treatment of 17β-hydroxyandrost-4-en-3-one (**1a**) with this reagent afforded an epimeric mixture of C-6-acetylated 17β-acetoxyandrost-4-en-3-ones (**5**). By extending the reaction period under more forcing conditions they obtained a compound which had undergone C acylation at both C-2 and C-6 positions. The use of perchloric acid as catalyst alters the reaction to produce the enol acetate of compound **5** as a final product. Both methods of acetylation have been postulated as proceeding *via* acetylium ion attack on the enol acetate **2**; however the difference in final products obtained suggests that the Δ4-3 ketone formed in the boron trifluoride catalyzed acetylation is probably not free but complexed with the reagent and only liberated on working up the reaction mixture. A further variation in the products obtained from the two methods of acylation is the absence of mono-C-acylated product at the C-2 position in the boron trifluoride catalyzed reaction. Using perchloric acid catalyst the major constituent of the reaction was 3,17β-diacetoxy-2-acetylandrosta-2,4-diene (**6**).

The glpc analytical results obtained indicate that there is no appreciable quantity of 3,17β-diacetoxyandrosta-2,4-diene (**4**) present under the equilibrating conditions of the reaction. However, there must be the transient formation of **4** to account for the C-2-acylated product. In cross-conjugated enol acetates, such as **4** or 3,17β-diacetoxy-5α-androsta-1,3-diene,[23] the enolic double bond reacts readily which would explain the high yield of compound **6** in our reaction products. The situation is analogous to that found in the dehydrogenation of Δ4-3 ketones where it has been suggested that the Δ2,4-dienol is formed by kinetic control and the Δ3,5-dienol by thermodynamic control.[25] The equilibrium point in the presence of acid is almost exclusively on the side of the Δ3,5-dienolic compound.[26] This would signify a rapid attack by acetylium ion on the Δ2,4-dienol acetate **4** which is formed either directly from the Δ4-3 ketone **1b** or from the equilibration of the Δ3,5-diene **2**.

(18) When the m/e 330 peaks in the spectra of **3** and **6** are corrected for the isotope effect from the m/e 329 peaks, it can be seen that this peak in the spectrum of **3** corresponds to a major fragmentation route, whereas in **6** it is hardly significant.

(19) R. H. Shapiro and C. Djerassi, *J. Amer. Chem. Soc.*, **86**, 2825 (1964).

(20) 17β-Acetoxy-6β-hydroxyandrost-4-en-3-one has been prepared by oxidizing 3,17β-diacetoxyandrosta-3,5-diene (**2**) with *t*-butyl chromate.[21] The physical properties agree with those of compound **8** isolated herein.

(21) K. Ysuda, *Chem. Pharm. Bull.* (Tokyo), **11**, 1167 (1963).

(22) J. R. Holum, *J. Org. Chem.*, **26**, 4814 (1961).

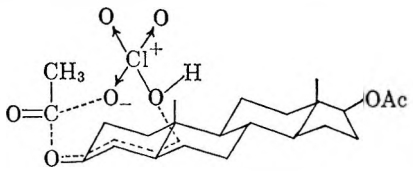
(23) O. R. Rodig and G. Zanati, *ibid.*, **32**, 1423 (1967).

(24) Although the identity of the acetylating species in perchloric acid catalyzed enol acetylations has not been unequivocally established, there is increasing evidence that the acetylium ion must play a significant role in these acetylations. For an excellent review, see D. P. N. Satchell, *Quart. Rev.* (London), **17**, 196 (1963).

(25) A. B. Turner and H. J. Ringold, *J. Chem. Soc.*, 1720 (1967).

(26) H. J. Ringold and K. Malhotra, *J. Amer. Chem. Soc.*, **86**, 1997 (1964).

The isolation of 17β-acetoxy-6β-hydroxyandrost-4-en-3-one is surprising because under strong acetylating conditions the 6β-hydroxyl group should have undergone almost instantaneous acetylation.[27,28] It is necessary to postulate a complex in which both the Δ⁴-3-ketone function and the hydroxyl group are involved. A complex of the type shown below would satisfy these conditions. Decomposition of such a complex during the work-up would liberate compound **8**.



Rodig and Zanati have isolated 3% of 1,17β-diacetoxy-4-methylestra-1,3,5(10)-triene from the enol acetylation of Δ¹-3-oxo-5α steroids.[23] To ascertain that none of the minor unidentified constituents of the reaction mixture was the same rearrangement product, the latter compound was synthesized from 17β-hydroxyandrosta-1,4-dien-3-one by dienone–phenol rearrangement.[29] Glpc analysis of the reaction mixture obtained from the perchloric acid catalyzed enol acetylation with authentic 1,17β-diacetoxy-4-methylestra-1,3,5,(10)-triene demonstrated that the phenolic compound was not formed in the reaction.

In view of the lack of C acylation at tertiary C atoms the enol acetylation of alkyl-Δ⁴-3 ketones is being investigated. Such compounds may provide a system in which the equilibrium between Δ²,⁴- and Δ³,⁵-dienol acetates may be studied.

Experimental Section

General.—Melting points were determined on an Electrothermal apparatus by the capillary method and are corrected. Rotations were measured in chloroform solution. The infrared spectra were recorded on a Perkin-Elmer Model 221 double-beam spectrophotometer. The ultraviolet spectra were determined in ethanol solution using a Bausch and Lomb Spectronic 502 recording spectrophotometer. The nmr spectra were determined on a Varian A-60A spectrometer in deuteriochloroform and chemical-shift values are given in parts per million (ppm) values measured downfield from tetramethylsilane used as an internal standard. Gas chromatography was carried out on a Model 810 F & M gas chromatograph equipped with dual flame detectors. The columns were 5% Fluoro Silicone FS-1265 (QF-1) on 60–80 mesh Diatoport "S," 8 ft × 4 mm o.d. The carrier gas was helium at a flow rate of 60 cc/min and the column temperature was 230°. Quantitative estimation of mixtures was made by trangulation of the signals. Preparative gas chromatography was carried out on an F & M Model 776 Prepmaster Jr. using 20% QF-1 on 10–60 mesh Diatoport "S" with 8 ft × 1 in. o.d. columns. The carrier gas was nitrogen at a flow rate of 0.8 l./min. The column temperature was 250°. The adsorbant for thin layer chromatography was Merck silica gel G and the solvent was benzene–ethanol (8:1). The mass spectra were carried out on a Hitachi-Perkin-Elmer Model RMU-6D at 50 eV.

3,17β-Diacetoxyandrosta-3,5-diene (2).—17β-Hydroxyandrost-4-en-3-one (1a, 4.5 g) was suspended in isopropenyl acetate (100 ml) and concentrated sulfuric acid (0.08 ml) was added. The mixture was refluxed for 1.5 hr and the solvent was then partially distilled under reduced pressure. After cooling, the residue was diluted with ether (100 ml) and extracted with 5% aqueous sodium bicarbonate (100 ml). The ether layer was washed with salt solution and dried (Na_2SO_4), and the solvent was evaporated to dryness. The residue (6.1 g) was crystallized from ether to give 3,17β-diacetoxyandrosta-3,5-diene (2.58 g), mp 143–147° (lit.[7] mp 149–150°).

The Reaction of 17β-Hydroxyandrost-4-en-3-one with Perchloric Acid–Acetic Anhydride Reagent.—To a solution of 17β-hydroxyandrost-4-en-3-one (1a, 1 g) in carbon tetrachloride (40 ml) and benzene (100 ml) was added a solution (10 ml) of acetic anhydride–70% perchloric acid (49:1). The mixture was stirred at room temperature for 40 min and the reaction was quenched by pouring it into sodium bicarbonate solution (150 ml). The organic material was extracted with two 150-ml portions of ether and the ether solution was dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure and the residual oil was analyzed by glpc. The product consisted of 3,17β-diacetoxyandrosta-3,5-diene (2, 72%) and 17β-acetoxyandrost-4-en-3-one (1b, 24%). The mixture was separated by preparative glpc. The first product collected was 3,17β-diacetoxyandrosta-3,5-diene (2, 700 mg), mp 145–146°; the mixture melting point determination with authentic material previously prepared showed no depression. The second compound isolated by preparative glpc was 17β-acetoxyandrost-4-en-3-one (1b, 300 mg), mp 141–143°; the mixture melting point with authentic material was undepressed.

In a similar reaction using 17β-hydroxyandrost-4-en-3-one (1a, 1 g) the reaction period was extended to 4 hr and the reaction was quenched as previously described. The crude product was analyzed by glpc and eight compounds were detected: at retention time 8.8 min, 6.3% 3,17β-diacetoxyandrosta-3,5-diene (2); at retention time 16.3 min, 10.2% 17β-acetoxyandrost-4-en-3-one (1b); at retention time 20.0 min, 0.6% unidentified product; at retention time 23.5 min, 0.2% unidentified product; at retention time 25.3 min, 0.4% unidentified product; at retention time 28.3 min, 4.5% 6β-hydroxyandrost-4-en-3-one (8); at retention time 38.8 min, 30.8% 3,17β-diacetoxy-6-acetylandrosta-3,5-diene (3); and, at retention time 42.4 min, 45.0% 3,17β-diacetoxy-2-acetylandrosta-2,4-diene (6).

The crude material was separated by preparative tlc using a 500-μ layer of silica gel and solvent system benzene–ethanol 19:1. The mixture was deposited (70 mg/20-cm-square plate) from methylene chloride solution as a 5-mm-wide band. The bands were detected by ultraviolet light (R_f 0.54, 0.57, 0.60, and 0.75) and aspirated from the plates. The products were eluted from the adsorbant by washing with acetone and filtering.

From the band at R_f 0.60 there was isolated an oil (100 mg) which was homogeneous by glpc analysis (retention time 38.8 min). Crystallization from acetone–hexane gave pure 3,17β-diacetoxy-6-acetylandrosta-3,5-diene (3, 88 mg): mp 140–141°; $[\alpha]^{28}D$ −168° (c 0.5); uv max, 281 mμ (ε 7900), 220 (8800); ir (CCl_4), 1758 (>C=C(–OCOCH₃)–), 1735 (–OCOCH₃), 1685 (>C=O), and 1657 cm⁻¹ (>C=C<); the nmr spectrum is recorded in Table I; mass spectrum, m/e (relative intensity) 414 (5), 373 (26), 372 (100), 357 (15), 330 (18), and 329 (23).

Anal.[30] Calcd for $C_{25}H_{34}O_5$: C, 72.43; H, 8.27. Found: C, 72.72; H, 8.43.

From the band at R_f 0.54 there was obtained an oil (70 mg) which was demonstrated by glpc analysis to consist of 17β-acetoxyandrost-4-en-3-one (1b, 26%), retention time 16.3 min, and 3,17β-diacetoxy-2-acetylandrosta-2,4-diene (6, 74%), retention time 42.4 min. Fractional crystallization from acetone–hexane gave pure 3,17β-diacetoxy-2-acetylandrosta-2,4-diene (6, 11 mg): mp 158–159°; $[\alpha]^{28}D$ 102° (c 0.5); uv max, 274 mμ (ε 9900), 242 (12,700); ir (KBr), 1759 (>C=C(–OCOCH₃)–), 1730 (–OCOCH₃), 1675 (>C=O), and 1653 cm⁻¹ (>C=C<); the nmr spectrum is recorded in Table I; mass spectrum, m/e (relative intensity) 414 (3), 373 (26), 372 (100), 357 (14), 330 (7), and 329 (25).

Anal. Calcd for $C_{25}H_{34}O_5$: C, 72.43; H, 8.27. Found: C, 72.45; H, 8.25.

From the band at R_f 0.75 there was obtained an oil (18 mg) which by glpc analysis was shown to consist of five compounds, the major constituent (53%, retention time 28.3 min) was 17β-acetoxy-6β-hydroxyandrost-4-en-3-one (8). The mixture also contained 20% 3,17β-diacetoxy-6-acetylandrosta-3,5-diene (3), retention time 38.8 min. The mixture was crystallized from acetone–hexane and there was obtained homogeneous (glpc)

(27) Recently it has been shown that steroidal Δ³,⁵-dienol ethers are autoxidized to give 6-hydroxy-Δ⁴-3 ketones[28] by a free-radical process. Obviously such a mechanism is not operating under our strong acidic conditions since no 3,6,17β-triacetoxyandrosta-3,5-diene was detected.

(28) R. Gardi and A. Lusignani, *J. Org. Chem.*, **32**, 2647 (1967).

(29) C. Djerassi, "Steroid Reactions," Holden-Day, Inc., San Francisco, Calif., 1963, p 371.

(30) Microanalyses were performed by Schwarzkopf Microanalytical Laboratories, Woodside, N. Y.

17β-acetoxy-6β-hydroxyandrost-4-en-3-one (**8**) (4 mg): mp 202–203.5°; uv max, 237 mμ (ε 19,600); ir (KBr), 3460 (–OH), 1730 (–$OCOCH_3$), 1668 (>C=O), and 1615 cm^{-1} (>C=C<); the nmr spectrum is recorded in Table I; the mass spectrum had a molecular ion peak at *m/e* 346.

The Oxidation of 17β-acetoxy-6β-hydroxyandrost-4-en-3-one (8).—A solution of 17β-acetoxy-6β-hydroxyandrost-4-en-3-one (**8**, 2 mg) in pyridine (0.5 ml) was added to a stirred suspension of chromium trioxide (67 mg) in pyridine (6 ml). The mixture was stirred for 17 hr and poured into sodium bicarbonate solution (25 ml) and extracted with ether (20 ml). The ether extract was washed with 3 *N* sulfuric acid (20 ml), saturated bicarbonate solution (20 ml), and salt solution until neutral. The ether solution was dried (Na_2SO_4) and filtered, and the solvent was evaporated to dryness. Glpc analysis of the product gave a single peak at retention time 29.6 min. The material failed to crystallize but demonstrated the spectral properties consistent with 17β-acetoxyandrost-4-ene-3,6-dione (**9**): uv max, 250 mμ (ε 17,000); ir (CCl_4), 1740 (–$OCOCH_3$), 1710 (>C=O), and 1690 cm^{-1} (>C=O). The product (1.5 mg) was partitioned between 5% sodium hydroxide (5 ml) and ether (5 ml). Glpc analysis indicated the retention of the product in the ether layer.

17β-Acetoxy-6β-acetylandrost-4-en-3-one (5).—A solution of 3,17β-diacetoxyandrosta-3,5-diene (**2**, 1.37 g) in acetic anhydride (20 ml) was treated with boron trifluoride etherate (4.1 ml) at 25° for 4 min, then poured into ice water (200 ml). The aqueous suspension was extracted with ether (100 ml), and the ether solution was washed with sodium bicarbonate solution (100 ml) and then with brine until neutral. The ether solution was dried ($MgSO_4$) and filtered, and the solvent was concentrated under reduced pressure. After cooling, the material was filtered and there was obtained 17β-acetoxy-6β-acetylandrost-4-en-3-one (**5**, 400 mg): mp 162–164°; uv max, 246 mμ (ε 12,000) [lit.[14] mp 165–166°; uv max, 246 mμ (ε 13,000)].

Saponification of Compounds 3 and 6. A.—To a solution of 3,17β-diacetoxy-6-acetylandrosta-3,5-diene (**3**, 20 mg) in methanol (5 ml) was added a saturated solution of sodium acetate (1 ml). The solution was refluxed for 3 hr, and the solvent was removed *in vacuo*. The residue was partitioned between ether (20 ml) and water (20 ml), the organic layer was dried (Na_2SO_4) and filtered, and the solvent was concentrated to dryness. Crystallization from acetone–hexane gave 17β-acetoxy-6β-acetylandrost-4-en-3-one (**5**, 6 mg): mp 151–155°, uv max, 246 mμ (ε 11,900); ir (KBr), 1735 (–$OCOCH_3$), 1712 (>C=O), 1678 (>C=C–C=O), and 1608 cm^{-1} (>C=C<). The ir spectrum was identical with that of an authentic sample. Admixture with authentic material gave a single tlc spot at R_f 0.86 and the mixture melting point was undepressed.

B.—Compound **6** (1 mg) was treated as above. The saponification product **7** had uv max 241 mμ; addition of 5% potassium hydroxide solution caused a bathochromic shift to 425 mμ. Insufficient material was available to characterize the compound further.

1,17β-Diacetoxy-4-methylestra-1,3,5(10)-triene.—To a solution of 17β-hydroxyandrosta-1,4-dien-3-one (1.0 g, mp 167–169°) in carbon tetrachloride (40 ml) and benzene (100 ml) was added a solution of acetic anhydride–70% perchloric acid (10 ml, 49:1). The mixture was stirred at room temperature for 2.5 hr after which the reaction mixture was diluted with ether (100 ml) and washed with two 150-ml portions of sodium bicarbonate solution. The ether layer was washed until neutral with brine and dried (Na_2SO_4). The solution was filtered and the solvent was removed under reduced pressure. Two crystallizations from acetone–hexane gave 1,17β-diacetoxy-4-methylestra-1,3,5(10)-triene (840 mg): mp 139–140° (lit.[31] mp 138.5–139°); uv max, 278 mμ (ε 257); ir (CCl_4), 1759 (>C=C–$OCOCH_3$) and 1740 cm^{-1} (–$OCOCH_3$).

An aliquot of the material was added to the reaction mixture consisting of **2** treated with acetic anhydride–perchloric acid reagent and a new peak was detected by glpc analysis at retention time 8.2 min.

Registry No.—Perchloric acid, 7601-90-3; acetic anhydride, 108-24-7; **1b**, 1045-69-8; **2**, 1778-93-4; **3**, 16853-04-6; **6**, 16803-41-1; **8**, 13096-48-5.

Acknowledgment.—We wish to thank Dr. G. Neville for the nmr spectra and Mr. A. Viau for technical assistance. We are also indebted to Professor P. Morand of the University of Ottawa for the mass spectral determinations.

(31) (a) A. L. Wilds and C. Djerassi, *J. Amer. Chem. Soc.*, **68**, 2125 (1946); (b) C. Djerassi, G. Rosenkranz, J. Romo, J. Pataki, and St. Kaufmann, *ibid.*, **72**, 4540 (1950).

Steroidal C-17 Allene Acetates and Their 17(20)-Unsaturated C-21 Aldehyde Derivatives

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A number of examples of steroid derivatives bearing an acetoxyallene side chain at C-17 have been synthesized. In the case of the 3-acetoxy-5-ene derivatives, both isomeric allenes **2a** and **3a** were isolated and the stereochemistry was established by their unique spectral properties. Hydrolysis of the allenic esters lead to conjugated C-21 aldehydes in high over-all yields.

The allenic structure has proven to be a most intriguing system to the chemist from the standpoint of theoretical interest as well as synthetic challenge. The great span of time from van't Hoff's early prediction of the existence of asymmetry in the system to the successful demonstration of this fact stemmed from the lack of good synthetic methods of preparation and resolution. The past several years has seen the development of new routes of stereospecific syntheses of allenes. These are enumerated in the recent review of allene chemistry by Taylor.[1]

Noting the absence of examples of steroidal allenes, some years ago we embarked on a program directed toward the incorporation of this rather novel system into a representative group of steroids.[2] In this first paper we will describe the preparation of a series of steroidal allenic esters and some of the unsaturated aldehydes derived therefrom. The products under consideration are isomeric with, and in fact derived from, a class of compounds of considerable physiolog-

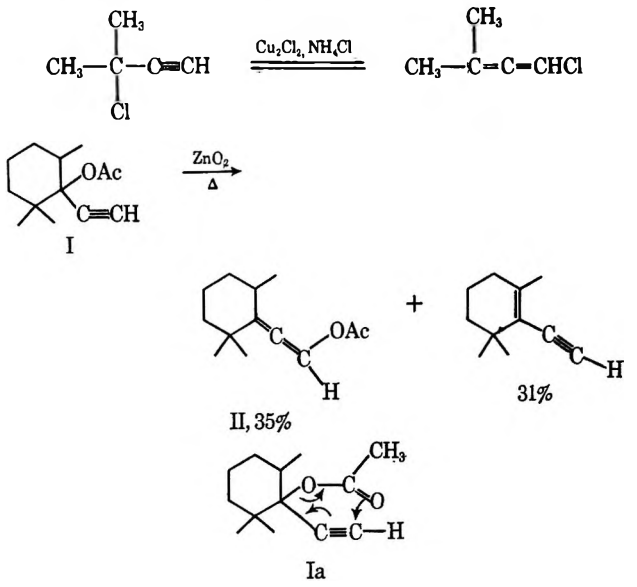
(1) (a) D. W. Taylor, *Chem. Rev.*, **67**, 317 (1967). (b) *Cf.* also the section on cumulenes in H. Fischer, "The Chemistry of Alkenes," S. Patai, Ed., Interscience Publishers, Inc., London, 1964, p 1025.

(2) Since this work has initiated, two papers have appeared describing examples of steroidal allenes: (a) R. Vitali and R. Gardi [*Gazz. Chim. Ital.*, **96**, 1125, 3203 (1966)] have employed the Claisen rearrangement of propargylic enol ethers to introduce the three carbon allenyl group adjacent to a carbonyl function; (b) *cf.* also N. K. Chaudhuri and M. Gut, *J. Amer. Chem. Soc.*, **87**, 3737 (1965).

ical importance, namely, steroidal C-17 ethynylcarbinols.[3] It appeared to us to be an attractive goal to synthesize the isomeric allenic esters in order to compare the biological activities with those of the parent compounds, as well as to study their use as intermediates for subsequent side-chain modifications.

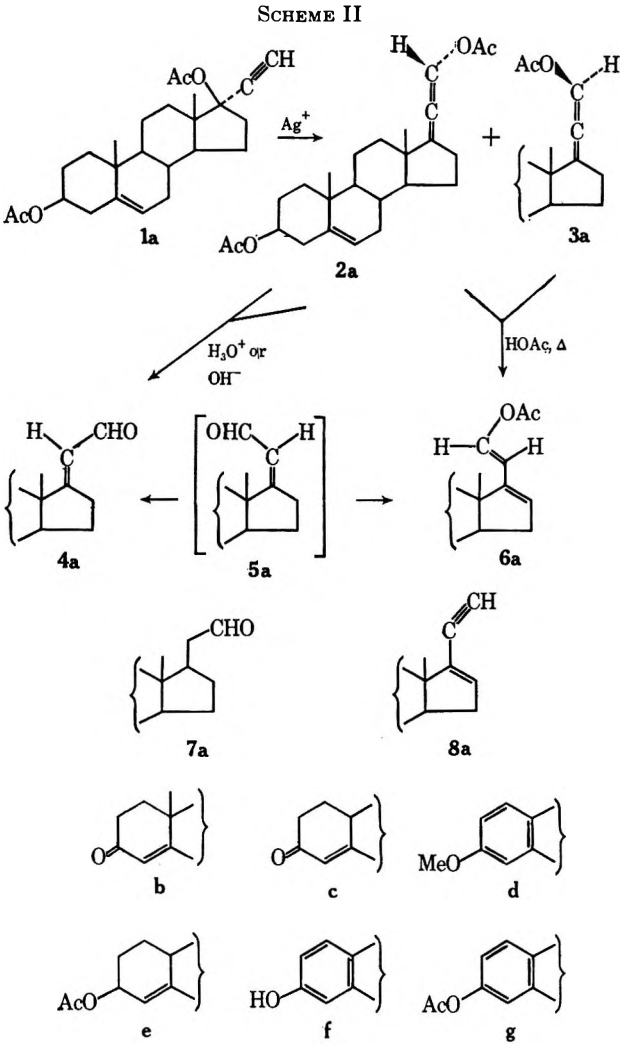
The most straightforward preparative method appeared to be the use of metal salts to catalyze the interconversion of acetylenic halides or esters to their isomeric allenes. Hennion[4] and coworkers in 1950 observed the catalytic influence of cuprous chloride on the equilibrium of a chloroacetylene with its isomeric allene (Scheme I). In 1956, Landor and Landor[5] demonstrated the influence of zinc salts on the acetylenic ester I to give a modest yield of the rearranged acetoxyallene II. Saucy[6] and coworkers at Hoffmann-La Roche found that silver salts were superior to copper and gold salts in catalyzing this latter type of transformation. The products were generally characterized by unique spectral properties and by hydrolysis to unsaturated aldehydes. The question of stereoisomerism of the acetoxyallenes was not considered in these papers. Landor[5] postulated that the migration occurred *via* an internal displacement involving a cyclic transition state such as Ia (Scheme I).

SCHEME I



We have found the silver ion catalyzed rearrangement to be a very facile method of preparing the desired steroidal allenes. Thus, when an acetone solution of 17α-ethynylandrost-5-ene-3β,17β-diol diacetate (**1a**) was maintained at reflux temperature together with about 5 mol % of silver perchlorate over a period of several days, thin layer chromatography (tlc) indicated the gradual disappearance of starting material and formation of two products in equal amounts. Precipitation of the catalyst as silver chloride followed by concentration of the acetone filtrate afforded by direct crystallization 42% of a pure product, **2a** (Scheme II). A second crystalline product, **3a**, having very similar spectral properties and tlc mobility, was isolated by chromatography of the filtrates. That these two products were the isomeric 21α- and 21β-acetoxy-17(20),20-allenes[7] resulting from the expected intramolecular rearrangement was shown by the characteristic 5.04-μ allenic stretching band in the infrared spectrum of each compound. The stereochemistry was established by inspection of the nmr spectra discussed below. Mild alkaline or acid hydrolysis afforded the known unsaturated *trans*-aldehyde **4a**.[8,9] These transformations may be considered as an example of a stepwise Meyer–Schuster rearrangement,[1b] in effect leading to hydration of the ethynyl group at the unsubstituted carbon. This route affords a convenient method for the synthesis of conjugated aldehydes of general structure **4**, generally in higher yields than had been observed by alternate synthetic procedures.[8]

SCHEME II



When the silver catalyzed rearrangement was carried out in boiling acetic acid, the initially formed allenes underwent a double-bond shift to give the 16,20-con-

(3) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, pp 476, 556, and 591.

(4) G. F. Hennion, J. T. Sheehan, and D. E. Maloney, *J. Amer. Chem. Soc.*, **72**, 3542 (1950).

(5) P. D. Landor and S. R. Landor, *J. Chem. Soc.*, 1015 (1956).

(6) (a) G. Saucy, R. Marbet, H. Lindlar, and O. Isler, *Helv. Chim. Acta*, **42**, 1945 (1959); (b) R. Marbet, *et al.*, U. S. Patent 3,211,780 (1965).

(7) Applying the sequence rule system of nomenclature to the isomeric allenes results in the *R* designation for the 21α-acetoxy compounds (**2**), and *S* for the 21β isomers (**3**). We feel that the conventional Fischer designation for the isomeric allenes is more descriptive to chemists working in this area. *Cf.* R. S. Cahn, *J. Chem. Educ.*, **41**, 116 (1964).

(8) H. Heusser, K. Eichenberger, and Pl. A. Plattner, *Helv. Chim. Acta*, **33**, 1088 (1950).

(9) When the mixture of epimeric allenes was subjected to very brief hydrolytic conditions there was evidence suggesting formation of some of the less stable *cis*-aldehyde **5a** (see Experimental Section).

jugated enol acetate **6**, together with some of the unsaturated aldehyde **4**. The interconversion of aldehyde **4b** and its enol acetate **6b** had been demonstrated by Miescher and coworkers.[10]

Variations in the ring-A portion of the molecule, while not affecting the nature of the acetylene–allene equilibrium, did influence the relative ease of isolation of the isomeric acetoxyallenes. Thus, in the estrane series with an aromatic A ring bearing either a 3-hydroxy (**1f**) or 3-acetoxy group (**1g**), only one of the isomeric allenes was isolated in crystalline form. In each case this proved to be the 21α isomer (**2f** and **2g**), the 21β epimer formed in equal amount remaining in the mother liquors. The 3-methoxy compound (**1d**) upon rearrangement afforded a noncrystalline 1:1 mixture of the isomeric allenes (**2d**:**3d**) which was hydrolyzed in good over-all yield to the *trans*-17(20)-aldehyde **4d**. Similarly the rearrangement of ethisterone acetate (**1b**) gave an equimolar mixture of 21 epimers that could not be separated nor crystallized. On the other hand, the corresponding 19-nor analog **1c** afforded a mixture of epimeric allenes from which the 21β isomer could be crystallized. In each case, however, hydrolysis led to a single crystalline aldehyde verifying the assignments made on the basis of spectral and elemental analyses. Compound **1e** underwent elimination of the 3-acetoxy function leading to an inseparable mixture of products. The 17(20) double bond of **4a** and **4d** could be selectively reduced over palladium on charcoal to give saturated 21-aldehydes **7a** and **7d**, respectively.

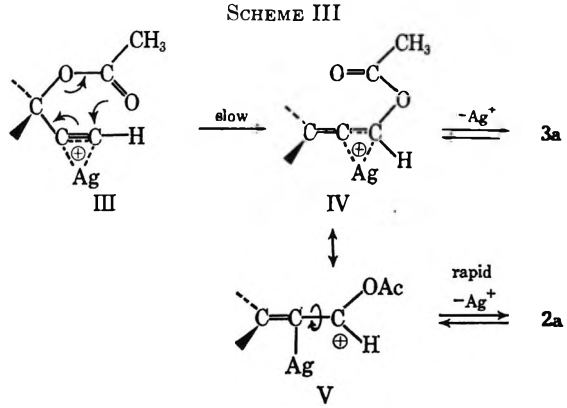
Stereochemistry.—The isolation of both crystalline isomers **2a** and **3a** permitted spectral comparison from which we may confidently make configurational assignments of the allene geometry. By examination of the positions of the C-18 angular methyl proton signals in the nmr spectra we have assigned the 21β-acetoxy configuration to that isomer having a C-18 methyl proton signal at lower field (**3a**, 57 Hz) relative to its isomer (**2a**, 53 Hz). The deshielding influence of a neighboring β-oriented acyloxy function on the C-18 protons is well documented.[11] In each series of compounds studied, the nmr spectrum of the total crude reaction product revealed the two C-18 methyl signals of about equal intensity separated by about 4 Hz, thus permitting the assignment of geometry to the crystalline form ultimately isolated.

The C-21 olefinic proton signal appeared as a triplet (J = 2.5 Hz) showing five-bond coupling with the C-16 protons. The C-21β proton of **2a** was centered at 439 Hz while the isomeric compound, **3a**, showed the C-21 proton signal at 446 Hz.[12] Lowe,[13] extrapolating from the principals of Brewster,[14] has studied the optical rotational properties of a series of allenes of known stereochemistry. He observed an apparent correlation in the sign of optical rotation and the handedness of the screw pattern of polarizability of substituents on the allene chain. In the present set of compounds the uncertainty as to the relative polarizability of the ring-D carbon substituents on the allene side chain reduces the reliability of any configurational assignments made on the basis of the relative signs of rotation of the isomers.

The ORD[15] spectra of the two isomers is noteworthy, generally bearing out the quasi-enantiomeric nature of the pair of compounds. Thus, the 21α-acetoxy compound **2a** has a negative curve with a plateau in the region 220–252 mμ, whereas the 21β-acetoxy compound **3a** shows a strong positive Cotton effect with a peak at 243 mμ.[16]

Any consideration of the mechanism of this silver ion catalyzed rearrangement must account for the apparent lack of stereospecificity. A significant point in this regard is the observation that pure acetoxyallene **2a** (or **3a**) together with 5 mol % of silver perchlorate in acetone, when held at reflux temperature for *24 hr*, equilibrated to an equimolar mixture of the two compounds. This was deduced on the basis of the equivalence of the heights of the C-18 methyl proton resonances relative to the single C-19 signal of the silver-free concentrate. This is in contrast with the several-day reaction period required for the initial rearrangement of the ethynyl ester. We believe the data to be consistent with the mechanism shown in Scheme III.

SCHEME III



Formation of a π complex between silver ion and allenic double bonds has received much less study than the corresponding acetylenic complex formation.[17] Nevertheless, such an intermediate as IV may explain the apparent loss of stereoselectivity of the rearrangement. Thus, a π complex or a bridged ion structure between silver and the acetylenic bond electrons (structure III) would result in increased electrophilicity of the terminal acetylenic carbon resulting in the initial stereospecific 1,3 migration of acetate. The intermediate IV, also bound to silver, may be expected to be in resonance with the symmetrical allyl cation form V. Reversible loss of argentous ion then gives either isomeric allene. Under the reaction conditions employed in this study the rate of equilibration of the products is

(10) K. Miescher, A. Wettstein, and C. Scholz, *Helv. Chim. Acta*, **22**, 892 (1939).

(11) *Cf.* W. R. Benn and R. M. Dodson, *J. Org. Chem.*, **29**, 1142 (1964), and references cited therein.

(12) Since this work was completed, two communications have appeared describing some acyclic, monocyclic, and bicyclic acetoxy allenes prepared by the general procedure described herein: (a) M. Apparu and R. Glenat, *C. R. Acad. Sci., Paris, Ser. C*, **265**, 400 (1967); (b) V. T. Ramakrishnan, K. V. Narayanan, and S. Swaminathan, *Chem. Ind.* (London), 2082 (1967). The nmr data cited by these groups, particularly that of the Indian authors, are entirely consistent with that observed in the present work.

(13) (a) G. Lowe, *Chem. Commun.*, 411 (1965); (b) *cf.* E. L. Eliel, *Tetrahedron Lett.*, No. 8, 16 (1960).

(14) J. H. Brewster, *J. Amer. Chem. Soc.*, **81**, 5475 (1959).

(15) We are indebted to Professor W. Klyne at the University of London, for making the ORD determinations of compounds **2a** and **3a** for us.

(16) *Cf.* S. F. Mason and G. W. Vane, *Tetrahedron Lett.*, 1593 (1965).

(17) Reference 1, p 342. For a recent discussion of the nature of the structure of the analogous mercurinium allene ion, see W. L. Waters and E. F. Kiefer, *J. Amer. Chem. Soc.*, **89**, 6261 (1967). These workers prefer the three-membered σ-bonded mercury bridge structure over the alternate simple polarized π complex.

greater than is the rate of the SNi′ rearrangement. This is analogous to the reaction of optically active ethynyl carbinols with thionyl chloride in which Landor and coworkers[18] observed retention of optical purity in the resulting chloroallene under anhydrous conditions and rapid racemization in the presence of traces of acid.

In light of the success of this reaction system, little attention was given to other catalysts or solvents. It is noteworthy that cuprous ion in either dimethyl sulfoxide or dimethylformamide resulted in loss of acetic acid to give the known enyne **8a**.[19] Landor and coworkers[20] observed an analogous result when chloroallenes were heated in the presence of cuprous cyanide in dimethylformamide suggesting an allene intermediate in the formation of **8a**.

Experimental Section[21]

Rearrangement of 17α-Ethynylandrost-5-ene-3β,17β-diol Diacetate. 5,17(20),20-Pregnatriene-3β,21α-diol Diacetate (2a).—A solution of 19.0 g of 17α-ethynylandrost-5-ene-3β,17β-diol diacetate and 619 mg (6 mol %) of silver perchlorate in 500 ml of dry acetone containing 10 drops of tetramethylguanidine (tmg) was refluxed under nitrogen for 96 hr. At the end of this time thin layer chromatography (tlc) indicated a spot corresponding to only a trace of starting material together with a single slightly less polar spot. The reaction mixture was cooled and 5 ml of saturated ammonium chloride solution was added. After stirring for 15 min the precipitated solids were removed by filtration and the filtrates concentrated to *ca.* two-thirds volume and allowed to cool slowly. From the acetone solution there was obtained by direct crystallization 7.03 g (42%) of the 21α-acetoxyallene (**2a**). Recrystallization from acetone containing a trace of pyridine (py) afforded analytically pure material: mp 199–202°; $[\alpha]_D$ −67.3°; ir (KBr) 3.25, 5.03, 5.76, and 8.05 μ; nmr signals appeared at 53 (18 H), 62.5 (19 H), 121 (3 Ac), 126.5 (21 Ac), 278 (3 H), 324 (6 H), and 439 Hz (t, J = 2.5 Hz, 21β-H).

Anal. Calcd for $C_{25}H_{34}O_4$: C, 75.34; H, 8.60. Found: C, 75.47; H, 8.86.

5,17(20),20-Pregnatriene-3β,21β-diol Diacetate (3a).—Concentration of the acetone filtrates above afforded upon cooling 1.5 g of a crystalline material melting at 122–130°. Concentration of the filtrate and chromatography over silica gel afforded more of this material from the fractions eluted by 1% ethyl acetate–benzene (total 23%). Crystallization from ether–petroleum ether (bp 64–68°) yielded pure **3a**: mp 128–131°; $[\alpha]_D$ −11°; ir (KBr) 3.29, 5.05, 5.68, 5.77, 8.05, and 8.20 μ; the nmr spectrum differed from that of the 21α isomer only in the position of the C-18 proton signal at 57 Hz and the 21α-H triplet at 446 Hz (J = 2.5 Hz).

Anal. Calcd for $C_{25}H_{34}O_4$: C, 75.34; H, 8.60. Found: C, 75.68; H, 8.60.

The lower melting isomer **3a** was isolated in lower yield than the higher melting material, **2a**. Nevertheless, in other experiments determination of the nmr spectrum on the total crude reaction product indicated equal amounts of the two compounds together with about 10% of the starting material (**1a**). A preliminary attempt to separate the isomers by vpc was unsuccessful.

Equilibration of 5,17(20),20-Pregnatriene-3β,21α-diol Diacetate.—**2a** (1 g) together with 68 mg of silver perchlorate was refluxed in 25 ml of acetone containing 1 drop of tmg for 24 hr. The reaction mixture was cooled, diluted with chloroform, washed with saturated ammonium chloride, dried, and concentrated to a noncrystalline residue. The nmr spectrum of the material was identical with that of a 1:1 mixture of the isomeric allenes **2a** and **3a**.

5,16,20-Pregnatriene-3β,21-diol Diacetate (6a).—A solution of 12.2 g of **1a** and 0.5 g of silver acetate in 250 ml of acetic acid and 100 ml of acetic anhydride was refluxed under nitrogen for 2 hr. The reaction mixture was concentrated under vacuum to one-half volume, poured into 800 ml of water, and then taken up in ether. The ether extract was washed with cold dilute sodium bicarbonate solution, dried over sodium sulfate, and concentrated to an amber gum weighing 11.1 g. This gum was chromatographed on silica and yielded, from the 2% ethyl acetate–benzene fractions, the conjugated enol acetate **6a**. Recrystallization from benzene–cyclohexane gave pure material: mp 145–150°; uv λ_{max} 247.5 mμ (18,650); ir (KBr) 3.21, 5.69, 5.78, 8,00, and 8.26 μ; the nmr spectrum displayed signals at 54.5 (18 H), 63.5 (19 H), 121.5 (3 Ac), 127.5 (21 Ac), 278, 322, 358.5 (d, J = 12.5 Hz, 20 H), and Hz 449 (d, J = 12.5 Hz, 21 H).

Anal. Calcd for $C_{25}H_{34}O_4$: C, 75.34; H, 8.60. Found: C, 74.97; H, 8.66.

The enol acetate was further characterized by hydrolysis to the unsaturated aldehyde **4a** (described below) by brief warming with 80% acetic acid. More polar eluates of the above chromatogram also afforded aldehyde **4a**.

***trans*-3β-Acetoxypregna-5,17(20)-dien-21-al (4a).**—A solution of 5 g of 5,17(20),20-pregnatriene-3β,21α-diol diacetate (**2a**) in 100 ml of 80% acetic acid was warmed on the steam bath under nitrogen for 1 hr and then diluted with 500 ml of water. The product was extracted with ether. The ether solution was washed with sodium carbonate solution and dried; the ether was then removed under reduced pressure affording 4.2 g of pale yellow prisms. Recrystallization from ethyl acetate–methylcyclohexane gave aldehyde **4a**: mp 180–185° (lit.[22] mp 184–185°); nmr 57 (18 H), 64 (19 H), 347 (20 H, doublet of triplets, J_{20-21} = 8, J_{20-16} = 2.5 Hz), and 594 Hz (d, J = 8 Hz, CHO).

Treatment of the isomeric allene **3a** or the enol acetate **6a** under these same conditions led to the identical aldehyde **4a**. Alternatively, the entire silver acetate–acetic acid–acetic anhydride reaction solution could be diluted with water such as to result in an 80% acetic acid solution. Warming for 1 hr followed by dilution with water afforded the unsaturated aldehyde **4a** directly in about 70% over-all yield. Hydrolysis of **2a**, **3a**, **6a**, or **4a** under alkaline conditions led to the corresponding 3-hydroxy-aldehyde, mp 181–190°[23] (lit.[22] mp 178–179°). The nmr spectrum showed the expected aldehyde proton doublet at 595 Hz (J = 7.5 Hz). In one experiment acetoxyallene **3a** was warmed in 80% acetic acid for 20 min. The nmr spectrum of the crude crystalline product obtained after work-up indicated the presence of what is believed to be the 17(20)-*cis*-aldehyde **5a**[24] as evidenced by an 18-methyl proton signal at 66 Hz. Attempts to separate the *cis* isomer from the more stable *trans* form were unsuccessful.

21α- and 21β-Acetoxypregna-4,17(20),20-trien-3-one (2b and 3b).—A solution of 8.0 g of 17β-acetoxy-17α-ethynylandrost-4-en-3-one in 150 ml of acetone containing 4 drops of tmg and 358 mg of silver perchlorate was refluxed under nitrogen for 2 days. The reaction mixture was cooled and 2 ml of saturated sodium chloride solution was added and stirred for 15 min. The precipitated solids were filtered off and the filtrates diluted with 300 ml of ether. This solution was then washed with saturated sodium chloride solution, dried over sodium sulfate, and concentrated to 8.0 g of a light yellow glass. This was taken up in benzene and chromatographed on silica gel. The product, eluted by the 2–5% ethyl acetate–benzene eluates, was obtained as a colorless glass consisting of a 1:1 mixture of 21α- and 21β-acetoxyallenes, **2b** and **3b** (36%). The absorption maximum in the ultraviolet spectrum occurred at 240 mμ (15,900); ir ($CHCl_3$) 5.05, 5.72, 6.01, 6.20, 8.10, and 8.18 μ. The nmr

(18) R. J. D. Evans, S. R. Landor, and R. T. Smith, *J. Chem. Soc.*, 1506 (1963); *Cf.* also ref 13b.

(19) E. B. Hershberg, E. P. Oliveto, C. Gerold, and L. Johnson, *J. Amer. Chem. Soc.*, **73**, 5073 (1951).

(20) P. M. Greaves, S. R. Landor, and D. R. J. Laws, *J. Chem. Soc., Sect. C*, 1976 (1966).

(21) Melting points were taken on a Kofler microstage. Rotations were taken in chloroform at about 1% concentration at 26 ± 2° and the ultraviolet spectra were determined in methanol. All spectral and analytical results were carried out under the direction of Dr. R. T. Dillon of the Analytical Department of G. D. Searle & Co. Nmr spectra were determined in deuteriochloroform using a Varian Associates A-60 spectrometer operating at 60 MHz. Resonances are expressed in cycles per second (Hz) in the direction of decreasing field strength relative to an internal tetramethylsilane standard.

(22) H. Heuser, K. Eichenberger, and Pl. A. Plattner, *Helv. Chim. Acta*, **33**, 370 (1950); *cf.* ref 10.

(23) Melting points of the unsaturated aldehydes taken on the micro hot stage tended to be broad, no doubt as a result of the tendency of these compounds to undergo air oxidation at elevated temperatures; *cf.* ref 10.

(24) J. Romo and A. Romo DeVivar, *J. Amer. Chem. Soc.*, **79**, 1118 (1957).

spectrum exhibited 18-methyl proton signals at 55 and 59 Hz of equal amplitude and half the amplitude of the 19 proton signal at 72 Hz; the 20 H resonances appeared at 443 and 446 Hz (t, J = 2.5 Hz). The glass was dried for 3 hr at 80° (0.01 mm).

Anal. Calcd for $C_{23}H_{30}O_3$: C, 77.93; H, 8.53. Found: C, 77.73; H, 8.53.

21-Acetoxypregna-4,16,20-trien-3-one (**6b**) and ***trans*-3-Keto-pregna-4,17(20)-dien-21-al** (**4b**).—This reaction was carried out in an identical manner as that described above for the preparation of **6a**. The enol acetate **6b** crystallized directly from a benzene solution of the reaction product: mp 193–200° (lit.[10] mp 192–194°); uv_{max} 244 mμ (32,500).

The unsaturated aldehyde **4b** was obtained by hydrolysis of the enol acetate, either with 80% acetic acid as described above for the preparation of **4a**, or by brief treatment with methanolic sodium bicarbonate at reflux. The over-all yield from **1b** was 74%. The ketoaldehyde was crystallized from ether to give an analytically pure sample: mp 148–150°; uv λ_{max} 242.5 mμ (31,000) (lit.[10] mp 149–152°).

21β-Acetoxy-19-norpregna-4,17(20),20-trien-3-one (**3c**).—A solution of 10.6 g of 17β-acetoxy-17α-ethynyl-19-norandrost-4-en-3-one and 365 mg (5 mol %) of silver perchlorate in 150 ml of acetone containing 8 drops of tmg was maintained at reflux (nitrogen atmosphere) for 72 hr. The reaction was worked up as described above for the preparation of **2a**. The product was allowed to crystallize from ethyl acetate (2.56 g, 24%), and was then recrystallized from acetone–petroleum ether (py) to give the 21β-acetoxyallene **3c** as cubes: mp 187–190°; $[\alpha]_D$ 144°; uv λ_{max} 238.5 mμ (19,550); ir (KBr) 5.03, 5.69, 5.61, 6.15, 9.91, and 8.06 μ. The nmr resonances appeared at 60.5 (18 H), 128 (Ac), 350 (4 H), and 445 Hz (t, J = 2.5 Hz, 21 H).

Anal. Calcd for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29. Found: C, 77.87; H, 8.24.

Additional quantities of this isomer were obtained by chromatography of the crystallization filtrates on silica gel. The 21α-acetoxyallene 2c, however, could not be isolated in crystalline form. Its presence in the crude reaction product and in the mother liquors following crystallization of isomer **3c** was established on the basis of the 18-methyl proton signal at 56.5 Hz as well as the characteristic allene absorption band in the infrared spectrum at 5.04 μ. On the basis of the greater deshielding of the 18-methyl protons the crystalline product was assigned the 21β configuration (**3c**) (see discussion).

21-Acetoxy-19-norpregna-4,16,20-trien-3-one (**6c**).—A solution of 4.9 g of 17β-acetoxy-17α-ethynyl-19-norandrost-4-en-3-one in 100 ml of acetic acid and 50 ml of acetic anhydride together with 200 mg of silver acetate was stirred under nitrogen at reflux temperature for 0.5 hr. The reaction mixture was cooled, decanted from deposited solids, and poured into 2 l. of water. After 1 hr, the suspension was extracted with ether. The organic phase was then washed successively with water, saturated sodium carbonate solution and saturated salt solution. The ether solution was dried, concentrated *in vacuo*, and chromatographed on silica gel. From the fractions eluted by 10–20% ether–benzene was obtained, following recrystallization from aqueous methanol, the conjugated enol acetate **6c** (52%) as rods: mp 122–129°; uv λ_{max} 243 mμ (33,200); ir (KBr) 5.69, 5.96, 6.15, and 8.18 μ.

Anal. Calcd for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29. Found: C, 77.62; H, 8.39.

***trans*-3-Keto-19-norpregna-4,17,(20)-dien-21-al** (**4c**).—Treatment of enol acetate **6c** or either acetoxyallene **2c** or **3c** with 80% acetic acid as described above resulted in hydrolysis to the unsaturated aldehyde **4c** in 80% yield. Recrystallization from aqueous acetone gave prisms having mp 142–145°; uv λ_{max} 242 mμ (35,500); ir (KBr) 3.59, 5.95, 6.11, and 6.15 μ; nmr 56.6 (18 H), 344 (m, 20 H), 347 (4 H), and 589 Hz (d, J = 8 Hz, CHO)

Anal. Calcd for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78. Found: C, 80.07; H, 8.76.

21α- and 21β-Acetoxy-19-norpregna-1,3,5(10),17(20),20-pentaen-3-ol 3-Methyl Ether (**2d and 3d**).—17β-Acetoxy-17α-ethynylestratr-1,3,5(10)-trien-3-ol 3-methyl ether (mestranol acetate, **1d**) was treated with silver perchlorate in acetone as described above. Integration of the nmr signals produced by the 18-methyl and acetate protons indicated the crude product to consist of **2d**, **3d**, and **1d** in the ratio 40:40:20. Passage through a column of silica separated the allene fraction as a pure 1:1 mixture of **2d** and **3d** in the form of colorless glass: $[\alpha]_D$ +25°; ir ($CHCl_3$) 5.05, 5.72, and 8.02 μ. Pertinent features of the nmr spectra consisted of signals of equal intensity at 54.5 and 58.5 Hz attributed to the 18-methyl protons of **2d** and **3d**, respectively. The C-21 proton signals were somewhat obscured by the ring-A aromatic proton signals at 438 to 448 Hz. The glass was dried for analysis for 3 hr at 75° (0.01 mm).

Anal. Calcd for $C_{23}H_{28}O_3$: C, 78.37; H, 8.01. Found: C, 78.44; H, 8.10.

***trans*-3-Methoxy-19-norpregna-1,3,5(10),17(20)-tetraen-21-al** (**4d**). **Alkaline Hydrolysis.**—A solution of 16.7 g of an equimolar isomeric mixture of **2d** and **3d** in 300 ml of methanol containing 15 ml of saturated sodium bicarbonate solution was refluxed under nitrogen for 45 min. Tlc at this time indicated no starting material. The product began to crystallize spontaneously from the reaction mixture. Cooling afforded 10.8 g of material having mp 170–172°, and a second crop of 0.55 g, mp 169–172° (77% from **1d**). The analytical sample was recrystallized from acetone–hexane and had mp 175–177°; $[\alpha]_D$ +63.5°; uv λ_{max} 234–242 mμ (20,900), λ_{inf} 276 and 285 mμ; ir (KBr) 3.63, 5.98, and 6.10 μ; nmr 54.5 (18 H), 227 (OCH_3), 348.5 (d of t, J = 8 and 2.5 Hz, 20 H), 399, 418 (q, aromatic), and 595 Hz (d, J = 8 Hz, CHO).

Anal. Calcd for $C_{21}H_{26}O_2$: C, 81.25; H, 8.44. Found: C, 81.19; H, 8.39.

The *trans*-unsaturated aldehyde **4d** could also be obtained by acid hydrolysis using 80% acetic acid as described above.

19-Norpregna-1,3,5(10),17(20),20-pentaene-3,21α-diol Acetate (**2f**).—Treatment of 15.6 g of the 17-monoacetate of 17α-ethynylestradiol (**1f**) under the conditions described above for the corresponding 3-methyl ether (**1d**) resulted in the isolation from ether of 7.1 g of crystalline material. Recrystallization from acetone and from ethyl acetate gave pure 21α-acetoxyallene **2f** as needles: mp 206–208° dec (sample inserted at 200°); $[\alpha]_D$ −6°; ir (KBr) 2.92, 3.24, 5.01, and 5.81 μ; nmr 54 (18 H), 127 and 438 Hz (t, J = 2.5 Hz, 21 H).

Anal. Calcd for $C_{22}H_{26}O_3$: C, 78.07; H, 7.74. Found: C, 78.26; H, 7.76.

Examination of the nmr spectrum of the residues from the isolation of the 21α-acetoxyallene (above) showed a signal at 57.5 Hz attributed to the 18-methyl proton resonance of the isomeric 21β acetate **3f**. Attempts to isolate this compound in pure form were unsuccessful.

***trans*-3-Hydroxy-19-norpregna-1,3,5(10),17(20)-tetraen-21-al** (**4f**).—Alkaline hydrolysis of either the pure 21α-acetoxyallene **2f** or a mixture of the two isomers **2f** and **3f** by sodium bicarbonate methanol treatment as described in the preparation of aldehyde **4d** led to the corresponding 3-hydroxy compound, **4f**. Purification by recrystallization from acetone–methylcyclohexane gave prisms: mp 243–248° dec (inserted at 240°); ir (KBr), 3.05, 6.05, 6.31 μ; nmr (pyridine) 46, 352 (d of t, J = 8, 2.5 Hz, 20 H) and 599 Hz (d, J = 8, CHO).

Anal. Calcd for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16. Found: C, 81.25; H, 8.11.

19-Norpregna-1,3,5(10),17(20)-pentaene-3,21α-diol Diacetate (**2g**).—Subjecting 16.5 g of 17α-ethynylestradiol diacetate (**1g**) to the silver perchlorate rearrangement conditions as described above gave, upon work-up, 12.26 g of a crystalline mixture of acetoxyallenes. Crystallization from acetone–hexane afforded one pure isomer, the 21α-acetoxy compound **2g** in 27% yield. A sample crystallized from ethyl acetate (py) as platelets: mp 145–148°; $[\alpha]_D$ −12.5°; ir (KBr) 3.23, 5.03, 5.68, and 8.09 μ; nmr 54 (18 H), 127.5 (21 Ac), 136 (3 Ac), and 440.5 Hz (m, 21 H, partly obscured by aromatic proton signals).

Anal. Calcd for $C_{24}H_{28}O_4$: C, 75.76; H, 7.42. Found: C, 75.90; H, 7.52.

Attempts to isolate the 21β isomer were unsuccessful. Impure samples of this material displayed 18-methyl proton resonance in the nmr at 58 Hz in a manner consistent with the other examples studied. Hydrolysis of the mixture of allene diacetates **2g** and **3g** under the alkaline conditions described above led to the same 3-hydroxy aldehyde **4f** in 70% over-all yield.

3β-Acetoxypregn-5-en-21-al (**7a**).[25]—A solution of 9.4 g of **4a** in 1 l. of ethanol was shaken in an atmosphere of hydrogen together with 3 g of 5% palladium on calcium carbonate at room temperature for 3.5 hr. Removal of the catalyst and recrystallization from acetone–petroleum ether afforded the product **7a** in 80% yield: mp 141–144°; ir (KBr) 3.66, 5.78, and 8.06 μ.

Anal. Calcd for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 76.85; H, 9.64.

(25) We are indebted to Dr. Robert Garland of these laboratories for the preparation of this compound.

3-Methoxy-19-norpregna-1,3,5(10)-trien-21-al (7d).—Unsaturated aldehyde **4d** (2 g) was shaken with 0.2 g of 5% palladium on charcoal in 600 ml of ethanol in an atmosphere of hydrogen at room temperature for 1 hr. Concentration of the filtrates following removal of catalyst and recrystallization from benzene–methylcyclohexane afforded pure **7d** in 75% yield: mp 110–112.5°; $[\alpha]_D$ +69°; ir (KBr) 3.65, 5.79 μ; nmr 38 (18 H), and 590 Hz (t, J = 2.5 Hz, CHO).

Anal. Calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.49; H, 9.18.

Catalytic Effect of Cuprous Ion.—When **1a** was refluxed with 10 mol % of cuprous cyanide in dimethylformamide for 2 hr and the reaction mixture concentrated and chromatographed over silica, the only crystalline product isolated was 17-ethynylandrosta-5,16-dien-3β-ol acetate, **8a**: mp 174–176°; $[\alpha]_D$ −68° {lit.[19] mp 174°, $[\alpha]_D$ −64.2° (di)}.

Registry No.—**2a**, 16934-40-0; **2b**, 16934-41-1; **2d**, 16934-42-2; **2f**, 16934-43-3; **2g**, 16960-05-7; **3a**, 16934-44-4; **3b**, 16934-45-5; **3c**, 16934-46-6; **3d**, 16934-47-7; **4a**, 16934-48-8; **4c**, 16934-49-9; **4d**, 16934-50-2; **4f**, 16934-51-3; **6a**, 16934-52-4; **6c**, 16934-53-5; **7a**, 16934-54-6; **7d**, 16934-55-7.

Carbon 1–Carbon 11 Interactions in Some Oxygenated 5β-Pregnanes and Androstanes[1]

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5β-Androstane-1,3,11,17-tetrone (**3**), 5β-androstane-1,3,17-trione (**6**), 5α-androstane-1,3,17-trione, and 25α_F-5α-spirostane-1,3-dione have been compared with regard to degree of enolization in methanol and dioxane solution and in KBr dispersion. In contrast to the normal behavior of the 11-deoxy-β diketones, the 11-keto-β diketone **3** is but half-enolized even in methanol solution, and is largely or wholly ketonized in less polar solvents. From an examination of the ratio of the enol methyl ethers prepared from each β diketone, it was shown that the tetrone **3** enolizes chiefly to the 1-hydroxy form **7**. Additional examples of 1,11 interaction include the observations that the two 1,11 diketones **26** and **28** are resistant to metal hydride or catalytic reduction, and that the chromic anhydride–pyridine oxidation of 5β-androstane- or 5β-pregnane-1β,3α-diols in the 11-deoxy series furnishes only the 1-keto-3α-ols, whereas similar oxidation of the corresponding 11-keto-1β,3α-diols also affords appreciable amounts of the 3-keto-1β-ols. These results are variously attributed to conformational distortion, hydrogen bonding, or polarization of keto groups.

In an earlier publication[2] we described the isolation from urine of 1β,3α,17α,20β,21-pentahydroxy-5β-pregnan-11-one (**1**, Scheme I) following the administration of 3α,17α,20β,21-tetrahydroxy-5β-pregnan-11-one (β-cortolone, a known metabolite of cortisol in man) to the senior author. The position of the metabolically introduced hydroxyl group in **1** was established by degrading it to the known 5β-androst-1-ene-3,11,17-trione; its configuration was determined primarily from the nuclear magnetic resonance (nmr) spectrum of a second degradation product, namely 1β-hydroxy-3α-acetoxy-5β-androstane-11,17-dione. In this paper the preparation of additional derivatives and degradation products of this metabolite, the partial synthesis of some related steroids, and evidence for the occurrence of various types of 1,11 interaction among certain of these compounds are described.

Oxidative cleavage of the side chain of **1** with sodium periodate[2] followed by further oxidation of the 17-keto steroid **2** thus obtained by Jones' method[3] gave the β diketone, 5β-androstane-1,3,11,17-tetrone (**3**). This product crystallized readily, analyzed correctly, and was chromatographically homogeneous, but its extinction coefficient in methanol (ϵ 6400 at 256 mμ) was only about half the value for the corresponding 11-deoxy-β diketone, namely 5β-androstane-1,3,17-trione [**6**, Scheme I, λ_{max} 258 mμ (ϵ 12,650)].[4] The latter was prepared from **1** *via* **4** and **5** by the sequence outlined in Scheme I.[2]

In view of this observation, we examined in detail the ultraviolet (uv) and infrared (ir) spectra of the tetrone **3** and the trione **6** as well as two β diketones in the 5α series.[5] Table I gives the λ_{max} values and extinction coefficients (ϵ) of these β diketones in neutral and alkaline methanol and in dioxane solution, and their principal bands in the infrared region. The tetrone **3**, which is highly enolized in alkaline methanol, is, like 5α-cholestane-1,3-dione and 25α_F-5α-spirostane-1,3-dione, largely ketonized in dioxane solution and wholly so in KBr dispersion. In contrast, the trione **6** and its 5 epimer are as fully enolized in dioxane solution and in KBr dispersion as they are in methanol.

Tamm and Albrecht[6] attributed the unusual stability of the keto form of 5α-cholestane-1,3-dione in KBr dis-

(1) Supported in part by a research grant, AM 01255, from the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, U. S. Public Health Service.

(2) J. J. Schneider and N. S. Bhacca, *J. Biol. Chem.*, **241**, 5313 (1966).

(3) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(4) Professor Ch. Tamm and his associates have prepared a number of 11-deoxy-1,3-diketo-5β steroids derived from sapogenins and cardenolides as well as members of the androstane and pregnane series. Their extinction coefficients at 256–257 mμ in ethanol ranged from 15,500 to 15,900 with a mean value of 15,700. We wish to thank Professor Tamm for supplying us with these data prior to publication as well as for samples of 5α-cholestane-1,3-dione and the enol methyl ethers derived from it.

(5) 5α-Androstane-1,3,17-trione was prepared from 5α-androstan-3β-ol-17-one (isoandrosterone) and 25α_F-5α-spirostane-1,3-dione from ruscogenin (see Experimental Section).

(6) Ch. Tamm and R. Albrecht, *Helv. Chim. Acta*, **43**, 768 (1960).

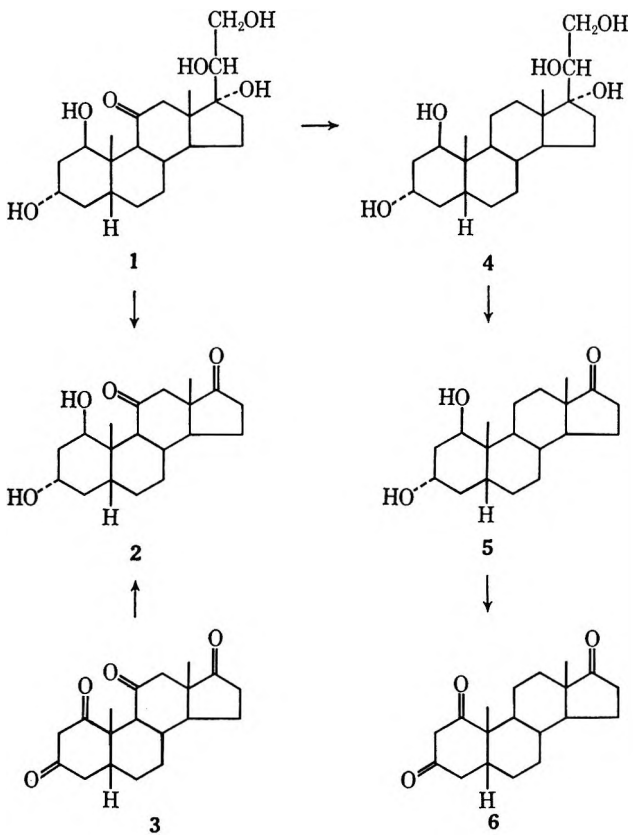
TABLE I

STEROIDAL β DIKETONES. PRINCIPAL BANDS IN ULTRAVIOLET AND INFRARED SPECTRA

Compound	λ_{max} mμ (ε) Methanol	Alkaline methanol[a]	Dioxane	Associated OH stretching band[b]	Associated C=O plus C=C stretching bands[c]
5β-Androstane-1,3,11,17-tetrone (**3**)	256 (6,400)	284 (20,700)	246 (2,050)	Absent	Absent
5β-Androstane-1,3,17-trione (**6**)	258 (12,650)	282 (25,500)	245 (12,500)	Strong	Strong
5α-Androstane-1,3,17-trione	255 (11,900)	284 (23,400)	245 (11,000)	Strong	Strong
25α_F-5α-Spirostane-1,3-dione	255 (12,000)	284 (24,300)	243 (1,650)	Absent	Absent
25α_F-Spirost-5-ene-1,3-dione[d]	256 (12,900)	283 (23,400)			
5α-Cholestane-1,3-dione[e]	255 (12,600)	285 (27,540)	301 (76)	Absent	Absent

[a] One milliliter of 1 *N* aqueous sodium hydroxide diluted to 100 ml with methanol. [b] 2750–2200 cm^{-1} (KBr dispersion). [c] 1680–1500 cm^{-1} (KBr dispersion). [d] C. W. Shoppee, R. E. Lack, and B. C. Newman, *J. Chem. Soc.*, 339 (1967) (neutral and alkaline ethanol). [e] Tamm and Albrecht[6] (neutral and alkaline ethanol).

SCHEME I



persion chiefly to the formation of an intramolecular hydrogen bridge between the 11α-hydrogen atom and the carbonyl group at C-1 which serves to impede enolization of the latter. It is to be noted, from Table I, that, although 5α-androstane-1,3,17-trione has the same structure as 25α_F-5α-spirostane-1,3-dione and 5α-cholestane-1,3-dione with regard to rings A, B, and C, it differs from them in being highly enolized in dioxane solution and in KBr dispersion. It may be suggested, as an alternative to Professor Tamm's proposal, that the suppression of enolization of 25α_F-5α-spirostane-1,3-dione and of 5α-cholestane-1,3-dione in nonpolar solvents may be due to a long-range effect of the side chain.

The limited enolization of the tetrone **3**, particularly in methanol solution, cannot be ascribed to the *cis* nature of the A/B ring juncture since the 5α- and 5β-11-deoxy-β diketones are equally enolized in various solvents. It seems probable that the aberrant enolization of the tetrone **3** is a consequence of marked conformational distortion of the ring system. The contrasting properties of the tetrone **3** and the trione **6** with respect to degree of enolization also were observed in their circular dichroism (CD) curves and by paper chromatographic means (*vide infra*).

Having established, from its extinction coefficient in methanol, that the tetrone **3** is but half-enolized even in polar solvents, it seemed of interest to determine the relative abundance of its two enolic forms (**7** and **8** in Scheme II). Two considerations make it certain that the 1-hydroxy-1-ene form **7** predominates. First, its formation would be promoted by the stabilizing influence of hydrogen bonding as depicted by **9**. The nmr spectrum of **3** is compatible with this view.[7] Second, the ratio of the enol methyl ethers (**10** and **11**) derived from **3** supports this conclusion. Tamm[8] found that the ratio of the 1-methoxy to the 3-methoxy derivative, obtained on treating 5α-cholestane-1,3-dione with diazomethane, was 0.76. This ratio corresponds reasonably well with the ratios of 0.94 and 0.85 which we noted for the corresponding ethers derived from 11-deoxy-β diketone **6** (**12** and **13**) and from 5α-androstane-1,3,17-trione (**14** and **15**), respectively, but contrasts with the ratio of 1.66 which we obtained in the case of 11-keto-β diketone **3**. Assuming, with Tamm, that the ratio of the enol methyl ethers isolated fairly approximates the ratio of the two enol forms present under the conditions of etherification, it follows that the principal enol in equilibrium with the tetrone **3** must be the 1-hydroxy derivative **7**. It is thus evident that the carbonyl group C-11 controls the *direction* of enolization, presumably through the agency of intramolecular hydrogen bonding, but it is not apparent by what mechanism it contributes to the observed *limit* of enolization.

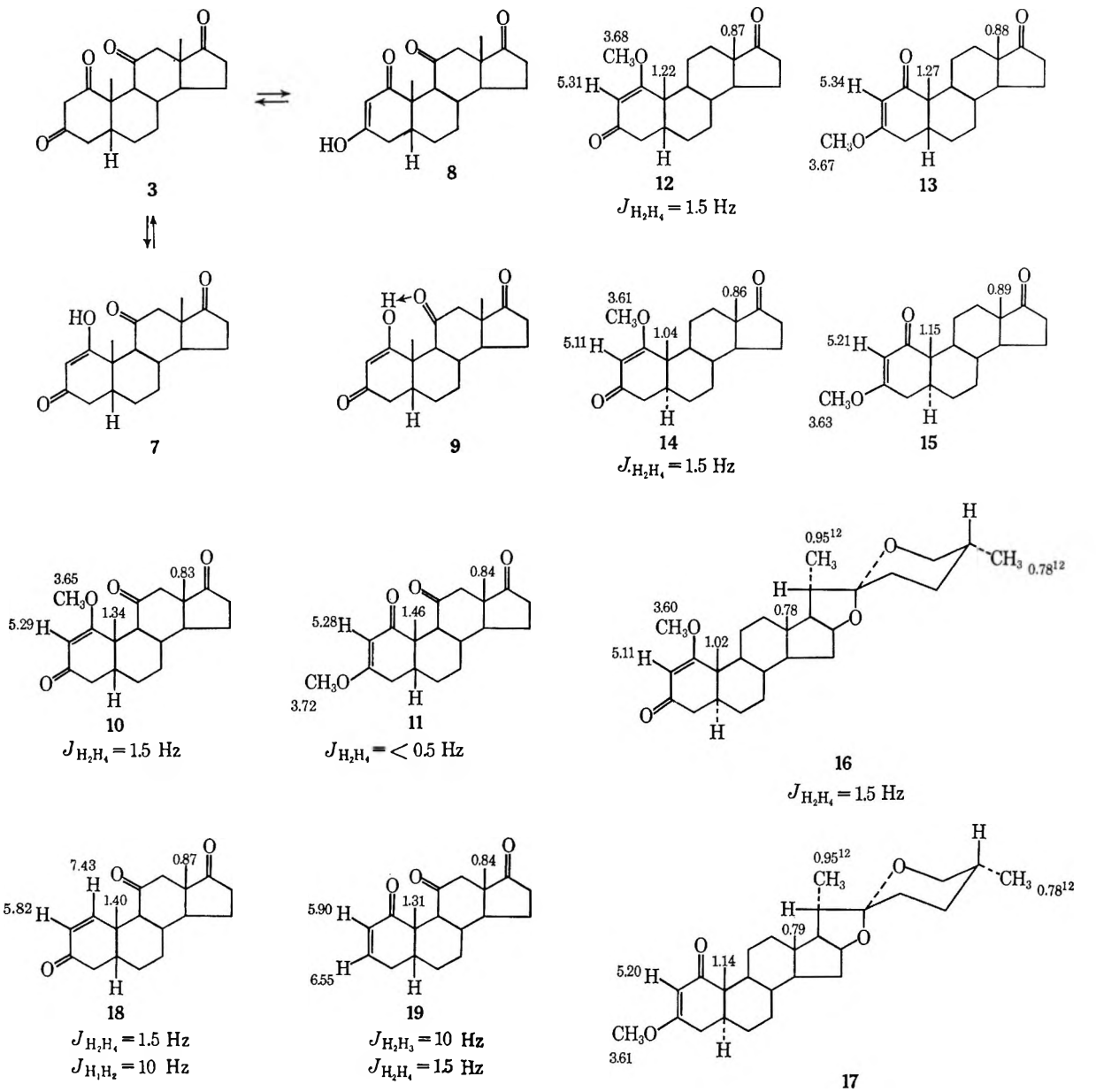
Nmr Spectroscopy Studies.—Proof of structure of the eight enol methyl ethers prepared in this study (Scheme II) required differentiating between individual members of the four pairs. The structures of the 11-keto enol methyl ethers **10** and **11** were distinguished by comparing their spectra with those derived from the unsaturated triketones **18** and **19**.[9] The distinction was made by examination of the nmr patterns caused by the proton α to the carbonyl function in the two ethers. The resonance pattern for H-2 appears as a pair of triplets in the spectrum of **19**. The large splitting of 10 Hz is caused by the interaction of this proton with H-3, whereas the smaller splittings of 1.5 Hz are due to long-range interactions of the C-4 methylene

(7) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry: Illustrations from the Steroid Field," Holden-Day, Inc., San Francisco, Calif., 1964, p 95.

(8) Ch. Tamm, *Helv. Chim. Acta*, **43**, 1700 (1960).

(9) The coupling constants and chemical shifts for **18** and **19** are given in Figure 7 of an earlier paper[2] and are reproduced here in order to facilitate comparisons.

SCHEME II



hydrogens with H-2. Since H-3 (the proton β to the carbonyl function) is replaced by a methoxyl group in **11**, the large splitting of 10 Hz in the resonance of H-2 (the proton α to the carbonyl group) disappears. Furthermore, the smaller couplings of 1.5 Hz due to interaction of H-2 with the methylene hydrogens which was discernible in **19** becomes much smaller in **11** owing to the presence of the methoxyl group at C-3. Thus H-2, which is α to the carbonyl group in **11**, appears as a broad singlet.

The nmr pattern for the proton α to the carbonyl function in **18** (H-2) occurs as a pair of doublets. The large coupling of 10 Hz is attributed to coupling with the β hydrogen (H-1). The smaller splitting of 1.5 Hz is due to long-range coupling[10] of H-2 through the carbonyl group to one of the methylene hydrogens at C-4. This small, very characteristic, coupling is present in the spectrum of **10** and also was observed in the spectra of the 11-deoxy ethers **12**, **14**, and **16**. This makes it possible to distinguish the various ethers in this series.

(10) See ref 7, pp 121–123.

The chemical shifts of C-19 methyl resonances in **18** and **19** are at variance with those of the 11-keto ethers **10** and **11**. This is due to a very unusual dipole–dipole interaction[11] between the C-1 and C-11 carbonyl groups. A detailed analysis of this interaction will be submitted for publication at a later date.

In Table II we have correlated the assigned structures of the eight enol methyl ethers with their absorption characteristics in the ultraviolet and infrared regions and their mobilities in four representative chromatographic systems. The two enol methyl ethers prepared from 5α-cholestane-1,3-dione by Tamm are included for comparison; their structures were determined by chemical means.

These data are in accord with and support the structure assignments. Thus the higher λ_{max} values and larger extinction coefficients for the 1-methoxy member

(11) (a) R. F. Zürcher, *Helv. Chim. Acta*, **46**, 2054 (1963); (b) see ref 7, pp 26, 27.

(12) K. Tori and K. Aono, *Ann. Rept. Shionogi Res. Lab.*, No. 14, 136 (1964).

TABLE II

STEROIDAL ENOL METHYL ETHERS. CORRELATION OF NMR STRUCTURE ASSIGNMENTS WITH OBSERVED CONSTANTS

No.	Nmr designation	Ultraviolet absorption[a] λ_{max}, mμ (ε)	Infrared maxima, cm^{-1}, for CH$_3$O—C=C—C=O system[b]		R_f in system[c] 1	2	3	4
10	1-Methoxy-5β-androst-1-ene-3,11,17-trione	258 (14,850)	1582	1638	0.18	0.17	0.08	
11	3-Methoxy-5β-androst-2-ene-1,11,17-trione	250 (12,430)	1619	1655	0.12	0.11	0.18	
12	1-Methoxy-5β-androst-1-ene-3,17-dione	254 (16,300)	1590	1655	0.72	0.56	0.19	
13	3-Methoxy-5β-androst-2-ene-1,17-dione	250 (14,700)	1619	1642	0.84	0.72	0.39	
14	1-Methoxy-5α-androst-1-ene-3,17-dione	255 (15,400)	1570	1648	0.66	0.50	0.19	
15	3-Methoxy-5α-androst-2-ene-1,17-dione	248 (13,030)	1616	1650	0.86	0.76	0.47	
16	1-Methoxy-25αF-5α-spirost-1-en-3-one	256 (16,770)	1575	1652				0.11
17	3-Methoxy-25αF-5α-spirost-2-en-1-one	248 (14,670)	1615	1660				0.38
	1-Methoxy-5α-cholest-1-en-3-one	242 (15,850)	1581	1655				0.18
	3-Methoxy-5α-cholest-2-en-1-one	237 (14,500)	1618	1658				0.48

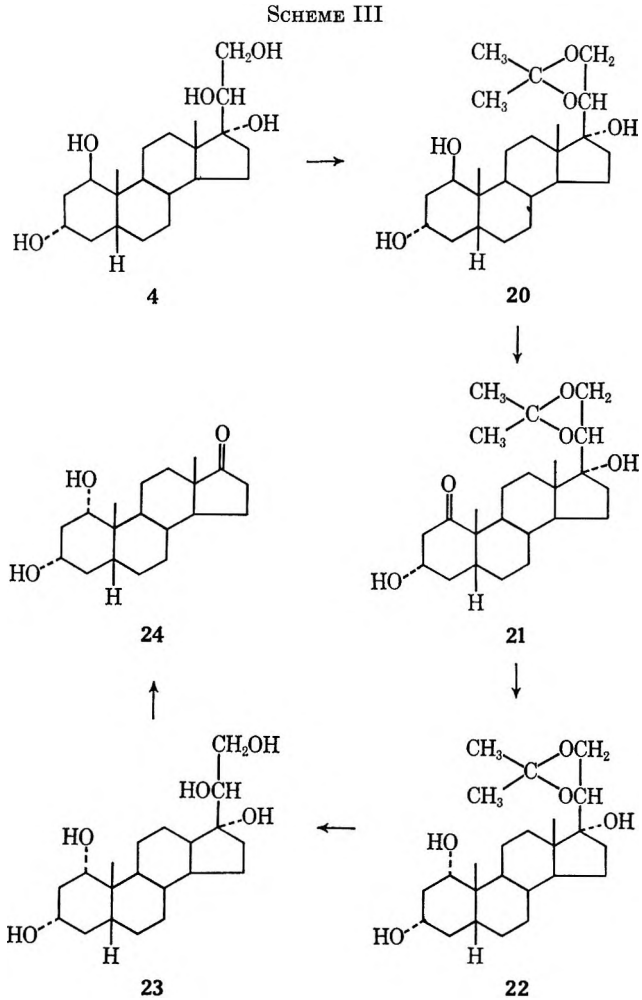
[a] Ultraviolet absorption spectra were obtained in methanol solution. [b] Infrared spectra were obtained in KBr dispersion; C=C stretching bands are in left column and C=O stretching bands in right column. [c] The composition of chromatographic systems referred to by number in this table and in the text appear in Table IV.

of each pair reflect the known differences between the 3-keto-1-ene and 1-keto-2-ene systems.[13] The feature of the infrared spectra useful in this connection is that the C=C stretching bands for the 3-methoxyl derivatives, including that prepared by Tamm, uniformly occur at significantly higher frequencies than is the case for the 1-methoxy forms. This relationship is not evident in the C=O stretching bands.

Partial Synthesis of 5β-Pregnane-1α,3α,17α,20β,21-pentol and of 1α,3α-Dihydroxy-5β-androstan-17-one.—Preparation of the 1 epimers of **1** and of **4** seemed straightforward since oxidation of the 1β,3α-diol (a, e) system under mild conditions would give the 1 ketone predominantly, which on reduction with sodium borohydride would furnish chiefly the more stable α (equatorial) alcohol. The route employed in the 11-deoxy series is outlined in Scheme III. Treatment of **4** with *p*-toluenesulfonic acid in acetone[14] furnished the 20,21-acetonide **20** in good yield, which on oxidation with chromic anhydride in pyridine,[15] reduction with sodium borohydride, and hydrolysis with aqueous acetic acid[16] gave successively the 1-ketoacetonide **21**, the 1α,3α,17α-trihydroxyacetonide **22**, and a product (**23**) which was assigned the structure 5β-pregnane-1α,3α,17α,20β,21-pentol, the 1 epimer of **4**. Sodium periodate oxidation of the pentol **23** provided 1α,3α-dihydroxy-5β-androstan-17-one (**24**), the 1 epimer of **5**.

Similarly, **1** gave a high-melting acetonide (**25**, Scheme IV) in excellent yield. Oxidation of this derivative as above furnished mainly 3α,17α-dihydroxy-20,21-isopropylidenedioxy-5β-pregnane-1,11-dione (**26**), which readily was converted into the unsaturated diketo-acetonide **27** by acetylation followed by percolation through neutral alumina.[2] Hydrolysis of the diketo-acetonide **26** as above furnished 3α,17α,20β,21-tetrahydroxy-5β-pregnane-1,11-dione (**28**), which on oxidation with sodium periodate provided the known[2] 3α-hydroxy-5β-androstane-1,11,17-trione (**29**). Treatment of the unsaturated diketoacetonide **27** with aqueous acetic acid followed by oxidation of the free compound with sodium periodate gave the known[2] 5β-androst-2-ene-1,11,17-trione (**30**).

SCHEME III



The aim then was to reduce selectively the C-1 carbonyl group of **26** and of **28** with sodium borohydride, using conditions where the C-11 carbonyl group would not be reduced, as in the preparation of 3α,17α,20β,-21-tetrahydroxy-5β-pregnan-11-one from 3α,17α,21-trihydroxy-5β-pregnane-11,20-dione.[2] Reduction did not occur under these conditions as judged by the fact that no substances more polar (less mobile) than **26** or **28** could be detected when the recovered neutral fractions were examined by paper chromatography. Subsequent trials showed that these two ketones were largely unaffected by even vigorous reducing agents such as lithium aluminum hydride (prolonged refluxing

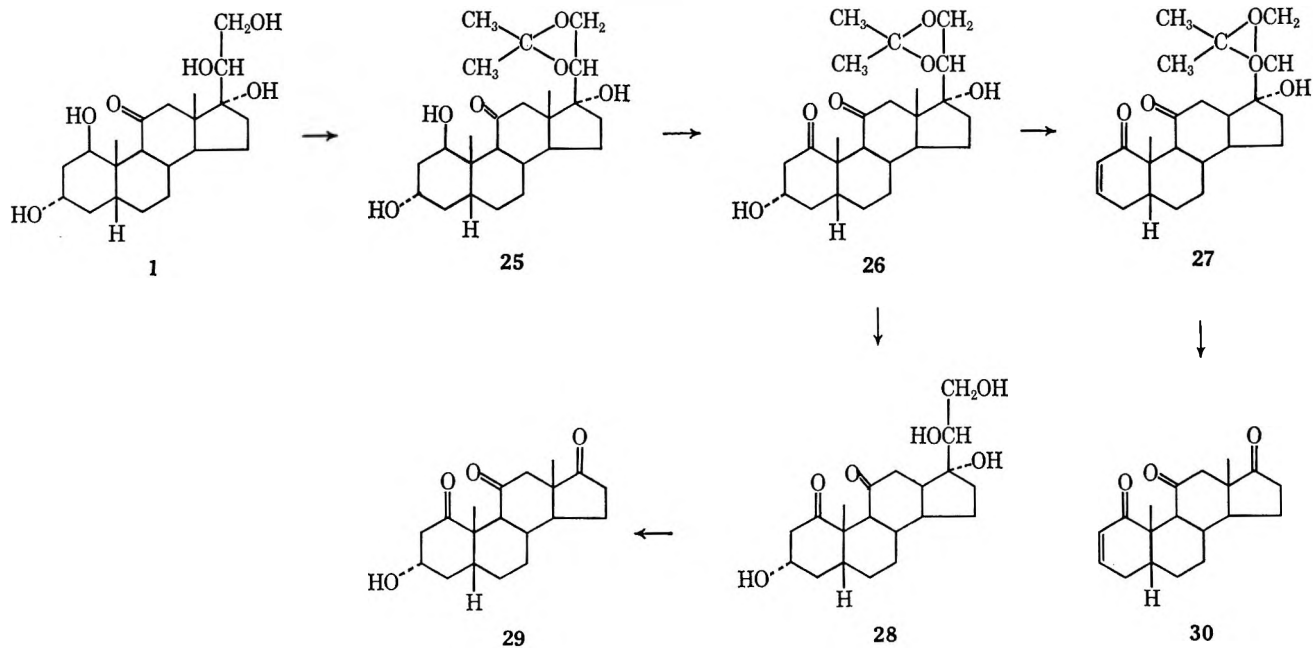
(13) J. P. Dusza, M. Heller, and S. Bernstein, in L. L. Engel, Ed., "Physical Properties of the Steroid Hormones," The Macmillan Co., New York, N. Y., 1963, p 82.

(14) J. H. Fried and A. N. Nutile, *J. Org. Chem.*, **27**, 914 (1962).

(15) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Amer. Chem. Soc.*, **75**, 422 (1953).

(16) M. L. Lewbart, *J. Org. Chem.*, **33**, 1695 (1968).

SCHEME IV



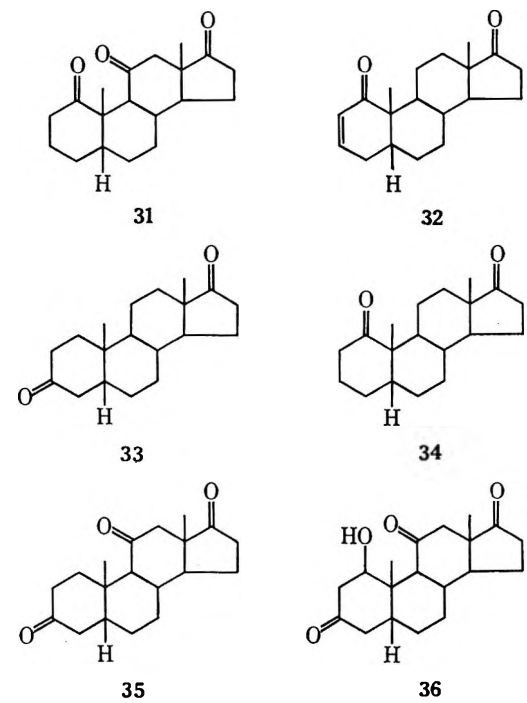
in ether) or hydrogenation at atmospheric pressure, using acetic acid as solvent and freshly prepared platinum catalyst.[17] We attribute this difficulty in reducing either of the two closely approaching carbonyl groups of these cisoid 1,4-diones to a reduction in the degree of polarization of both groups with a consequent reduction in the positive charge on each carbon atom. The adverse effect of this charge distribution on metal hydride reductions is well known.

A similar 1,4 interaction was referred to in our earlier paper.[2] It was noted that the chromic anhydride–pyridine oxidation of **2** gave both 1β-hydroxy-5β-androstane-3,11,17-trione (**36**) and 3α-hydroxy-5α-androstane-1,11,17-trione (**29**), whereas similar oxidation of the 11-deoxydiolone **5** furnished 3α-hydroxy-5β-androstane-1,17-dione as the only recoverable product. The present work provides a second example of this effect. As detailed in the Experimental Section, oxidation of the 11-deoxyacetonide **20** (Scheme III) with this reagent yielded only the 1-ketoacetonide **21**, whereas similar oxidation of the 11-ketoacetonide **25** (Scheme IV) gave the 1,3,11 triketone, the 1-hydroxy-3,11 diketone, and, as the major product, the 3-hydroxy-1,11 diketone **26**. The reduced lability of the C-1 axial hydroxyl group of **2** and of **25** to oxidative attack probably is a manifestation of hydrogen bonding between the oxygen substituents at C-1 and C-11, but it is also possible that the approach of the pyridine–chromic anhydride complex is sterically hindered.

In connection with the evidence indicating interactions in 1,11 diketones, it is of interest to consider the report of Jones and DiGiorgio[18] who examined Dreiding models of the unsaturated triketone **30** (Scheme IV) and the corresponding saturated triketone **31** (Scheme V) and determined their ir spectra in chloroform and carbon disulfide solution. They found that there was no more interaction between the C-1 and C-11 carbonyl groups of these compounds, as judged by displacement of the C-11 band, than in 11,17 diketones generally.

(17) H. C. Brown and C. A. Brown, *J. Amer. Chem. Soc.*, **84**, 1494 (1962).
(18) R. N. Jones and J. B. DiGiorgio, *Can. J. Chem.*, **43**, 182 (1965).

SCHEME V



This is surprising since they noted that the C-1 and C-11 carbonyl groups of **30** are separated by only 3.7 Å (ring-B boat conformation) while those of **31** are separated by 2.8 Å (ring-B chair conformation). As there was no marked absorption above 3000 cm^{-1}, it was concluded that neither steroid was appreciably enolized.

Circular Dichroism Studies.—These results are summarized in Table III. The Cotton effects observed experimentally in the 300-mμ region for the saturated carbonyl chromophores in compounds **1**, **2**, **25**, and **32**–**34** are in reasonably good agreement with the calculated values (obtained by simple addition of the Cotton effect associated with each carbonyl group). In this respect, the weak Cotton effect of **34** clearly shows that the strong negative effect of the 1 ketone is cancelled by the strong positive optical activity associated with the

TABLE III

CD DATA IN 300-mμ REGION, EXPRESSED AS MOLECULAR ELLIPTICITIES [θ]

Compound	[θ] observed in this work	Calcd Cotton effect[a]
11-Ketocorticoid (**25**)	+600	~+1,200
11-Ketocorticoid (**1**)	+1,250	~+1,200
17-Ketoandrostene derivative (**32**)	+10,500	~+11,400
3,17-Diketo-5β-androstane (**33**)	+9,000	~+10,000
11,17-Diketoandrostene derivative (**10**)	+32,000	~+12,600
11,17-Diketoandrostene derivative (**11**)	+31,300	~+12,600
11,17-Diketoandrostene derivative (**30**)	+18,300	~+12,600
1,17-Diketo-5β-androstane (**34**)	+800	~+300
1β,3α-Dihydroxy-11,17-diketo-5β-androstane (**2**)	+14,000	~+12,600
1,3,17-Triketo-5β-androstane (**6**)	+9,500	~−1,200
1,11,17-Triketo-5β-androstane (**31**)	+15,800	~+1,500
3,11,17-Triketo-5β-androstane (**35**)	+15,200	~+11,000
1β-Hydroxy-3,11,17-triketo-5β-androstane (**36**)	+14,100	~+11,000
1,11-Diketocorticoid (**26**)	+1,900	~−10,000
1,11-Diketocorticoid (**28**)	+1,300	~−10,000
3α-Hydroxy-1,11,17-triketo-5β-androstane (**29**)	+14,000	~+1,500
1,3,11,17-Tetraketo-5β-androstane (**3**)	+23,800	~0

[a] By simple summation of various ketones.

17 chromophore. Conversely, differences are noted between the calculated values and the experimental data observed for steroids **3**, **6**, **10**, **11**, **26**, **28–31**, **35**, and **36**.

It is well known from the work of Djerassi, *et al.*,[19] that the Cotton effect associated with the carbonyl group at C-11 is temperature- and solvent-dependent, probably indicative of the conformational mobility of ring C. Stereochemical and electronic factors could be responsible for conformational changes occurring in ring C of compounds **2**, **3**, **10**, **11**, **26**, **28–31**, **35**, and **36**. However, it is well established that the "additivity rule of chromophores" suffers numerous exceptions in the case of polyketonic compounds presenting the 11-keto chromophore.[20] In particular, it has been shown that the rule is not applicable either to 11,17 diketones[21] or to 3,11,17-triketo steroids.[22] This explains the discrepancies observed between the calculated and observed Cotton effects for numerous compounds in Table III.

The strong positive Cotton effect of the trione **6** around 300 mμ is in agreement with other evidence (Table I) that the β-diketonic system is enolized. This is confirmed by the multiple weak Cotton effects observed at *ca.* 350 mμ which indicates the presence of an α,β-unsaturated ketone. The absence of such effects at *ca.* 350 mμ in the CD curve of the tetrone **3** is in harmony with the view that this compound is largely ketonized under most circumstances. However, it may be argued that in the presence of such an intense Cotton effect the n–π* transition of an α,β-unsaturated ketone may not be detected.

The large positive Cotton effect shown by the saturated triketone **31** suggests that it is conformationally distorted since the molecular ellipticity around 300 mμ is similar to that of the unsaturated triketone **30**. It is to be recalled that there is no evidence from their ir spectra[18] that these ketones are enolized.

Paper Chromatographic Effects.—Interaction in 1,11 diketones also is evident in their partition paper chromatography. For example, we observed (Table II) that the paper chromatographic order of mobility of the six enol methyl ethers **10–15** in systems 1 and 2 (and in a variety of other partitioning systems) was not in harmony with the assigned structures. When it was found that a regular order of mobility was obtained using thin layer (adsorption) chromatography, the R_f values with system 3 constituting an example, it was clear that the noted irregularity consists of a reversal of the relative mobilities of **10** and **11**. When the contribution to polarity of the C-11 carbonyl group in a number of 1,11 diketones was assessed in terms of ΔR_{Mg} values,[23] it was found that this reversal is due to an aberrantly high polarity (low mobility) of **11**, and of all other 1,11 diketones thus far examined, in partitioning systems. A detailed study of this effect and a consideration of possible explanations will be submitted for publication at a later date.

Experimental Section

Melting points were determined with a Fisher-Johns apparatus and are reported uncorrected. Optical rotations were obtained at 26 ± 1°, in methanol solution unless otherwise indicated, at a concentration of around 1% in a Zeiss 0.005° photoelectric polarimeter. Extinction coefficients were determined in a Zeiss PRQ 20A recording spectrophotometer. Infrared spectra were recorded with a Beckman IR-8 instrument. The mass spectrum of 25αF-5α-spirostane-1β,3β-diol' was determined by Dr. H. D. Fisher of the West Coast Technical Service using a Hitachi-Perkin-Elmer RMU-6D instrument and an ionization voltage of 70. A description of and references to our paper, thin layer, and column chromatographic techniques appear in a previous publication.[2] For composition of paper, thin layer, and column chromatographic systems, see Table IV. Elementary analyses were carried out by E. Thommen, Basel, Switzerland, Aug. Peisker-Ritter, Brugg, Switzerland, and the Hoffman Laboratories, Wheatridge, Colo. Circular dichroism curves were obtained in dioxane solution with a Jouan dichrograph at the University of Strasbourg, through the kind cooperation of Professor G. Ourisson. Nmr spectra were determined with Varian A-60 or HR-100 spectrometers, using $CDCl_3$ as the solvent and tetramethylsilane as an internal standard of reference.

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(20) P. Crabbé, "Applications de la Dispersion Rotatoire Optique et du Dichroisme Circulaire en Chimie Organique," Gauthier-Villars, Paris, 1968, Chapter VI.

(21) (a) L. Velluz, M. Legrand, and M. Grosjean, "Optical Circular Dichroism. Principles, Measurements and Applications," Verlag-Chemie, Weinheim, 1965; (b) L. Velluz and M. Legrand, *Angew. Chem.*, **73**, 603 (1961).

(22) A. M. Giroud, A. Rassat, and T. Rull, *Bull. Soc. Chim. Fr.*, 2563 (1963).

(23) I. E. Bush, "The Chromatography of Steroids," Pergamon Press Inc., New York, N. Y., 1961, pp 84, 85.

TABLE IV

COMPOSITION OF PAPER, THIN LAYER, AND COLUMN CHROMATOGRAPHIC SYSTEMS

System no.	Composition[a]
1	EA, 40; Iso, 160; AM, 80; HOH, 120 ml
2	Tol, 60; Iso, 140; AM, 150; HOH, 50 ml
3	EA, 20, diluted to 25 ml with Iso
4	EA, 10, diluted to 25 ml with Iso
5	Tol, 120; Iso, 80; AM, 50; HOAc, 20; HOH, 130 ml
6	Iso, 155; III-bu, 45; HOH, 150 ml
7	Tol, 70; Iso, 130; AM, 70; HOAc, 50; HOH, 80 ml
8	Tol, 20; Iso, 180; AM, 160; HOH, 40 ml
9	EA
10	Tol, 45; Iso, 155; AM, 70; HOAc, 50; HOH, 80 ml
11	EA, 5, diluted to 25 ml with Iso
12	Tol, 70; Iso, 130; AM, 160; HOH, 40 ml
13	Tol, 100; Iso, 100; AM, 150; HOH, 50 ml
14	Tol, 150; III-bu, 50; AM, 70; HOH, 80 ml
15	Tol, 140; Iso, 60; AM, 160; HOH, 40 ml

[a] EA = ethyl acetate; Iso = isooctane (2,2,4-trimethylpentane); AM = methanol; Tol = toluene; HOAc = glacial acetic acid; III-bu = *t*-butyl alcohol.

Preparation and Enol Etherification of 5β-Androstane-1,3,11,-17-tetrone (3).—To a solution of 150 mg (0.5 mmol) of 1β,3α-dihydroxy-5β-androstane-11,17-dione (2)[2] in 30 ml of acetone (distilled from $KMnO_4$) at 5° and in a nitrogen atmosphere, 0.45 ml (1.2 mmol) of a solution of 2.67 g of CrO_3 and 2.3 ml of concentrated sulfuric acid diluted to 10 ml with water was added in one portion. After 5 min at 5°, water was added and the solution was extracted with ethyl acetate. The combined extracts were washed with neutral brine, dried with anhydrous sodium sulfate, and evaporated *in vacuo*. Crystallization of most of the product from methanol followed by chromatography of the mother liquor on a 16 × 650 mm Celite column (system 5) gave a total of 95 mg of **5β-androstane-1,3,11,17-tetrone (3)** as needles: mp 182–183°; $[\alpha]_D$ +99°; R_f 0.29 (system 5).

Anal. Calcd for $C_{19}H_{24}O_4$: C, 72.12; H, 7.65. Found: C, 71.80; H, 7.83.

A solution of 60 mg of 5β-androstane-1,3,11,17-tetrone in 3 ml of methanol was allowed to stand at room temperature for 8 hr with an excess of ethereal diazomethane. Examination of the crude product by paper chromatography (system 6), and employing ultraviolet light scanning and the Zimmermann reagent[24] as the detecting methods, showed that the β diketone had reacted completely, giving unequal amounts of two ultraviolet light absorbing, Zimmermann-positive substances with R_f values of 0.16 and 0.30. Chromatography on a 20 × 550 mm Celite column prepared with system 6 easily effected their separation giving, from acetone–ether, 27.8 mg of the mobile ether, **1-methoxy-5β-androst-1-ene-3,11,17-trione (10)**, and, from the same solvent system, 16.7 mg of the polar ether, **3-methoxy-5β-androst-2-ene-1,11,17-trione (11)**. Constants for **10** are mp 181.5–182.5° and $[\alpha]_D$ +163°.

Anal. Calcd for $C_{20}H_{26}O_4 \cdot 0.5C_3H_6O$ (**10**): C, 71.90; H, 8.14; OCH_3, 8.07. Found: C, 72.06; 72.09; H, 8.15, 8.19; OCH_3, 10.72.

Constants for **11** are mp 247–247.5° and $[\alpha]_D$ +28°.

Anal. Calcd for $C_{20}H_{26}O_4$ (**11**): C, 72.70; H, 7.93; OCH_3, 9.39. Found: C, 72.82; H, 8.06; OCH_3, 9.43.

Preparation and Enol Etherification of 5β-Androstane-1,3,17-trione (6).—Oxidation of 60 mg of 1β,3α-dihydroxy-5β-androstan-17-one (5)[2] in the manner described above gave, from methanol–ether, 42 mg of **5β-androstane-1,3,17-trione (6)**: mp 239–241°; $[\alpha]_D$ +26°; R_f 0.25 (system 7).[25]

Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.60; H, 8.80.

Treatment of 69 mg of 5β-androstane-1,3,17-trione in methanol solution with an excess of ethereal diazomethane for 12 hr at room temperature, followed by chromatography of the crude extract on a 20 × 650 mm Celite column (system 8), gave two well-separated components. The mobile component furnished, from methanol–ether, 22 mg of **3-methoxy-5β-androst-2-ene-1,17-dione (13)** as needles: mp 191–191.5°; $[\alpha]_D$ −49°; R_f 0.42 (system 8).

Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 76.20; H, 9.07.

Crystallization of the polar component from ethyl acetate–*n*-hexane gave 21 mg of **1-methoxy-5β-androst-1-ene-3,17-dione (12)** as needles: mp 184–184.5°; $[\alpha]_D$ +190°; R_f 0.23 (system 8).

Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 76.11; H, 9.06.

5α-Androstane-1,3,17-trione and Its Enol Methyl Ethers.—Isoandrosterone (3 g) was incubated with shaking for 24 hr at 26° with a flourishing culture of a *Penicillium* species, ATCC 12556.[26] Chromatography of the crude extract on a 50 × 840 mm column of silica gel (system 9) gave, from methanol–ethyl acetate, 685 mg (22%) of needles: mp 202–203°; $[\alpha]_D$ +103°. Its melting point was unaltered on admixture with an authentic sample of **1α,3β-dihydroxy-5α-androstan-17-one**, and their ir spectra in KBr dispersion were identical.

Oxidation of 120 mg of 1α,3β-dihydroxy-5α-androstan-17-one as above, followed by chromatography of the crude product on a 20 × 680 mm Celite column (system 10), gave 65 mg of prisms from methanol (mp 198–199°, $[\alpha]_D$ +274°) assigned the structure **5α-androstane-1,3,17-trione** [lit.[26] mp 157–159°, 199–200°; λ_{max} 254 mμ (ε 12,000)].

Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.19; H, 8.63.

Reaction of 50 mg of 5α-androstane-1,3,17-trione with an excess of ethereal diazomethane as in the previous examples, followed by chromatography of the crude extract on a 16 × 450 mm Celite column (system 8), gave two well-separated components. The mobile fraction, designated **3-methoxy-5α-androst-2-ene-1,17-dione (15)**, gave 19 mg of needles from ethyl acetate: mp 199–200°; $[\alpha]_D$ +278°; R_f 0.51 (system 8).

Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.90; H, 8.80.

The polar component, assigned the structure **1-methoxy-5α-androst-1-ene-3,17-dione (14)**, furnished 14 mg of needles from ethyl acetate–*n*-hexane: mp 172.5–173.5°; $[\alpha]_D$ +126°; R_f 0.19 (system 8).

Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.88; H, 8.90.

Preparation and Enol Etherification of 25αF-5α-Spirostane-1,3-dione.—A 500-mg sample of 25αF-spirost-5-ene-1β,3β-diol [ruscogenin[27] mp 209–210°; $[\alpha]_D$ −122° ($CHCl_3$)], obtained by saponification of the diacetate, was hydrogenated over a 3-hr period at atmospheric pressure in neutral ethanol–cyclohexane using 5% palladium on carbon (Engelhard Industries) as catalyst. Crystallization of the product from aqueous acetone gave prisms or plates assigned the structure **25αF-5α-spirostane-1β,3β-diol**: mp 211–212°; $[\alpha]_D$ −75° ($CHCl_3$); R_f 0.17 in system 3 (orange fluorescence after spraying with *p*-toluenesulfonic acid and heating at 120°; in this system ruscogenin has an R_f of 0.21 and displays a blue fluorescence). Its mass spectrum showed a single molecular ion (M^+) at *m/e* 432 amu.

Anal. Calcd for $C_{27}H_{44}O_4$: C, 74.95; H, 10.25. Found: C, 74.68; H, 10.20.

Treatment of the free diol with acetic anhydride and pyridine at room temperature followed by crystallization of the product from aqueous acetone and from acetone gave **25αF-5α-spirostane-1β,3β-diol diacetate**[28] as needles: mp 249–250°; $[\alpha]_D$ −72° ($CHCl_3$).

Anal. Calcd for $C_{31}H_{48}O_6$: C, 72.06; H, 9.36; CH_3CO, 16.66. Found: C, 72.32; H, 9.39; CH_3CO, 16.59.

Oxidation of 200 mg of the free diol with Jones' reagent as in the previous examples gave 110 mg of **25αF-5α-spirostane-1,3-**

(24) R. Neher, "Steroid Chromatography," Elsevier, Amsterdam, 1964, p 125.

(25) In addition to its general utility in this study, the paper chromatographic technique made an unique contribution in the case of the β diketones **3** and **6**. Prior to determining their extinction coefficients, the limited enolization of the former readily has demonstrated by comparing the paper chromatographic characteristics of the two ketones. In the absence of acetic acid in the system, both compounds streaked markedly, and it was easily determined how much acid was required in each case to eliminate streaking, presumably by suppressing enolization. Much less acid was required in the system suitable for the tetrone **3** (compare systems 5 and 7, Table IV).

(26) S. Noguchi and D. K. Fukushima, *J. Org. Chem.*, **30**, 3552 (1965).

(27) H. Lapin and C. Sannié, *Bull. Soc. Chim. Fr.*, 1552 (1955).

(28) 25αF-5α-Spirostane-1β,3β-diol has not to our knowledge been prepared previously. Its 5 epimer, isorhodeasapogenin, has these constants: mp 241–243°; $[\alpha]_D$ −71° ($CHCl_3$); diacetate, mp 205° [H. Nawa, *Pharm. Bull.* (Tokyo), **6**, 255 (1958)].

dione as needles from methylene chloride–ethyl acetate: mp 244–245°, $[\alpha]D$ +9° ($CHCl_3$).

Anal. Calcd for $C_{27}H_{40}O_4$: C, 75.66; H, 9.41. Found: C, 75.80; H, 9.46.

To a solution of 100 mg of 25α_F-5α-spirostane-1,3-dione in 2 ml of methylene chloride, an excess of ethereal diazomethane was added. After 12 hr at room temperature, the solvents were evaporated, and the residue was chromatographed on a 20 × 765 mm silica gel column prepared with system 11 (changed to system 4 after emergence of the mobile component). The mobile fraction gave, from methylene chloride–methanol, 40 mg of **3-methoxy-25α_F-5α-spirost-2-en-1-one** (**17**) as plates: mp 213–214°; $[\alpha]D$ +53° ($CHCl_3$); R_f 0.38 (system 4).

Anal. Calcd for $C_{28}H_{42}O_4$: C, 75.97; H, 9.57. Found: C, 75.94; H, 9.55.

Crystallization of the polar component from acetone–*n*-hexane gave 32 mg of **1-methoxy-25α_F-5α-spirost-1-en-3-one** (**16**) as needles: mp 203–204°; $[\alpha]D$ −72° ($CHCl_3$); R_f 0.11 (system 4).

Anal. Calcd for $C_{28}H_{42}O_4$: C, 75.97; H, 9.57. Found: C, 75.94; H, 9.61.

Preparation of 5β-Pregnane-1α,3α,17α,20β,21-pentol (23).—To a solution of 200 mg of 5β-pregnane-1β,3α,17α,20β,21-pentol (**4**, mp 252–253°; $[\alpha]D$ +6°)[2] in 50 ml of acetone, 50 mg of *p*-toluenesulfonic acid was added. After 30 min at room temperature, 0.3 ml of 1 *N* aqueous sodium hydroxide was added, and the solution was concentrated *in vacuo* to near dryness. The crystalline suspension was dissolved in ethyl acetate, and the solution was washed with dilute sodium hydroxide and neutral brine, dried with anhydrous sodium sulfate, and evaporated. Crystallization of the product from methanol gave 192 mg of stout needles (mp 243–244°; $[\alpha]D$ +13°) designated as **20,21-isopropylidenedioxy-5β-pregnane-1β,3α,17α-triol** (**20**).[29]

Anal. Calcd for $C_{24}H_{40}O_5$: C, 70.55; H, 9.87. Found: C, 70.73; H, 10.08.

Oxidation of 100 mg of 20,21-isopropylidenedioxy-5β-pregnane-1β,3α,17α-triol with chromic anhydride in pyridine as in our previous publication[2] furnished, from acetone–*n*-hexane and from acetone, 70 mg of **3α,17α-dihydroxy-20,21-isopropylidenedioxy-5β-pregnan-1-one** (**21**): mp 218–219°; $[\alpha]D$ −73°; R_f 0.36 (system 12).

Anal. Calcd for $C_{24}H_{38}O_5$: C, 70.90; H, 9.42. Found: C, 70.80; H, 9.40.

To a solution of 60 mg of 3α,17α-dihydroxy-20,21-isopropylidenedioxy-5β-pregnan-1-one in 5 ml of methanol, 40 ml of sodium borohydride was added in one portion. After 3 hr at room temperature, acetic acid was added, and the solution was extracted with ethyl acetate after dilution with brine. The organic phase was washed with dilute sodium hydroxide and neutral brine, dried with anhydrous sodium sulfate, and evaporated *in vacuo*. Crystallization from acetone–*n*-hexane gave 40 mg of needles [mp 203–204°; $[\alpha]D$ +16°; R_f 0.20 (system 13)] assigned the structure **20,21-isopropylidenedioxy-5β-pregnane-1α,3α,17α-triol** (**22**). On admixture with a sample of **20**, its 1 epimer (mp 243–244°), the melting range was 191–195°; their ir spectra were dissimilar.

Anal. Calcd for $C_{24}H_{40}O_5$: C, 70.55; H, 9.87. Found: C, 70.22; H, 9.68.

A solution of 43 mg of 20,21-isopropylidenedioxy-5β-pregnane-1α,3α,17α-triol in 43 ml of 60% (v/v) aqueous acetic acid was allowed to stand at room temperature for 4 hr. The solution was concentrated to dryness *in vacuo*, and the residue was chromatographed on a 16 × 560 mm Celite column prepared with system 14. Crystallization of the recovered product from methanol–ether gave 28 mg of needles [mp 228–229°; $[\alpha]D$ +10°; R_f 0.21 (system 14)] designated as **5β-pregnane-1α,3α,17α,20β,-21-pentol** (**23**). On admixture with a sample of its 1 epimer (**4**, mp 252–253°), the melting range was 214–218°; their ir spectra were dissimilar.

Anal. Calcd for $C_{21}H_{36}O_5$: C, 68.44; H, 9.85. Found: C, 68.34; H, 9.80.

Oxidation of a 16-mg sample of 5β-pregnane-1α,3α,17α,20β,21-pentol with sodium periodate as previously described[2] gave 9 mg of prisms (mp 230–232°; $[\alpha]D$ + 101°) assigned the structure **1α,3α-dihydroxy-5β-androstan-17-one** (**24**). Its 1 epimer (**5**) has mp 204–204.5° and $[\alpha]D$ +95°.[2] A mixture of **5** and **24** melted at 188–192°, and their ir spectra were dissimilar.[30]

Preparation of 3α,17α,20β,21-Tetrahydroxy-5β-pregnane-1,11-dione (28).—Reaction of 400 mg of 1β,3α,17α,20β,21-pentahydroxy-5β-pregnan-11-one (**1**) with *p*-toluenesulfonic acid in acetone as in the preparation of **20** from **4** gave, from methanol–acetone, 405 mg of **1β,3α,17α-trihydroxy-20,21-isopropylidenedioxy-5β-pregnan-11-one** (**25**) as prisms: mp 261–262°; $[\alpha]D$ +15°.

Anal. Calcd for $C_{24}H_{38}O_6$: C, 68.22; H, 9.06. Found: C, 68.20; H, 9.00.

Oxidation of 300 mg of 1β,3α,17α-trihydroxy-20,21-isopropylidenedioxy-5β-pregnan-11-one with chromic anhydride in pyridine as in the preparation of **21** from **20**, followed by chromatography on a 38 × 755 mm Celite column (system 15) furnished three products. The most mobile fraction gave, from ethyl acetate–*n*-hexane, 40 mg of impure **17α-hydroxy-20,21-isopropylidenedioxy-5β-pregnane-1,3,11-trione**. The fraction of intermediate mobility provided, from ethyl acetate, 85 mg of **1β,17α-dihydroxy-20,21-isopropylidenedioxy-5β-pregnane-3,11-dione**: mp 236–238°; $[\alpha]D$ +25°. The least mobile (most polar) fraction yielded, from acetone, 145 mg of **3α,17α-dihydroxy-20,21-isopropylidenedioxy-5β-pregnane-1,11-dione** (**26**): mp 278–279°; $[\alpha]D$ −15°; R_f 0.18 (system 15).

Anal. Calcd for $C_{24}H_{36}O_6$ (**26**): C, 68.54; H, 8.63. Found: 68.53; H, 8.49.

A solution of 30 mg of 3α,17α-dihydroxy-20,21-isopropylidenedioxy-5β-pregnane-1,11-dione in 1 ml each of acetic anhydride and pyridine was allowed to stand at room temperature overnight. The product was recovered in the usual fashion and percolated through a small column of neutral alumina as described in a previous publication.[2] The product was eluted with 0.15% ethanol in benzene and furnished, from methanol, 20 mg of prisms [mp 237–238°; $[\alpha]D$ +3°; λ_{max} 225 mμ (ϵ 7450)] which were assigned the structure **17α-hydroxy-20,21-isopropylidenedioxy-5β-pregn-2-ene-1,11-dione** (**27**).

Anal. Calcd for $C_{24}H_{34}O_6$: C, 71.61; H, 8.51. Found: C, 71.39; H, 8.54.

Hydrolysis of a sample of 17α-hydroxy-20,21-isopropylidenedioxy-5β-pregn-2-ene-1,11-dione with aqueous acetic acid followed by oxidation of the free compound with sodium periodate gave needles from acetone–*n*-hexane, mp 223–224°. On admixture with an authentic sample of **5β-androst-2-ene-1,11,17-trione** (**30**), mp 223.5–224.5°,[2] its melting point was unaltered. The ir spectra of the two ketones were identical.

Hydrolysis of 3α,17α-dihydroxy-20,21-isopropylidenedioxy-5β-pregnane-1,11-dione (40 mg) with aqueous acetic acid as in the previous examples, followed by crystallization of the product from methanol–ethyl acetate, gave 26 mg of needles (mp 253–254°; $[\alpha]D$ −1°) designated as **3α,17α,20β,21-tetrahydroxy-5β-pregnane-1,11-dione** (**28**).

Anal. Calcd for $C_{21}H_{32}O_6$: C, 66.29; H, 8.48. Found: C, 66.04; H, 8.50.

Oxidation of a sample of 3α,17α,20β,21-tetrahydroxy-5β-pregnane-1,11-dione with sodium periodate followed by crystallization of the product from methanol gave needles, mp 262–263°. The melting point was unchanged on admixture with an authentic sample of **3a-hydroxy-5β-androstane-1,11,17-trione** (**29**),[2] and their ir spectra were identical.

Registry No.—**1,** 10535-94-1; **2,** 10535-95-2; **3,** 2061-61-2; **6,** 16963-70-5; **10,** 16963-71-6; **11,** 16963-72-7; **12** and **13,** not yet resolved; **14,** 16963-75-0; **15,** 16963-76-1; 5α-androstane-1,3,17-trione, 4171-02-2; 25$_{\alpha F}$-5α-spirostane-1β,3β-diol, 16963-78-3; 25$_{\alpha F}$-5α-spirostane-1β,3β-diol diacetate, 16976-44-6; 25$_{\alpha F}$-5α-spirostane-1,3-dione, 16963-79-4; **16,** 16963-80-7; **17,** 16963-81-8; **20,** 16963-82-9; **21,** 16976-45-7; **22,** 16963-83-0; **23,** 16963-84-1; **25,** 16963-85-2; **26,** 16976-46-8; **27,** 16963-86-3; **28,** 16963-87-4; **29,** 10535-97-4; **30,** 16963-89-6; **31,** 2785-91-3; **32,** 16963-91-0; **33,** 1229-12-5; **34,** 10536-04-3; **35,** 1429-06-7; **36,** 10535-96-3; 1-methoxy-5α-

(29) We are engaged in a study of the preparation, hydrolysis, and properties of steroidal 17,20- and 20,21-acetonides. The principal bands in the ir region of the acetonides prepared in this paper are in close agreement with those found generally for members of the second class.

(30) The forthcoming paper chromatographic study will include an examination of the relative mobilities of the members of five pairs of epimeric 1-ols, including the pairs 4/23 and 5/24.

cholest-1-en-3-one, 16963-96-5; 3-methoxy-5α-cholest-2-en-1-one, 16963-97-6.

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A Synthesis of Estrone *via* Novel Intermediates. Mechanism of the Coupling Reaction of a Vinyl Carbinol with a β Diketone[1]

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An investigation of the coupling reaction of vinylcarbinols with β diketones as exemplified by the condensation of 1-vinyl-1-hydroxy-6-methoxy-1,2,3,4-tetrahydronaphthalene with 2-methylcyclopentane-1,3-dione is presented. Quantitative conversion of 1-vinyl-1-hydroxy-6-methoxy-1,2,3,4-tetrahydronaphthalene into a crystalline isothiuronium salt has provided a versatile intermediate in an improved condensation providing the tricyclic precursor to estrone, **3**. Selective as well as stereospecific reduction of the latter system with lithium tri-*t*-butoxyaluminum hydride afforded the ketol **8**, a key optically resolvable intermediate in the synthesis of estrone.

Ten years have elapsed since Nazarov and collaborators[2] successfully prepared the important vinylcarbinol, 1-vinyl-1-hydroxy-6-methoxy-1,2,3,4-tetrahydronaphthalene (**1**); their attempts, however, to convert **1** into the allylic bromide **4** (X = Br) for purposes of condensation with reactive enolates proved abortive.[3,4] Subsequently, Ananchenko and Torgov discovered that the vinylcarbinol **1** it selfwas capable of direct coupling with 2-methylcyclohexane-1,3-dione in the presence of strong base to give the homolog of the tricyclic diketone **3** in 50% yield.[5] These authors further examined a variety of catalysts to promote this condensation although they later employed Triton B (benzyltrimethylammonium hydroxide) almost exclusively.[6] This procedure has since been generally adopted by contemporaries in the field in its application to the synthesis of estrone employing 2-methylcyclopentane-1,3-dione (**2**) as donor component.[7]

The coupling of a vinylcarbinol with an enolate under presumed conditions of basic catalysis presented a unique reaction type for which a fitting analogy was lacking. By way of rationalization both a simulated Michael process[8] and an SN2′ displacement reaction[9] have been proposed. A close formal analogy of this condensation to the so-called Carroll reaction[10] has already been noted elsewhere.[11] In the latter reaction, for example, acetoacetic ester condenses with phenylvinylcarbinol in the presence of potassium acetate at 200° to give cinnamylacetone. The Carroll reaction has been shown to proceed *via* initial ester exchange to a derived acetoacetate followed by Cope rearrangement.[12] More pertinent to the case at hand are the observations of Marbet and Saucy[10b] that tertiary vinylcarbinols rearrange *via* their isopropenyl ethers to γ,δ-unsaturated carbonyl systems. The possibility of a formal Carroll reaction in the case of the condensation of **1** and **2** *via* an intermediate enol ether was ruled out by our own observations through the employment of vinylcarbinol possessing ^{18}O in the carbinol grouping. In the event of a formal Carroll reaction the carbinol ^{18}O would have been transferred to the pertinent carbonyl function of the cyclopentandione moiety, a consequence not observed.

It appeared to us on the basis of the prior art to be patently unsound that alkali should catalyze the condensation of **1** with **2**. To gain substantiation for this point of view the two components were allowed to react in the presence of 1 equiv of alkali instead of the fractional equivalent which had always been employed previously.[6,7] Under the conditions that employed 1 mol equiv of alkali *no condensation* whatsoever was observed between **1** and **2**. It was thereby evident that the condensation of Torgov and Ananchenko is not base catalyzed, but is in fact an acid-catalyzed reaction with the β diketone functioning autocatalytically. It was likewise evident that the previous success of this condensation was due to the extent that the β diketone had not been converted into its salt by added alkali, mistakenly believed to catalyze the reaction. In substantiation thereof we observed that, when **1** and **2** were warmed together in *t*-butyl alcohol in the absence of any external catalyst, coupling proceeded smoothly to give **3** directly

(1) For preliminary accounts of this work, see (a) C. H. Kuo, D. Taub, and N. L. Wendler, *Angew. Chem.*, **77**, 1142 (1965); *Angew. Chem. Intern. Ed. Engl.*, **4**, 1083 (1965); (b) *Chem. Ind.* (London), 1340 (1966).

(2) I. N. Nazarov, I. V. Torgov, and G. Verkhaletova, *Dokl. Akad. Nauk SSSR*, **112**, 1067 (1957).

(3) D. J. Crispin and J. S. Whitehurst [*Proc. Chem. Soc.*, 22 (1963)] have more recently reported on the preparation of this bromide in a preliminary note.

(4) For an excellent review of recent advances in the synthesis of 19-nor steroids, see T. B. Windholz and M. Windholz, *Angew. Chem. Intern. Ed. Engl.*, **3**, 353 (1964).

(5) S. N. Ananchenko and I. V. Torgov, *Dokl. Akad. Nauk SSSR*, **127**, 553 (1959).

(6) S. N. Ananchenko, T'ao Jeng-O, and I. V. Torgov, *Izv. Akad. Nauk SSSR, Otd. Khim.*, 298 (1962).

(7) (a) T. B. Windholz, J. H. Fried, and A. A. Patchett, *J. Org. Chem.*, **28**, 1092 (1963); (b) G. H. Douglas, J. M. H. Groves, D. Hartley, G. A. Hughes, B. J. McLaughlin, J. Siddal, and H. Smith, *J. Chem. Soc.*, 5072 (1963). These workers employed alkali metal hydroxides and bicarbonate as catalysts: (c) T. Miki, K. Hiraga, and T. Asako, *Proc. Chem. Soc.*, 139 (1963); *Chem. Pharm. Bull. Jap.*, **13**, 1285 (1965); (d) S. N. Ananchenko and I. V. Torgov, *Tetrahedron Lett.*, 553 (1963).

(8) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965, p 209.

(9) J. S. Whitehurst, *Ann. Rept. Chem. Soc.* (London), 426 (1963).

(10) (a) M. F. Carroll, *J. Chem. Soc.*, 704, 1266 (1940); 507 (1941); (b) R. Marbet and G. Saucy, *Chimia*, **14**, 362 (1960); *Helv. Chim. Acta*, **50**, 2091, 2095 (1967).

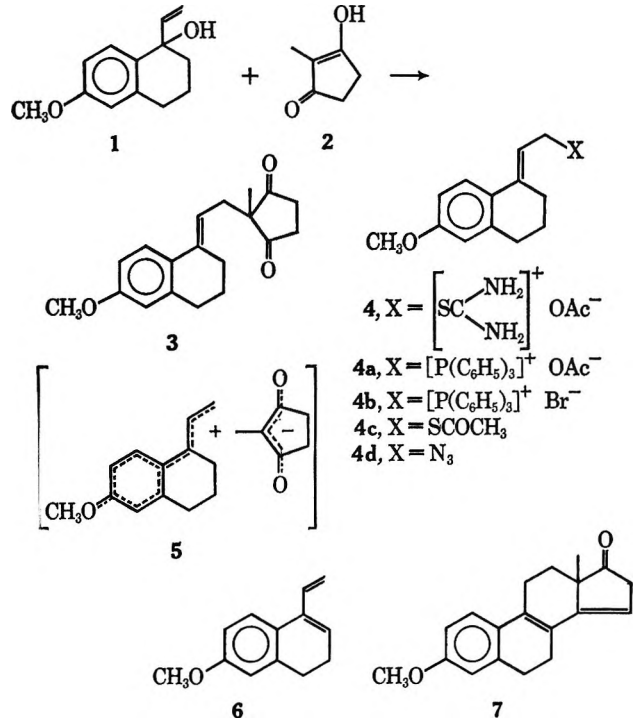
(11) D. P. Strike, T. Y. Jen, G. A. Hughes, C. H. Douglas, and H. Smith, *Steroids*, **8**, 309 (1966).

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

in over 70% yield.[13] On the other hand when **1** and **2** were heated in acetic acid and xylene at 120° there was afforded a 60% yield of the crystalline pentaene **7** resulting from coupling followed by cyclization. This method is actually the most convenient preparative procedure for this compound.

The vinylcarbinol **1** is extremely acid labile and when warmed in acetic acid readily undergoes dehydration to diene **6** which subsequently dimerizes *via* a Diels–Alder reaction.[14] That this diene, moreover, is not an intermediate in the coupling reaction of **1** with **2** was evident from its inability to react with dione **2** to give **3** under the prescribed reaction conditions. These facts suggested therefore that the coupling of 2-methylcyclopentane-1,3-dione **2** (pK_a 4.5) with vinylcarbinol **1** might be best interpreted as an acid–base reaction proceeding *via* an ion-pair intermediate **5**. In this context it was found that the vinylcarbinol **1** in acetic acid reacted rapidly with thiourea, added as a carbonium-ion scavenger, to give the crystalline isothiuronium salt **4**, mp 125–127°, in essentially quantitative yield. This salt in turn coupled in aqueous media at room temperature with the cyclopentanedione **2** to give crystalline **3** in 90% yield.

The reaction of **1** with **2** in *t*-butyl alcohol was further found to be essentially unaffected by the addition of triphenylphosphine, again added as carbonium-ion scavenger. On the other hand **1** itself rapidly formed the crystalline phosphonium salts **4a** and **4b** on reaction with triphenylphosphine in acetic acid and triphenylphosphine hydrobromide in methylene chloride, respectively. Likewise the thioacetate **4c** and azide **4d** were formed by treating **1** with thioacetic acid in *t*-butyl alcohol–xylene and sodium azide in acetic acid, respectively. The phosphonium salts **4a** and **4b**, in contrast to the isothiuronium salt **4**, were unreactive in attempted coupling with **2**. From these observation it appears reasonable to conclude that the ion-pair intermediate **5** involved in the coupling of **1** with **2** is associated and inaccessible to external nucleophiles.[15]

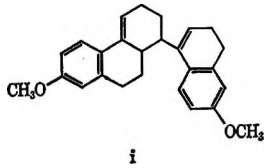


The advantages of employing the isothiuronium salt **4** in the coupling reaction, *inter alia*, with 2-methylcyclopentane-1,3-dione (**2**) are several. In the form of the crystalline isothiuronium salt the otherwise labile carbinol **1** can be easily handled and stored without deterioration; secondly, superior yields in the coupling reactions are observed; and finally, this salt exhibits a greater versatility in the application of this condensation reaction to other enolate systems. In the latter connection several instances of derived cyclopentane-1,3-diones, *e.g.*, 4-acetoxy-2-methylcyclopentane-1,3-dione[16] and cyclopentane-1,3-dione itself, either do not couple at all with **1** or only in very poor yield. By contrast the isothiuronium salt **4** condenses with these same diones in good to acceptable yields to afford the desired products. Recently, **4** has been utilized in a condensation with α,γ-dimethyltetronic acid to provide an efficient synthesis of bisdehydrodoisynolic acid.[17]

In pursuit of a novel approach to estrone from the tricyclic diketone **3**, the latter was submitted to reduction with lithium tri-*t*-butoxyaluminum hydride. Surprisingly, this reduction not only proved to be completely selective in reducing exclusively one carbonyl group but was also found to be highly stereospecific in yielding one epimer (85–90%), namely, the *dl*-17α-ketol **8** (steroid nomenclature).[18] The structure of the latter was established by cyclization of its acetate derivative **8c** to *dl* **9a** which was found to be distinct from its 17β counterpart and could in turn be further transformed indepen-

(13) Yields obtained by previous workers employing Triton B as recommended by Ananchenko and Torgov[6] have been of the order of magnitude of 50–60% (see ref 7). Smith, *et al.*,[11] have recently claimed to have achieved yields as high as 80%, although an experimental account supporting this does not appear to have been published.

(14) Previous references to the dimerization of **6** [*cf.* I. V. Torgov and I. N. Nazarov, *Zh. Obshch. Khim.*, **29**, 787 (1959)] do not include specific structural proposals. We observed the formation of two dimers: i [mp 168–170° (reported, *ibid.*, mp 168–170°); λ_{max}^{MeOH} 265 mμ (ϵ 30,500), 212 (36,400); nmr δ 5.82 (1 H triplet, J = 7 cps) and 6.25 (1 H multiplet), 2-vinyl protons (Found: C, 83.63; H, 7.53. Calcd for $C_{28}H_{28}O_2$: C, 83.83; H, 7.58)] and ii [mp 135–137° (reported, *ibid.*, mp 134–135°); λ_{max}^{MeOH} 272.5 mμ (ϵ 24,200); nmr δ 5.76 (1 H triplet, J = 7 cps), 1-vinyl proton (Found: C, 83.71; H, 7.80; mol wt, 378 (vapor phase osmometry). Calcd for $C_{28}H_{28}O_2$: C, 83.83; H, 7.78; mol wt, 372.5]. The perhydro-1-naphthyl- rather than -2-naphthylphenanthrene structures are selected by virtue of the Alder–Stein rule: K. Alder and G. Stein, *Angew. Chem.*, **50**, 510 (1937).



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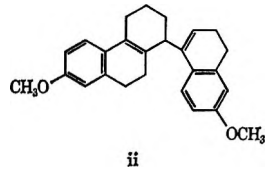

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(15) Subsequent to the publication of our original communication[1a] on the mechanism of this coupling reaction, pertinent papers have appeared in which the acid-catalyzed character of this reaction has also been recognized and earlier points of view correspondingly accommodated. See ref 11 and A. V. Zakharychev, D. R. Logidze, and S. N. Ananchenko, *Tetrahedron Lett.*, 803 (1967).

(16) R. D. Hoffsommer, D. Taub, and N. L. Wendler, *J. Org. Chem.*, **32**, 307+ (1967).

(17) W. R. J. Simpson, D. Babbe, J. A. Edward, and J. H. Fried, *Tetrahedron Lett.*, 3209 (1967). For the use of the isothiuronium salt **4** in a synthesis of 13-amino-19-nor steroids, see D. B. R. Johnston, F. S. Waksmunski, T. B. Windholz, and A. A. Patchett, *Chimia*, **22**, 84 (1968). See also the synthesis of A-nor-1-thia-3-aza steroids: C. Lehmann, H. Schick, B. Lücke, and C. Hilgetag, *Chem. Ber.*, **101**, 787 (1968).

(18) While our original communication[1b] was still in press, a preliminary note [H. Gibian, *et al.*, *Tetrahedron Lett.*, 2321 (1966)] appeared noting the stereospecific semireduction of **3** microbiologically to give optically active 17β-ol of the natural series and 17α-ol in the unnatural series, the latter having no utility in a synthesis of *d*-estrone.

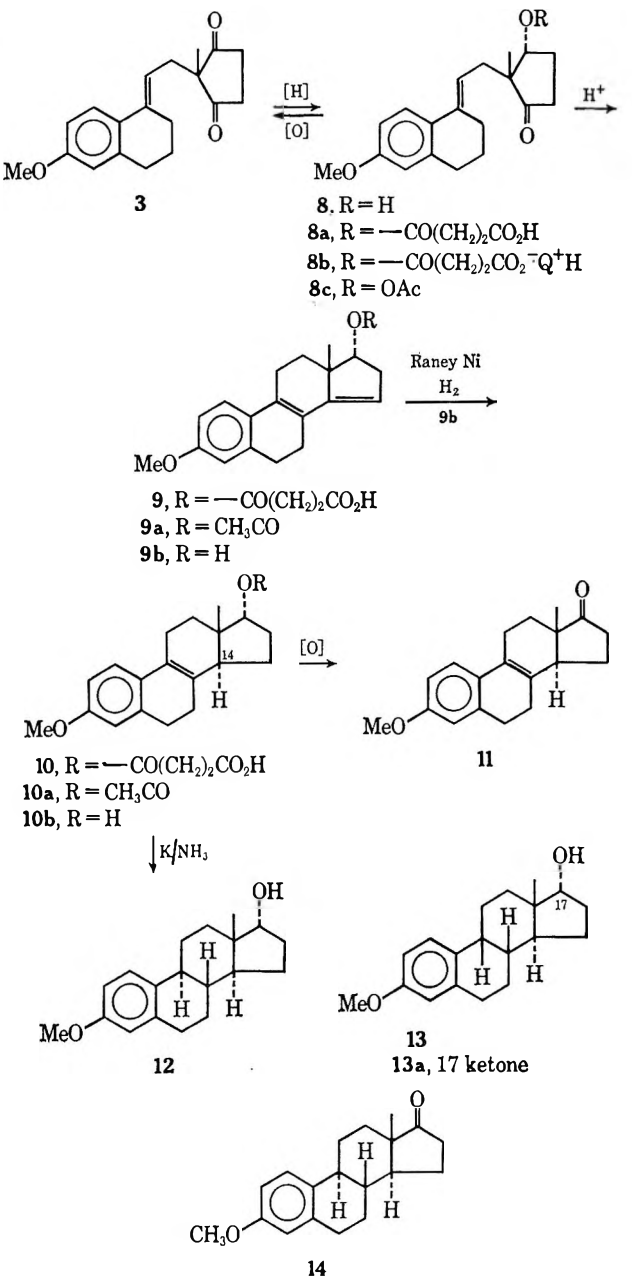
dently to *dl*-estrone **14** *via* the sequence **9a** → **10a** → **12** → **14**.

The ketol, **8**, provided the key intermediate in our sequence, not only for purposes of optical resolution, but also in providing a novel sequence of intermediates *en route* to estrone. The ketol was converted essentially quantitatively into its hemisuccinate derivative **8a** which in turn was resolved *via* the corresponding quinine salt **8b** (Q = quinine). Although the desired enantiomorph appeared in the mother liquors after initial separation of its dextrorotatory isomer, it could nevertheless be isolated in good yield and in turn hydrolyzed to the (−)-ketol **8**: mp 100–102°; $[\alpha]_D$ −45° (dioxane). Hydrolysis of the undesired enantiomeric hemisuccinate in turn provided the corresponding (+)-ketol: mp 100–102°; $[\alpha]_D$ +45° (dioxane) {lit.[18] $[\alpha]_D$ +47° (ethanol)}. The latter ketol together with extraneous hydrolyzed hemisuccinate residue could be essentially quantitatively reoxidized to starting diketone **3** by the method of Moffatt and Pfitzner (see Experimental Section). The latter sequence thereby permits utilization of the unwanted isomer by recycling it in the resolution process *via* the indicated oxidation–reduction pathway (**3** ⇌ **8**).

Cyclization of the (−)-ketol **8** could be effected either as its acetate derivative **8c** or as the hemisuccinate **8a** obtained from the resolution step. Ring closure was carried out by the conventional technique[7] with *p*-toluenesulfonic acid in benzene to give both the 17-hemisuccinate (**9**) and 17-acetate (**9a**) of 8,14-bisdehydro-17-isoestradiol-3-methyl ether, both in 85–90% yield. Hydrogenation of the latter **9a** over palladium on carbon afforded essentially a 70:30 mixture[19] of 14α and 14β **10a**, respectively, which was very difficult to separate. The hemisuccinate derivative **9** gave an even poorer ratio (55:45) of the corresponding 14α and 14β **10**. These ratios were determined by integration of the C-18 methyl peaks at δ 0.76 and 1.00 for 14α and 14β, respectively, in the nmr spectra. Initial removal of the ester function at C-17, either hydrolytically or reductively with $LiAlH_4$, followed by hydrogenation of the free 17α-ol **9b** in dioxane over Raney nickel, afforded a 92:8 (14α:14β) ratio of the desired 8-dehydro-17-isoestradiol-3-methyl ether (**10b**): mp 118–120°; $[\alpha]_D$ −36°. This result demonstrates that, contrary to expectations based on the usual steric considerations, hydrogenation of the 14,15 double bond in the 17α-OH series from the α face can be made to proceed with a selectivity equal to that in the 17β-OH series.

Oxidation of the 17α-ol **10b** either by the Oppenauer procedure or that of Moffatt and Pfitzner led to optically active 8-dehydroestrone methyl ether **11** which, as the racemate, had previously been converted into estrone.[7] Chromium trioxide treatment of **10b**, either in pyridine or acetone–sulfuric acid, produced only minor amounts of **11**. The major reaction pathway was dehydrogenation to napthalenoid products (*cf.* ref 7c).

Reduction of the 8,9 double bond of **10b** with lithium or potassium in liquid ammonia produced preponderantly 17-isoestradiol 3-methyl ether **12**, mp 103–106°, $[\alpha]_D$ +55° (MeOH),[20] together with a minor amount of the 9β isomer **13**, $[\alpha]_D$ −75.4° (MeOH), identified by comparison of the ir spectrum of the corresponding 17



ketone **13a**, $[\alpha]_D$ +43° (MeOH), with that reported for the *dl* isomer.[21,22] Oxidation of **12** with chromic acid yielded *d*-estrone methyl ether **14** identical in all respects with an authentic specimen.

Experimental Section

Melting points were taken on a microscope hot-stage apparatus and are uncorrected. Uv spectra were determined in MeOH on a Cary Model II PMS spectrometer and ir spectra on a Perkin-Elmer Infracord instrument. Nmr spectra were recorded on a Varian A-60 spectrometer using TMS as an internal standard. Optical rotations were measured with a Zeiss photoelectric

(19) C. Ruter, E. Schröder, and R. Vössing, *Ann.*, **701**, 206 (1967).

(20) (a) A. Butenandt and C. Groergens [*Z. Physiol. Chem.*, **248**, 129 (1937)] reported mp 109–110°. (b) C. H. Robinson, O. Gnoj, and E. P. Oliveto [*J. Org. Chem.*, **25**, 2247 (1960)] reported $[\alpha]_D$ +53° (dioxane).

(21) W. S. Johnson, I. A. David, H. C. Dehm, R. J. Highet, E. W. Warnhoff, W. D. Wood, and E. Jones, *J. Amer. Chem. Soc.*, **80**, 661 (1958).

(22) Use of lithium as the reductant generally produced some phenolic material by methyl ether cleavage [*cf.* K. K. Koshoev, S. N. Ananchenko, and I. V. Torgov, *Khim. Prirodn Soedin, Akad. Nauk Uz SSR*, **1**, 172 (1965)] isolated in our *dl* series and identified as 1,3,5(10),8-estratetraene-3,17α-diol. In the previously described metal–ammonia reductions of the analogous 8-dehydro-17β-ol and 17-one systems (see ref 7) the formation of 9β-estratriene by-product has not been noted, although the 9β isomer of 19-nortestosterone was a significant by-product in the further reduction of the above 8-dehydro systems [K. K. Koshoev, S. N. Ananchenko, and I. V. Torgov, *ibid.*, 180 (1965)].

polarimeter employing a 0.5-dc tube. Tlc was carried out on silica gel G coated glass plates. We wish to thank Mr. R. N. Boos and his associates for the elemental analyses, Mr. A. Kalowsky for the ultraviolet spectra, and Dr. N. R. Trenner and Mr. J. Beck for the ^{18}O mass spectral determinations.

6-Methoxy-1,2,3,4-tetrahydronaphthylideneethylisothiuronium Acetate (4).—To a stirred mixture of purified vinyl carbinol 1,[23] (3.06 g, 15 mmol) and thiourea (1.14 g., 15 mmol) was added 12 ml of acetic acid, and the reaction mixture was stirred at 25° for 4 hr.[24] At the end of this period 80 ml of ether was added with stirring and the precipitated salt was filtered to afford 3.73 g of **4**. The filtrate was concentrated to a solid residue, triturated with benzene–ether, and filtered to give an additional 1.04 g which was combined with the first crop to give a total of 4.77 g of **4** (98%): mp 125–127°; λ_{max} 300 mμ (ε 8590), 275 (19,400); nmr (DMSO-d_6), δ 1.79 [s, $CH_3C(=O)$-], 3.75 (s, MeO–), 5.98 (t, vinylic proton).

Anal. Calcd for $C_{16}H_{22}O_3N_2S$: C, 59.60; H, 6.88; N, 8.69; S, 9.95. Found: C, 59.47; H, 6.95; N, 8.59; S, 9.73.

6-Methoxy-1,2,3,4-tetrahydronaphthylidineethyltriphenylphosphonium Acetate (4a).—A solution of 1-vinyl-6-methoxy-1-tetralol (**1**, 1.02 g, 5 mmol) and triphenylphosphine (1.31 g, 5 mmol) in 10 ml of acetic acid was magnetically stirred at 25° for 3 hr. The reaction mixture was concentrated *in vacuo* to a yellow oil which was triturated with ether. The residual oil crystallized from acetone–ether to afford **4a**: first crop, 1.11 g; mp 101–106°; λ_{max} 303 mμ (ε 10,900), 275 (17,100), 270 (16,450), 225 (34,600), $\lambda_{max}^{chloroform}$ 2.8 (w), 3.1–3.3 (bonded), 5.9, 6.22, 6.38, 6.70, 6.98, 7.25, 7.60, 7.85, 8.10, 8.60, 8.98, 9.60, 10.0, 14.45 μ. This material was difficult to obtain in a solvent-free form suitable for elemental analysis, but could be converted into the corresponding bromide by salt exchange in acetone with an equivalent of lithium bromide at room temperature. The bromide so obtained was identical with an authentic sample (see below).

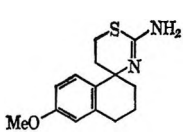
6-Methoxy-1,2,3,4-tetrahydronaphthylideneethyltriphenylphosphonium Bromide (4b).—To a stirred solution of triphenyl phosphine hydrobromide (1.37 g, 4 mmol; prepared from triphenylphosphine and hydrogen bromide in ethyl acetate at 25°) in 15 ml of methylene chloride under nitrogen, was added a solution of vinylcarbinol **1** (1.02 g, 5 mmol) in 10 ml of methylene chloride at 0–10°. The reaction mixture was then stirred at 25° for 16 hr. The solvent was removed under reduced pressure and the crystalline residue was filtered from acetone to afford 1.514 g of **4b**: mp 189–192°; $\lambda_{max}^{chloroform}$ 2.80 (w), 3.05 (m), 6.21 (s), 6.37 (w), 6.69 (s), 6.83 (w), 6.96, 8.98, 9.60, 9.99, 10.70, 14.45 μ. An analytical sample was prepared by recrystallization from acetone–ether: mp 190–192° (needles); λ_{max}^{MeOH} 301 mμ (ε 13,400), 276 (22,000), 268 (22,200), 250 (24,600), 226 (105,700); nmr, δ 1.50 (2 H, multiplet), 3.78 (3 H, singlet), 4.68, 4.92, (2 H, two doublets), 5.75 (1 H, multiplet).

Anal. Calcd for $C_{31}H_{30}OPBr$: C, 70.32; H, 5.71; P, 5.71 Br, 15.04. Found: C, 70.13; H, 5.59; P, 5.86; Br, 15.32.

6-Methoxy-1,2,3,4-tetrahydronaphthylidineethyl Thioacetate (4c).—A solution of 1-vinyl-6-methoxy-1-tetralol (**1**, 408.5 mg, 2 mmol), thioacetic acid (152.2 mg, 2 mmol), 1.5 ml of dry xylene, and 0.7 ml of *t*-butyl alcohol was refluxed for 3 hr. The solvents were removed *in vacuo* and the residue was extracted into ether. The latter was washed with water, 5% $NaHCO_3$, and aqueous NaCl, dried over $MgSO_4$, and concentrated *in vacuo* to an oil which was purified chromatographically (10 g of silica gel, 15-ml fractions). The benzene eluates gave 400 mg of single-spot **4c** as an oil: λ_{max} 269 mμ (ε 19,750), $\lambda_{max}^{chloroform}$ 5.95, 6.21, 6.28, 6.7 μ.

(23) This material was purified by short-path distillation: bp 111° (0.02 mm); λ_{max}^{MeOH} 283 mμ (ε 2060), 276 (2210), 227 (8,950), 223 (8760) (*Anal.* Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.30; H, 7.93). *Cf.* R. Seltzer and W. J. Considine, *Chem. Ind.* (London), 1729 (1965).

(24) Under hot conditions (refluxing xylene–acetic acid 2:1) no isothiuronium salt was obtained. The product was the spiran iii: mp 253–255°; λ_{max} 284 mμ (ε 1700), 275 (2200), 244 (18,500); λ_{max}^{Nujol} 3.21, 6.20, 6.40, 6.45, 6.57, 6.69, 6.86, 7.30, 7.50, 7.95, 8.30, 8.85, 9.65 μ (*Anal.* Calcd for $C_{14}H_{18}ON_2S$: C, 64.08; H, 6.91; N, 10.68; S, 12.22. Found: C, 63.81; H, 6.69; N, 10.91; S, 11.60).



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Anal. Calcd for $C_{15}H_{18}O_2S$: C, 68.67; H, 6.91; S, 12.22. Found: C, 68.70; H, 6.89; S, 11.29.

In the same manner 408.5 mg of vinylcarbinol in 3 cc of acetic acid reacted with 130 mg of sodium azide at 25° for 3 hr. After the usual work-up 6-methoxy-1,2,3,4-tetrahydronaphthylidineethyl azide (**4d**) was obtained as an oil: $\lambda_{max}^{chloroform}$ 4.78, 5.99, 6.20, 6.38, 6.68, 6.81, 7.00 μ.

The ^{18}O Series. 6-Methoxytetralone-^{18}O.—Oxygen-18-labeled water (0.3 ml, 20% $H_2{}^{18}O$) was added to a stirred solution of 6-methoxytetralone (528 mg, 3 mmol) in 3 ml of anhydrous methanol. One drop of concentrated HCl was added and the reaction mixture was heated at 80° for 20 min. The solvent was removed *in vacuo* and the residue was triturated with dry benzene to provide crystalline-labeled 6-methoxytetralone, mp 74–76°. Recrystallization from ether gave 456 mg, mp 76–78°. Mass spectrometry indicated 19 atom % ^{18}O content.

1-Vinyl-6-methoxytetralol-^{18}O (1) was obtained by reaction of the above 6-methoxytetralone-^{18}O (740 mg, 4.2 mmol) with vinylmagnesium bromide in tetrahydrofuran under the standard conditions.[7,25] The product (1.20 g of pale yellow oil) was purified by short-path distillation, bp 111° (0.02 mm). Direct mass spectral ^{18}O determination could not be performed because of elimination of the tertiary hydroxyl group as water. However, analysis by $H_2O \rightleftarrows CO_2$ equilibration of the eliminated water showed **1** to contain 17–18% ^{18}O.

3-Methoxy-8(14)-seco-1,3,5(10),9(11)-estratetraene-14,17-dione (3). A.—A mixture of the above vinylcarbinol-^{18}O (198 mg, 0.97 mmol), 2-methylcyclopentane-1,3-dione (**2**, 109 mg, 0.97 mmol), dry xylene (0.9 ml), and *t*-butyl alcohol (0.9 ml) was refluxed under nitrogen for 3 hr. Solvents were removed at reduced pressure and the residue was triturated with benzene. Ether was added and the crystals were filtered to give 51 mg of recovered **2**. The filtrate was washed with water, 5% $NaHCO_3$, and saturated aqueous NaCl, dried over $MgSO_4$, and concentrated *in vacuo* to afford 110 mg of **3**, mp 75–77°. Direct mass spectrometry showed the product to contain 1.6 mol % ^{18}O. As shown in the control experiment (B) this small percentage of ^{18}O is attributable to exchange with the ^{18}O liberated during the condensation and present in the reaction medium.

B.—To a stirred mixture of normal dione **3** (448 mg, 1.5 mmol), 2-methylcyclopentane-1,3-dione (**2**, 506 mg, 4.5 mmol) in 2.6 ml of dry xylene, and 2.5 ml of *t*-butyl alcohol was added 0.027 ml (1.5 mmol, 20% H_2O^{18}) of H_2O^{18}. The system was refluxed for 3 hr under nitrogen, concentrated *in vacuo*, and triturated with benzene. Ether was added and the recovered crystalline dione **2** was removed by filtration. The filtrate was washed with water, 5% $NaHCO_3$, and saturated aqueous NaCl, dried over $MgSO_4$, and concentrated *in vacuo* to 326 mg of **3**, mp 76–78°, which mass spectrometry indicated to have 2 mol % of ^{18}O.

Attempted Condensation of 1 and 2 in the Presence of 1 *M* Equiv of Base.—A stirred mixture of vinylcarbinol **1** (530 mg, 2.6 mmol), 2-methylcyclopentane-1,3-dione (**2**, 290 mg, 2.6 mmol), and 1.60 ml of 1.7 *M* methanolic Triton B in 3 ml of xylene and 0.8 ml of *t*-butyl alcohol was refluxed under nitrogen for 2 hr. The mixture was cooled, treated with ethyl acetate and water, extracted with excess 5% $KHCO_3$ and saturated aqueous NaCl, dried over $MgSO_4$, and concentrated to dryness. The neutral oily residue (520 mg) possessed no carbonyl absorption in its infrared spectrum ($CHCl_3$) which was identical with that of vinylcarbinol **1**. From the aqueous extract, **2** could be recovered on acidification and concentration.

Direct Condensation of 1 and 2 without External Catalyst.—A stirred mixture of 1-vinyl-6-methoxytetralol (**1**,[25] 700 mg, 3.7 mmol) and 2-methylcyclopentane-1,3-dione (**2**, 420 mg, 3.7 mmol) in 4 ml of xylene and 2 ml of *t*-butyl alcohol was refluxed under nitrogen for 90 min. The mixture was cooled, ether was added, and precipitated, unreacted dione **2** was removed by filtration (115 mg). The filtrate was washed with water, 5% $KHCO_3$, and saturated aqueous NaCl, dried over $MgSO_4$, and concentrated to dryness. Crystallization of the residue from methanol gave 575 mg of **3**, mp 76–78°, in two crops (70% based on **2** consumed) with additional material in the mother liquor.

(±)-3-Methoxy-1,3,5(10),8,14-estrapentaene-17-one (7). One-Step Process from 1 and 2.—To a stirred solution of 7.00 g of

(25) I. N. Nazarov, I. V. Torgov, and G. N. Verkholetova, *Dokl. Akad. Nauk SSSR*, **112**, 1067 (1957). Vinylcarbinol **1** is normally *ca.* 85–90% pure as prepared by Grignard reaction of 6-methoxytetralone and vinyl magnesium bromide.

vinylcarbinol **1** (*ca.* 90% pure, 30 mmol) in 40 ml of xylene was added 3.90 g (35 mmol) of 2-methylcyclopentane-1,3-dione (**2**) and 20 ml of acetic acid. The mixture was refluxed under nitrogen for 2 hr and concentrated to a small volume, ether–benzene 1:1 was added, and the precipitated unreacted **2** was recovered by filtration and washed with ether (1.11 g). The combined filtrate and washes were extracted with 5% $KHCO_3$ and saturated salt solution, dried over $MgSO_4$, and concentrated to dryness. Trituration with ether gave 3.73 g of single-spot (tlc with $CHCl_3$) **7**, mp 106–108°. Concentration of the mother liquor to dryness and crystallization of the residue from methanol gave an additional 1.32 g of single-spot **7**: mp 106–108°; total yield 5.05 g (60% based on **1**, 70% based on **2** consumed); λ_{max} 332 mμ infl (ε 24,600), 311 (29,000), 239 infl (11,000), 233 (13,600), 228 (13,300); identical with an authentic sample.[7]

dl **Series. 3-Methoxy-8(14)-seco-1,3,5-(10),9(11)-estratetraene-14,17-dione (3). By the Isothiuronium Salt Method A.**—To a stirred mixture of the isothiuronium acetate **4** (645 mg, 2.0 mmol) and 2-methylcyclopentane-1,3-dione (**2**, 449 mg, 4.0 mmol) was added 14 ml (1:1) of aqueous ethanol. A clear solution was observed within 5 min followed by precipitation of product after an additional 5 min. The reaction mixture was stirred at room temperature for 3 hr, chilled, and filtered to give 476 mg of dione **3**, mp 76–78°. The ethanol was removed from the filtrate under reduced pressure and the aqueous phase was saturated with NaCl and extracted with ethyl acetate. The latter extract was washed with 5% $NaHCO_3$ and saturated aqueous NaCl, dried over $MgSO_4$, and concentrated *in vacuo* to give 140 mg of partly crystalline residue which was purified by tlc (silica gel, chloroform) to provide an additional 59 mg of **3**, mp 76–78° (total yield 90%).

B.—A mixture of 1.63 g (5 mmol) of isothiuronium salt **4**, 700 mg (6.3 mmol) of 2-methylcyclopentane-1,3-dione (**2**), 30 ml of water, 15 ml of benzene, and 15 ml of ether was stirred at 20–25°.[26] Essentially all of the material dissolved after 30 min. After a total time of 1.5 hr, 50 ml of water and 25 ml of 1:1 ether–benzene were added, and the layers were separated. The aqueous layer was extracted twice with 1:1 ether–benzene. The combined organic layers were washed with excess 5% $KHCO_3$ and saturated aqueous NaCl and dried over $MgSO_4$. Concentration to dryness on the water pump gave a yellow oil, 1.44 g, which solidified on cooling and scratching. Crystallization from methanol gave 1.05 g of dione **3**: mp 77–79°; λ_{max} 295 mμ (ε 5640), 267 (17,500); tlc (silica gel 5% acetone–chloroform) showed the mother liquor to be rich in product.

(±)-3-Methoxy-8(14)-seco-1,3,5(10),9(11)-estratetraene-17α-ol-14-one (8).—A solution of 4.20 g of lithium tri-*t*-butoxyaluminum hydride in 150 ml of freshly distilled tetrahydrofuran was added to a magnetically stirred solution of 4.48 g of 3-methoxy-8(14)-seco-1,3,5(10),9(11)-estratetraene-14,17-dione (**3**), in 120 ml of tetrahydrofuran at 0° under nitrogen during ~45 min. The reaction mixture was stirred at 20–25° for 16 hr. Saturated aqueous Na_2SO_4 (210 ml) was then added dropwise at 0°. Inorganic salts were removed by filtration and washed thoroughly with benzene and ether. The combined organic phase was washed with saturated aqueous NaCl, dried over $MgSO_4$, and concentrated *in vacuo* to 4.52 g of (±) **8**: λ_{max} 295 mμ (ε 3970), 265 (18,200), 210 (19,400). The composition of this product as ~85–90% of the 17α epimer was determined by cyclization of its acetate derivative (see below) to tetracyclic pentaene followed by chromatographic isolation of the desired 17α isomer **9a**. Purification of the reduction product *via* its hemisuccinate derivative followed by hydrolysis (see below under Optically Active Series) afforded crystalline (±) **8**: mp 74–76°; $\lambda_{max}^{chloroform}$ 2.82, 2.95 (sh), 5.75, 6.21, 6.36, 6.69, 6.82 μ.

Anal. Calcd for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 75.83; H, 7.95.

In subsequent reductions (±) **8** could be obtained crystalline directly by seeding.

The (±)-ketol **8** afforded a **semicarbazone** crystallized from EtOAc–$CHCl_3$: mp 196–199°; λ_{max}^{MeOH} 295 mμ (ε 3520), 266 (20,420), 214 (28,800); λ_{max}^{Nujol} 2.95, 3.15, 5.95, 6.22, 6.40, 6.60, 6.70, 6.88 μ.

Anal. Calcd for $C_{20}H_{27}O_3N_3$: C, 67.20; H, 7.61; N, 11.76. Found: C, 67.58; H, 7.60; N, 11.67.

(±)-3-Methoxy-1,3,5(10),8,14-estrapentaene 17α-Acetate (9a).—Total crude lithium tri-*t*-butoxyaluminum hydride reduction product **8** (4.52 g) was acetylated with acetic anhydride (2 ml) in 8 ml of dry pyridine at 25° for 16 hr. The reaction mixture was concentrated *in vacuo* to a brown oil, **9a**, which was cyclized without further purification with anhydrous *p*-toluenesulfonic acid (17.3 g) in 300 ml of dry benzene at 25° for 16 hr. After filtration of the formed *p*-toluenesulfonic acid monohydrate, the organic phase was washed with 5% Na_2CO_3, dried over $MgSO_4$, and concentrated *in vacuo* to 4.85 g of product which was chromatographed on 500 g of silica gel, and the eluates were collected in 500-ml fractions. The initial compound eluted was **3-methoxy-1,3,5(10),8,14-estrapentaene 17β-acetate**:[27] 227 mg; mp 110–112° (from acetone–methanol); nmr ($CDCl_3$), δ 1.00 (s, CH_3-C–), 2.13 [s, CH_3–C(=O)–], 5.07 (t, J = 8 cps, 17α-H), 5.51 (m, vinyl H). This was followed by the 17α-acetate **9a**: 2.17 g; mp 95–98° (analytical sample needles were recrystallized from acetone–methanol, mp 97–99°); λ_{max} 320 mμ (ε 23,600), 311 (30,800), 302 (25,800), 240 (10,520), 239 (13,580), 228 (13,600), 220 (13,500); $\lambda_{max}^{chloroform}$ 5.80, 6.22, 6.40, 6.70, 6.85, 7.00, 7.95, 8.00 μ; nmr ($CDCl_3$), δ 1.04 (s, CH_3–C–), 2.05 (s, CH_3C=O), 3.83 (s, CH_3O), 5.17 (d, J = 5 cps, 17β-H), 5.60 (m, vinyl H).

Anal. Calcd for $C_{21}H_{24}O_3$: C, 77.75; H, 7.46. Found: C, 77.66; H, 7.51.

(±)-3-Methoxy-1,3,5(10),8-estratetraene 17α-Acetate (10a).—The (±)-pentaene acetate **9a** (324 mg, 1 mmol) in 10 ml of dry benzene was hydrogenated over 10% palladium on charcoal at atmospheric pressure. Uptake of 1 mol of hydrogen was realized within 10 min. The reduction was terminated and the catalyst was removed by filtration. The filtrate was concentrated *in vacuo* to an oil which crystallized upon addition of ether. The crystals were filtered to give a first crop of 207 mg, mp 103–110° (*ca.* 70:30 mixture of **10a** and its 14β epimer by comparison of the respective nmr 18-methyl singlets at δ 0.76 and 1.00). Pure **10a** (rosettes) was obtained by preparative tlc: mp 112–115°; λ_{max} 320 mμ (ε 1140), 308 (2980), 278 (16,000), 213 (18,600); $\lambda_{max}^{chloroform}$ 5.82, 6.22, 6.40, 6.70, 8.05, 8.20 μ.

Anal. Calcd for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03. Found: C, 77.14; H, 8.06.

(±)-17-Isoestradiol 3-Methyl Ether (12).—To a stirred solution of 200 mg of (±)-3-methoxy-1,3,5(10),8-estratetraene 17α-acetate (**10a**) in 14 ml of drytetrahy drofuran and 25 ml of NH_3 was added 56 mg of lithium at −50°. At the end of 2 hr, the deep blue color of the reaction mixture was discharged by addition of solid NH_4Cl. Following evaporation of the ammonia, water (80 ml) was added and the mixture was extracted with ether. The ether extract was washed with water and saturated aqueous Na_2SO_4, dried over $MgSO_4$, and concentrated *in vacuo* to an oil. Partial crystallization took place upon addition of ether to give 42 mg of **1,3,5(10),8-estratetraene-3,17α-diol**: mp 233–235°; λ_{max}^{MeOH} 276 mμ (ε 14,900), 212 (19,000); λ_{max}^{Nujol} 3.00, 3.30, 6.23, 6.70, 6.90, 7.30, 9.60 μ.

Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 79.34; H, 8.34.

Preparative thin layer chromatography (5% ether in $CHCl_3$) of the mother liquor gave 64 mg of pure **12** (needles): mp 92–95°; λ_{max} 287 mμ (ε 1760), 279 (1840), 219 (7700); $\lambda_{max}^{CHCl_3}$ 2.85, 3.40, 3.50, 3.55, 6.20, 6.36, 6.69, 6.84, 6.90 μ.

Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.88; H, 9.32.

(±)-Estrone Methyl Ether (14).—To a stirred solution of (±)-17-isoestradiol 3-methyl ether (**12**, 30 mg) in acetone (3 ml) was added 0.08 ml of Jones' reagent.[28] The reaction mixture was stirred at 25° for 5 min and excess reagent was destroyed by addition of 1.5 ml of MeOH and dilution with 15 ml of water to give a colorless crystalline precipitate which was filtered and air dried to yield 20.4 mg of **14**: mp 139–141°; $\lambda_{max}^{CHCl_3}$ 5.75, 6.18, 6.22, 6.65, 6.81, 6.86 μ; tlc (5% ether in $CHCl_3$), R_f 0.65; identical with an authentic sample (mixture melting point, ir spectroscopy, tlc).

Optically Active Series. (±)-3-Methoxy-8(14)-seco-1,3,5-(10),9(11)-estratetraene-17α-ol-14-one 17-Hemisuccinate (8a).—(±)-3-Methoxy-8(14)-seco-1,3,5(10),9(11)-estratetraene-17α-ol-14-one (**8**, 300 mg, 1 mmol, mp 74–76°) and succinic anhydride (450 mg, 2.5 mmol) in dry pyridine (8 ml) was stirred and

(26) Comparable results were obtained on refluxing the reactant in *t*-butyl alcohol for 3 hr.

(27) K. K. Koshoev, S. N. Ananchenko, A. V. Platonova, and I. V. Torgov [*Ivv. Akad. Nauk SSSR, Ser. Khim.*, 2058 (1963)] report mp 110–111°.

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

heated under nitrogen at 100° for 52 hr.[29] The dark reaction mixture was concentrated *in vacuo* to a residue. Ether and water were added and the reaction mixture was made acidic with 2 *N* sulfuric acid. Precipitated excess succinic anhydride was removed by filtration. The ether extract was washed with water and 5% K_2CO_3, dried over $MgSO_4$, and concentrated to a neutral residue (11 mg). The acidic product was isolated from the carbonate extract by acidification with 2 *N* H_2SO_4 and extraction with ether. The ether extract was washed with water, dried over $MgSO_4$, and concentrated *in vacuo* to afford 398 mg of crystalline succinate **8a**, mp 101–104°. The analytical sample was prepared by recrystallization from ether–petroleum ether: mp 102–104°; λ_{max} 293 mμ (ε 3940), 265 (20,000), 213 (20,200); $\lambda_{max}^{chloroform}$ 2.9–3.3, 5.75, 5.80 (sh), 6.21, 6.36, 6.69, 8.15, 8.65, 9.41, 9.60 μ; nmr ($CDCl_3$), δ 1.07 (s, 3 H, CH_3–C–).

Anal. Calcd for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05. Found: C, 69.21; H, 7.15.

Saponification of the crystalline (±) hemisuccinate **8a** (801 mg, 2 mmol) was effected by treatment with cold aqueous KOH (1.36 g in 40 ml of water) under nitrogen at 25°. (Neutral product precipitated in part.) After stirring for 15 min, the reaction mixture was briefly warmed on the steam cone for 15 min and cooled to room temperature and the residue was dissolved in methylene chloride. The latter solution was washed with water and saturated aqueous NaCl, dried over $MgSO_4$, and concentrated *in vacuo* to afford 612 mg of colorless oil which completely crystallized from ether–petroleum ether, mp 70–72°. Recrystallization from ether–petroleum ether gave a first crop of 517 mg of the racemic ketol **8**, mp 74–76°. (See above for earlier description of this substance.)

(−)-3-Methoxy-8(14)-seco-1,3,5(10),9(11)-estratetraene-17α-ol-14-one 17-Hemisuccinate (8a).—(±) hemisuccinate **8a** (41.48 g, 104 mmol), quinine trihydrate (39.17 g, 104 mmol), and acetone (1 l.) were warmed briefly on the steam bath to achieve homogeneity. The reaction mixture was cooled slowly with stirring. The resulting precipitate was aged before filtration to provide 40.65 g of the (+)-quinine salt **8b**: mp 160–162°; $[\alpha]^{29}D$ −39.2° (MeOH); $\lambda_{max}^{chloroform}$ 3.0–3.4 (broad), 5.75, 6.16, 6.21, 6.25, 6.35, 6.62, 6.68 μ. The filtrate was concentrated to a foam {39.00 g, $[\alpha]D$ −121° (MeOH)}, dissolved in benzene–ethyl acetate (1:1), and washed four times with 10% H_2SO_4, water, and saturated aqueous NaCl. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to afford 21.8 g of crude noncrystalline hemisuccinate (−) **8a**: $\lambda_{max}^{chloroform}$ 2.8–3.3, 5.75, 5.80 (sh), 6.21, 6.38 μ. The ir spectrum was similar to that of (±) **8a**.

(−)- and (+)-3-Methoxy-8(14)-seco-1,3,5(10),9(11)-estratetraene-17α-ol-14-one (8).—Cold aqueous base (37.2 g of KOH in 1 l. of water) was added to 21.80 g of the crude (−) hemisuccinate **8a** with swirling under nitrogen. The cloudy reaction mixture was heated on the steam bath for 15 min with occasional swirling resulting in precipitation of neutral **8**. The mixture was chilled before filtration. The precipitate was washed with water and air dried to give 14.72 g of crude (−)-ketol **8** (91%), mp 94–98°. The filtrate was saturated with NaCl and extracted with methylene chloride and the extract was washed with water and saturated aqueous NaCl, dried over $MgSO_4$, and concentrated *in vacuo* to give an additional 120 mg of product. The total ketol was recrystallized from acetone–ether–petroleum ether to provide 13.12 g of prismatic needles, mp 98–100°. An analytical sample was prepared by recrystallization from ether–petroleum ether: mp 100–102°; $[\alpha]D$ −45° (dioxane).

Anal. Calcd for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 76.11; H, 7.75.

The (+) hemisuccinate (319 mg) was saponified in a similar manner to afford 218 mg of (+) **8** (92%): mp 100–102°; $[\alpha]D$ +45° (dioxane).

Oxidative Reconversion of (+) 8 into 3.—(+)-3-Methoxy-8(14) seco-1,3,5(10),9(11)-estratetraene-17α-ol-14-one (**8**, 300 mg, 1 mmol) was dissolved in anhydrous dimethyl sulfoxide (1.5 ml) and benzene (1.5 ml) containing pyridine (0.08 ml), and trifluoroacetic acid (0.04 ml) was added. After addition of 0.62 g of dicyclohexylcarbodiimide, the reaction mixture was kept at 25° for 16 hr.[30] Ether (25 ml) was added, followed by a solution of oxalic acid (270 mg, 3 mmol) in methanol (2.5 ml). After gas evolution had ceased (~30 min), water (25 ml) was added and the insoluble dicyclohexylurea was removed by filtration. The organic phase was then extracted twice with 5% $NaHCO_3$ and water, dried over Na_2SO_4, and evaporated to dryness to provide 300 mg of crude crystalline **3** which was filtered from ether–petroleum ether to give 291 mg in three crops: mp 75–77°; tlc ($CHCl_3$), R_f 0.5.

3-Methoxy-1,3,5(10),8,14-estrapentaene 17α-Hemisuccinate (9).—(+)-3-Methoxy-8(14)-seco-1,3,5(10),9(11)-estratetraene-17α-ol-14-one 17-hemisuccinate (**8a**, 2.0 g, 5 mmol) in 50 ml of dry benzene was added to a stirred slurry of anhydrous *p*-toluenesulfonic acid (from 5.71 g of the monohydrate in 40 ml of dry benzene taken to dryness) in 40 ml of dry benzene under nitrogen and the reaction mixture was stirred at 25° for 16 hr. The *p*-toluenesulfonic acid hydrate which precipitated was filtered and the filtrate was washed with water and saturated aqueous NaCl, dried over $MgSO_4$, and concentrated *in vacuo* to 1.93 g of crystalline solid. The product was triturated with ether–petroleum ether and filtered to give 1.74 g of tetracyclic acid **9**: mp 133–135°; $[\alpha]D$ 0° ($CHCl_3$); λ_{max} 324 mμ (ε 24,100), 311 (31,700), 302 infl (26,300), 242 (10,580), 235 (13,730), 228 (13,500), 223 (12,510); $\lambda_{max}^{chloroform}$ 2.9–3.3, 5.8, 6.21, 6.39 μ; nmr, δ^{CCl_4} 1.0 (s, 3 H, >C–CH_3), 3.81 (s, 3 H, –O–CH_3), 5.17 (broad doublet, 1 H, –CH–O–), 5.57 (m, 1 H, vinylic), 10.3 (1 H, –CO–OH).

Anal. Calcd for $C_{23}H_{26}O_5$: C, 72.23; H, 6.85. Found: C, 72.33; H, 6.82.

(−)-3-Methoxy-1,3,5(10),8,14-estrapentaene 17α-Acetate (9a).—Acetylation of (−) **8** (1.00 g) and cyclization as described above for (±) **8** gave (−) 17α-acetate **9a** (860 mg): mp 125–127°; $[\alpha]D$ −182° ($CHCl_3$).

Anal. Calcd for $C_{21}H_{24}O_3$: C, 77.75; H, 7.46. Found: C, 77.33; H, 7.40.

(−)-3-Methoxy-1,3,5(10),8,14-estrapentaene-17α-ol (9b). A.—The pentaene acetate **9a** (1.30 g, 3 mmol) in dry tetrahydrofuran (52 ml) was added dropwise to a stirred slurry of lithium aluminum hydride (656 mg) in ether (104 ml) at 25°, and the reaction mixture was stirred at room temperature for 3 hr. With caution, ethyl acetate (24 ml) was added followed by 40 ml of saturated aqueous Na_2SO_4. Sufficient solid $MgSO_4$ was added to remove all the water. Inorganics were removed by filtration and the filtrate was concentrated *in vacuo* to 1.22 g of solid **9b**: mp 89–94°; $\lambda_{max}^{chloroform}$ 2.85, 3.0, 6.21, 6.26 (sh), 6.40, 6.70, 6.85, 7.00 μ. This compound became purple on standing. Because of its instability, further purification was not attempted and it was immediately hydrogenated.

B.—Under nitrogen, methanolic KOH (1.70 ml, 0.85 *N*) was added to a stirred solution of the hemisuccinate **9** (382 mg, 1 mmol) in 3 ml of methanol. The clear reaction mixture was stirred at 25° for 3 hr. Water was then added and methanol was removed *in vacuo*. The final aqueous solution was saturated with NaCl and extracted with ethyl acetate. The latter was washed with saturated aqueous NaCl, dried over $MgSO_4$, and concentrated *in vacuo* to 238 mg of crude 17α-ol **9b**; because of its instability **9b** was immediately hydrogenated without further purification.

(−)-3-Methoxy-1,3,5(10),8-estratetraene-17α-ol (10b).—(−)-3-Methoxy-1,3,5(10),8,14-estrapentaene-17α-ol (**9b**, 850 mg, 3 mmol) in 16 ml of dry dioxane was added to Raney nickel catalyst (850 mg) in 20 ml of dry dioxane pre-equilibrated with hydrogen, and the reaction mixture was hydrogenated at 1 atm of pressure in a wrist-action shaker. Three millimoles of hydrogen were absorbed within 5 hr. The catalyst was removed by filtration, and the filtrate was concentrated *in vacuo* to a crystalline residue: 859 mg; mp 107–117°; nmr, δ 0.68 (s), 0.93 (s); ratio 92:8 of **10b** and its 14 β epimer. Vpc of the trimethylsilyl ether (t, 210°; 5% F 60 silicone oil on Gas-Chrom P) confirmed the nmr result. Recrystallization from ether–petroleum ether gave 738.7 mg of **10b** in two crops, mp 116–119°. The analytical sample was recrystallized from ether–petroleum ether: mp 118–120°; $[\alpha]D$ −36° ($CHCl_3$); λ_{max}^{MeOH} 278 mμ (ε 14,000), 214 (16,400).

Anal. Calcd for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.20; H, 8.43.

(−)-3-Methoxy-1,3,5(10),8-estratetraene 17α-Acetate (10a).—(−)-3-Methoxy-1,3,5(10),8-estrapentaen-17α-ol (**10b**, 950 mg)

(29) In earlier runs in which esterification was effected at 100° for 18 hr, 80% yields of the hemisuccinate resulted, whereas, when the crude ketol **8** was employed under the same conditions, a yield of 65% was realized. Therefore, in the preparation of this hemisuccinate employing total reduction product, an over-all yield of 80% of 17α-succinate can be expected.

(30) Procedure of K. E. Pfitzner and J. G. Moffatt, *J. Amer. Chem. Soc.*, **87**, 5661, 5670 (1965).

was acetylated with acetic anhydride (1.5 ml) in dry pyridine (6 ml) at 25° for 16 hr. The reaction mixture was concentrated *in vacuo* to a crystalline residue. Recrystallization from ether–petroleum ether gave a first crop of 875 mg of 17α-acetate **10a**: mp 116–118°; $\lambda_{max}^{chloroform}$ 5.80, 6.20, 6.36, 6.68, 6.82, 7.00 μ.

(+)-17-Isoestradiol 3-Methyl Ether (12) and (−)-17-Iso-9β-estradiol 3-Methyl Ether (13). A.—To a stirred solution of 326.4 mg of 3-methoxy-1,3,5(10),8-estratetraene 17α-acetate (**10a**) in 23 ml of dry tetrahydrofuran and 40 ml of ammonia was added 91.5 mg of lithium ribbon at −50°. At the end of 2 hr, the deep blue color of the reaction mixture was discharged with solid ammonium chloride and the ammonia was evaporated yielding a solid residue. Water (~130 ml) was added and the organic mixture was extracted into ether. The latter extract was washed with water and saturated aqueous Na_2SO_4, dried over $MgSO_4$, and concentrated *in vacuo* to give a solid residue, mp 101–104°, which was separated by preparative tlc (silica gel, 5% ethyl acetate–chloroform) into two isomers, (+)-17-isoestradiol 3-methyl ether (**12**)[20] as needles {171.3 mg; mp 103–106°; [α]D +55° (MeOH); λ_{max} 288 mμ (ε 1770), 279 (1840), 218 (7730); $\lambda_{max}^{chloroform}$ 2.83, 2.98, 6.21, 6.35, 6.69 μ} and the corresponding 9β epimer **13** {52 mg; mp 84–95, 98–116°; [α]D −75.4 (MeOH); λ_{max} 288 μ (ε 1520), 279 (1675), 223 (6980); $\lambda_{max}^{chloroform}$ 2.82, 3.00, 6.2, 6.35, 6.69 μ}.

B.—A solution of (−)-3-methoxy-1,3,5(10),8-estratetraene 17α-ol (**10b**, 284.4 mg, 1 mmol) in 16 ml of tetrahydrofuran and 9 ml of ether was added at a temperature of −40 to −50° to ~18 ml of liquid ammonia which had been dried by passing through a soda lime tube. At −50 to −60°, 312 mg of potassium, in small pieces was added to the resulting solution and the mixture was allowed to stand for 1.5 hr at the same temperature. Solid ammonium chloride (882 mg) was carefully added. After evaporation of the ammonia, the residue was treated with water (at −5 to 0°) and was extracted with ether. The ethereal extract was neutralized with solid carbon dioxide, washed with water, and dried over sodium sulfate. After removal of the solvent, an oil was obtained which readily crystallized upon addition of ether to give 286.9 mg of product. Vpc of the trimethylsilyl derivative indicated two major peaks comprising about 90% of the total area with retention time 6.4 min (**12**) and 7.8 min (**13**) in the ratio of 4:1 (column temperature 222°; 6 ft × 0.25 in. glass column; packing, 3% F-60, 1.5% SE-30 on silonized Gas-Chrom P).

***d*-Estrone Methyl Ether (14).**—To a magnetically stirred solution of 17-isoestradiol 3-methyl ether (**12**, 60 mg) in 6 ml of acetone was added 0.16 ml of Jones' reagent[28] and the reaction mixture was stirred at 25° for 5 min. Excess chromic acid was destroyed with *ca.* 2 ml of methanol and 25 ml of water was added. The green chromate complex gradually dissolved followed by precipitation of colorless crystals which were filtered and washed with water to give 55 mg of *d*-estrone methyl ether (**14**), mp 158–162°. A sample crystallized from methanol had mp 164–166°; [α]D +156° (dioxane) {authentic sample had [α]D +159° (dioxane)}; nmr δ 0.97 (3 H) 3.78 (3 H). The infrared spectrum was identical with that of an authentic sample.

(+)-9β-Estrone Methyl Ether (13a).—A solution of 3-methoxy-9β-estradiol (**13**, 30 mg) in 3 ml of acetone was oxidized in the described manner with 0.08 ml of Jones' reagent for 5 min to give 31 mg of oil which was further purified by preparative tlc to afford 21 mg of a colorless oil: [α]D +43° (MeOH). The infrared spectrum of this material was identical with that of *dl*-9β-estrone 3-methyl ether prepared by W. S. Johnson, *et al.*,[21] with $\lambda_{max}^{chloroform}$ 2.9–3.0 (w), 3.39, 3.48, 5.76 (s), 6.20, 6.34, 6.68, 6.81, 6.88, 7.11, 7.29, 7.41, 7.60, 7.70, 7.75, 7.78, 8.02, 8.43, 8.59, 8.70, 8.85, 8.99, 9.19, 9.33, 9.45, 9.60, 9.80, 9.98, 10.18, 10.30, 10.47, 10.73, 11.0, 11.28, 11.47, 11.63, 12.1–12.3 μ; nmr δ 0.97, 3.78.

3-Methoxy-1,3,5(10),8-estratetraen-17-one (11). A.—3-Methoxy-1,3,5(10),8-estratetraen-17α-ol (**10b**, 286.4 mg, 1 mmol) was dissolved in anhydrous dimethyl sulfoxide (1.5 ml), benzene (1.5 ml) containing dry pyridine (0.08 ml), and trifluoroacetic acid (0.04 ml). After addition of dicyclohexylcarbodiimide (0.62 g, 3 mmol), the reaction mixture was stirred at 25° for 16 hr. Ether (25 ml) was then added, followed by a solution of oxalic acid (270 mg, 3 mmol) in methanol (2.5 ml). After gas evolution had ceased, 25 ml of water was added, solid dicyclohexylurea was filtered off, and the organic phase was washed with 5% $NaHCO_3$ and water, dried over anhydrous Na_2SO_4, and concentrated to give a crystalline residue (472.4 mg) which still contained a small amount of dicyclohexylurea. After filtration from a benzene–ether mixture (1:1) the crystalline product from the filtrate was recrystallized from ether–petroleum ether plus a few drops of methanol. The ketone **11** was obtained in two crops totaling 158 mg (56% of theory): mp 116–119° (needles); [α]D +30.4° ($CHCl_3$); λ_{max} 320 mμ (ε 700), 280 (16,420), 275 (15,750), 213 (18,050), 208 (18,630); $\lambda_{max}^{chloroform}$ 2.79, 2.8–3.0, 5.75, 6.20, 6.35, 6.68, 6.85, 7.0 μ.

Anal. Calcd for $C_{19}H_{22}O_2$: C, 80.81; H, 7.85. Found: C, 80.63; H, 7.72.

B.—To a boiling solution of aluminum isoproxide (408.5 mg, 2 mmol) in 11.7 ml of Na-dried toluene and 2.67 ml of freshly distilled cyclohexanone under nitrogen was added over a 10-min period 286.4 mg of the tetraene alcohol **10b** in 8 ml of dry toluene. The reaction mixture was stirred and refluxed for an additional 2 hr (reflux temperature 108°). Saturated aqueous Rochelle salt solution (2.0 ml) was added dropwise and the reaction mixture was mechanically pumped to near dryness. Cyclohexylidinecyclohexanone was removed by steam distillation for 4 hr. The aqueous solution was extracted with benzene–ether (2:1) and the organic extract was washed with saturated aqueous NaCl, dried over $MgSO_4$, and concentrated *in vacuo* to 301 mg of a reddish oil which crystallized from ether to afford a first crop of 86 mg of **11**, mp 116–119°. The filtrate was purified by tlc (silica gel, 2% methanol–chloroform) to provide an additional 86.6 mg, mp 116–119° (totaling 172.6 mg or 61%).

Registry No.—**1**, 16973-91-4; **3**, 4820-46-6; **4**, 5060-00-4; **4a**, 5541-17-3; **4b**, 16976-23-1; **4c**, 16976-24-2; **4d**, 16994-39-1; **7**, 1456-50-4; (±) **8**, 16976-26-4; (±) **8** semicarbazone, 16976-27-5; (−) **8**, 16976-39-9; (+) **8**, 6563-81-1; (±) **8a**, 16976-28-6; (−) **8a**, 16976-29-7; **8b**, 16976-30-0; **9**, 16976-31-1; **9a**, 10003-15-3; **9b**, 17004-84-1; **10a**, 10003-16-4; **10b**, 17021-76-0; **11**, 6885-44-5; **12**, 16994-40-4; **13**, 7021-78-2; **13a**, 1923-52-7; **14**, 1091-94-7; estrone, 53-16-7; 6-methoxytetralone-O[18], 16973-92-5.

Synthesis of Epimeric 15-Hydroxyestriols, New and Potential Metabolites of Estradiol[1]

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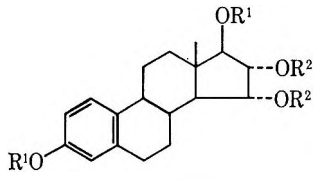
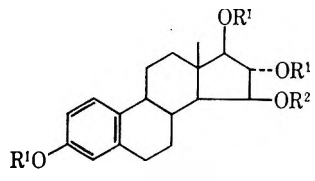
The synthesis of estra-1,3,5(10)-triene-3,15α,16α,17β-tetrol, a new metabolite of estradiol, and of estra-1,3,5(10)-triene-3,15β,16α,17β-tetrol, a potential metabolite, are described. The nuclear magnetic resonance spectra of the corresponding tetraacetates which were instrumental in assigning the correct structures are discussed.

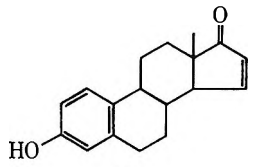
A new polar metabolite of estradiol was isolated from both pregnancy and neonatal urine.[2-4] It constitutes the main product of fetal metabolism and apparently is not produced at all by the adult.[3] Initial chemical characterization on the very small amounts available indicated the compound to be a tetrol, but the location of the hydroxyl groups was undetermined. It was apparent that a definite structure assignment for this novel and interesting metabolite required the synthesis of possible estrogen tetrols for comparison purposes. A most likely candidate was estra-1,3,5,(10)-triene-3,15α,16α,17β-tetrol (Ia) and the synthesis of this compound was undertaken. The epimeric 15β-hydroxytetrol represents another potential natural substance and the preparation of estra-1,3,5(10)-triene-3,15β,-16α,17β-tetrol (IIa) was also initiated. The successful synthesis of 15α-hydroxyestriol Ia described below permitted its comparison[5] with the unknown metabolite and thus their complete identity was established. The structure of the major fetal metabolite of estradiol could therefore be described as the tetrol Ia.



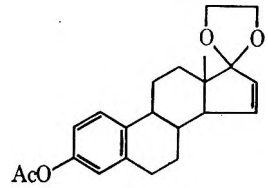
Ia, $R^1 = R^2 = H$
b, R^1 = Ac; $R^2 = H$
c, $R^1 = R^2$ = Ac



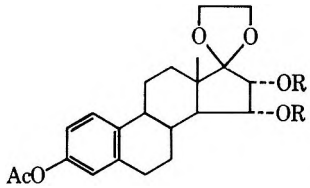
IIa, $R^1 = R^2 = H$
b, R^1 = Ac; $R^2 = H$
c, $R^1 = R^2$ = Ac



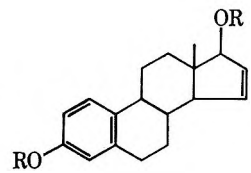
III



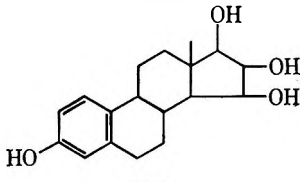
IV



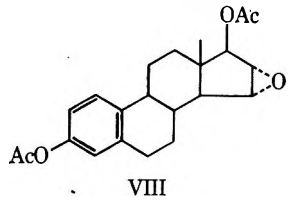
Va, R = H
b, R = Ac



VIa, R = H
b, R = Ac



VII



VIII

The initial route to estra-1,3,5(10)-triene-3,15α,-16α,17β-tetrol (Ia) involved *cis* hydroxylation of the double bond in the known α,β-unsaturated ketone III.[6] The advantage of this particular starting material resided in the possibility of preparing the two C-17 epimeric tetrols upon reduction of the 17-ketone intermediate. Because of the instability of the highly strained cyclopentenone structure[7] with the attendant possibilities of double-bond migration prior to hydroxylation the dioxolane derivative IV was chosen as the substrate for the OsO_4 oxidation. Oxidation of IV gave the 17,17-ethylenedioxyestra-1,3,5(10)-triene-3,15α,16α-triol 3-acetate (Va) as the major product, isolated as the triacetate Vb. The orientation of the D-ring hydroxyl groups was confirmed as α on the basis of nmr evidence presented later. Attempts to remove the dioxolane group of Vb with toluenesulfonic acid in acetone at room temperature failed completely. When aqueous sulfuric acid in warm dioxane was used, hydrolysis of the acetate groups took place and the resultant rearrangements gave a mixture containing a multitude of products. The stability of Vb is in contrast to the dioxolane derivatives of both the α,β-unsaturated and saturated 17 ketones which react readily under mild conditions. The apparent cause is the presence of substituent at C-16 since the 16α-bromo-17-diethylene ketal derivative[6] is similarly inert to mild deketalizing conditions. Whether this effect[8] is limited to 16α substituents only or is also produced by 16β substitution requires further study.

Oxidation of the Δ^{15} double bond by OsO_4 in the presence of a preformed 17β-hydroxy group was the next method of choice. Reaction of the 3-hydroxyestra-1,3,5(10),15-tetraen-17-one (III) with $NaBH_4$ even under the mildest conditions resulted in reduction of the double bond to give estradiol-17β as the sole product. $LiAlH_4$ at 0° in ether, however, gave the desired allylic alcohol, estra-1,3,5(10),15-tetraene-3,-17β-diol (VIa), isolated as the diacetate VIb, in sat-

(1) Part of this work has been reported in a preliminary form: J. Fishman and H. Guzik, *Tetrahedron Lett.*, 2929 (1967).

(2) A. A. Hagen, M. Barr, and E. Diczfalusy, *Acta Endocrinol.* (Copenhagen), **49**, 207 (1965).

(3) E. Gurpide, J. Schwers, M. T. Welch, and S. Lieberman, *J. Clin. Endocrinol. Metab.*, **26**, 1355 (1966).

(4) J. Schwers, E. Gurpide, R. L. Vande Wiele, and S. Lieberman, *ibid.*, **27**, 1403 (1967).

(5) G. Zucconi, B. P. Lisboa, E. Simonitsch, L. Roth, A. A. Hagen, and E. Diczfalusy, *Acta Endocrinol.*, **56**, 413 (1967).

(6) E. W. Cantrall, R. Littell, and S. Bernstein, *J. Org. Chem.*, **29**, 214 (1964).

(7) W. S. Johnson and W. F. Johns, *J. Amer. Chem. Soc.*, **79**, 2005 (1955).

(8) This effect is not likely to be due to steric hindrance but may involve a greater preference for a tetrahedral C-17 in the presence of a C-16 substituent: M. M. Kreevoy, C. R. Morgan, and R. W. Taft, Jr., *ibid.*, **82**, 3064 (1960).

isfactory yield.[9] Reduction of the 17 ketone in III led stereoselectively to the β alcohol at C-17 since catalytic hydrogenation of VIb gave only estradiol 17β-diacetate with no evidence for the presence of estradiol 17α-diacetate.

Oxidation of the allylic diacetate VIb with OsO_4 produced as the major product estra-1,3,5(10)-triene-3,15α,16α,17β-tetrol 3,17-diacetate (Ib). A small amount of another product tentatively assigned the isomeric 15β,16β-diol structure VII, was isolated by preparative thin layer chromatography; the amount of material obtained prevented further characterization. The desired estrogen tetrol Ia was obtained from either the diacetate Ib or the tetraacetate Ic by heating with K_2CO_3 in methanol; more drastic alkaline or acid conditions or reductive cleavage with $LiAlH_4$ resulted in poorer yields of the free tetrol.

Estra-1,3,5(10),15-tetraene-3,17β-diol diacetate (VIb) also served as the starting material for the preparation of the isomeric tetrol IIa. Reaction of VIb with per acid gave 15α,16α-epoxyestra-1,3,5(10)-triene-3,17β-diol diacetate (VIII) as the main product. The location and orientation of the epoxide oxygen in VIII was confirmed by $LiAlH_4$ cleavage which gave estra-1,3,5(10)-triene-3,16α,17β-triol as the only product. The opening of the 15α,16α-epoxide with $LiAlH_4$ adheres to the established preference for axial hydroxyl generation[10] in that the bisectional 16α-hydroxyl rather than the pseudo-equatorial 15α-hydroxyl is produced.

In view of the direction of reductive opening of the epoxide in VIII it was expected that acetic acid would also yield the axial product. In fact the only identified product of the reaction of VIII with glacial acetic acid was estra-1,3,5(10)-triene-3,15β,16α,17β-tetrol 3,15,17-triacetate (IIb), isolated as the tetraacetate IIc. Hydrolysis of IIc with K_2CO_3 in aqueous methanol at room temperature gave the tetrol IIa. The milder hydrolytic conditions were required in view of the demonstrably lesser stability of the 15β-tetrol IIa compared with that of the 15α-tetrol Ia.

Nmr spectroscopy was instrumental in assigning the orientation of the newly introduced hydroxyl groups. *A priori* one may expect that the 15β substituent would produce a much larger effect on the chemical shift of the C-18-methyl group than a corresponding 15α substituent.[11,12] This follows not only from the β orientation but also from 1,3 diaxial relationship of the C-18 methyl with the 15β substituent. The C-18-methyl shifts of the various compounds of interest are listed in Table I. It is apparent from these data that the chemical shifts are fully consistent with the assigned orientations. It has been emphasized[13] that the assignment of ring-D substituent orientations on the basis of C-18-methyl shifts is hazardous. This is true with respect to the bisectional C-16 substituents, but C-15 substituents which have pseudo- axial and -equatorial conformations can be firmly assigned on this basis.

The nmr of the C-15, -16, and -17 protons in the isomeric tetrol acetates Ic and IIc further confirms their structures. The first-order analysis of the spectrum of the 15α-acetoxy compound Ic permits assignment of a doublet at 303 cps ($J \sim 6$ cps) to the 17α-H. A pair of doublets ($J \sim 6$, 8 cps) centered at 325 cps represents the 16β-H, while a multiplet at 310 cps is assigned to the pseudo-axial 15β-H, and reflects its coupling with both the 16β and 14α protons. The spectrum of the 15β-acetoxy compound IIc presents a substantially different picture. The 17α-H resonance appears as a doublet at 292 cps owing to coupling with the 16β-H with an apparent coupling constant of 6 cps. The 16β proton now appears as a doublet ($J = 6$ cps at 312 cps) on which is superimposed a broad singlet at 310 cps representing the 15α proton. The assignments in both spectra were confirmed wherever possible by double resonance studies. The significant feature of these spectra is the identical coupling of the 17α-H in both indicating the same orientation of the 16α-acetoxy substituent in both compounds. Also significant is the greatly decreased coupling of the 15 proton in IIc in accord with its equatorial α orientation. These findings are pertinent since on the basis of the C-18-methyl chemical shifts alone (64 cps observed *vs.* 59 cps calculated) the possibility of opening the epoxide in VIII to give a 15α,16β,17β product would have to be considered.

The demonstrated dextorotatory effect of 15α substituents and the levorotatory shift of 15β substituents[14] permitted a further confirmation of the orientation of the C-15 substituents in the new tetrols. The molecular rotation differences calculated for compounds Ia and IIa show ΔM_D +226 for Ia and ΔM_D −61 for IIa and are in accord with the assigned structures.

TABLE I

CHEMICAL SHIFTS OF C-18-METHYLS

Compound	C-18 methyl[a] Obsd	Calcd
Estra-1,3,5(10)-triene-3,16α,17β-triol triacetate	51	...
Estra-1,3,5(10)-triene-3,15α,16α,17β-tetrol tetraacetate (Ic)	56	55
Estra-1,3,5(10)-triene-3,15β,16α,17β-tetrol tetraacetate (IIc)	64	64
Estra-1,3,5(10)-triene-3,16β,17β-triol triacetate	55	...
Estra-1,3,5(10)-triene-3,15α,16β,17β-tetrol tetraacetate	...	59
17,17-Ethylenedioxyestra-1,3,5(10)-trien-3 ol	54	...
17,17-Ethylenedioxyestra-1,3,5(10)-triene-3,15α,16α-triol triacetate (Vb)	63	61

[a] The chemical shift values are in cycles per second downfield from tetramethylsilane.

Experimental Section[15]

17,17-Ethylenedioxyestra-1,3,5(10)-triene-3,15α,16α-triol Triacetate (Vb).—A 0.5-g sample of 17,17-ethylenedioxyestra-1,3,5(10),15-tetraen-3-ol acetate (IV) dissolved in 12 ml of benzene and 1 ml of pyridine was treated with 0.5 g of osmium-tetroxide for 45 hr at room temperature. The solvents were removed *in vacuo* and the residue was stirred at room temperature for 4 hr in 34 ml of water, 12 ml of benzene, and 23 ml of methanol containing 3 g of sodium sulfite and 3 g of potassium bicarbonate. Chlorofom was then added, the mixture was filtered,

(9) The use of hydrocarbon solvents to prevent coreduction of the double bond in α,β-unsaturated ketones has been reported recently: E. I. Snyder, *J. Org. Chem.*, **32**, 3531 (1967).

(10) A. Furst and A. Plattner, *Helv. Chim. Acta*, **32**, 275 (1949); A. Furst, and R. Scotoni, *ibid.*, **36**, 1332 (1953).

(11) R. F. Zurcher, *Helv. Chim. Acta*, **46**, 2054 (1963).

(12) L. L. Smith, *Steroids*, **4**, 395 (1964).

(13) A. D. Cross and C. Beard, *J. Amer. Chem. Soc.*, **86**, 5317 (1964).

(14) E. W. Cantrall, R. Littell, and S. Bernstein, *J. Org. Chem.*, **29**, 64 (1964).

(15) Melting points were determined on a hot-stage apparatus and are corrected. Nmr spectra were obtained on a Varian A-60 instrument in deuteriochloroform with tetramethylsilane as an internal standard. Analyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich.

and the precipitate was washed with hot chloroform. The combined filtrates were washed with saturated sodium chloride solution to neutrality, dried, and evaporated. The oily residue was acetylated with acetic anhydride in pyridine and after work-up was chromatographed on 40 g of acid-washed alumina. Elution with ether–chloroform 1:1 gave 186 mg of material which was crystallized from ether–petroleum ether (bp 40–60°) and melted at 145–147°. The nmr spectrum in deuteriochloroform showed C-18 absorption at 63 cps. The acetate bands appeared at 122 (6 H) and 136 cps (3 H). The analytical sample melted at 146–148°.

Anal. Calcd for $C_{26}H_{32}O_8$: C, 66.08; H, 6.83. Found: C, 66.12; H, 6.97.

Attempted Deketalization of Vb.—A 10-mg sample of Vb was stirred at room temperature overnight in 1 ml of acetone containing 2 mg of *p*-toluenesulfonic acid. Thin layer chromatography of the reaction mixture in ethyl acetate–cyclohexane 1:1 showed the presence of only starting material. Similar results were obtained using either glacial acetic acid or *p*-toluenesulfonic acid in dioxane at room temperature. When the reaction was attempted with 10% sulfuric acid in dioxane–water 1:1 at 50° for 4 hr, a mixture of at least six compounds was obtained, none of which provided sufficient material for further work.

Estra-1,3,5(10),15-tetraene-3,17β-diol Diacetate (VIb).—A solution of 387 mg of 3-hydroxyestra-1,3,5(10),15-tetraen-17-one (III) in 400 ml of ether was stirred at 0° with 100 mg of $LiAlH_4$ for 1 hr. The excess reagent was decomposed by the addition of water and the mixture was acidified with ice-cold 5% sulfuric acid. The ether layer was washed with water, dried, and evaporated. The residue was acetylated with acetic anhydride in pyridine to give after the usual work-up 340 mg of oil. Chromatography on 20 g of alumina and elution with petroleum ether–benzene 8:2 gave 285 mg of VIb which crystallized from petroleum ether and melted at 90–92°. The nmr spectrum revealed C-18-methyl absorption at 54 cps and acetate methyls at 128 and 138 cps, $[\alpha]^{26}D$ −19° ($CHCl_3$).

Anal. Calcd for $C_{22}H_{26}O_4$; C, 74.55; H, 7.39. Found: C, 74.86; H, 7.26.

Hydrogenation of VIb.—A 10-mg sample of VIb was dissolved in 5 ml of ethanol and an equal weight of 10% Pd on charcoal was added. After hydrogenation had proceeded for 30 min, filtration and evaporation of solvent gave 10 mg of crystals, mp 120–124. The infrared spectrum was identical with that of estradiol 17β-diacetate.

Estra-1,3,5(10)-triene-3,15α,16α,17β-tetrol 3,17-Diacetate (Ib).—A 260-mg sample of the allylic diacetate VIb was oxidized with 250 g of OsO_4. The reaction and work-up conditions were as described above for the oxidation of IV. The product, an oil weighing 245 mg, was chromatographed on 15 g of alumina. Elution with benzene afforded 123 mg of Ib which crystallized from acetone–hexane and melted at 186–190°. The analytical sample obtained by further crystallization had a melting point of 189–192°. The nmr spectrum showed the C-18-methyl resonance at 51 cps and acetate methyls at 130 and 138 cps.

Anal. Calcd for $C_{22}H_{28}O_6$: C, 68.02; H, 7.27. Found: C, 67.82; H, 7.06.

The tetraacetate Ic was obtained from Ib with acetic anhydride and pyridine. Crystallization from methanol gave material melting at 174–178°, $[\alpha]^{23}D$ +92° ($CHCl_3$).

The nmr spectrum of the tetraacetate Ic exhibited C-18-methyl resonance at 58 and acetate methyl absorptions at 122 (3 H), 125 (6H), and 138 cps (3 H). The 17α hydrogen appeared as a doublet ($J \sim 6$ cps) at 303 cps. A pair of doublets at 325 cps was assigned to the 16β-H, while a multiplet at 310 cps was assigned to the 15β-H. Irradiation at 325 cps caused collapse of the 303-cps doublet to a singlet.

Anal. Calcd for $C_{26}H_{32}O_8$: C, 66.08; H, 6.83. Found: C, 66.28; H, 6.23.

Estra-1,3,5(10)-triene-3,15α,16α,17β-tetrol (Ia).—A 100-mg sample of tetrol diacetate Ib obtained directly from the alumina column was dissolved in 20 cc of methanol containing 20 mg of anhydrous potassium carbonate. The mixture was refluxed under N_2 for 2 hr, cooled, filtered, and taken down to dryness. The residue was separated by preparative thin layer chromatography on silica gel in the system 10% CH_3OH–90% ethyl acetate into two crystalline products. The less polar one (2 mg, mp 240–242°) was tentatively assigned the structure of the 3,15β,-16β,17β-tetrol (VII). The more polar material (22 mg) was crystallized from ethyl acetate (mp 230–235°) and represented the desired α-tetrol Ia, $[\alpha]^{25}D$ +135° (EtOH). The analytical sample melted at 234–236°.

Anal. Calcd for $C_{18}H_{24}O_4$; C, 71.02; H, 7.05. Found: C, 69.54; H, 7.86.

15α,16α-Epoxyestra-1,3,5(10)-triene-3,17β-diol Diacetate (VIII).—A solution of 400 mg of the allylic diacetate VIb in 6 ml of $CHCl_2$ was mixed with 300 mg of *m*-chloroperbenzoic acid in 8 ml of $CHCl_3$ and allowed to stand at 5° for 40 hr. After dilution with 100 ml of $CHCl_3$ the solution was washed with 5% sodium bicarbonate and then water, dried, and evaporated. The residue was chromatographed on 40 g of alumina. Elution with benzene–petroleum ether 1:1 yielded 215 mg of crystalline material, mp 165–171°. Recrystallization from acetone–petroleum ether gave the analytical sample of VIII which melted at 168–172°. The nmr spectrum showed the C-18-methyl resonance at 62 and two acetate methyl bands at 128 and 136 cps.

Anal. Calcd for $C_{22}H_{26}O_5$: C, 71.33; H, 7.08. Found: C, 70.67; H, 6.87.

$LiAlH_4$ Reduction of VIII—Reduction of 20 mg of VIII with excess $LiAlH_4$ in refluxing ether gave, after the usual work-up, 7 mg of estra-1,3,5(10)-triene-3,16α,17β-triol, mp 248°. The material, which was isolated by preparative thin layer chromatography on silica gel in ethyl acetate, was identical by mixture melting point and infrared spectral comparison with authentic estriol.

Acetolysis of VIII.—A solution of 165 mg of the epoxide VIII in 10 ml of glacial acetic acid was refluxed for 18 hr. The acetic acid was removed *in vacuo* and the residue, by thin layer chromatography, consisted of a mixture of tri- and tetraacetates IIb and IIc, respectively. The material was therefore acetylated with acetic anhydride in pyridine. After work-up and preparative thin layer chromatography in the system 1:1 cyclohexane–ethyl acetate a homogenous tetraacetate IIa was obtained, which, however, resisted crystallization. The nmr spectrum of IIc showed the C-18-methyl singlet at 64 and the acetate methyls appeared at 122 (6 H), 133 (3 H), and 138 cps (3 H). The methine hydrogens were assigned as follows: 17α-H at 292 (doublet, $J \sim 6$ cps), 16β-H at 312 (doublet, $J \sim 6$ cps), and 15α-H at 310 cps (singlet). Irradiation at 312 cps collapsed the 17α-H doublet to a singlet.

Estra-1,3,5(10)-triene-3,15β,16α,17β-tetrol (IIa).—A solution of 23 mg of the oily tetraacetate IIc in 5 ml of methanol containing 5 mg of potassium carbonate was stirred overnight at room temperature under N_2. The solution was neutralized with dilute acetic acid, and the solvents were removed *in vacuo*. The residue was taken up in chloroform–ethanol 4:1, washed with water, dried, and evaporated. The solid residue was purified by preparative thin layer chromatography in the system 10% methanol–90% ethyl acetate. The material obtained weighed 6 mg and melted at 250–257°. Recrystallization from acetone–petroleum ether gave the analytical sample of IIa: mp 257–262°; $[\alpha]^{24}D$ +40° (EtOH).

Anal. Calcd for $C_{18}H_{24}O_4 \cdot H_2O$: C, 67.06; H, 8.13. Found: C, 67.47; H, 8.03.

Registry No.—Ia, 15183-37-6; Ib, 16127-99-4; Ic, 16934-35-3; IIa, 16934-36-4; IIc, 16960-04-6; Vb, 16127-97-2; VIb, 16127-98-3; VIII, 16934-39-7.

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The Structure of *Leuconostoc mesenteroides* Strain C Dextran. I. Methylation Analysis[1a]

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The extracellular dextran elaborated by *Leuconostoc mesenteroides* strain C (NRRL B-1298), which gives a strong precipitin reaction with type-12 pneumococcus antiserum and with concanavalin A, has been shown by methylation analysis to be composed of D-glucopyranose units linked by 1 → 6 glycosidic bonds with branches at C-2 and at C-3. Methylation and subsequent hydrolysis of the dextran afforded 2,3,4,6-tetra- (20.2 mol %), 2,3,4-tri- (53.3 mol %), 2,4,6-tri- (1.0 mol %), 3,4-di- (12.0 mol %), 2,4-di- (7,7 mol %), and 4-*O*-methyl-D-glucose (5.7 mol %); the molar proportions of the methylated sugars correspond to $\overline{CL}$ 4–5.

The dextrans constitute a heterogeneous class of extracellular D-glucans elaborated by bacteria primarily of the genus *Leuconostoc*.[2,3] These polymers apparently possess a common structural feature of chains of α-D-glucopyranose residues consecutively linked by 1 → 6 glycosidic bonds.[2] Most dextrans are somewhat branched at C-2, C-3, or C-4. They vary in the degree of branching from the *L. mesenteroides* NRRL B-512 dextran with 4% branch points at C-3[4] to the highly branched dextrans from *L. mesenteroides*, Birmingham strain, which has 15% branch points at C-3,[5] and B-1416 strain with 17% branch points at C-3 and C-4.[6] Preliminary studies have indicated that certain dextrans are still more highly branched with as many as 30 and 40% branched units.[7]

Substitution at C-3 now appears to be common in dextrans and indeed may be a structural feature typical of all dextrans.[8] Evidence has been presented that in one dextran the 1 → 3 linkages occur in the main chain as well as at branch points.[7] The occurrence of 1 → 2 linkages in certain dextrans was suggested first by the optical rotational shifts associated with cuprammonium dextran complex formation[9] and was confirmed later by the isolation of kojibiose from acetolysates of several dextrans.[8,10-12] Serological data[13] provided additional evidence for the presence of 1 → 2 linkages when kojibiose was found to be an inhibitor of the precipitin reaction of certain dextrans with antisera.

There is a marked similarity[8,14] in the capacity of the dextrans to precipitate concanavalin A,[15,16] a globulin in Jack bean meal, and their activity toward type-12 pneumococcus antiserum;[14] both of these precipitin reactions correlate with the content of 1 → 2 linkages (as revealed by the amount of kojibiose liberated during acetolysis).[8]

Relatively few dextrans have been submitted to a detailed structural examination and those dextrans containing 1 → 2 linkages have been examined by acetolysis fragmentation or by cuprammonium complex formation only.[17] Neither technique provides quantitative data for the proportion of the individual linkages and the degree of branching in the polymers. This paper is concerned with the constitution of the dextran elaborated by *Leuconostoc mesenteroides* strain C[18,19] which reacts strongly with concanavalin A and type-12 pneumococcus antiserum and has been shown[8] to contain the relatively rare 1 → 2 linkage.

L. mesenteroides strain C when grown on a medium containing sucrose as a carbon source produces two extracellular polysaccharides: the dextran, described herein, and a fructan.[20] The two polymers were separated readily by fractional precipitation with ethanol since the dextran was insoluble in 45% aqueous ethanol while the fructan ($[\alpha]^{25}D$ −40° in water) remained in solution. The crude dextran ($[\alpha]D$ +175° in water), representing 68% of the polysaccharide mixture, was purified further by fractional precipitation of the dextran acetate. The major fraction of the dextran acetate ($[\alpha]^{27}D$ +187° in chloroform) was recovered in 61% yield while a minor fraction ($[\alpha]^{27}D$ +190° in chloroform) was isolated in 11% yield. All structural studies were conducted on the major acetate fraction which on deacetylation gave the purified dextran having $[\alpha]^{27}D$ +182° in water.

Complete hydrolysis of the dextran in refluxing 1 *N* sulfuric acid liberated D-glucose as the only sugar detectable by paper chromatographic analysis. Since these conditions promote extensive degradation of fructose, the dextran was also subjected to hydrolytic conditions designed to cleave fructosyl bonds with minimum degradation of fructose. This demonstrated the efficiency of the fractionation procedures for removing

(1) (a) This paper, No. 6261 Scientific Journal Series, Minnesota Agricultural Experiment Station, was presented at the National Meeting of the American Chemical Society, Phoenix, Ariz., 1966, and forms part of the thesis submitted by M. J. S. to the Graduate faculty of the University of Minnesota in partial fulfillment of the requirements for the degree of Ph.D., July 1966. (b) Deceased.

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the fructan since even these mild conditions failed to reveal fructose.

The dextran was methylated by the Haworth and Purdie procedures giving the methylated product in 62% yield (OCH_3 44.93%). Fractional precipitation of the methylated dextran gave a major fraction ($[\alpha]^{25}D$ +222° in chloroform) in 90% yield. A minor fraction, which was recovered from the mother liquor, appeared to be structurally different as revealed by the lower rotation ($[\alpha]^{25}D$ +101° in chloroform) and was not examined further. With the exception of this minor fraction, the dextran was predominantly homogeneous by these fractionation procedures.

Cleavage of the methylated dextran into the component methylated glucosides by methanolysis was only partially successful. Refluxing with 1% hydrogen chloride in methanol for 33 hr did not effect complete solution of the methylated dextran. The soluble portion of the methanolysate (fraction i) was separated from the insoluble portion (fraction ii) by centrifugation and hydrolyzed in refluxing 1 *N* sulfuric acid. The methylated sugars from fraction i (see Table I) were separated by hydrocellulose column chromatography and identified by paper chromatography, by paper electrophoresis, and by comparison of physical constants of the crystalline compounds or their derivatives.

TABLE I

CLEAVAGE FRAGMENTS OF THE METHYLATED DEXTRAN

O-Methyl-D-glucose	Fraction i, mol %[a]	Fraction ii, mol %[a]
2,3,4,6-Tetra-	25.5	5.1
2,3,4-Tri-	48.2	69.5
2,4,6-Tri-	1.2	...
2,4-Di-	6.1	12.6
3,4-Di-	13.1	7.6
4-	6.1	5.2

[a] Fractions i and ii refer to the methanol-soluble and -insoluble fractions, respectively, formed during methanolysis of the methylated dextran. Fraction ii represents 21% by weight of the original methylated dextran.

Fraction ii, which represented 21% of the methylated dextran, was resistant to both methanolysis and dilute acid hydrolysis and was therefore treated successively with cold 72% sulfuric acid and refluxing 1 *N* sulfuric acid. The methylated sugars obtained thus were separated by paper chromatography and shown to be identical with those obtained from fraction i although they were obtained in different proportions from the two fractions (see Table I).

In view of the fact that an unusually low proportion of tetra-*O*-methyl-D-glucose was obtained from fraction ii as shown in Table I, it is reasonable to assume that this insoluble fraction had arisen by fragmentation of the original methylated polymer through the loss of side chains (and hence tetra-*O*-methyl-D-glucosyl residues). The possibility that the low proportion of tetra-*O*-methyl-D-glucose resulted from partial demethylation during treatment of fraction ii with cold 72% sulfuric acid is unlikely since it was demonstrated in a control experiment that more 2,3,4,6-tetra-*O*-methyl-D-glucose is degraded during the methanolysis and subsequent hydrolysis with 1 *N* sulfuric acid (10% degradation) than with the 72% sulfuric acid–1 *N* sulfuric acid treatment (7% degradation). In both cases the predominant methylated sugar formed was tri-*O*-methyl-D-glucose. Similar observations have been reported by Croon and coworkers.[21]

Since there is no evidence to indicate that fractions i and ii reflect a heterogeneity in the original dextran, the proportions of the different linkages in the dextran are based on the combined yields of the methylated sugars from fractions i and ii. Cleavage of the methylated dextran therefore afforded the methylated sugars in the following mole proportions: 2,3,4,6-tetra- (20.2 mol %), 2,3,4-tri- (53.3), 2,4,6-tri- (1.0), 3,4-di- (12.0), 2,4-di- (7.7), and 4-*O*-methyl-D-glucose (5.7).

The methylation data show that the dextran has a framework of (1 → 6)-linked D-glucopyranose residues with branches joined to some of these residues through C-2 and to a lesser extent through C-3. The ratio of 3,4-di- to 2,4-di-*O*-methyl-D-glucose indicates 50% more branches at C-2. A few of these residues may be branched at both C-2 and C-3 since the proportion of 4-*O*-methyl-D-glucose obtained from the methylated dextran is greater than can be attributed to incomplete methylation of the dextran considering the methoxyl content. The proportion of 2,3,4,6-tetra-*O*-methyl-D-glucose is somewhat lower than that required by the di-*O*-methyl and mono-*O*-methyl sugars present and corresponds to an average chain length ($\overline{CL}$) of 5, whereas the $\overline{CL}$ calculated from the proportion of branch points is about 4. This is apparently one of the most highly branched dextrans that have been characterized although preliminary studies[7] indicate that a dextran with $\overline{CL}$ 2.5 occurs.

The identification of 3,4-di-*O*-methyl-D-glucose establishes that the 1 → 2 linkages previously demonstrated by acetolysis[8] represent branch points rather than linear residues. The structural significance of the 2,4,6-tri-*O*-methyl-D-glucose is questionable; this small amount could have arisen by demethylation of the tetra-*O*-methyl-D-glucose or by incomplete methylation of the dextran since C-3 is the most difficult to alkylate.

Experimental Section

All concentrations were effected *in vacuo* at 35–45° (bath temperature). Paper chromatography was performed on Whatman No. 1 paper, unless stated otherwise, by the descending method using the following solvent systems: (A) pyridine–ethyl acetate–water (2:5:7, upper phase), (B) 1-butanol–ethanol–water (3:2:1), (C) 2-butanone–water azeotrope, and (D) benzene–ethanol–water–ammonium hydroxide (200:47:15:1, upper phase). Paper electrophoresis was carried out on Whatman No. 1 paper using 0.1 *M* sodium tetraborate at 600 V for 1–2 hr.[22]

Chromatograms were sprayed with ammoniacal silver nitrate (for detection of sugars and polyols),[23] *p*-anisidine hydrochloride (reducing sugars),[24] or *p*-anisidine trichloroacetate (reducing sugars). Components were detected on electropherograms by spraying with *p*-anisidine trichloroacetate containing 2% phosphoric acid or by the Trevelyan method[25] after removal of borates with 10% hydrogen fluoride in acetone.[26]

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Thin layer chromatography (tlc) was performed on layers of silica gel G by the ascending method. Glass plates (20 × 20 cm) were coated mechanically and activated for 1 hr at 100°. Microscope slides (5 × 7.5 cm) were coated manually with a slurry of silica gel G in chloroform–methanol (1:1) and air dried for 30–60 min. Compounds were detected on air-dried plates with iodine vapor or with sulfuric acid and subsequent charring.

Optical rotations were obtained with a Rudolph Model 80 or a Bendix ETL-NPL automatic polarimeter, type 143A. Melting points were determined on a Fisher-Johns apparatus and are uncorrected.

The precipitin reaction with concanavalin A was performed as described previously[27] and the reactivity of the polysaccharide is expressed as the glycogen value (GV) with calf liver glycogen assigned a GV of 1.00.

Fractionation of the Extracellular Polysaccharides. Isolation of the Dextran.—The extracellular polysaccharides elaborated by *Leuconostoc mesenteroides* strain C (NRRL B-1298)[28] when grown on a medium containing sucrose were fractionated by alcohol precipitation. The crude polysaccharide mixture (25 g) was dissolved in water (1 l.), and the dextran was precipitated as a gel with ethanol (825 ml). The gel was collected by centrifugation, dissolved in water (180 ml), and poured into ethanol (2 l.). The fibrous dextran was washed with ethanol and petroleum ether (bp 30–60°) and dried *in vacuo:* yield 16.5 g (66% of the crude mixture); $[\alpha]^{25}D$ +171° (*c* 0.1 in water); GV 7.3. In two additional experiments the fractionation performed in the same manner afforded the dextran in yields of 68% with $[\alpha]^{21}D$ +175 and +181°.

Acetylation of the Dextran.—Dextran (10 g) was dissolved in formamide (200 ml) and treated with pyridine (110 ml) and acetic anhydride (74 ml) at room temperature for 24 hr.[29] The acetate, which precipitated as the reaction mixture was poured into water, was collected (centrifuge), washed with water, ethanol, and petroleum ether, and air dried. The product was reacetylated in the same manner except that the reaction mixture was held at 50–55° for the first 2 hr. The acetylated dextran was isolated as before and dried *in vacuo*. Fractional precipitation of the dextran acetate from chloroform (800 ml) with petroleum ether (550 ml) gave fraction A which was collected (centrifuge), washed with petroleum ether, and dried *in vacuo:* yield 11 g (61%); $[\alpha]^{27}D$ +187° (*c* 0.8 in chloroform). Addition of petroleum ether (550 ml) to the supernatant solution from the precipitation of fraction A afforded fraction B: yield 2 g (11%); $[\alpha]^{27}D$ +190° (*c* 0.5 in chloroform). Fraction B was not investigated further.

Dextran acetate A (12.5 g) was deacetylated in chloroform (600 ml) with 1 *N* methanolic potassium hydroxide (220 ml). The precipitate which separated after 10 min was washed with ethanol and dissolved in 0.3 *N* sodium hydroxide to ensure saponification of all acetyl groups. After 45 min the solution was neutralized with acetic acid and poured into ethanol (2 l.). The precipitate was removed, dissolved in water (150 ml), and again precipitated in ethanol (2 l.). The white fibrous dextran was washed with ethanol and petroleum ether and dried *in vacuo:* yield 7.8 g; $[\alpha]^{27}D$ +182° (*c* 0.7 in water); GV 8.2.

The dextran was treated with 0.1 *N* sulfuric acid at 55° for 6 hr, and the solution was deionized. No monosaccharides or oligosaccharides which moved from the origin were detected by paper chromatographic examination (solvent A). Hydrolysis of the dextran with refluxing 1 *N* sulfuric acid for 7 hr afforded glucose only which was characterized by conversion into *N*-*p*-nitrophenyl-D-glucopyranosylamine: mp 180–182° and $[\alpha]^{29}D$ −194° (*c* 0.7 in pyridine) (lit.[30] mp 180–182° and $[\alpha]D$ −191°).

Methylation.—Dextran acetate A (4.35 g) was dissolved in acetone (200 ml) and methylated with 30% sodium hydroxide (360 ml) and dimethyl sulfate (110 ml) over a period of 3 hr. The bath temperature was kept at 25° for the first 2 hr and at 55° for 1 hr; it was then raised to 100° for 0.5 hr. The excess alkali was neutralized and the reaction mixture was dialyzed. The dialyzed material was concentrated to a small volume and the methylation was repeated four times in the same way with the bath temperature maintained at 55°; acetone was added into keep the product in solution.

After the fifth methylation the product was extracted with chloroform, and the extract was washed with dilute acetic acid and water and concentrated to a syrup (3.37 g). The syrupy product was methylated with methyl iodide (50 ml) and silver oxide (6 g, added in 12 portions) with continual stirring and refluxing for 22 hr. The product was extracted with chloroform and after removal of solvent it was remethylated four times in the same manner (yield 1.96 g; OCH_3, 44.93%). On fractionation of the methylated dextran from chloroform with petroleum ether, 90% of the product precipitated at 90–92% petroleum ether: $[\alpha]^{25}D$ +222° (*c* 0.7 in chloroform). A second fraction ($[\alpha]^{25}D$ +101 in chloroform) recovered by concentration of the mother liquor was not investigated further.

Identification of the Hydrolysis Products of the Methylated Dextran.—The methylated dextran (1.28 g) was heated in refluxing 1% methanolic hydrogen chloride (100 ml) for 33 hr. A small amount of insoluble methylated dextran (fraction ii, 0.27 g) was removed by centrifugation and the supernatant solution (fraction i) was neutralized with lead carbonate, filtered, and concentrated. The methyl glycosides (fraction i) were hydrolyzed in refluxing 1 *N* sulfuric acid (100 ml) for 20 hr. The hydrolysate was neutralized with barium carbonate, filtered, and concentrated, and the mixture (1.04 g) was separated on a hydrocellulose column[31] with solvent C.

The components were identified by direct comparison with authentic compounds by paper electrophoresis and paper chromatography using solvents B, C, and D. The identification was confirmed by crystallization of the component or a derivative.

A. 2,3,4,6-Tetra-*O*-methyl-D-glucose (0.237 g) had mp 86–88° and $[\alpha]^{26}D$ +82.7° (*c* 0.2 in water) after recrystallization from petroleum ether (lit.[32] mp 95–96° and $[\alpha]D$ +83.8° in water).

B. 2,3,4-Tri-*O*-methyl-D-glucose (0.442 g) had $[\alpha]^{27}D$ +73.2° (*c* 3.0 in methanol) (lit.[32] $[\alpha]D$ +69.1° in methanol). Treatment of component b with aniline afforded *N*-phenyl-2,3,4-tri-*O*-methyl-D-glucosylamine which was recrystallized from ethyl ether: mp 142–143°, and $[\alpha]^{23}D$ −88° (*c* 0.3 in ethanol) (lit.[33] mp 150° and $[\alpha]^{23}D$ −103° in ethanol). Acylation of component b with *p*-nitrobenzoyl chloride in pyridine at 80° for 2 hr afforded a mixture of the anomeric di-*p*-nitrobenzoates as revealed by tlc with benzene–ethyl acetate (95:5) as solvent (α anomer, R_f 0.14, and β anomer, R_f 0.35). The mixture was separated by chromatography on a column of silica gel using the same solvent to give the following esters of 2,3,4-tri-*O*-methyl-D-glucose: β-1, 6-di-*p*-nitrobenzoate, mp and mmp 135–136° and $[\alpha]^{29}D$ −13.6° (*c* 1.0 in chloroform), after recrystallization from methanol (lit.[34] mp 138–139° and $[\alpha]^{22}D$ −12° in chloroform); α-1, 6-di-*p*-nitrobenzoate, mp 151–152° (recrystallized from methanol) and $[\alpha]^{29}D$ +22.6° (*c* 1.1 in chloroform).

Anal. Calcd for $C_{23}H_{24}O_{12}N_2$: C, 53.0; H, 4.7; N, 5.4. Found: C, 53.0; H, 4.7; N, 5.4.

Reduction with sodium borohydride and subsequent oxidation with periodic acid of the 2,3,4-tri-*O*-methyl-D-glucose afforded one component identical with 2,3,4-tri-*O*-methyl-L-xylose as revealed by paper chromatography using solvents B and C.

C. 2,4,6-Tri-*O*-methyl-D-glucose (0.012 g) had $[\alpha]^{22}D$ +72.5° (*c* 0.4 in methanol) (lit.[35] $[\alpha]D$ +70° in methanol).

D. 3,4-Di-*O*-methyl-α-D-glucose (0.112 g) had mp 118–120° and $[\alpha]^{22}D$ +139° → +100° (*c* 0.3 in ethanol) (recrystallized from ethyl acetate) (lit.[36] mp 114–118.5° and $[\alpha]D$ +80 → +76° in water for the α anomer; lit.[37] mp 113° and $[\alpha]^{16}D$ +94.5 → +99.5° in ethanol for the β anomer).

E. 2,4-*O*-methyl-D-glucose (0.052 g) had $[\alpha]D$ +63.8° (*c* 0.9 in water) (lit.[38] $[\alpha]D$ +76.5° in water). Component e was converted into the crystalline *N*-*p*-nitrophenyl-2,4-di-*O*-methyl-D-glucosylamine, mp and mmp 250–251° and $[\alpha]^{26}D$ −250 → −262° (*c* 0.2 in pyridine) (after recrystallization from ethanol) (lit.[38] mp 250–251° and $[\alpha]D$ −252 → −268° in pyridine).

F. 4-*O*-Methyl-D-glucose (0.049 g) had $[\alpha]^{31}D$ +63° (*c* 0.4 in methanol) (lit.[39] $[\alpha]^{20}D$ +53° in water). This fraction afforded

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4-O-methyl-D-glucosazone, mp 154–155°, after recrystallization from 30% aqueous acetone (lit.[39] mp 158°).

A portion of the insoluble methylated dextran (0.157 g) which resisted methanolysis (fraction ii) was solubilized in 72% sulfuric acid (2 ml) at 5° for 3 days. The solution was diluted with water to give 1 *N* sulfuric acid and refluxed for 11 hr. The hydrolysate was neutralized with barium carbonate, filtered, and concentrated. The methylated sugars were separated by chromatography (Whatman 3 MM paper, solvent C) giving 2,3,4,6-tetra- (0.006 g), 2,3,4-tri- (0.077 g), 2,4-di- (0.013 g), 3,4-di- (0.008 g), and 4-O-methyl-D-glucose (0.004 g). Each sugar was identified by paper electrophoresis and paper chromatography as described previously.

Methyl 2,3,4,6-tetra-O-methyl-α-D-glucoside was subjected to the two procedures that were used for cleavage of the methylated dextran, namely, (A) methanolysis followed by 1 *N* sulfuric acid hydrolysis (for fraction i) and (B) 72% sulfuric acid followed by 1 *N* sulfuric acid hydrolysis (for fraction ii). The extent of demethylation and degradation of the methylated sugar was ascertained by quantitative analysis (phenol–sulfuric acid method[40]) of each component of the hydrolysates after separation by paper chromatography (solvent C). Methanolysis (procedure A) resulted in a loss of 10% of the tetra-O-methyl-D-glucose, whereas 7% was lost in the 72% sulfuric acid method (procedure B); in both procedures tri-O-methyl-D-glucose was the major methylated sugar formed by demethylation.

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Registry No.—2,3,4-Tri-O-methyl-D-glucose α-1,6-di-*p*-nitrobenzoate, 16780-52-2.

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The Structure of *Leuconostoc mesenteroides* Strain C Dextran. II. Fragmentation Analysis[1a]

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Partial acid hydrolysis of the dextran produced by *Leuconostoc mesenteroides* strain C (NRRL B-1298) has afforded the homologous series of isomaltodextrins, whereas acetolysis gave kojibiose, nigerose, isomaltose, and, in addition, trisaccharides derived from the branch points. Further evidence for the detailed structure of the dextran was obtained from periodate oxidation studies.

Methylation studies (part I of this series[2]) have shown that the dextran synthesized by *Leuconostoc mesenteroides* strain C (NRRL B-1298) is a highly branched D-glucan (CL 4-5) linked predominantly by 1 → 6 glycosidic bonds. Twelve per cent of the D-glucose units have branches at C-2 and 7.7% at C-3, while a few units appear to be doubly branched at these positions. To obtain further information on the sequential arrangement of the linkages and to confirm the α-anomeric configuration suggested by the high positive rotation of the dextran and its derivatives, the dextran was fragmented by partial acid hydrolysis, by partial acetolysis, and by Smith degradation.

Since the order of stability of glycosidic linkages involving primary and secondary hydroxyls is reversed in acid hydrolysis compared with acetolysis, these two reactions are complimentary methods for fragmentation of glycans containing mixed linkages. Thus (1 → 6)-linked oligosaccharides are obtained from such glycans by partial acid hydrolysis, whereas glycosidic linkages involving secondary hydroxyls tend to be preserved in the oligosaccharides resulting from partial acetolysis.[3,4]

When the dextran was heated in 0.1 *N* oxalic acid, the homologous series of isomaltodextrins from isomaltose to isomaltooctaose was obtained in addition to D-glucose. Each oligosaccharide was identified by paper chromatography and by partial acid hydrolysis to give the lower homologs of the series. Isolation of this homologous series of oligosaccharides establishes the presence in this dextran of sequences of consecutive (1 → 6)-linked D-glucopyranose units.

Acetolysis of the dextran afforded D-glucose pentaacetate and a mixture of oligosaccharide acetates. After deacetylation the oligosaccharides were separated by gradient elution from a charcoal column and purified further by paper chromatography. The disaccharides were obtained in good yield and were characterized by conversion into crystalline derivatives. In two separate experiments kojibiose and nigerose were isolated in yields of 7–13 and 2%, respectively, whereas isomaltose was obtained in only 2–3% yield. The yield of kojibiose in particular (35% of the maximum yield theoretically possible on the basis of the methylation data) confirms previous observations[5,6] on the value of this procedure for obtaining non-(1 → 6)-linked oligosaccharides. These results are in accordance with those of Suzuki and Hehre[5] who isolated kojibiose and nigerose from this dextran in yields of 11.7 and 2.5%, respectively, under similar acetolysis conditions.

The trisaccharide fraction obtained from the ace-

(1) (a) This paper, was presented in part at the National Meeting of the American Chemical Society, Phoenix, Ariz., 1966, and forms part of the thesis submitted by M. J. S. to the Graduate faculty of the University of Minnesota in partial fulfillment of the requirements for the degree of Ph.D., 1966. (b) Deceased.

(2) B. A. Lewis, M. J. St. Cyr, and F. Smith, *J. Org. Chem.*, **33**, 3136 (1968).

(3) K. Matsuda, H. Watanabe, K. Fujimoto, and K. Aso, *Nature*, **191**, 278 (1961).

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(6) I. J. Goldstein and W. J. Whelan, *J. Chem. Soc.*, 170 (1962).

tolysis reaction contained six components of which four were obtained sufficiently pure for structural studies. Altering the acetolysis conditions increased the yield of the trisaccharide fraction somewhat while lowering the yield of kojibiose. The repeated paper chromatographic separations required to give pure components, however, led to poor recoveries of the individual trisaccharides. Three trisaccharides were identified as isomaltotriose, *O*-α-D-glucopyranosyl-(1 → 2)-*O*-α-D-glucopyranosyl-(1 → 6)-D-glucopyranose (**1**), and 2,6-di-*O*-(α-D-glucopyranosyl)-D-glucopyranose (**2**). A fourth trisaccharide (**3**) corresponded to either *O*-α-D-glucopyranosyl-(1 → 6)-*O*-α-D-glucopyranosyl-(1 → 3)-D-glucopyranose or 3,6-di-*O*-(α-D-glucopyranosyl)-D-glucopyranose. These structural assignments are based on the following observations.

Trisaccharides **1** and **2** had identical mobilities on paper chromatography in three different solvent systems but could be distinguished by paper electrophoresis in 0.1 *M* borate buffer and by paper chromatography of the borohydride-reduced trisaccharides. The structural studies were carried out on a mixture of the two trisaccharides. Partial acid hydrolysis afforded glucose, kojibiose, and isomaltose as revealed by paper chromatography, whereas the borohydride-reduced trisaccharides gave rise to glucose, sorbitol, kojibiose, and isomaltitol indicating that the reducing glucose unit in each trisaccharide was substituted at C-6.

Trisaccharides **1** and **2** were methylated by the Kuhn and Purdie techniques until no hydroxyl absorbance was detected in the infrared spectrum. Acid hydrolysis of the methylated trisaccharides afforded 2,3,4,6-tetra, 2,3,4-tri-, 3,4,6-tri-, and 3,4-di-*O*-methyl-D-glucoses which were isolated and identified by paper chromatography and paper electrophoresis. The identification of 3,4-di-*O*-methyl-D-glucose established the branched structure of trisaccharide **2** while the two tri-*O*-methyl-D-glucoses must originate from a trisaccharide having 1 → 6 and 1 → 2 linkages. From the partial acid hydrolysis data then, trisaccharide **1** must have the structure assigned with isomaltose at the reducing terminal. The ratio of di- to tri- to tetra-*O*-methyl-D-glucose of 1.00:1.74:3.11 suggests that the two trisaccharides were present in approximately equal amounts.

Partial acid hydrolysis of trisaccharide **3** gave isomaltose, nigerose, and glucose as revealed by paper chromatography. It was established that the 1 → 3 linkage was at the reducing end of the trisaccharide since periodate oxidation, reduction, and hydrolysis afforded glycerol and arabinitol but no glucose. However, these data do not distinguish between the linear and the branched trisaccharide.

Another trisaccharide fraction isolated in small quantity gave glucose, nigerose, and kojibiose on partial acid hydrolysis. When this fraction was treated successively with periodate, sodium borohydride, and refluxing methanolic hydrogen chloride, arabinitol, methyl α-D-glucopyranoside, and glycerol were obtained. This evidence suggests that this fraction was a mixture of the two linear trisaccharides containing both 1 → 2 and 1 → 3 linkages [D-G_p-(1 → 3)-D-G_p-(1 → 2)-D-G_p and D-G_p-(1 → 2)-D-G_p-(1 → 3)-D-G_p]. It does not rule out the alternate possibility that there was present a mixture of nigerotriose and kojitriose. However, there is no evidence from periodate oxidation studies for the presence of consecutive 1 → 3 linkages which would give rise to nigerotriose. In view of the small proportion of this trisaccharide fraction containing both (1 → 2)- and (1 → 3)-linked glucopyranose units and the relative stability to acetolysis of these linkages compared with the 1 → 6 linkages, it would appear that sequences of consecutive 1 → 2 and 1 → 3 linkages are not a common structural feature in this dextran.

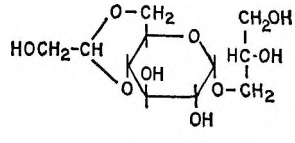
Additional evidence for the structure of the dextran was provided by periodate oxidation studies. The dextran was oxidized by periodate with a reduction of 1.58 mol of periodate per glucose unit while 0.66 mol of formic acid was liberated per glucose unit. These values are in good agreement with the values predicted by the methylation data (1.59 and 0.73, respectively). The dextran polyaldehyde showed little tendency to overoxidize; the periodate consumption reached a maximum in 40 hr and remained constant for an additional 55 hr.

For further studies the dextran polyaldehyde was reduced to the polyalcohol with sodium borohydride. On complete hydrolysis of the polyalcohol glucose and glycerol were obtained in the mole ratio 1.00:7.60 as determined by colorimetric analysis after separation of the two components by paper chromatography. This ratio is somewhat different from that indicated by the methylation results (1.00:5.98) but it is shifted in the direction expected if part of the 2,4,6-tri-, 2,4-di-, or 4-*O*-methyl-D-glucose had arisen by either incomplete methylation of the dextran or by partial demethylation of the methylated sugars during cleavage of the methylated dextran.

Partial fragmentation of the dextran polyalcohol was accomplished most satisfactorily with methanolic hydrogen chloride at room temperature. The methanolysate was examined by gas–liquid partition chromatography revealing glycerol, glycolaldehyde dimethyl acetal, and glyceraldehyde dimethyl acetal, the latter arising from 1 → 2 linkages. Several less volatile components were detected by paper chromatography. The components of the methanolysate were isolated by paper chromatography and identified as follows.

Glycerol, the major component, was identified by chromatography and as the tri-*p*-nitrobenzoate. It is derived from the linear segments of the dextran chain, the nonreducing terminal units, and the units branched at C-2.

1-*O*-α-D-Glucopyranosyl-L-glycerol was isolated along with two of its acetals containing glycolaldehyde (**4** and **5**). These three glucosides arise from glucose



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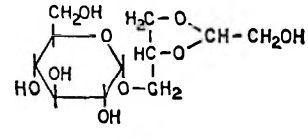

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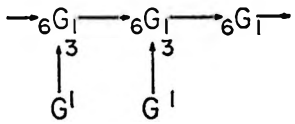
units substituted at C-3 and at C-1 by periodate-labile units. Since the methylation study revealed that most, if not all, of the 3-substituted glucose units represent branch points, then C-6 of this glucose unit is also substituted by an oxidizable residue. These periodate-

sensitive units can be nonreducing terminal units, linear 1 → 6 units, or the C-2 branched units.

A fifth component in the methanolysate was identified as 1-*O*-α-isomaltosyl-L-glycerol (**6**) by chromatographic comparison with the authentic compound. In addition partial acid hydrolysis of **6** afforded isomaltose, 1-*O*-α-glucopyranosylglycerol, glucose, and glycerol while complete hydrolysis liberated glucose and glycerol in the mole ratio of 2:1. If **6** is structurally significant and is not an artifact created by incomplete oxidation, then it must originate from two adjacent glucose units in the (1 → 6)-linked chain each branched at C-3 as in the linkage sequence depicted by **7**. This structural feature has been observed previously in a dextran.[7] A trace of 1-*O*-α-isomaltotriosyl-L-glycerol was obtained also.



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The isolation of **6** suggests some randomness in the distribution of C-3 branches. However the preponderance of the glucosylglycerol and its acetals **4** and **5** indicates that most of the 3-linked branches occur in isolated rather than in adjacent positions along the (1 → 6)-linked chain. No glycosides of nigerose were isolated from the polyalcohol suggesting that consecutive 1 → 3 linkages are not present in the dextran.

Cleavage of the dextran polyalcohol with aqueous acid, the method used previously for fragmenting these polyalcohols, gave the same components and, in addition, several other compounds which were condensation products with glyceraldehyde or glycol aldehyde. This complicated both the isolation and identification procedures. It seems advisable therefore to subject polyalcohols derived from (1 → 2)-linked polysaccharides to methanolysis thereby converting glyceraldehyde into the less reactive dimethyl acetal.

The structures of the two glycolaldehyde acetals of 1-*O*-α-D-glucopyranosyl-L-glycerol were established in the following manner. The rapid mobility of **4** and **5** on paper chromatograms and their acid lability suggested their acetal nature. Acetal **4** on partial acid hydrolysis gave 1-*O*-α-glucopyranosylglycerol, glucose, and glycerol. Methylation by the Kuhn procedure gave the methyl ether of **4** which on hydrolysis with dilute sulfuric acid afforded 2,3-di-*O*-methylglucose. The methyl ether of **4** was methanolyzed giving rise to methoxyacetaldehyde dimethyl acetal and 1,2-di-*O*-methylglycerol which were identified by glpc. The identification of these components establishes that **4** is 1-*O*-[4,6-*O*-(2-hydroxyethylidene)-α-D-glucopyranosyl]-L-glycerol.

Acetal **5** on partial acid hydrolysis gave 1-*O*-α-glucopyranosylglycerol which was identified by paper chromatography. Glycolaldehyde dimethyl acetal was detected in the methanolysate of **5** by glpc. Methylation of **5** and subsequent hydrolysis gave 2,3,4,6-tetra-*O*-methylglucose and glycerol, while methoxyacetaldehyde dimethyl acetal was obtained by methanolysis. The structure *O*-α-D-glucopyranosyl-(1 → 1)-2,3-*O*-(2-hydroxyethylidene)-L-glycerol was assigned to **5** from these results. Although the stereochemistry of the glycerol moiety in acetals **4** and **5** and in isomaltosylglycerol (**6**) has not been established for the isolated compounds, the configuration was assigned on the basis of its derivation from a 6-substituted D-glucopyranose unit.

Acetals **4** and **5** apparently arise through incomplete methanolysis of the dextran polyalcohol. The possibility that they were synthesized from glucosylglycerol and glycolaldehyde during methanolysis seems unlikely under the dilute conditions employed for methanolysis. Indeed when a mixture of 1-*O*-α-D-glucopyranosyl-L-glycerol and glycolaldehyde was treated with methanolic hydrogen chloride under conditions similar to those used for the polyalcohol, acetals **4** and **5** were not detected. The structural significance of **4** and **5** then depends on whether acid-catalyzed structural rearrangements took place during methanolysis. If acid-catalyzed rearrangements of the glycolaldehyde moiety of **4** and **5** did not occur, then these two compounds would have additional structural significance since the glycolaldehyde moiety of **4** and **5** can only be derived from a linear (1 → 6)-linked glucose unit and not from a C-2 branched unit.

Authentic 1-*O*-α-D-glucopyranosyl-L-glycerol was prepared from isomaltitol by oxidation with 1 mol of lead tetraacetate, followed by reduction with sodium borohydride. The oxidant attacks the glucitol moiety preferentially[8] and a mixture of glycosides is produced; 1-*O*-α-D-glucopyranosyl-L-glycerol was the major product isolated after reduction, and it was characterized as the crystalline hexa-*p*-nitrobenzoate.

Definitive evidence for the fine structure of dextrans has been lacking particularly with reference to the nature of the branches. Physical studies have suggested the presence of single unit branches as well as long branches.[9] The pattern of oligosaccharides formed by the action of dextranases[7,10] and recent chemical studies[7] indicate that the majority of branches in certain dextrans consist of a single α-D-glucopyranosyl unit.

The evidence obtained from these studies on the strain C dextran does not distinguish between single-unit branches and long branches or a ramified structure. The oligosaccharides obtained by acetolysis and periodate fragmentation could arise from C-2 and C-3 branch points terminated by either single α-D-glucopyranosyl units or chains of (1 → 6)-linked α-D-glucopyranose units.

Experimental Section

The general conditions are described in part I of this series.[2] The following chromatography solvent systems were used in addition to these described previously: (E) 1-propanol–ethyl acetate–water (65:10:25), (F) isoamyl alcohol–pyridine–water (1:1:1, upper phase), (G) pyridine–ethyl acetate–water (4:10:3), (H) 1-butanol–pyridine–water (6:4:3). Mobilities are expressed relative to glucose (R_G), isomaltose (R_{IM}), isomaltotriose (R_{IMT}), and glycerol (R_{GEY}).

Unless stated otherwise partial acid hydrolyses were performed with Amberlite IR-120 (H^+) cation-exchange resin as catalyst,

(7) D. Abbott, E. J. Bourne, and H. Weigel, *J. Chem. Soc., Sect. C*, 827 (1966).

(8) A. J. Charlson and A. S. Perlin, *Can. J. Chem.*, **34**, 1200 (1956).

(9) W. B. Neely, *Advan. Carbohydrate Chem.*, **15**, 341 (1960).

(10) R. W. Bailey, D. H. Hutson, and H. Weigel, *Biochem. J.*, **80**, 514 (1961); D. H. Hutson and H. Weigel, *ibid.*, **88**, 588 (1963).

and the reaction mixtures were heated in a boiling-water bath. Sulfuric acid hydrolyses were neutralized with barium carbonate or ion-exchange resins.

An F & M 500 gas chromatograph equipped with a thermal conductivity detector and a column (1.8 m × 6 mm) of 20% diethylene glycol succinate on acid-washed Chromosorb W, 60–80 mesh, was used for gas–liquid partition chromatography (glpc). Helium was used as carrier gas at a flow rate of 1 ml/sec and inlet pressure of 30 psi. All runs were linearly programmed at a rate of 7.9°/min from 40 to 200°. The components are defined by their retention time (R_t) in minutes and the temperature (T) at which they emerged from the column.

Fragmentation of the *L. mesenteroides* Strain C Dextran by Acid Hydrolysis.—Dextran (0.10 g) was heated in 0.1 *N* oxalic acid (2 ml) in a sealed tube in a boiling water bath for 5 hr. The acid was neutralized with calcium carbonate, and the solution was filtered and concentrated. The components were separated by chromatography on Whatman 3 MM paper using solvent G. Paper chromatography on solvents A, E, and F indicated that the components represented the homologous series of isomaltodextrins from isomaltose to isomaltooctaose as well as free glucose. Partial hydrolysis of each oligosaccharide at 95° for 2 hr with Amberlite IR-120 (H^+) resin as catalyst gave rise to the lower molecular weight homologs of the series as revealed by paper chromatography.

Fragmentation by Acetolysis.—Dextran acetate (12.4 g) was dissolved in acetic anhydride (170 ml) at 5° and treated with a cold 5:1 mixture of acetic anhydride–sulfuric acid (78 ml) for 15 min. The reaction mixture was allowed to warm to room temperature (2 hr) and then held at 35° for 45 hr. The acetates were recovered by centrifugation after pouring the reaction mixture into water, and the supernatant was extracted with chloroform to remove the remaining acetates. The combined acetates were dissolved in chloroform, washed with sodium bicarbonate solution and water, and concentrated to a syrup (yield 14.0 g). The syrup was extracted with methanol and the methanol-soluble material was deacetylated catalytically with sodium methoxide (yield 4.0 g). The methanol-insoluble acetate fraction was deacetylated in chloroform with methanolic potassium hydroxide and shown by chromatography to be primarily large oligosaccharides (yield 1.5 g). This latter fraction was not investigated further.

The deacetylated acetolysate (4.0 g) was resolved by cocoanut charcoal column chromatography,[11] giving the disaccharides in a yield of about 17% (1.16 g) and the trisaccharides in 5% yield (0.30 g).[12] The yields are calculated as the percentage by weight of the dextran (12.4 g of dextran acetate correspond to 7.1 g of dextran). Fractions eluted from the carbon column were purified further by chromatography on Whatman 3 MM paper with solvents E and G giving the following oligosaccharides.

A. **3-*O*-α-D-Glucopyranosyl-D-glucopyranose (Nigerose).**—Fraction a (yield 0.14 g, 2%) was chromatographically (paper) identical with nigerose: R_G 0.51, 0.74, and 0.85 in solvents A, E, and F, respectively; $[\alpha]^{26}D$ +128.2° (*c* 1.2, water) (lit.[6] $[\alpha]^{18}D$ +131° in water). Acetylation with acetic anhydride and sodium acetate afforded the β-octaacetate: mp 145–147°; $[\alpha]^{26}D$ +89° (*c* 0.6, chloroform) after recrystallization from ethanol (lit.[6,13] mp 149, 152–154; $[\alpha]D$ +83° in chloroform).

B. **2-*O*-α-D-Glucopyranosyl-α-D-glucopyranose (Kojibiose).**—Fraction b (yield 0.51 g, 7%) was recrystallized from aqueous ethanol: mp 186–187°; $[\alpha]^{25}D$ +161° (10 min) → +136.5° (80 min) (*c* 0.9, water) (lit.[14] α-kojibiose: anhydrous, mp 193–194°; hydrate, mp 195–196°, $[\alpha]D$ +145.8° → +135.2° in water). This fraction was identical with kojibiose by paper chromatography in solvents A, E, and F (R_G 0.37, 0.68, and 0.76, respectively). Acetylation with acetic anhydride and sodium acetate afforded the β-octaacetate which was recrystallized from ethanol: mp and mmp 117–119°; $[\alpha]^{26}D$ +130.5° (*c* 0.2, chloroform) (lit.[15] mp 118°; $[\alpha]D$ +113° in chloroform).

Kojibiose was reduced with sodium borohydride to the syrupy kojibiitol, $[\alpha]^{23}D$ +83.5° (*c* 1.5 in water) and R_G 0.70 in solvent E. On oxidation with 0.015 *M* periodic acid at 5°, kojibiose reduced 2.9 mol of periodate in 23 hr, unchanged after 42 hr, and thereafter was overoxidized reducing 5.2 mol in 76 hr and 6.5 mol in 165 hr.

Methylation of kojibiose (0.072 g) using dimethylformamide (6 ml), methyl iodide (1.8 ml), and silver oxide (3.5 g)[16] gave the octamethyl ether (0.074 g): $[\alpha]^{27}D$ +113° (*c* 1.9, chloroform). The octa-*O*-methylkojibiose was refluxed for 8 hr and the methylated sugars were separated by paper chromatography (solvent C) giving equimolar quantities of 2,3,4,6-tetra-*O*-methyl-D-glucose, mp 88–90°, and 3,4,6-tri-*O*-methyl-D-glucose, $[\alpha]^{29}D$ +55° (*c* 0.7, water) (lit.[17] $[\alpha]D$ +78° in water). The mobility of the 3,4,6-tri-*O*-methyl-D-glucose on paper electrophoresis in 0.1 *M* borate buffer established that C-2 was not methylated since the other tri-*O*-methyl-D-glucoses do not form borate complexes under these conditions.[18]

C. **6-*O*-α-D-Glucopyranosyl-D-glucopyranose (Isomaltose).**—Fraction c (yield 0.23 g, 3%) was identical with isomaltose by paper chromatography in solvents A, E, and F (R_G 0.26, 0.58, and 0.64, respectively), and G (R_{IMT} 1.90). Acylation with *p*-nitrobenzoyl chloride in pyridine at 85° for 3.5 hr gave the β-octa-*p*-nitrobenzoate which was recrystallized from 2-butanone: mp 226–228°; $[\alpha]^{22}D$ +83.8° (*c* 0.3 in acetonylacetone) {lit.[19] mp 188°; $[\alpha]D$ +22.0° (*c* 1.3 in acetonylacetone) after recrystallization from acetone}. Authentic isomaltose β-octa-*p*-nitrobenzoate prepared in this laboratory with *p*-nitrobenzoyl chloride and pyridine and recrystallized from 2-butanone had mp 223–225° and $[\alpha]^{23}D$ +78.8° (*c* 0.6 in acetonylacetone).

Anal. Calcd for $C_{68}H_{46}N_8O_{35}$: C, 53.2; H, 3.0; N, 7.3. Found: C, 53.0; H, 3.3; N, 7.2.

Recrystallization of the β-octa-*p*-nitrobenzoate from acetone gave crystals which melted at 189–190°, solidified at 200°, and remelted at 236–237°.

Fraction c was transformed into isomaltitol by reduction with sodium borohydride. Recrystallization of the isomaltitol from methanol gave crystals with mp 137–138° and $[\alpha]^{29}D$ +90.3° (*c* 0.7, water) (lit.[20] mp 165.5–167° and $[\alpha]^{28}D$ +89° in water).

D. **Isomaltotriose.**—Fraction d (0.05 g) was chromatographically identical with isomaltotriose in solvents E, F, and G and had $[\alpha]^{27}D$ +142° (*c* 0.8, water) (lit.[21] $[\alpha]D$ +142° in water). Partial hydrolysis liberated glucose and isomaltose only.

E. **Trisaccharides 1 and 2.**—Fraction e (0.060 g), $[\alpha]D$ +83° (*c* 0.8, water), contained two components which had similar mobilities on paper chromatograms in solvents E, F, and G (R_{IMT} 1.12 in solvent G) but were distinguished by paper electrophoresis. When this fraction was partially hydrolyzed, glucose, kojibiose, and isomaltose were detected by paper chromatography. Treatment of fraction e with sodium borohydride afforded the two reduced trisaccharides with R_{IM} 0.68 and 0.79 in solvent E and R_{IMT} 1.08 and 1.38 in solvent G. Partial hydrolysis of the mixture of reduced trisaccharides gave glucose, sorbitol, kojibiose, and isomaltitol as revealed by paper chromatography.

The trisaccharide mixture (36 mg) was subjected to three Kuhn and five Purdie methylations until no hydroxyl absorption was observed in the infrared. The methylated trisaccharides were hydrolyzed in refluxing 1 *N* sulfuric acid, and the methylated sugars were isolated by paper chromatograph in solvent C. Assay of each fraction by the phenol–sulfuric acid method[22] gave the ratio 1.00:1.74:3.11 for the the di-, tri-, and tetra-*O*-methyl-D-glucoses. The following components of the hydrolysate were identified by comparison with the authentic compounds by paper chromatography in solvents B and C and by paper electrophoresis in 0.1 *M* borate buffer: (i) 3,4-di-*O*-methyl-D-glucose, (ii) 3,4,6-tri-*O*-methyl-D-glucose, (iii) 2,3,4-tri-*O*-methyl-D-glucose, and (iv) 2,3,4,6-tetra-*O*-methyl-D-glucose. Reduction of

(11) F. W. Barth and T. E. Timell, *Can. J. Chem.*, **36**, 1321 (1958).

(12) When the dextran was subjected to acetolysis using a longer reaction time and a higher concentration of acid (similar to the conditions described by Suzuki and Hehre[6]), the oligosaccharides were isolated in the following yields: isomaltose (2%), kojibiose (13%), nigerose (2%), and trisaccharides (1%).

(13) K. Matsuda, H. Watanabe, and K. Aso, *Tohoku J. Agr. Res.*, **12**, 351 (1961).

(14) K. Takiura and K. Koizumi, *J. Pharm. Sci. Jap.*, **82**, 852 (1962).

(15) K. Matsuda, *Nature*, **180**, 985 (1957).

(16) R. Kuhn, H. Trischmann, and I. Löw, *Angew. Chem.*, **67**, 32 (1955).

(17) R. L. Sundberg, C. M. McCloskey, D. E. Rees, and G. H. Coleman, *J. Amer. Chem. Soc.*, **67**, 1080 (1945).

(18) H. Weigel, *Advan. Carbohyd. Chem.*, **18**, 61 (1963).

(19) E. M. Montgomery, F. B. Weakley, and G. E. Hilbert, *J. Amer. Chem. Soc.*, **71**, 1682 (1949).

(20) M. L. Wolfrom, A. Thompson, A. N. O'Neill, and T. T. Galkowski, *ibid.*, **74**, 1062 (1952).

(21) J. R. Turvey and W. J. Whelan, *Biochem. J.*, **67**, 49 (1957).

(22) M. Dubois, K. A. Gilles, J. K. Hamilton, P. A. Rebers, and F. Smith, *Anal. Chem.*, **28**, 350 (1956).

iii with sodium borohydride and subsequent oxidation with 0.037 *M* periodic acid at 5° for 40 hr afforded 2,3,4-tri-*O*-methylxylose as revealed by paper chromatography. This establishes conclusively that iii is 2,3,4-tri-*O*-methyl-D-glucose.

No glucose was detected by paper chromatography when the trisaccharide mixture was oxidized with periodic acid for 24 hr, reduced with borohydride, and hydrolyzed.

F. Trisaccharide 3.—Fraction f (0.043 g) had R_{IM} 0.63 and R_{IMT} 1.31 on paper chromatography in solvent G. Partial hydrolysis released glucose, isomaltose, and nigerose. The trisaccharide was oxidized with 0.1 *M* periodic acid at 5° for 24 hr, and the product was reduced with sodium borohydride for 3 days. The reduced product was hydrolyzed with 0.1 *N* hydrochloric acid at room temperature for 22 hr. Paper chromatography of the deionized hydrolysate showed considerable streaking of the components and the hydrolysate was re-treated with sodium borohydride and again deionized. Glycerol and arabinitol were the only components detected by paper chromatography.

G. Trisaccharides 8 and 9.—Fraction g (0.013 g) showed two components by paper chromatography in solvent G (R_{IMT} 1.52 and 1.74). Partial hydrolysis of fraction g yielded glucose, nigerose, and kojibiose. Fraction g was oxidized with 0.1 *M* periodic acid at 5° for 15 hr, and the product was reduced with sodium borohydride and refluxed with 1 *N* methanolic hydrogen chloride for 2 hr. The deionized methanolysate was shown by paper chromatography (solvents A, B, and H) to contain arabinitol, methyl α-D-glucopyranoside, and glycerol.

Periodate Oxidation of Dextran.—Dextran (0.2044 g), purified *via* the acetate, was oxidized with 0.075 *M* periodic acid (100 ml) at 5°. Aliquots (2 ml) were titrated for periodate by the Fleury–Lange method,[23] and formic acid was titrated on 5-ml aliquots to the phenolphthalein end point with 0.009 *N* sodium hydroxide after reduction of the excess periodate with ethylene glycol (Table I).

TABLE I

	Time, hr					
	22	26	39	63	65	113
Periodate reduced, mol/glucose unit	1.44	1.45	1.58	1.56	...	...
Formic acid released, mol/glucose unit	...	...	...	...	0.65	0.66

For further studies dextran (5.11 g) was oxidized with 0.1 *M* periodic acid (1 l.) at 5° for 95 hr (1.58 mol of periodate reduced/glucose unit). The acid was neutralized with barium carbonate, and the solution was filtered and treated with sodium borohydride (5 g) for 22 hr. The excess borohydride was destroyed with acetic acid, and the solution was concentrated to 200 ml.

Methanolysis of the Dextran Polyalcohol.—A portion of the solution (100 ml) was passed through a column of Amberlite IR-120 (H^+), and the eluate was concentrated nearly to dryness and treated with methanol (75 ml). The solution was concentrated to a syrup and again treated with methanol; this process was repeated four times. The residue was dissolved in methanol (80 ml) and treated with 1 *N* methanolic hydrogen chloride (30 ml) for 16 hr at 23°. The acid was neutralized with silver carbonate, the mixture was filtered, and the solution was concentrated to 10 ml. Examination of this methanolysate by glpc revealed glycolaldehyde dimethyl acetal (R_t 8.6 min, *T* 120°), glyceraldehyde dimethyl acetal (R_t 16.6 min, *T* 180°), and glycerol, which were confirmed by cochromatography[24] with the authentic compounds. The remainder of the methanolysate was concentrated to dryness (yield 0.93 g).

A. Glucose–Glycerol Ratio.—A portion of the methanolysate (19 mg) was hydrolyzed in refluxing 1 *N* sulfuric acid for 21 hr. The solution was deionized [Duolite A4 (OH^-)] and concentrated, and the components were separated by paper chromatography in solvent A. Glucose and glycerol were each eluted with water and analyzed respectively by the phenol–sulfuric acid[22] and the periodate–chromotropic acid[25] methods giving a glucose–glycerol molar ratio of 1.00:7.60.

B. Identification of the Components of the Methanolysate. The methanolyzate (0.745 g) was separated on Whatman 3 MM paper using solvent A. The components were eluted with water and identified as follows.

i. Glycerol (0.197 g).—Fraction i was chromatographically identical with glycerol in solvents A, B, and H and gave the tri-*p*-nitrobenzoate, mp 192–193°.

ii. 1-*O*-[4,6-*O*-(2-Hydroxyethylidene)-α-D-glucopyranosyl]-L-glycerol (4) (0.054 g).—Compound **4** had $[\alpha]^{28}D$ +79° (*c* 0.3, methanol) and R_{GEY} 0.81 in solvent A. Partial hydrolysis of **4** for 30 min gave 1-*O*-α-D-glucopyranosylglycerol, glycerol, and glucose as revealed by paper chromatography. The original compound could not be detected after hydrolyzing for 60 min.

Compound **4** (6 mg) was methylated twice by the Kuhn procedure, and a portion was hydrolyzed with 1 *N* sulfuric acid at 100° for 12 hr. Examination of the hydrolysate by paper chromatography in solvents C and H and by electrophoresis revealed one visible component corresponding to 2,3-di-*O*-methyl-D-glucopyranose. The remainder of the methyl ether of **4** was heated in 1 *N* methanolic hydrogen chloride in a sealed tube in a boiling-water bath for 14 hr. Examination of the methanolysate by glpc showed peaks corresponding to methoxyacetaldehyde dimethyl acetal (*T* 91°, R_t 7.4 min) and 1,2-di-*O*-methylglycerol (*T* 76°, R_t 2.5 min) which were confirmed by cochromatography.

iii. 1-*O*-α-D-Glucopyranosyl-2,3-*O*-(2-hydroxyethylidene)-L-glycerol (5) (0.042 g).—Compound **5** had $[\alpha]^{18}D$ +44° (*c* 1.6, methanol) and R_{GLY} 0.45 in solvent A. Partial hydrolysis of **5** for 15 min gave 1-*O*-α-D-glucopyranosylglycerol and a trace of glucose as revealed by paper chromatography; the original compound could not be detected. Methanolysis of **5** in a sealed tube at 95° for 6 hr afforded glycolaldehyde dimethyl acetal (*T* 122°) detected by glpc and confirmed by cochromatography.

Compound **5** was methylated two times by the Kuhn procedure and subjected to methanolysis. Glpc of the methanolysate showed a peak corresponding to methoxyacetaldehyde dimethyl-acetal (*T* 98°, R_t 7.1 min). Mono- and di-*O*-methylglycerol were not detected. The remainder of the methanolysate was refluxed with 1 *N* sulfuric acid for 9 hr. Paper chromatography of the concentrated hydrolysate using solvents A and C revealed 2,3,4,6-tetra-*O*-methyl-D-glucose and glycerol.

iv. 1-*O*-α-D-Glucopyranosyl-L-glycerol (0.084 g).—Fraction iv had $[\alpha]^{29}D$ +122.8° (*c* 1.4, water); it was chromatographically identical with the authentic compound on solvents A, B, and H (R_G 0.71, 1.04, and 0.95, respectively) and on partial hydrolysis afforded glucose and glycerol in addition to iv. Acylation with *p*-nitrobenzoyl chloride and pyridine gave the hexa-*p*-nitrobenzoate which was recrystallized from acetone and from 2-butanone: mp and mmp 219–220° (melted at 134–136° and resolidified); $[\alpha]^{25}D$ +53.9° (*c* 0.6, acetone).

v. *O*-α-D-Glucopyranosyl-(1 → 6)-*O*-α-D-glucopyranosyl-(1 → 1)-L-glycerol (1-*O*-α-Isomaltosyl-L-glycerol) (6).—Fraction v was purified further by paper chromatography giving 15 mg of **6**. Compound **6** was chromatographically identical with authentic 1-*O*-α-isomaltosyl-L-glycerol[26] in solvents A, E, and F (R_G 0.24, 0.57, and 0.60, respectively) and had $[\alpha]^{28}D$ +109° (*c* 0.2, water); authentic, $[\alpha]D$ +165° (*c* 0.7, water). Partial acid hydrolysis of **6** for 30 min afforded isomaltose, 1-*O*-glucopyranosylglycerol, glucose, and glycerol which were revealed by paper chromatography. The original compound was still detected after 2 hr but not after 3 hr. Complete hydrolysis of **6** with refluxing 1 *N* sulfuric acid for 12 hr afforded glucose and glycerol in the mole ratio 1.00:0.55; glucose was analyzed by the phenol–sulfuric acid method[22] and glycerol by the periodate–chromotropic acid technique.[25]

vi. 1-*O*-α-Isomaltotriosyl-L-glycerol.—Fraction vi was chromatographically identical with 1-*O*-α-isomaltotriosyl-L-glycerol[26] on solvents A, E, and F (R_{IM} 0.28, 0.42, and 0.55, respectively). Partial hydrolysis for 30 min gave 1-*O*-isomaltosylglycerol, isomaltose, 1-*O*-glucopyranosylglycerol, glucose, and glycerol which were detected by paper chromatography.

(23) R. D. Guthrie in "Methods in Carbohydrate Chemistry," Vol. I, R. L. Whistler and M. L. Wolfrom, Ed., Academic Press Inc., New York, N. Y., 1962, p 437.

(24) Cochromatography refers to chromatography of an admixture of the authentic specimen and the compound being examined.

(25) B. A. Lewis, F. Smith, and A. M. Stephen in "Methods in Carbohydrate Chemistry," Vol. I, R. L. Whistler and M. L. Wolfrom, Ed., Academic Press Inc., New York, N. Y., 1962, p 472.

(26) The 1-*O*-α-isomaltosyl-L-glycerol and 1-*O*-α-isomaltotriosyl-L-glycerol required as reference compounds were prepared by partial periodate oxidation of NRRL B-512 dextran.

C. Attempted Condensation of Glycolaldehyde with 1-*O*-α-D-Glucopyranosyl-L-glycerol.—A mixture of 1-*O*-α-D-glucopyranosyl-L-glycerol (21 mg, 0.082 mmol) and glycolaldehyde (32 mg, 0.53 mmol) in methanol (1 ml) was treated with 1 *N* methanolic hydrogen chloride (0.38 ml) for 18 hr at 20°. The reaction mixture was neutralized with silver carbonate and filtered, and the solution was concentrated. The unreacted glucosylglycerol was the only component visible by paper chromatography in solvents A and E. Acetals 4 and 5 could not be detected.

Hydrolysis of the Dextran Polyalcohol.—The dextran polyalcohol was hydrolyzed with 0.1 *N* hydrochloric acid at 25° for 18 hr, and the reaction mixture was neutralized and treated with sodium borohydride. The components of the deionized hydrolysate were separated by paper chromatography. The same components (i–vi) were identified, but in addition there were small amounts of several components which appeared to be condensation products of these components with glycolaldehyde or glyceraldehyde. These were not investigated further.

Synthesis of 1-*O*-α-D-Glucopyranosyl-L-glycerol.—A solution of isomaltitol (0.245 g) in water (1 ml) was diluted with acetic acid (75 ml) and treated with lead tetraacetate (0.350 g, 1.1 molecular proportions). The reaction mixture was shaken vigorously until the lead tetraacetate had dissolved and, after 2.5 hr at room temperature, oxalic acid (0.368 g) in acetic acid (10 ml) was added. The mixture was filtered and the solution was concentrated. The residue was dissolved in water and deionized with Amberlite IR-120 (H^+) and Duolite A-4 (OH^-) resins. Sodium borohydride (0.20 g) was added, and after 15 hr the solution was neutralized with acetic acid and the sodium ions were removed with Amberlite IR-120 (H^+). The solution was concentrated, and the residue was treated with methanol to remove boric acid.

Preparative paper chromatography (solvent G) of the syrupy product (0.204 g) afforded pure 1-*O*-α-D-glucopyranosyl-L-glycerol (0.070 g) in addition to isomaltitol (0.054 g), 1-*O*-α-D-glucopyranosyl-L-erythritol (0.011 g), and hydroxyethyl α-D-glucopyranoside (0.030 g). The 1-*O*-α-D-glucopyranosyl-L-glycerol had $[\alpha]^{29}D$ +123.9° (*c* 1.2, water) and on heating with pyridine and *p*-nitrobenzoyl chloride at 95° for 3.5 hr it gave a hexa-*p*-nitrobenzoate which was recrystallized from acetone–ethanol (1:1): mp 121–125°, solidifying and remelting at 222–223°; $[\alpha]^{24}D$ +57.4° (*c* 1.0, acetone).

Anal. Calcd for $C_{61}H_{36}N_6O_{26}$: C, 53.3; H, 3.2; N, 7.3. Found: C, 53.2; H, 3.2; N, 7.1.

Registry No.—Isomaltose β-acta-*p*-nitrobenzoate, 16780-53-3; 1-*O*-α-D-glucopyranosyl-L-glycerol hexa-*p*-nitrobenzoate, 16808-40-5.

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Deoxophylloerythroetioporphyrin[1a]

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A method of preparation of deoxophylloerythroetioporphyrin using the chlorophyll derivative, pheophytin, as the starting material has been worked out. In the procedure pheophytin is first converted into pyropheophorbide which is further degraded to deoxophylloerythrin in a single composite reaction based on the Wolff–Kishner reduction. Deoxophylloerythrin is then decarboxylated to yield deoxophylloerythroetioporphyrin by a seven-step reaction which includes Curtius rearrangement, Hofmann degradation, and catalytic hydrogenation.

The natural occurrence of deoxophylloerythroetioporphyrin (DPEP) was suspected by A. Treibs when he extracted from a Swiss marl a porphyrin with a visible spectrum identical with that of deoxophylloerythrin (for structures see Table I) and chemical properties indicating the absence of carboxyl groups.[2] The central position of DPEP in the geochemistry of the fossil porphyrins[3] required that the suggested structure be confirmed by synthesis. Using the usual synthetic approach of the Fischer school based on the appropriate pyrromethenes, an authentic sample of DPEP was prepared. However, the yields were dishearteningly low; for example, 12 mg of DPEP was obtained from 30 g of pyrromethenes.[4] A later attempt by other workers to repeat the synthesis produced only fractional milligrams of the desired porphyrin and they reported that the major product was etioporphyrin.[5] The comparative ease with which quantities of the chlorophyll derivative, pheophytin, can be obtained from natural sources suggested that a different approach might be more fruitful. Since it already contains the required carbon skeleton, the choice of pheophytin as the starting point would avoid much of the tedium of the pyrromethene synthesis. Furthermore, now that the structure of chlorophyll has been confirmed,[6] it is sound to use it as a starting point for the synthesis of compounds of related structures.

Thus, a logical starting point for the synthesis of DPEP was pheophytin a + b (see Table II). Pheophytin is produced by extraction from chlorophyll-rich plants and may be obtained commercially. It is known to be readily converted into pyropheophorbide a + b by refluxing in concentrated HCl, and so could be made available in quantity without undue labor. A glance

(1) (a) Porphyrin Studies. XXXVI. Paper XXXV: C. B. Storm, A. H. Corwin, R. R. Arellano, M. Martz, R. Weintraub, *J. Amer. Chem. Soc.*, **88**, 2525 (1966). This work supported in part by the Petroleum Research Fund administered by the American Chemical Society and in part by Public Health Service Research Grant No. FR 55801-5 from the General Research Support Branch. (b) Mellon Institute. (c) Johns Hopkins University.

(2) A. Treibs, *Ann.*, **509**, 103 (1934).

(3) (a) For the orginal proposal of the organic geochemistry of the porphyrins, see A. Treibs, *Angew. Chem.*, **49**, 682 (1936); (b) for a recent discussion, see E. W. Baker, in "Organic Geochemistry: Methods and Results," G. Eglinton and M. Murphy, Ed., Springer-Verlag, New York, N. Y., 1968.

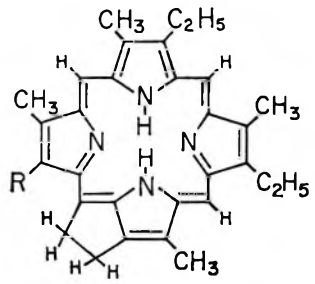
(4) H. Fischer and H. J. Hoffmann, *Ann.*, **517**, 274 (1935).

(5) J. M. Sugihara and L. R. McGee, *J. Org. Chem.*, **22**, 795 (1957). These workers suggest etioporphyrin I as the major product from the reaction mixture. However, the proximate 2-carbon side chains (3′-ethyl and 3-bromovinyl) on the pyrromethene component which forms the III and IV rings of the porphyrin seem to contradict this and etioporphyrin III would be the product if the isocyclic ring did not close.

(6) (a) R. B. Woodward, *Pure Appl. Chem.*, **2**, 383 (1961); (b) R. B. Woodward, *et al.*, *J. Amer. Chem. Soc.*, **82**, 3800 (1960); (c) for a complete discussion of all details of this synthesis and prior work, see W. Lwowski in "The Chlorophylls," L. P. Vernon and G. R. Seely, Ed., Academic Press, New York, N. Y., 1966, p 119.

TABLE I

STRUCTURE AND NAMES OF PORPHYRINS



Compound name: trivial (systematic)	Compd no.	R	Reactants and conditions
Deoxophylloerythrin (1,3,5,8-tetramethyl-2,4-diethyl-6,γ-ethanoporphine-7-propionic acid)	V	CH_2CH_2COOH	CH_3OH, HCl
Deoxophylloerythrin methyl ester (1,3,5,8-tetramethyl-2,4-diethyl-6,γ-ethanoporphine-7-propionic acid methyl ester)	VI	$CH_2CH_2COOCH_3$	$NH_2NH_2 \cdot H_2O$
Deoxophylloerythrin hydrazide (1,3,5,8-tetramethyl-2,4-diethyl-6,γ-ethanoporphine-7-propionic acid methyl ester)	VII	$CH_2CH_2CONHNH_2$	HNO_2, MeOH
Deoxophylloerythrin ethyl-ω-methylurethan [1,3,5,8-tetramethyl-2,4-diethyl-6,γ-ethano-7-(ethyl-ω-methylurethan)porphine]	VIII	$CH_2CH_2NHCOOCH_3$	10% HCl, 130°
Deoxophylloerythrin ethyl-ω-amino hydrochloride [1,3,5,8-tetramethyl-2,4-diethyl-6,γ-ethano-7-(ethyl-ω-amino hydrochloride)porphine]	IX	$CH_2CH_2NH_3^+Cl^-$	OH^-, $(CH_3)_2SO_4$
Deoxophylloerythrin ethyl-ω-dimethylamino dimethyl sulfate [1,3,5,8-tetramethyl-2,4-diethyl-6,γ-ethano-7-(ethyl-ω-dimethylamino dimethyl sulfate)-porphine]	X	$CH_2CH_2N^+(CH_3)_3SO_4CH_3^-$	KOH, heat
Protodeoxophylloerythroetioporphyrin (1,3,5,8-tetramethyl-2,4-diethyl-7-vinyl-6,γ-ethanoporphine)	XI	$CH{=}CH_2$	H_2–Pt, THF
Deoxophylloerythroetioporphyrin (1,3,5,8-tetramethyl-2,4,7-triethyl-6,γ-ethanoporphine)	XII	CH_2CH_3	

at the formulas shows that the route from pyropheophorbide to DPEP crosses two major hurdles. The oxidation level of a number of the substituents (reduction of carbonyl and vinyl) as well as that of the aromatic system (oxidation of chlorin to porphyrin) must be changed and decarboxylation of a propionic acid side chain must be performed. Decarboxylation of unactivated carboxyl groups is difficult and in this case is more so owing to the ponderance of the molecule. Methods of decarboxylation of the propionic acid group were considered and the Curtius and Hofmann degradative method was the obvious choice because of its demonstrated utility on porphyrin carboxylic acids. All reactions in this sequence proceed under relatively mild conditions such that the integrity of the porphyrin moiety is known to be preserved.[7] The reaction sequence is somewhat lengthy (eight steps) and yields are considerably less than quantitative. These considerations dictated that deoxophylloerythrin would have to be made available in sizable quantities. To this end then, first attention was devoted to streamlining and simplifying the standard methods of reducing the functional groups of pyropheophorbide and oxidizing it to a porphyrin.

It was known that the Wolff–Kishner reaction run under mild conditions would reduce both the vinyl and carbonyl functions of pyropheophorbide a or b to give, along with several other products, deoxomesopyropheophorbide (III).[8] Under more severe Wolff–Kishner conditions, some deoxophylloerythrin and etioporphyrin III were formed.[9] Reduction of the carbonyl functions and the aromatization are, of course, not unexpected but clean reduction of the vinyl group does not occur under Wolff–Kishner conditions in a sealed tube. The fact that the effective reductant is not hydrazine but its oxidation product, diimide, explains this observation.[10]

Thus, an improved procedure, based on the above considerations and incorporating the Huang-Minlon modification of the Wolff–Kishner reduction, was formulated. Pyropheophorbide a + b is converted into deoxophylloerythrin in one composite reaction without isolation of the intermediates. Three distinct reactions take place sequentially: reduction of the vinyl group, reduction of the carbonyl functions, and dehydrogenation of ring IV. The early stages of the reaction are run in the presence of air to obtain reduction of the vinyl group. If oxygen is carefully excluded from the reaction mixture, a sizable yield of what appears to be the 2-vinyl analog of deoxophylloerythrin is obtained; however, some reduction of the vinyl group still occurs even in the absence of oxygen. In a later stage of the reaction, base is added and the temperature raised to 150° to decompose the hydrazone (IV). Finally, the temperature is raised to 190–200° and the reaction mixture changes from dull green to reddish brown indicating conversion into the porphyrin, which after work-up is obtained in about 65% yield. A small yield of chlorin is also obtained which spectral evidence indicates is deoxomesopyropheophorbide (III).[8]

(7) For example, see (a) mesoporphyrin IX to etioporphyrin III, E. W. Baker, M. Ruccia, and A. H. Corwin, *Anal. Biochem.*, **8**, 512 (1964), and H. Fischer, E. Haarer, and F. Stadler, *Z. Physiol. Chem.*, **241**, 201 (1936); (b) koproporphyrin I to 1,3,5,7-tetramethyl-2,4,6,8-tetravinylporphine, H. Fischer, *et al.*, *ibid.*; (c) pyrroporphyrin XV to pyrroetioporphyrin, H. Fischer and E. Haarer, *ibid.*, **229**, 55 (1934).

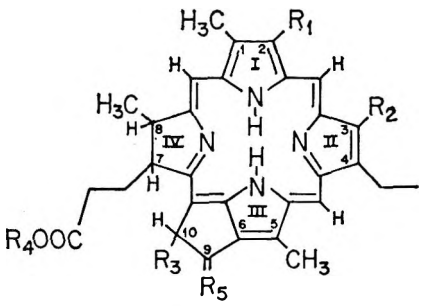
(8) (a) H. Fischer and H. Gibian, *Ann.*, **552**, 153 (1942); (b) *ibid.*, **548**, 183 (1941).

(9) H. Fischer, E. Lakatos, and J. Schnell, *ibid.*, **509**, 212 (1934).

(10) (a) E. J. Corey, W. L. Mock, and D. J. Pasto, *Tetrahedron Lett.*, No 11, 347 (1961); (b) E. J. Corey, D. J. Pasto, and W. L. Mock, *J. Amer. Chem. Soc.*, **83**, 2957 (1961).

TABLE II

STRUCTURE OF PHORBIDES



Name	Compd no.	R_1	R_2 a	R_2 b	R_3	R_4	R_5
Pheophytin	I	$CH{=}CH_2$	CH_3	CHO	$COOCH_3$	$C_{20}H_{39}$	O
Pyropheophorbide	II	$CH{=}CH_2$	CH_3	CHO	H	H	O
Deoxomesopyropheophorbide	III	CH_2CH_3	CH_3	CHO	H	H	H_2
Pyropheophorbide hydrazone	IV	$CH{=}CH_2$	CH_3	$CH{=}NNH_2$	H	H	NNH_2

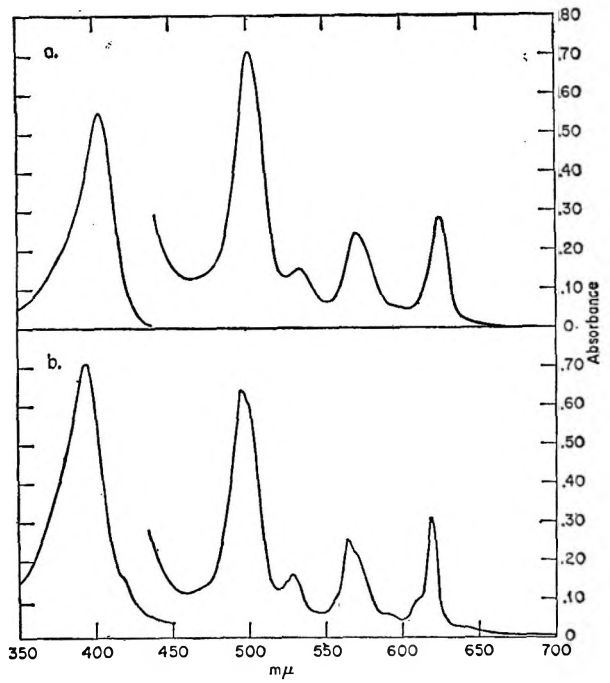


Figure 1.—(a) Electronic spectrum of protodeoxophylloerythroetioporphyrin; (b) electronic spectrum of deoxophylloerythroetioporphyrin.

Deoxophylloerythrin was then decarboxylated to yield DPEP by the series of reactions shown schematically in Table I. In all reactions, the conditions used were essentially those reported for the conversion of mesoporphyrin IX into etioporphyrin III,[7a] except for the formation of deoxophylloerythrin hydrazide. Conditions under which no mesoporphyrin dimethyl ester was reduced, produced chlorin as the major product when deoxophylloerythrin methyl ester was treated with hydrazine hydrate. To obtain deoxophylloerythrin hydrazide, less severe conditions were employed; and the unconverted material was recovered and recycled. The reaction conditions reported (see Experimental Section) represent a compromise between unproductive recycling and loss of material by reduction. Except for the quaternary salt (X), all intermediates in the decarboxylation sequence were crystallized and characterized. Not surprisingly, the quaternary salt undergoes elimination so readily that pure crystalline material was not obtained. This ready elimination is in no way detrimental to the synthesis; and, as the procedures evolved, it was found that higher yields were obtained by treating the total precipitate with base and recovering the vinyl compound (XI). The vinyl compound (proto DPEP) was catalytically hydrogenated to DPEP. In the product, a small absorption in the chlorin region (645 mμ) was observed. Mesoporphyrin does not reduce to chlorin under similar conditions even on extended hydrogenation. It is clear from these results that the isocyclic ring causes the molecule to be much more readily reduced.

Preparation of Metallo Chelates.—Vanadyl sulfate and acetic acid are effective in introducing vanadyl into porphyrins of the etio series; however, the insoluble vanadyl porphyrin coats the vanadyl sulfate particles and prevents the reaction from going to completion.[11] Addition of a cosolvent such as pyridine or dimethylformamide provides a homogeneous reaction mixture and overcomes this problem. Dimethylformamide is the cosolvent of choice when higher temperatures are required. Interestingly, the effect of the isocyclic ring was again noticed in the preparation of the vanadyl complexes. Considerably higher temperatures than those needed for the preparation of vanadyl mesoporphyrin failed to produce vanadyl deoxophylloerythrin. Addition of a small amount of trichloroacetic acid causes the reaction to proceed at a temperature of *ca.* 130°.

The formation of nickel chelates did not seem to be subject to such effects, and they were prepared in the standard way with nickel acetate in glacial acetic acid.

Electronic Spectra.—The visible spectra of all the derivatives of deoxophylloerythrin were identical (compounds V–X). Since only alterations to the side chain 2 or more carbons from the ring were being performed, this is expected. Only when the quaternary salt (X) decomposed to give a vinyl group in conjugation with the ring, did a noticeable change occur (compare parts a and b of Figure 1). The spectrum of the vinyl compound was shifted 6 mμ to longer wavelength compared to deoxophylloerythrin and much of the fine

(11) J. G. Erdman, V. G. Ramsey, N. W. Kalenda, and W. E. Hanson, *J. Amer. Chem. Soc.*, **78**, 5844 (1956).

structure which can be easily seen in the other spectra is missing (note especially the near absence of the Ia peak at 588 mμ). These spectral differences are analogous to those in protoporphyrin and etioporphyrin where much more fine structure can be seen in the etio spectrum and a shift of *ca.* 6 mμ per conjugated vinyl group has been noted.[12]

Steric Factors.—In a number of other cases where the hydrazides of porphyrin carboxylic acids were prepared by Fischer and coworkers under much more severe conditions (up to 30-hr reaction time) than employed here, no examples of reduction to chlorins are reported.[13] In none of the cases, however, did the porphyrin carboxylic acids contain an isocyclic ring.

An explanation for the ease of reduction of certain specifically substituted porphyrins has been advanced by Woodward.[6] The lower periphery of porphyrins (as the formula is usually drawn) derived from chlorophyll (such as DPEP) is so heavily laden with substituents that there is not room for all of them to lie in the plane of the ring. Hence, there is considerable distortion of bond angles and lengths. Removal of hydrogen atoms from the 7 and 8 positions of a 6,γ,7-substituted chlorin (for example, pyropheophorbide) transforms carbons 7 and 8 from tetrahedral to trigonal hybridization.

In the trigonal hybridization, substituents are forced into the plane of the ring with resultant distortion of bond angles and lengths. Conversely, there is a strong steric factor which favors the conversion of trigonal carbons, 7 and 8, into tetrahedral ones. Said another way, this means that such porphyrins (*i.e.*, DPEP) are rather easily reduced to chlorins. If the steric factor is absent as in the case of etioporphyrins, the reduction to chlorins occurs only under severe conditions.

Steric arguments similar to those advanced above probably also obtain for the reduction of the 9-carbonyl group to CH_2. The planar oxygen substituent is replaced by two *nonplanar* protons thus alleviating the peripheral crowding. At the same time, the carbonyl carbon is converted from trigonal (120°) into tetrahedral (109°) hybridization, with the concomitant approach to the unstrained 108° interior angle of a five-membered ring.

Naming of Compounds.—It has been convenient to use trivial names in accord with the conventions of Fischer for the new compounds rather than systematic names as substituted porphines. For example, compound (XI) has been called protodeoxophylloerthroetioporphyrin (proto DPEP) rather than 1,3,5,8-tetramethyl-2,4-diethyl-7-vinyl-6,γ-ethanoporphine. The prefix proto in this case showing the same relationship as protoetioporphyrin does to etioporphyrin.[14] The earlier compounds in the series were designated as derivatives of deoxophylloerythrin. Both systematic and trivial names are given in Table I including those for new compounds VII–XI.

(12) J. E. Falk, "Porphyrins and Metalloporphyrins," Elsevier Publishing Co., New York, N. Y., 1964, p 77.

(13) See examples in ref 8 and also H. Fischer and E. Thurner, *Z. Physiol. Chem.*, **204**, 79 (1932).

(14) H. Fischer and H. Orth, "Die Chemie des Pyrrols," Vol. II, part I, Akademie Verlag, Leipzig, 1937, p 218.

Experimental Section[15]

Pyropheophorbide a + b.—Pheophytin a + b[16] (I) (4.0 g) was stirred with acetone (250 ml) in a Waring Blendor for 5 min. The solution was decanted into a 4-l. beaker and the solvent was evaporated on a steam bath under nitrogen until a gummy residue remained. (Allow some acetone to remain to promote solubility in the ether.) Peroxide-free ether (800 ml) was added with stirring to dissolve the pheophytin. Concentrated (36%) HCl (2 l.) was added slowly and the solution was heated on steam bath at boiling temperature for 1 hr. Cold water (800 ml was added and the solution was transferred to a 6-l. separatory funnel. After two extractions with ether (1 l.) to remove the phytol, one-half of the acid solution was placed in a 6-l. separatory funnel, and cold water (2.5 l.) was added. Extraction with successive 1-l. portions of ether (total 6 to 7 l.) was continued until the aqueous layer was pale green. The aqueous layer was then discarded and the second portion was treated in a like manner. The ether extracts were combined and evaporated giving bright green glassy flakes,[17] yield 1.85–1.95 g (65–70%).

Deoxophylloerythrin (V).—Pyropheophorbide a + b (2.0 g) was added to triethylene glycol (300 ml) and 99% hydrazine hydrate (15 ml) in a 500-ml, round-bottom flask fitted with a heater and stirrer. The mixture was heated at 100° for 2 hr in contact with air with constant stirring. NaOH (15 g) was added, the solution was blanketed with nitrogen, and the temperature was raised *carefully* to 150–160° when loss of nitrogen, from hydrazone occurred with frothing of the solution. When the gas evolution was complete, the temperature was raised to 190–210° and maintained for 1 hr. During this time, the reaction mixture changed from a dull green to a reddish brown indicating the formation of porphyrin. The reaction mixture was cooled and poured into 5% HCl (1 l.). After extracting twice with 750-ml portions of ether to remove unconverted chlorin, anhydrous sodium acetate was added to the aqueous layer to pH 5. The precipitate, coagulated by warming, was cooled, filtered, washed with distilled water, and dried at 60° to obtain 1.2–1.35 g (60–68%) of vermillion powder: low resolution mass spectra, 70 eV, *m/e* (%) 520 (100) (P), 505 (6) (P − CH_3^+), 416 (17) (P − CH_2COOH^+). The molecular ion at 492 may indicate that devinylation rather than reduction occurs to a small degree (3%) to give 2-desethyl deoxophylloerythrin. The molecular ion at 494 is not easily explainable but could indicate rupture and loss of the carbocyclic ring. The electronic spectrum was identical with that of the methyl ester (VI).

Deoxophylloerythrin Methyl Ester (VI).—To deoxophylloerythrin (V) (2.0 g) in a 500-ml flask was added absolute MeOH (200 ml), and *dry* nitrogen was passed through for a short time. Gaseous HCl was then added at a rapid rate until the solution was saturated and initial generation of heat was finished. After 20 min, the flow of HCl was reduced and the reaction flask was cooled with an ice bath; however, cooling is probably not necessary since, in some cases, higher yields were obtained without cooling. Slow HCl flow was continued for 1 hr. Then the methanol–HCl solution was poured into a 6-l. separatory funnel containing 2 l. of ice water and ether (1 l.) added. The solution was neutralized to pH 5 with dilute aqueous ammonia (1:1)

(15) Elemental analyses were performed by Mr. J. Walter at the Chemical Laboratories of The Johns Hopkins University. Mass spectra and exact molecular weights were determined on an AEI MS9 double-focusing mass spectrometer by Mr. R. E. Rhodes of Research Services at the Mellon Institute. Electronic spectra were recorded on a Beckman DK-2 spectrophotometer.

(16) Pheophytin a + b is obtainable commercially from a number of suppliers. Alfalfa meal is generally the source of domestic supplies whereas the European source is more commonly stinging nettle leaves. In our hands the latter material was easier to process, being less prone to form persistent emulsions in the phytol separation step and giving pyropheophorbide without gummy contaminants. However, experience with a wide variety of starting materials, some of questionable purity, showed that all were workable and apparently all produce equivalent purity material at the deoxophylloerythrin methyl ester stage. For details on methods of extraction of chlorophyll from plant sources, see R. Willstatter and A. Stoll, "Investigations on Chlorophyll, translated by F. Schertz and A. Merz, Science Printing Press, Lancaster, Pa., 1928, p 48.

(17) The visible spectrum showed peaks at 663, 655, 604, 560, 530, and 501 mμ indicative of a mixture of pyropheophorbide a + b. The procedure was checked by treatment of the a component obtained by acid fractionation (ref 14, part II, p 56). The product in that case showed absorption peaks at 663, 605, 560, 533, and 501 mμ identical with those of authentic pyropheophorbide a [A. Stoll and E. Wiederman, *Helv. Chim. Acta*, **17**, 837 (1934)] and did not give a phase test.

while keeping the temperature at 0–5° by the addition of cracked ice. After separation and reextraction of the water layer with successive 1-l. portions of ether, the unesterified material which precipitated at the interface was recovered by filtration of the water layer. The ether extracts were combined and passed through a 35 × 150 mm column of Alcoa Grade F 80–200 mesh alumina. The ether was reduced to low volume on a steam bath and the product was recovered by filtration. A yield of raw product of 1.3–1.5 g (65–75%) was obtained. The product was recrystallized from 1:10 chloroform–methanol to give blue-black prisms: mp 262° (lit.[18] 264°); spectrum in benzene, λ_{max} 619 mμ (ε 7.1 × 10³), 562 (6.8 × 10³), 527 (3.8 × 10³), 495 (17 × 10³), 393 (220 × 10³) [lit.[19] 615 (6.5 × 10³) 564 (6.3 × 10³), 530 (3.56 × 10³), 496 (16.67 × 10³)].

Vanadyl Deoxophylloerythrin Methyl Ester.—Deoxophylloerythrin methyl ester (0.2 g) and vanadyl sulfate (0.2 g) were dissolved in DMF (10 ml) in a three-necked flask equipped with a nitrogen inlet tube, a stirrer, and condenser. Trichloroacetic acid (1.0 g) dissolved in glacial acetic acid (10 ml) was added and the solution was heated to 120–130° for 1 hr. Warm water (7 ml) was added dropwise, and, after cooling, the crude product was recovered by filtration to yield 0.2 g.

The crude material was dissolved in benzene and chromatographed on Davison No. 62 silica gel. Unreacted deoxophylloerythrin methyl ester was eluted with 50:50 benzene–cyclohexane and the vanadyl chelate was eluted with benzene. The eluant was reduced to low volume and five parts of methanol was added to induce crystallization: in benzene, λ_{max} 568, 528, 405 mμ; rel OD 1.0, 0.77, *ca.* 15.

Anal. $C_{34}H_{36}N_4O_3V$: C, 68.1; H, 6.05. Found: C, 68.3; H, 6.03.

Deoxophylloerythrin Hydrazide (VII).—Deoxophylloerythrin methyl ester (2.0 g) was treated with 98% hydrazine hydrate (8 ml) in absolute MeOH (50 ml) for 7.5 hr at 125°, in a glass-lined bomb tube fitted to a low speed shaker. After cooling, the product was separated by filtration and washed with a small quantity of cold MeOH. The deep green filtrate was diluted with water and filtered to recover the reduced by-product. The yield of hydrazide was 1.35 g (68%). The analytical sample was recrystallized from chloroform–methanol. The spectrum is identical with that of the methyl ester.

Anal. Calcd for $C_{33}H_{38}ON_6$ (534.68): C, 74.1; H, 7.16. Found: C, 73.9; H, 7.32.

The yield of reduced by-product obtained depended on the conditions of the reaction, with longer reaction times leading to greater amounts. Spectrally, the material resembles deoxomesopyropheophorbide (III): spectrum in benzene, λ 643, 584, 528, 492, 387 mμ; rel OD, 1.0, 0.12, weak, 0.38, 4.7 (lit.[8b] 647, 584, 524, 493 mμ); order of intensity, I, IV, II, III.

Deoxophylloerythrin Ethyl-ω-methylurethan (VIII).—Deoxophylloerythrin hydrazide (1.0 g) was dissolved in ice-cold 5% HCl (100 ml) and cold 10% sodium nitrite solution added dropwise until potassium iodide paper turned blue. After standing 1.5 hr in the refrigerator, the reaction mixture was dissolved in ethylene dichloride (1.5 l.), and the aqueous layer was separated and reextracted with ethylene dichloride (0.5 l.). The combined ethylene dichloride extracts were washed with 5% NaOH solution (0.5 l.) and then with distilled water (1.0 l.). The ethylene chloride solution was reduced in volume to *ca.* 500 ml on a rotary evaporator and heated on a steam bath to boiling, MeOH was added (200 ml), and the volume further reduced to *ca.* 200 ml. The remainder of the ethylene dichloride was displaced by the addition of methanol (100 ml) and further heating. The methanol solution was chilled overnight in a refrigerator and the product was recovered by filtration to yield 0.55 g (53%).

The visible spectrum was identical with that of the methyl ester.

Anal. Calcd for $C_{34}H_{39}O_2N_5$ (549.69): C, 74.3; H, 7.15. Found: C, 74.3; H, 7.26.

Deoxophylloerythrin Ethyl-ω-amino Hydrochloride (IX).—Deoxophylloerythrin ethyl-ω-methylurethan (1.0 g) was heated with 10% HCl (150 ml) in a glass-lined bomb with shaking for 10 hr. After cooling (16 hr) the crystallized hydrochloride was recovered by filtration and washed with a little 10% HCl. The yield was small and the compound was very hygroscopic. The spectrum in 10% HCl was identical with that of the dication of the methyl ester: λ_{max} 596, 552, and 404 mμ.

Anal. Calcd for $C_{32}H_{40}N_6Cl_3$(600.04): C, 64.05; H, 6.55. Found: C, 62.3; H, 6.67.

Protodeoxophylloerythroetioporphyrin (XI).—Deoxophylloerythrin ethyl-ω-methylurethan (1.0 g) was treated with 10% HCl (150 ml) in a glass-lined bomb with shaking at 130° for 7.5 hr. The amine was precipitated by the addition of 10% sodium acetate, and recovered by centrifugation. While still wet, it was treated with 10% sodium hydroxide (100 ml) and dimethyl sulfate (10 ml) and shaken vigorously for 2 hr at 30°. The precipitated quaternary amine sulfate (X) was recovered by filtration and extracted from the filter with hot methanol. The methanol was reduced in volume to 100 ml and KOH (10.0 g) added. The solution was refluxed for 3.0 hr and cooled. The product was collected by filtration and washed with water, yield 240 mg. The visible spectrum in benzene is shown in Figure 1a: λ_{max} 624 mμ (ε 6.2 × 10³), 571 (5.3 × 10³), 533 (3.3 × 10³), 502 (15.5 × 10³), 404 (183 × 10³).

Deoxophylloerythroetioporphyrin (XII).—Protodeoxophylloerythroetioporphyrin (XI) (200 mg) was dissolved in tetrahydrofuran (200 ml) and PtO_2 catalyst (0.10 g) was added. The reduction was carried out for 20 hr at 1 atm of hydrogen pressure. The solution was filtered to remove the catalyst and the solvent was evaporated to give an essentially quantitative yield of crude product. The visible spectrum showed in addition to the deoxophylloerythrin type spectrum (Figure 1b) a small peak in the 645-mμ region.

The crude product (120 mg) was chromatographed over 30 g of Davison No. 62 silica gel, with 1:1 benzene–cyclohexane as the eluant. [The forerun contained the green (645 mμ) material.] The solvent was removed under vacuum to yield 100 mg of product with the visible spectrum shown in Figure 1b. A portion was recrystallized from benzene–methanol: low resolution mass spectrum, 70 eV, *m/e* (%) 478 (6) (P + 2⁺), 477 (33) (P + 1⁺), 476 (100) (P⁺), 461 (27) (P − CH_3^+) 477 (3) (P + 1 − $2CH_3^+$), 446 (5) (P − $2CH_3^+$), 431 (6), 429 (6); low resolution mass spectrum, 12 eV, *m/e* (%) 478 (7), 477 (31), 476 (100). No other peaks were observed above the noise level between *m/e* 478 and 239. (Calcd for parent peak $C_{32}H_{36}N_4$: 476.291. Found by high resolution mass spectrometry: 476.284.) The electronic spectrum in benzene had absorptions at λ_{max} 618 mμ (ε 7.3 × 10³), 563 (6.6 × 10³), 528 (3.9 × 10³), and 495 (19 × 10³).

Vanadyl Deoxophylloerythroetioporphyrin.—Crude deoxophylloerythroetioporphyrin (20 mg) was dissolved in DMF (5 ml) and treated with vanadyl sulfate (50 mg), trichloroacetic acid (0.5 g), and glacial acetic acid (5 ml). The reaction mixture was blanketed with nitrogen and heated to 125–135° for 1 hr. The mixture was cooled, diluted with water, and filtered. The crude product was taken up in a minimum of benzene and chromatographed over silica gel. A forerun of a small amount of uncomplexed porphyrin was eluted with 50:50 benzene–cyclohexane and the vanadyl complex was recovered by elution with benzene. The eluant was reduced to low volume and five volumes of methanol was added to induce crystallization. The product was recovered as purplish black pyramids:[20] yield 10 mg; in benzene λ_{max} 570, 529, 405 mμ; rel OD 1.0, 0.77 (Calcd for $C_{32}H_{34}N_4VO$: 541.217. Found by high resolution mass spectrometry: 541.210.).

Nickel Deoxophylloerythroetioporphyrin.—Crude deoxophylloerythroetioporphyrin (50 mg) was treated with nickel acetate (50 mg) in glacial acetic acid (10 ml) at reflux temperature for 0.5 hr. The volume of acetic acid was reduced to *ca.* 4 ml with a stream of nitrogen, and the reaction mixture was allowed to cool. The nickel chelate was recovered by filtration as very small red crystals: yield 8 mg; spectrum in benzene, λ_{max} 550, 521, 392 mμ; rel OD, 1.0, 0.51 (Calcd for $C_{32}H_{34}N_4Ni$: 532.214. Found by high resolution mass spectrometry: 532.214).

Registry No.—VII, 16980-15-7; VIII, 16980-11-3; IX, 16980-12-4; XI, 16980-13-5; XII, 16980-14-6; vanadyl deoxophylloerythrin methyl ester, 15550-18-2; vanadyl deoxophylloerythroetioporphyrin, 17000-55-4.

Acknowledgment.—The authors thank Dr. A. Stoll for a generous gift of pheophytin.

(18) Reference 14, part II, p 199.

(19) A. Stern and H. Wenderlein, *Z. Physik. Chem.* (Leipzig), **174**, 81 (1935).

(20) The crystal structure of this material has been determined by R. C. Pettersen and L. E. Alexander, *J. Amer. Chem. Soc.*, **89**, 3873 (1968).

Conformations of Iridolactones and the Stereochemistry in the Syntheses

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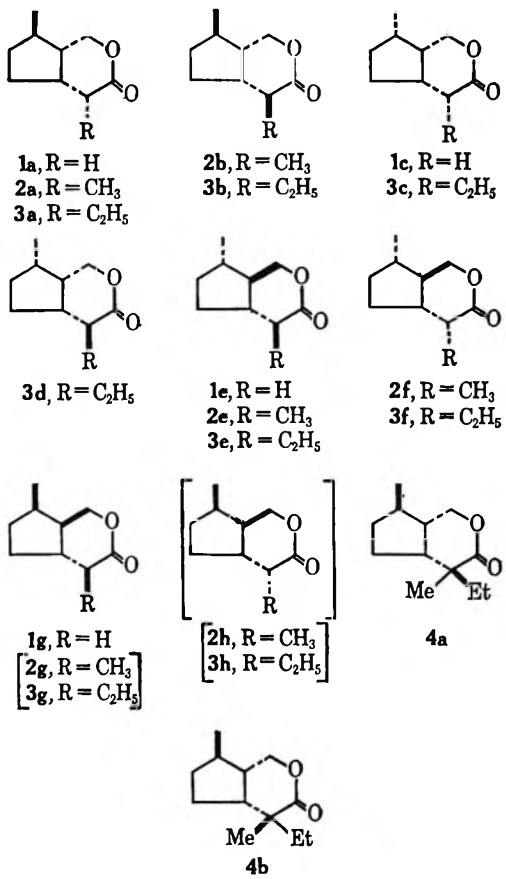
To obtain further information on stereoselective syntheses, six out of eight possible racemic stereoisomers of the lactone of 2-(2-hydroxymethyl-3-methylcyclopentyl)butyric acid (**3a–f**) were prepared from ethyl 2-(3-methyl-2-oxocyclopentyl)butyrate. The stereochemistry of the reactions was compared with the stereochemistry of the lower homologs. Configurations and conformations of these compounds and those of iridomyrmecin, boshnialactone, and their stereoisomers were studied by means of infrared spectra, spin–spin coupling constants, and solvent-induced chemical shifts.

Monoterpenoids with a cyclopentane ring including nepetalactone,[1] iridomyrmecin[2] (**2a**), isoiridomyrmecin[3] (**2b**), and boshnialactone[4] (**1c**) have recently received attention in that the 1,2,3-substituted cyclopentanes are regarded as biogenetic precursors of complex indole alkaloids.[5] The physiological activities[4,6] of these δ-lactones themselves are also interesting because of insecticidal, bactericidal, cat-attracting, and stimulating effects. The synthesis of these lactones was studied.[4,7–10] Stereoselective syntheses starting from 2-carbethoxy-5-methylcyclopentanone[11] carried out in this laboratory[12,13] furnished iridomyrmecin, boshnialactone, and the stereoisomers in racemic forms.

In continuation of these synthetic studies, the preparation of homologs of iridomyrmecin, *i.e.*, 2-(2-hydroxymethyl-3-methylcyclopentyl)butyric acid lactone (**3a–f**) was effected to obtain further information on the stereoselectivity of the syntheses. The fact that the differences in the biological activities of irido- (**2a**) and isoiridomyrmecin (**2b**) (Chart I) seemed to depend on the over-all shapes of the respective molecules but not on their epimeric relationship[14] aroused also an interest in the activities of the homologs. The conformation of iridolactones has been studied since the discovery of these compounds,[3c] but no conclusions except those based on an X-ray crystallographic analysis[14] were obtained. Conformations in solution have not been reported.

Stereoselective Syntheses.—Syntheses of the lactones of 2-(2-hydroxymethyl-3-methylcyclopentyl)butyric acid were carried out by procedures previously used for iridomyrmecin[12] and boshnialactone,[13] the stereochemistry of each process being checked (Charts II and III).

CHART I



Starting from 2-carbethoxy-5-methylcyclopentanone and ethyl 2-bromobutyrate, 2-(2-hydroxymethyl-3-methylcyclopentyl)butyric acid *cis* lactones (**3a–d**) were obtained *via* **5–10**.

Olefinic esters (**7–10**) should be a mixture of racemic *trans* olefins [(±) **7** and (±) **8**] and racemic *cis* olefins [(=) **9** and (±) **10**] in a ratio of 90:10. This ratio was determined, as described below, by the analysis of diacetates (**15–18**) derived from the olefinic esters (**7–10**) as shown in Chart IV. It was assumed that the methylene moiety of the *cis* isomers **9** and **10** would be attacked readily by the bulky dialkylborane from the side opposite the two *cis* group, while the *trans* isomers **7** and **8** were expected to resist attack because of hindrance by either one of the two substituents.[13] When the hydroboration followed by oxidation of the mixture

(1) (a) S. M. McElvain and E. J. Eisenbraun, *J. Amer. Chem. Soc.*, **77**, 1559 (1955); (b) J. Meinwald, *ibid.*, **76**, 4571 (1954).

(2) (a) M. Pavan, *Chim. Ind.* (Milan), **37**, 714 (1955); *Chem. Abstr.*, **50**, 13311c (1956); (b) R. Fusco, R. Trave, and A. Vercellone, *Chim. Ind.* (Milan), **37**, 251 (1955); *Chem. Abstr.*, **50**, 8451*f* (1956).

(3) (a) G. W. K. Cavill, D. L. Ford, and H. D. Locksley, *Chem. Ind.* (London), 465 (1956); (b) G. W. K. Cavill, D. L. Ford, and H. D. Locksley, *Aust. J. Chem.*, **9**, 288 (1956); (c) G. W. K. Cavill and H. D. Locksley, *ibid.*, **10**, 352 (1957).

(4) T. Sakan, H. Murai, Y. Hayashi, Y. Honda, T. Shono, M. Nakajima, and M. Kato, *Tetrahedron*, **23**, 4635 (1967).

(5) (a) W. I. Taylor, *Science*, **163**, 954 (1966); (b) A. R. Battersby, R. T. Brown, R. S. Kapil, A. O. Plunkett, and J. B. Taylor, *Chem. Commun.*, 46 (1966); (c) A. R. Battersby, R. T. Brown, J. A. Knight, J. A. Martin, and A. O. Plunkett, *ibid.*, 346 (1966); (d) E. S. Hall, F. McCapra, T. Money, K. Fukumoto, J. R. Hanson, B. S. Mooto, G. T. Phillips, and A. I. Scott, *ibid.*, 348 (1966).

(6) T. Sakan, A. Fujino, and F. Murai, *Nippon Kagaku Zasshi*, **81**, 1320, 1324 (1960); *Chem. Abstr.*, **56**, 11644*b*, 11644*c* (1962).

(7) K. J. Clark, G. I. Fray, R. H. Jaeger, and R. Robinson, *Tetrahedron*, **6**, 217 (1959).

(8) F. Korte, J. Falbe, and A. Zschocke, *ibid.*, **6**, 201 (1959).

(9) F. Korte, J. H. Büchel, and A. Zschocke, *Chem. Ber.*, **94**, 1952 (1961).

(10) J. Wolinsky, T. Gibson, D. Chan, and H. Wolf, *Tetrahedron*, **21**, 1248 (1965).

(11) K. Sisido, K. Utimoto, and T. Isida, *J. Org. Chem.*, **29**, 2781 (1964).

(12) K. Sisido, K. Utimoto, and T. Isida, *ibid.*, **29**, 3361 (1964).

(13) K. Sisido, T. Kageyama, H. Mera, and K. Utimoto, *Tetrahedron Lett.*, 1553 (1967).

(14) J. F. McConnell, A. M. Mathieson, and B. P. Schornborn, *ibid.*, 445 (1962).

CHART II

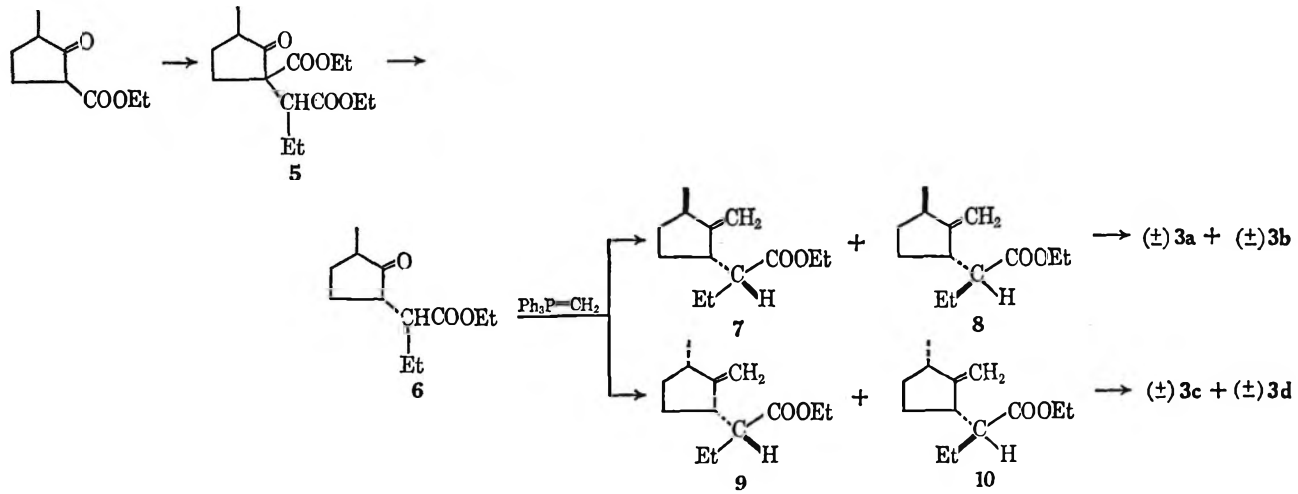


CHART III

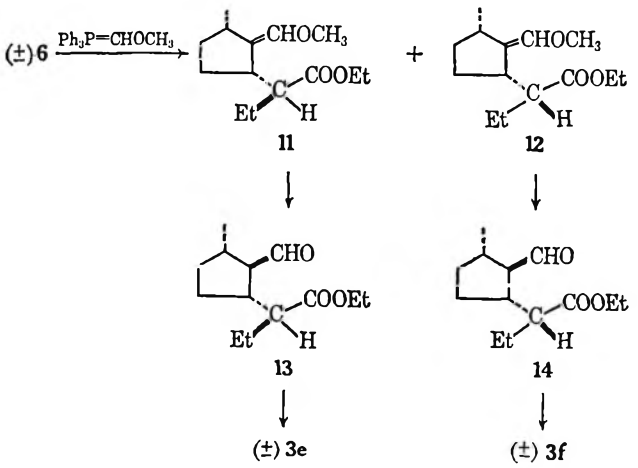
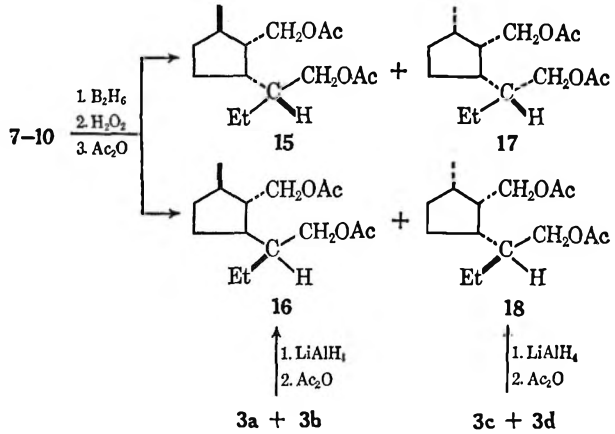


CHART IV



of *cis* and *trans* olefinic esters **7–10** was carried out with an insufficient amount of disiamylborane,[15] the *trans* isomers **7** and **8** remained unattacked. The reaction products afforded, when lactonized after removal[16] of the unchanged olefinic ester, *cis,cis* lactones [(±) **3c** and (±) **3d**]. Hydroboration of the recovered olefinic ester with unsubstituted borane, *i.e.*, diborane, gave *cis,trans* lactones [(±) **3a** and (±) **3b**] by attack from the side holding the less bulky methyl group. Since the synthetic mixture of (±) **3a** and (±) **3b** did not contain the *trans* lactones (**3g** and **3h**), it was proved that the attack of borane did not occur from the side of the butyrate group. In the case of boshnialactone [(±) **1c**], which contains the less bulky acetate group, the attack could occur also from the side of the acetate and compound (±) **1g** was produced.[13]

The lactone (±) **3a** was obtained in crystalline forms, but gas chromatography was utilized for the separation of (±) **3b**, (±) **3c**, and (±) **3d**.

Because it was difficult to carry out configurational studies on the olefinic esters **7–10**, they were converted into the corresponding diols, 2-(2-hydroxymethyl-3-methylcyclopentyl)butanol, and were compared with those prepared from **3a–d**, whose stereochemistry was determined as described below. The olefinic esters **7–10**, on hydroboration and reduction using excess diborane followed by oxidation, gave diols[12] which were acetylated to diacetates (**15–18**). The same diacetates (**15–18**) were prepared from **3a–d** *via* lithium aluminum hydride reduction followed by acetylation. Since the yield of each acetylation was nearly quantitative, it was considered that the acetylations proceeded independently of the isomeric relationships. Gas chromatographic comparison showed that the diacetates **15–18** derived directly from the olefinic esters **7–10** contained 90% *cis,trans* isomers (**15** and **16**) and 10% *cis,cis* isomers (**17** and **18**). It was deduced, therefore, that the olefinic esters obtained by the Wittig reaction was composed of 90% *trans* isomer (**7** and **8**) and 10% *cis* isomer (**9** and **10**) and that diborane attacked the methylene moiety from the direction opposite to the carboxypropyl group.

The *trans* lactones (**3e** and **3f**) were obtained from keto ester **6** *via* **11–14** in a similar way[12,13] as reported previously. Other *trans* lactone isomers [(±) **3g** and (±) **3h**] were not found among the products. This was in accord with the situation prevailing during the preparation of the *trans* isomer of boshnialactone, where the same synthetic route gave only one stereoisomer (**1e**). The methyl group of the cyclopentane ring was, therefore, *cis* to the 1-carboxypropyl group, that is, **3e** and **3f** were considered to be *trans,trans* lactones.

(15) (a) H. C. Brown, "Hydroboration," W. A. Benjamin, Inc., New York, N. Y., 1962; (b) G. Zweifel and H. C. Brown, *Org. Reactions*, **13**, 1 (1963).

(16) If this separation procedure was omitted, *i.e.*, when the lactonization was carried out on the reaction mixture including unchanged acid, the resulted δ-lactone contained γ-lactone, 2-(2,3-dimethyl-2-hydroxycyclopentyl)-butyric acid lactone, separation of which caused a difficult problem.

The keto ester **6** was presumed to be an equilibrium mixture of *cis* and *trans* isomers[17] containing predominantly the *trans* isomer which, however, might readily be subjected to epimerization owing to the existence of an enolizable carbonyl group.

From the fact that the methoxymethylene derivatives gave only **3e** and **3f** and not **3g** and **3h**, the methoxymethylene derivatives were considered to contain only **11** and **12**, *i.e.*, *cis* compounds. In the reaction with **6**, methoxymethylenetriphenylphosphorane seemed to have condensed only with the sterically unhindered *cis* isomer of **6** with the *trans* isomer epimerizing to the *cis* isomer and thus yielding **11** and **12** in high purity.

A similar epimerization was observed by Marshall, Pike, and Carroll,[18] the less reactive isomer being isomerized to the more reactive epimer which then was consumed to produce the olefin. In a different situation,[19] however, when the ketone was not easily epimerized, only the less-hindered isomer reacted to form olefin and the other isomer remained.

In an earlier paper[12] the configurations of the ring methyl group of two *trans* lactones of 2-(2-hydroxymethyl-3-methylcyclopentyl)propionic acid was not established. The two compounds were assumed to be (±) **2g** and (±) **2h** (*trans,cis* lactones), but, as suggested in a later paper,[13] the correct structures should be **2e** and **2f** (*trans,trans* lactones). This matter has now been reinvestigated. The configuration of the methyl group on the lactone ring has been determined by means of solvent-induced chemical shifts.

When heated with quinoline, **3a** and **d** gave a mixture of **3a** and **b**, as well as **3c** and **d**, respectively. These facts suggested that **3a** and **b** as well as **3c** and **d** have the same configuration at the methyl group of the cyclopentane ring but opposite at the ethyl group of the lactone ring. When an equimolar mixture of **3a–d** was heated with sodium methoxide in methanol, the contents of **3b** and **d** were enriched. From the fact that iridomyrmecin [(+) **2a**] could be converted into isoiridomyrmecin [(−) **2b**] by treatment with sodium methoxide,[3c] it was assumed that **3b** and **d** had the same configuration as isoiridomyrmecin [(−) **2b**] with regard to the ethyl group at the lactone ring and that **3a** and **3c** were similar to iridomyrmecin [(+) **2a**].

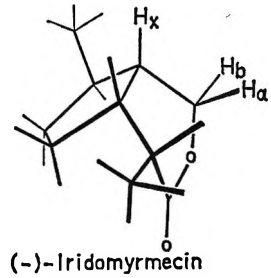
To determine the configuration of the methyl group on the cyclopentane ring, **3a** was alkylated with methyl iodide. This gave a 31:69 mixture of the two 2-methyl-2-(2-hydroxymethyl-3-methylcyclopentyl)butyric acid lactones (**4a** and **b**). Similarly (+)-isoiridomyrmecin[4] [(+)**2b**], on treatment with ethyl iodide, gave a mixture of **4a** and **b** in a 86:14 ratio. The configuration of the methyl group at the cyclopentane ring of **3a** and **2b** is, therefore, the same, which in turn determines the configurations of **3a–d**. Configurations of **3e** and **3f** were determined by physical methods as described below.

The ratios of the formations of **4a** and **4b** supported the conclusions about the configurations. Although the conformation of the iridomyrmecin (**2a**) analog **3a** is different from that of isoiridomyrmecin (**2b**)[2] as shown below, the conformation of the intermediate carbanions derived from **3a** and **2b** were considered to be similar. The alkylations by methyl iodide and ethyl iodide, respectively, would occur preferentially from the sterically less hindered side, that is, from the direction opposite to the cyclopentane ring; thus the entering alkyls should situate preferentially on opposite sides of the cyclopentane ring. Therefore, **3a** gave mainly **4b** and isoiridomyrmecin (**2b**) gave mainly **4a**.

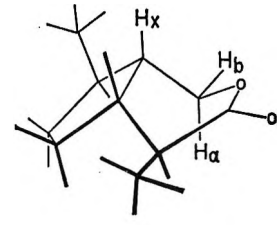
Conformational Analyses.—Configurations of the natural products, *i.e.*, **1c**,[4] **2a**,[2] and **2b**,[3] had already been determined. As to the synthetic compounds **1a**, **3a**, and **3b**, configurations had been determined by comparison with the natural products or by conversion into compounds whose stereochemistry was established as described above. For the remaining ten lactones in Chart I, configurations of the ring junctures were determined by infrared spectroscopy.[12]

According to Cheung, *et al.*,[20] δ-lactones can be assigned a boat or a half-chair form on the basis of their carbonyl absorptions. Thus, lactone rings of **1a**, **1c**, **2a**, **2b**, **3a**, **3b**, **3c**, **3d**, **4a**, and **4b**, whose carbonyl-stretching frequencies $\nu_{C=O}$ were at 1750–1765 cm^{-1}, could be classified as boat forms, while **1e**, **1g**, **2e**, **2f**, **3e**, and **3f**, showing $\nu_{C=O}$ at 1730–1740 cm^{-1}, could be classified as half-chair forms.

Inspection of Dreiding models indicated that a half-chair δ-lactone must have a rigid *trans* configuration and a boat δ-lactone must have a flexible *cis* configuration of either iridomyrmecin or isoiridomyrmecin type[14] as shown below, which shows antipodes of natural iridomyrmecin and isoiridomyrmecin. The lactone ring of these *cis* compounds are slightly folded.



(-)-Iridomyrmecin



(+)-Isoiridomyrmecin

For all lactones the same conclusion as to the stereochemistry of ring juncture was established by the respective synthetic routes.[12,13]

An attempt was also made to elucidate configurations and conformations of these lactones by nmr coupling

(17) K. Sisido, S. Kurozumi, K. Utimoto, and T. Ishida, *J. Org. Chem.*, **31**, 2795 (1966), showed that in the equilibrium mixture of 2-isopropyl-5-methylcyclopentanone 70% was the *trans* isomer and 30% was the *cis* isomer. An effort to analyze **6** was unsuccessful owing to the difficulty of the separation by gas chromatography.

(18) J. A. Marshall, M. T. Pike, and R. D. Carroll, *ibid.*, **31**, 2933 (1966).

(19) E. J. Corey, R. B. Mitra, and H. Uda, *J. Amer. Chem. Soc.*, **86**, 485 (1964).

(20) K. K. Cheung, K. H. Overton, and G. A. Sim, *Chem. Commun.*, 634 (1965).

constants and solvent-induced shifts was also made in view of previous reports.[21-26]

Application of the Karplus equation[27] to the dihedral angles of H_a and H_x as well as H_b and H_x measured from Dreiding models (Table I) gave theoretical

TABLE I
DIHEDRAL ANGLES AND COUPLING CONSTANTS OF IRIDOMYRMECIN AND ISOIRIDOMYRMECIN

	Dihedral angle, obsd,[a] deg		Coupling constant—J_{ax}, Hz—		—J_{bx}, Hz—	
	H_aH_x	H_bH_x	Calcd	Obsd	Calcd	Obsd
Iridomyrmecin (2a)	57	63	2.2	3.0	1.7	3.0
Isoiridomyrmecin (2b)	175	55	9.2	10.1	2.5	5.9

[a] Approximate value measured on the Dreiding models.

values for spin–spin coupling constants which were compared with the observed ones (Table I). Considering the fact that there is some dependence of coupling constant on the conformational relationship between protons and the electronegative oxygen[28,29] and that the calculated constants tend to give smaller values than the observed ones,[30] these measurements made with samples in solution are in good agreement with calculated values based on the conformations of the crystalline iridomyrmecin (**2a**) and isoiridomyrmecin (**2b**)[14] and suggest that these lactones have similar conformations both in the crystalline state and in solution.

Coupling constants J_{ax} and J_{bx} might be regarded as possible mean classifying the *cis* lactones into an iridomyrmecin or an isoiridomyrmecin type. By this procedure, lactones **1a**, **1c**, **2a**, **3a**, **3c**, **4a**, and **4b** were classified as of iridomyrmecin types and lactones **2b**, **3b**, and **3d** as of isoiridomyrmecin types (Table II). Dreiding models indicated that the methyl or ethyl group on the lactone ring was in a quasi-equatorial position in these *cis* lactones.

It is reasonable to assume that, within a certain series of similar compounds, solvent induced shifts of nmr signals as well as the spin–spin coupling constants (J_{ax} and J_{bx}) have nearly equal values when the compounds in solution have the same configuration. The values of iridomyrmecin-type *cis* lactones in Table II, those of isoiridomyrmecin-type *cis* lactones in Table III, and those of *trans* lactones in Table IV were compared with each other.

It was concluded that, with respect to the methyl group at the cyclopentane ring, **1a**, **2a**, **3a**, **4a**, and **4b** (iridomyrmecin-type *cis* lactones), **2b** and **3b** (isoiridomyrmecin-type *cis* lactones), as well as **1e**, **2e**, **2f**, **3e**, and **3f** (*trans* lactones) have the same configuration, respectively, and that, because known lactones of

TABLE II
IR AND NMR DATA OF IRIDOMYRMECIN-TYPE *cis* LACTONES

	J_{ax}, Hz	J_{bx}, Hz	J_{ab}, Hz	Methyl group at	ΔR,[a] ppm	δ_{CDCl_3},[b] ppm	$\delta_{C_6H_6}$,[c] ppm	$\nu_{C=O}$, cm^{-1}
1a	3.0[d]	3.0	−12.0	Cyclopentane	0.34	1.04	0.70	1755
1c	5.0	1.0	−10.5	Cyclopentane	0.38	1.00	0.62	1755
2a	3.0[d]	3.0	−11.4	Cyclopentane	0.32	1.05	0.73	1755
				Lactone	0.10	1.13	1.03	
3a	3.1[d]	3.1	−11.4	Cyclopentane	0.32	1.05	0.73	1755
				Ethyl group	0.14	0.98	0.84	
3c	4.1	1.1	−12.0	Cyclopentane	0.21	1.07	0.86	1755
				Ethyl group	0.13	0.98	0.85	
4a	4.6	1.1	−11.7	Cyclopentane	0.31	1.05	0.74	1750
				Lactone	0.06	1.16	1.10	
				Ethyl group	0.13	0.93	0.80	
4b	5.6	3.4	−11.5	Cyclopentane	0.35	1.05	0.70	1750
				Lactone	0.33	1.27	0.94	
				Ethyl group	0.18	0.91	0.73	

[a] $\Delta R = \delta_{CDCl_3} - \delta_{C_6H_6}$. [b] δ_{CDCl_3} means the chemical shift in $CDCl_3$ solution. [c] $\delta_{C_6H_6}$ means the chemical shift in benzene solution. [d] Nmr spectra of these protons were very simple; *cf.* pp 363 and 364 of ref 30.

TABLE III
IR AND NMR DATA OF ISOIRIDOMYRMECIN-TYPE *cis* LACTONES

	J_{ax}, Hz	J_{bx}, Hz	J_{ab}, Hz	Methyl group at	ΔR,[a] ppm	δ_{CDCl_3},[b] ppm	$\delta_{C_6H_6}$,[c] ppm	$\nu_{C=O}$, cm^{-1}
2b	10.1	5.9	−11.0	Cyclopentane	0.42	1.07	0.65	1755
				Lactone	0.14	1.20	1.06	
3b	9.8	5.9	−10.5	Cyclopentane	0.39	1.05	0.66	1755
				Ethyl group	−0.06	0.99	1.05	
3d	10.7	5.9	−11.0	Cyclopentane	0.47	1.00	0.53	1755
				Ethyl group	−0.01	1.05	1.06	

[a] $\Delta R = \delta_{CDCl_3} - \delta_{C_6H_6}$. [b] δ_{CDCl_3} means the chemical shift in $CDCl_3$ solution. [c] $\delta_{C_6H_6}$ means the chemical shift in benzene solution.

TABLE IV
IR AND NMR DATA OF *trans* LACTONES

	J_{ax}, Hz	J_{bx}, Hz	J_{ab}, Hz	Methyl group at	ΔR,[a] ppm	δ_{CDCl_3},[b] ppm	$\delta_{C_6H_6}$,[c] ppm	$\nu_{C=O}$, cm^{-1}
1e	10.5	4.5	−10.5	Cyclopentane	0.39	1.04	0.65	1738
2e	9.8	4.7	−10.7	Cyclopentane	0.40	1.04	0.64	1740
				Lactone	0.12	1.26	1.14	
2f	9.7	4.7	−10.7	Cyclopentane	0.38	1.03	0.65	1740
				Lactone	0.21	1.21	1.00	
3e	9.7	4.7	−10.7	Cyclopentane	0.39	1.04	0.65	1740
				Ethyl group	0.04	0.94	0.90	
3f	9.7	4.4	−10.7	Cyclopentane	0.39	1.04	0.65	1740
				Ethyl group	0.02	1.04	1.02	
1g	10.5	5.0	−10.5	Cyclopentane	0.49	0.88	0.39	1740

[a] $\Delta R = \delta_{CDCl_3} - \delta_{C_6H_6}$. [b] δ_{CDCl_3} means the chemical shift in $CDCl_3$ solution. [c] $\delta_{C_6H_6}$ means the chemical shift in benzene solution.

established stereochemistry are included in this group, the methyl group was *trans* with respect to the lactonized hydroxymethyl group.

If the benzene–lactone complex formed between the carbonyl and the π electrons is assumed to be similar to that of the benzene–ketone complex described by Williams and Wilson,[26] the coordinating benzene molecule may be considered to be at the less hindered side of the lactone carbonyl group. From the observation of the Dreiding models, the solvent induced shift values of *cis*-methyl groups of the cyclopentane ring were expected to be smaller than those of *trans*-methyl groups in the case of iridomyrmecin-type lactones, and larger in the case of isoiridomyrmecin-type lactones and *trans* lactones. The exceptionally high value of **1c** was accounted for assuming repulsion due to the three groups, being situated in the *cis,cis* configuration. A somewhat modified shape of the iridomyrmecin type must be invoked for **1c**, because **1c** has no substituents. The fact

(21) N. S. Bhacca and D. H. Williams, "Application of NMR Spectroscopy in Organic Chemistry. Illustrations from the Steroid Field," Holden-Day, Inc., San Francisco, Calif., 1964.

(22) M. Fetizon, J. Core, P. Laszlo, and B. Waegell, *J. Org. Chem.*, **31**, 4047 (1966).

(23) J. Ronayne and D. H. Williams, *Chem. Commun.*, 712 (1966).

(24) G. Di Maio, P. A. Tardella, and C. Iavarone, *Tetrahedron Lett.*, 2825 (1966).

(25) J. D. Connoly and R. McCrindle, *Chem. Ind.* (London), 379, 2066 (1965).

(26) D. H. Williams and D. A. Wilson, *J. Chem. Soc., B*, 144 (1966).

(27) M. Karplus, *J. Amer. Chem. Soc.*, **85**, 2870 (1963), and references cited therein.

(28) H. Boothe, *Tetrahedron Lett.*, 411 (1963), and references cited therein.

(29) Reference 21, pp 52, 53.

(30) J. W. Emsley, J. Feeney, and L. H. Sutcliff, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Pergamon Press, Oxford, 1965, pp 166–170.

that **3c**, which has also the *cis,cis* configuration, showed a smaller value might be explained by assuming that the unfolding of the lactone ring owing to the repulsion was somewhat hindered by the interaction of the ethyl group with the cyclopentane ring.

In lactones containing ethyl groups, solvent-induced shifts of the methyl moieties of the ethyl groups were effected to be less important in helping to establish the configurations, because the methyl moiety can rotate around the carbon–carbon bond of the ethyl group. Nevertheless, although the configuration of **4a** and **b** were deduced from the synthetic routes, as described above, confirmation was provided by a comparison of the solvent-induced shift of the lactone methyl group of **4a** (ΔR = 0.06 ppm) with that of iridomyrmecin (**2a**) (ΔR = 0.10 ppm). Since **4b** showed an entirely different value of 0.33 ppm, the methyl group of **4a** apparently had the same configuration as that of iridomyrmecin (**2a**).

Since, according to the Dreiding models, the methyl group on the lactone ring of **2e** is closer to the "carbonyl plane"[31] than that of **2f**, the solvent-induced shift of the methyl group of **2e** must be smaller than that of **2f**. The observed values, ΔR = 0.12 ppm for **2e** and ΔR = 0.21 ppm for **2f**, agree with the expectation. Owing to the difficulty of determining the configuration of the ethyl groups of the lactone ring by solvent-induced shifts as described above, comparison of the coupling constants (J_{ax} and J_{bx}, shown in Table IV) and the chemical shifts [δ (H_a) and δ (H_b)] of **3e** and **3f** with those of configurationally known **2e** and **2f** was utilized. Signals of the methylene protons of hydroxymethyl group of **2e** were observed at δ 4.02 and 4.49 ppm, and these values were equal to those of **3e**. The analogous protons of **2f** had signals at δ 3.95 and 4.46 ppm, equal to those of **3f**. From this, **2e** and **3e** as well as **2f** and **3f** were considered to be of similar conformation.

Thus the configuration and conformation of boshnialactone, iridomyrmecin and homolog, and their stereoisomers in solutions were determined. The conformation of iridomyrmecin in solution was found to be the same as that established for crystalline iridomyrmecin and its stereoisomers.[14]

Experimental Section

Infrared spectra were determined on Shimadzu IR-27. Gas chromatography was carried out on Shimadzu GC-2C and Shimadzu GC-1B for packed column and Hitachi K-23 for Goley column. Nmr spectra were measured at 60 MHz with Varian Associates A-60 and Japan Electron Optics C-60-H in 5% solution. For microelemental analyses Yanagimoto Automatic Analyser CHN Corder MT-1 was used.

All identifications of the compounds were carried out by the comparison of infrared spectra and gas chromatograms.

Ethyl 2-(1-Carbethoxy-3-methyl-2-oxocyclopentyl)butyrate (5).—Analogous procedure to the synthesis of ethyl 2-(1-carboethoxy-3-methyl-2-oxocyclopentyl)propionate[12] gave the product in 70% yield: bp 123–125° (3 mm); n^{30}D 1.4545; ir (liquid film) 1765 (C=O), 1740 (ester C=O), 1200, 1025 cm^{-1}.

Anal. Calcd for $C_{15}H_{24}O_5$: C, 63.36; H, 8.51. Found: C, 63.09; H, 8.66.

2-(3-Methyl-2-oxocyclopentyl)butyric Acid.—According to the procedure of Linstead and Jones,[32] from 263 g (0.93 mol) of ethyl 2-(1-carbethoxy-3-methyl-2-oxocyclopentyl)butyrate (**5**) there was obtained 119 g (0.65 mol; yield 70%) of 2-(3-methyl-2-oxocyclopentyl)butyric acid, bp 147–148° (5 mm), which solidified to give small crystals: mp 71–87°; ir (KBr) 1740 (C=O), 1700 (acid C=O), 1240, 925 cm^{-1}.

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.05; H, 8.78.

The **2,4-dinitrophenylhydrazone** had mp 205° dec.

Anal. Calcd for $C_{16}H_{20}O_6N_4$: C, 52.74; H, 5.53. Found: C, 52.53; H, 5.70.

Ethyl 2-(3-Methyl-2-oxocyclopentyl)butyrate (6).—Esterification of 71 g (0.39 mol) of the above-mentioned keto acid by the Linstead and Jones procedure[32] gave 75 g (0.36 mol; yield 92%) of ethyl 2-(3-methyl-2-oxocyclopentyl)butyrate (**6**): bp 94–95° (1 mm); n^{20}D 1.4552; ir (liquid film) 1735, 1180, 1025 cm^{-1}.

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 68.14; H, 9.23.

The **2,4-dinitrophenylhydrazone** had mp 159–160°.

Anal. Calcd for $C_{18}H_{24}O_6N_4$: C, 55.09; H, 6.19. Found: C, 55.10; H, 5.89.

Ethyl 2-(3-Methyl-2-methylenecyclopentyl)butyrate (7–10).—According to Greenwald, Chaykovsky, and Corey[33] and analogous to our previous report,[12] 17 g of **6** and 40.4 g of methyltriphenylphosphonium iodide in dimethyl sulfoxide gave 7.5 g (yield 45%) of ethyl 2-(3-methyl-2-methylenecyclopentyl)butyrates (**7–10**): bp 85–90° (5 mm); n^{25}D 1.4533; ir (liquid film) 3065, 1740, 1650, 880 cm^{-1}.

Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.21; H, 10.32.

Hydroboration of Ethyl 2-(3-Methyl-2-methylenecyclopentyl)-butyrate (7–10) with Diborane. Preparation of *cis* Lactone Mixture (3a–d).—The hydroboration was carried out with 0.61 g (16 mmol) of sodium borohydride, 10.1 g (48 mmol) of ethyl 2-(3-methyl-2-methylenecyclopentyl)butyrate (**7–10**), and 2.3 g (16 mmol) of boron trifluoride etherate in 40 ml of diglyme. After oxidation with 30% hydrogen peroxide solution in an alkaline medium acidification gave *cis* lactone mixture (**3a–d**), bp 102–110° (3 mm), yield 1.9 g (10 mmol; 22%). By gas chromatographic analyses this lactone mixture was found to contain 2-(2-hydroxymethyl-3-methylcyclopentyl)butyric acid lactones (**3a–d**) (78%) and an isomeric mixture of γ-lactones (22%), 2-(2-hydroxy-2,3-dimethylcyclopentyl)butyric acid lactones, which were identified by comparison with an authentic sample synthesized as described below.

Gas chromatography of **3a–d** revealed that this mixture contained 90% *cis,trans* lactones (**3a** and **b**) and 10% *cis,cis* lactones (**3c** and **d**).

2-(2-Hydroxy-2,3-dimethylcyclopentyl)butyric Acid Lactone.—An ethereal solution of methylmagnesium iodide prepared from 7.6 g (53.5 mmol) of methyl iodide and 1.3 g (53.5 mg-atoms) of magnesium was added to an ethereal solution of 8.5 g (40 mmol) of ethyl 2-(3-methyl-2-oxocyclopentyl)butyrate (**6**) in the course of 15 min, and the reaction mixture was heated under reflux for 1 hr. The reaction complex was decomposed by addition of an aqueous ammonium chloride solution and extracted with ether. After evaporation of ether, 40 ml of water and 2.5 g of sodium hydroxide were added to the residue, and the mixture was heated for 4 hr under reflux. After removal of unsaponified material, the aqueous layer was acidified to pH 3 with hydrochloric acid and heated for 30 min under reflux. The cooled reaction mixture was extracted with ether. On evaporation of ether, there was obtained 1.5 g (65%) of 2-(2-hydroxy-2,3-dimethylcyclopentyl)butyric acid lactone: bp 97–107° (4 mm); n^{24}D 1.4624; ir (liquid film) 1770 cm^{-1}.

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.21; H, 9.97.

Selective Hydroboration Synthesis of (±)-*cis,cis*-2-(2-Hydroxymethyl-3-methylcyclopentyl)butyric Acid Lactones (3c and 3d).—To a solution of 1.55 g (0.022 mol) of 2-methyl-2-butene in 15 ml of tetrahydrofuran (THF), 4.1 ml of a THF solution of diborane (containing 0.010 mol of BH_3) was added at 0° under an atmosphere of nitrogen, and the mixture was stirred for 1 hr at 0° and for 2 hr at room temperature. The mixture was cooled to 0° and 4.2 g (0.020 mol) of ethyl 2-(3-methyl-2-methylenecyclopentyl)butyrate (**7–10**) was added and stirred for 2 hr at 0°. After standing overnight at room temperature, to the reaction mixture was added, at 0°, 1 ml of water, 5 ml of 3 *N* sodium hydroxide solution, and 5 ml of 30% hydrogen peroxide in a course of 15 min. After vigorous stirring for an additional 30 min

(31) "Carbonyl plane" means the plane drawn through the carbon of the carbonyl group normal to the axis of the carbonyl bond.

(32) R. P. Linstead and R. L. Jones, *J. Chem. Soc.*, 616 (1936).

(33) R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, **28**, 1128 (1963).

at room temperature, the product was extracted with ether. Ether extract was washed with saturated sodium chloride solution, dried (Na_2SO_4), and concentrated. Evaporation residue afforded, on vacuum distillation, 2.5 g (60% recovery) of unchanged olefinic esters, bp 95–110° (3 mm), which were proved by vpc and ir spectroscopy to be a mixture of **7** and **8**. The residue of the vacuum distillation (1.1 g) was added to a solution of 30 ml of aqueous 3 *N* sodium hydroxide solution containing 1 ml of ethanol and heated under reflux for 5 hr with vigorous stirring. After cooling to room temperature, the solution was extracted with ether to remove unsaponified materials. The aqueous layer was acidified with hydrochloric acid and was extracted with ether. The ether extract was washed with water, dried (Na_2SO_4), concentrated, and distilled giving 0.4 g (0.0022 mol; 11%) of (±)-*cis,cis*-2-(2-hydroxymethyl-3-methylcyclopentyl)butyric acid lactones, **3c** and **d**, bp 100–115° (5 mm). Gas chromatography revealed that this *cis,cis* lactone mixture, **3c** and **d**, contained 9% *cis,trans* lactones, **3a** and **3b**.

From vpc, these *cis,cis* lactones were considered to be an about 1:2 mixture of **3c** and **d**. Pure **3c** and **d** were obtained by preparative vpc.

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.62; H, 9.70.

Compound **3c** had the following spectral data: ir (liquid film), 1755, 1120, 1050, 1020 cm^{-1}; nmr ($CDCl_3$) δ 1.07 (d, 3, J = 6 Hz, CH_3–CH), 0.98 (t, 3, J = 7 Hz, CH_3–CH_2), 1.20–3.00 (m, 10), 4.31 (m, 2, –CH_2–O).

Compound **3d** had the following spectral data: ir (liquid film), 1755, 1160, 1100, 1055, 1020 cm^{-1}; nmr ($CDCl_3$) δ 1.00 (d, 3, J = 6 Hz, CH_3–CH), 1.05 (t, 3, J = 7 Hz, CH_3–CH_2), 1.20–3.00 (m, 10), 4.15 (m, 2, –CH–O).

(±)-*cis,trans*-2-(2-Hydroxymethyl-3-methylcyclopentyl)butyric Acid Lactones (3a and 3b).—To a THF (10 ml) solution of 2.4 g (11.4 mmol) of the *trans* olefinic ester (**7** and **8**), recovered as an unchanged residue in the above preparation, 3.5 ml of a THF solution of diborane containing 8.36 mmol of BH_3 was added at 0° under an atmosphere of nitrogen. After usual treatment there was obtained a mixture of *cis,trans* lactones, **3a** and **b**: bp 114–116° (5 mm); yield 1.0 g (48%). Vpc showed that this mixture contained 3% *cis,cis* lactones, **3c** and **d**, but no **3g** and **h**.

The separation of **3a** and **b** proceeded with difficulty by ordinary vpc (packed column with HVSG, PEG-6000, Apiezon-L or succinate polyester). However, from this mixture, **3a** crystallized out and recrystallization from petroleum ether (bp 60–80°) gave a pure sample, mp 55°. Pure **3b** was prepared by preparative vpc on an HVSG column.

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.41; H, 10.14.

Compound **3a** had the following spectral data: ir (liquid film), 1755, 1175, 1160, 1110, 1080, 920, 755 cm^{-1}; nmr ($CDCl_3$) δ 1.05 (d, 3, J = 5 Hz, CH_3–CH), 0.98 (t, 3, J = 7 Hz, CH_3–CH_2), 1.20–2.90 (m, 10), 4.22 (m, 2, –CH_2–O).

Compound **3b** had the following spectral data: ir (liquid film) 1755, 1160, 1125, 1105, 1055, 1025 cm^{-1}; nmr ($CDCl_3$) δ 1.05 (d, 3, J = 5 Hz, CH_3–CH), 0.99 (t, 3, J = 7 Hz, CH_3–CH_2), 1.10–2.30 (m, 10), 4.10 (m, 2, –CH_2–O).

Ethyl 2-(2-Methoxymethylene-3-methylcyclopentyl)butyrates (11 and 12).—To a mixture of 70 ml of 1,2-dimethoxyethane, 1.45 g (60 mmol) of sodium hydride (2.9 g of 50% suspension in mineral oil) and 1 drop of ethanol was added 20.6 g (60 mmol) of methoxymethyltriphenylphosphonium chloride.[34,35] To the phosphorane was added 6.35 g (30 mmol) of ethyl 2-(3-methyl-2-oxocyclopentyl)butyrate (**6**). Treatment as reported previously[12] afforded 5.6 g (24 mmol; yield 78%) of ethyl 2-(2-methoxymethylene-3-methylcyclopentyl)butyrate: bp 107–109° (2 mm); $n^{20}D$ 1.4640; ir (liquid film) 1740, 1680, 1120 cm^{-1}.

Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07. Found: C, 69.87; H, 9.96.

Ethyl 2-(2-Formyl-3-methylcyclopentyl)butyrates (13 and 14).—According to the procedure of Levine,[34] hydrolysis of methoxymethylene group was effected by adding 2.15 g (8.95 mmol) of ethyl 2-(2-methoxymethylene-3-methylcyclopentyl)butyrates (**11** and **12**) to 30 ml of ether saturated with 70% perchloric acid to give 1.9 g (94% yield) of ethyl 2-(2-formyl-3-methylcyclopentyl)butyrate: bp 107–109° (3 mm); $n^{24}D$ 1.4543; ir (liquid film) 2700, 1735 cm^{-1}.

Anal. Calcd for $C_{13}H_{22}O_3$: C, 69.99; H, 9.80. Found: C, 68.92; H, 9.95.

The **2,4-dinitrophenylhydrazone** had mp 180–181°.

Anal. Calcd for $C_{19}H_{26}O_6N_4$: C, 56.14; H, 6.45; N, 13.79. Found: C, 56.15; H, 6.49; N, 13.65.

(±)-*trans,trans*-2-(2-Hydroxymethyl-3-methylcyclopentyl)butyric Acid Lactones (3e and 3f).—A solution of 1.0 g (4.4 mmol) of ethyl 2-(2-formyl-3-methylcyclopentyl)butyrates (**13** and **14**), 50 mg (1.3 mmol) of sodium borohydride, and 15 ml of ethanol was stirred for 1 hr. After decomposition of the residual active hydride with dilute hydrochloric acid, the reaction mixture was added to a solution of 5 g of sodium hydroxide in 20 ml of water and boiled for 4 hr under vigorous stirring. During the heating, ethanol was distilled off. After cooling, unsaponified materials were removed by extraction with ether. The aqueous solution was acidified with hydrochloric acid and refluxed for 30 min. The cooled reaction mixture was extracted with ether, and the ether extract was washed with water and dried (Na_2SO_4). When ether was evaporated, 0.5 g (2.8 mmol; yield 63%) of *trans,trans*-2-(2-hydroxymethyl-3-methylcyclopentyl)butyric acid lactones, **3e** and **f**, was obtained: bp 120–130° (5 mm); $n^{23}D$ 1.4748.

As determined by vpc peak areas, this mixture contained 79% **3e** and 21% **3f**. Using Goley column (BDS-45), this mixture was shown to be a mixture of only two components (**3e** and **f**) out of the possible four isomers (**3e–h**). Pure **3e** and **f** were obtained by preparative vpc.

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.59; H, 10.08.

Compound **3e** had the following spectral properties: ir (liquid film) 1740, 1170, 1130, 1105, 1080, 1020 cm^{-1}; nmr ($CDCl_3$) δ 1.04 (d, 3, J = 5 Hz, CH_3–CH), 0.94 (t, 3, J = 7 Hz, CH_3–CH_2), 1.00–2.50 (m, 9), 3.45 (q, 1, J = 7 Hz, —CH—C=O), 4.02 (m, 1, –CH–O–), 4.49 (m, 1, –CH–O–).

Compound **3f** had the following spectral properties: ir (liquid film) 1740, 1190, 1105, 1060, 1020 cm^{-1}; nmr ($CDCl_3$) δ 1.04 (d, 3, J = 5 Hz, CH_3–CH), 1.04 (t, 3, J = 7 Hz, CH_3–CH_2), 1.10–2.40 (m 9), 2.60 (m 1, —CH—C=O), 3.95 (m, 1, –CH–O–), 4.46 (m, 1, –CH–O–).

(±)-*trans,trans*-Iridolactones (2e and f).—Pure **2e** and **f** were separated from the products reported previously[12] by preparative vpc.

Compound **2e** had the following spectral data: ir (liquid film) 1740, 1175, 1135, 1110, 1070, 1040, 1010 cm^{-1}; nmr ($CDCl_3$) δ 1.04 (d, 3, J = 5 Hz, CH_3-cyclopentane), 1.26 (d, 3, J = 7 Hz, CH_3-lactone), 1.00–2.50 (m, 8), 4.02 (m, 1, –CH–O–), 4.49 (m, 1, –CH–O–).

Compound **2f** had the following spectral data: ir (liquid film) 1740, 1220, 1195, 1105, 1040, 1010 cm^{-1}; nmr ($CDCl_3$) δ 1.04 (d, 3, J = 5 Hz, CH_3-cyclopentane), 1.23 (d, 3, J = 7 Hz, CH_3-lactone), 0.90–2.50 (m, 7), 2.87 (m, 1, –CH–C=O), 3.95 (m, 1, –CH–O–), 4.46 (m, 1, –CH–O–).

Conversion of 3a into 3b.—According to the procedure for conversion of isoiridomyrmecin into an equilibrium mixture of iridomyrmecin and isoiridomyrmecin,[36] 25 mg of **3a** in 2.5 ml of quinoline was heated at reflux temperature for 50 hr under an atmosphere of nitrogen. Vpc analysis of the reaction mixture showed that the product was about 1:1 mixture of **3a** and **3b**.

Conversion of 3d into 3c.—In the same way as described above, 10 mg of **3d** was treated with quinoline. Vpc analysis of the reaction mixture showed that it was composed of 24% **3c** and 76% **3d**.

Treatment of 3a through 3d with Sodium Methoxide.—According to Cavill and Locksley,[3c] 100 mg of an equimolar mixture of **3a** through **3d** was added to a solution of 110 mg of sodium dissolved in 15 ml of methanol. After refluxing for 2 hr, methanol was evaporated. The reaction mixture was acidified with dilute hydrochloric acid and was extracted with ether. The ether extract was washed with water and dried over anhydrous sodium sulfate. Evaporation of ether gave 85 mg of an oily substance. Vpc analysis of the substance indicated the disappearance of **3a** and **c**.

Methylation of Lactone 3a.—To 23 ml of a freshly prepared ethereal solution containing 3.45 mmol of triphenylmethylsodium, 0.50 g (2.75 mmol) of **3a** dissolved in 5 ml of ether was added under an atmosphere of nitrogen at room temperature. To this orange solution 1.0 g of methyl iodide was added and, after standing overnight at room temperature, the reaction mixture was added to a solution of 0.5 ml of acetic acid and 10 ml of water.

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The organic layer was extracted with ether, and the ethereal solution was washed with water and 10% sodium carbonate. The solution was kept over anhydrous sodium sulfate, ether was removed, and the residue was distilled to give 0.5 g of a mixture of lactones, bp 115–120° (5 mm). Vpc on HVSG showed that the mixture was composed of a mixture (89%) of **4a** and **b**, whose ratio was 31:69, and a mixture (11%) of unchanged **3a** and its epimeric lactone **3b**. Accordingly, the yield of a mixture of **4a** and **b** was found to be 80%.

Pure **4a** and **b** were separated by preparative vpc.

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.21; H, 9.99.

Ethylation of Isoiridomyrmecin (2b).—From 0.93 g (5.5 mmol) of (+)-isoiridomyrmecin [(+) **2b**], $[\alpha]_D$ +58°, prepared from citronellal according to Robinson, *et al.*,[7] 45 ml of an ethereal solution containing 6.7 mmol of triphenylmethylsodium and 2.0 g of ethyl iodide, there was obtained 1.0 g of a mixture of lactones, bp 122–125° (6 mm). Vpc analysis showed the presence of a mixture of **4a** and **4b** (88%), whose ratio was 86:14, and 12% unchanged isoiridomyrmecin and epimeric iridomyrmecin. The yield of **4a** and **4b** was therefore 81%.

Pure **4a** and **b** were separated by preparative vpc and their ir spectra were identical with those of samples obtained by methylation of **3a**, respectively.

Compound **4a** had the following spectral properties: ir (liquid film) 1750, 1120 cm^{-1}; nmr ($CDCl_3$) δ 1.05 (d, 3, J = 5 Hz, CH_3–CH), 0.93 (t, 3, J = 7 Hz, CH_3–CH_2), 1.16 (s, 3, CH_3–C), 1.00–2.50 (m, 9), 4.33 (m, 2, –CH_2–O).

Compound **4b** had the following spectral properties: ir (liquid film) 1750, 1120 cm^{-1}; nmr ($CDCl_3$) δ 1.05 (d, 3, J = 5 Hz, CH_3–CH), 0.91 (t, 3, J = 7 Hz, CH_3–CH_2), 1.27 (s, 3, CH_3–C), 1.10–2.50 (m, 9), 4.33 (m, 2, –CH_2–O).

2-(2-Hydroxymethyl-3-methylcyclopentyl)butanol from Olefinic Esters, 7–10.—To a solution of 1.80 g (8.6 mmol) of ethyl 2-(3-methyl-2-methylenecyclopentyl)butyrate (**7–10**) in 15 ml of anhydrous THF was added 5 ml of a THF solution containing 5 mmol of diborane at 0°. After stirring for 3 hr at 0° and standing overnight at room temperature, 10 ml of a THF solution containing 10 mmol of diborane was added once again. After keeping at room temperature for 2 days, 1 ml of water was added to the reaction mixture to decompose excess active hydride. Oxidative cleavage of carbon–boron bond was operated by addition of 15 ml of 3 *N* sodium hydroxide and 5 ml of 30% hydrogen peroxide with vigorous stirring over a 10-min period. About 20 ml of THF was distilled off; the reaction mixture was heated at reflux for 5 hr. After cooling, the organic layer was extracted three times with ether, and the ether extract was washed with saturated sodium chloride solution and dried (Na_2SO_4). Distillation gave 1.5 g (94% yield) of the isomeric mixture of the diols: bp 143–146° (2 mm); $n^{23}D$ 1.4875; ir (liquid film) 3340, 1030 cm^{-1}.

Anal. Calcd for $C_{11}H_{22}O_2$: C, 70.92; H, 11.90. Found: C, 71.03; H, 11.78.

2-(2-Acetoxymethyl-3-methylcyclopentyl)butyl Acetates (15–18).—To 1.1 g (5.9 mmol) of the diol mixture was added 15 ml of pyridine together with 15 ml of acetic anhydride and the solution was kept at room temperature overnight. The reaction mixture was treated as usual to give 1.3 g (4.8 mmol; yield 82%) of the diacetates (**15–18**): bp 141–142° (3 mm); $n^{20}D$ 1.4573; ir (liquid film) 1745, 1240, 1035 cm^{-1}.

Anal. Calcd for $C_{15}H_{26}O_4$: C, 66.63; H, 9.69. Found: C, 66.85; H, 9.64.

Diacetate 15 and 16 from Lactones 3a and 3b.—To a stirred slurry of 50 mg of lithium aluminum hydride in 10 ml of dry ether was added 80 mg (0.44 mmol) of *cis,trans* lactones **3a** and **b**, and 30 mg of triphenylmethane which was used as an internal standard for the gas chromatographic yield calculation. After refluxing for 3 hr the complex was decomposed with 5 ml of saturated sodium chloride solution and 10 ml of 10% sulfuric acid. The reaction mixture was extracted three times with ether, washed once with saturated sodium chloride solution, and dried over anhydrous sodium sulfate. Evaporation of ether gave an oily substance whose ir spectrum indicated no carbonyl absorption. To this oil was added 2 ml of pyridine together with 2 ml of acetic anhydride. The reaction mixture was kept at room temperature overnight and worked up as described above. Vpc analysis of the oily product indicated the presence of 109 mg (0.40 mmol; yield 92%) of the *cis,trans* diacetates **15** and **16**. Pure mixture of **15** and **16** was obtained by preparative vpc. Ir spectrum of this mixture was identical with that of diacetates obtained directly from the olefinic esters **7–10**.

Diacetates 17 and 18 from Lactones 3c and 3d.—In the same way, from 71 mg (0.39 mmol) of *cis,cis* lactones **3c** and **d**, there was obtained 93 mg (0.34 mmol; yield 88%) of the isomeric mixture of *cis,cis* diacetates **17** and **18**, whose pure sample was obtained by preparative vpc. Ir spectrum of this mixture was almost identical with that of the mixture of **15** and **16**, but the retention times of vpc on HVSG or PEG-6000 column was different from each other.

Comparison of the Vapor Phase Chromatograms of the Diacetates 15–18.—Vpc analysis of the diacetates **15–18** derived directly from the olefinic esters **7–10** showed that the diacetates were composed of 90% *cis,trans* isomers **15** and **16** and 10% *cis,cis* isomers **17** and **18**.

Registry No.—**1a**, 16802-11-2; **1c**, 16802-12-3; **1e**, 16802-13-4; **1g**, 16802-14-5; (−) **2a**, 16802-15-6; (+) **2b**, 16802-16-7; **2e**, 16802-17-8; **2f**, 16802-18-9; **3a**, 16802-19-0; **3b**, 16802-20-3; **3c**, 16802-21-4; **3d**, 16802-22-5; **3e**, 16802-23-6; **3f**, 16802-24-7; **4a**, 16802-25-8; **4b**, 16802-26-9; **5**, 16802-27-0; *cis* **6**, 16802-30-5; 2,4-dinitrophenylhydrazone of *cis* **6**, 16802-31-6; free acid of *cis* **6**, 16802-28-1; 2,4-dinitrophenylhydrazone of free acid of *cis* **6**, 16802-29-2; *trans* **6**, 16802-07-6; 2,4-dinitrophenylhydrazone of *trans* **6**, 16802-08-7; free acid of *trans* **6**, 16802-09-8; 2,4-dinitrophenylhydrazone of free acid of *trans* **6**, 16802-10-1; 2-(2-hydroxy-2,3-dimethylcyclopentyl)butyric acid lactone, 16802-32-7; **7**, 16802-33-8; **8**, 16802-34-9; **9**, 16802-35-0; **10**, 16802-36-1; **11**, 16802-37-2; **12**, 16802-38-3; **13**, 16802-39-4; 2,4-dinitrophenylhydrazone of **13**, 16802-40-7; **14**, 16802-41-8; 2,4-dinitrophenylhydrazone of **14**, 16802-42-9; **15**, 16802-43-0; **16**, 16802-44-1; **17**, 16802-45-2; **18**, 16802-46-3.

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Simple Methods to Find the Stereochemistry of the Side Chain of γ-Lactones[1,2]

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The preferred conformation of the side chain C_{11}–CH_3 in γ-lactones on the eudesmane skeleton is discussed in the light of thermodynamic studies recently conducted on some of these compounds. Reasons are advanced to justify the results, which are contrary to earlier assumptions. Two simple methods, one depending on solvent shifts and the other on coupling constants, are presented to find directly the stereochemistry of this methyl group in any γ-lactone.

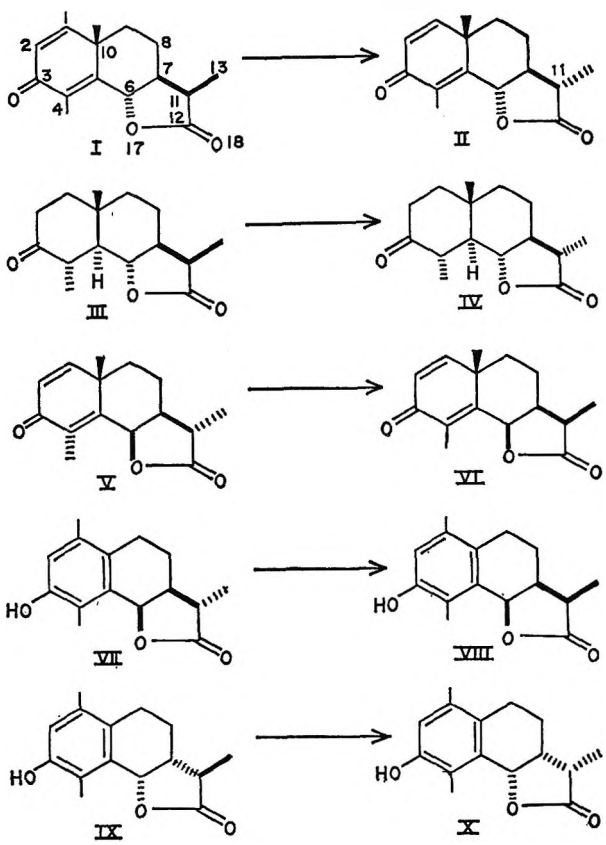
A variety of γ-lactones fused to cyclohexane systems such as santonin, artemisin, alantolactone, etc.,[4] has been known for a long time and new ones are also being found or made. All of these have a methyl side chain next to the lactone carbonyl. There is no simple or direct chemical method, nor was there any physical method to find the stereochemistry of this side chain.

The C_{11}–CH_3 in α-santonin (II, Scheme I) was deduced to be β oriented, because of stability considerations, based on equilibration reactions of this methyl group in the lactone.[5,6] Subsequently, all other related γ-lactones were assigned stereochemistry at C_{11}, either by chemically relating them to an α-santonin derivative or by equilibrating the methyl group and applying the stability considerations referred to above. A series of rules[7] detailing the particular type of lactone and the relation of C_{11}–CH_3 with C_7–H, etc., in each case has been proposed to describe the above assumed stability order and these were applied to assign the stereochemistry at C_{11} of newly found lactones.[8]

However, more recent X-ray studies of 2-bromodihydroisophoto-α-santonic lactone acetate[9] and 2-bromo-α-santonin[10] and independent chemical studies[11,12] have conclusively shown that α-santonin has its C_{11}-methyl group actually α oriented. Hence the previous stereochemical assignment at C_{11}, for all santonin derivatives and related lactones, had to be reversed. The present assignments are given in Schemes I and II.

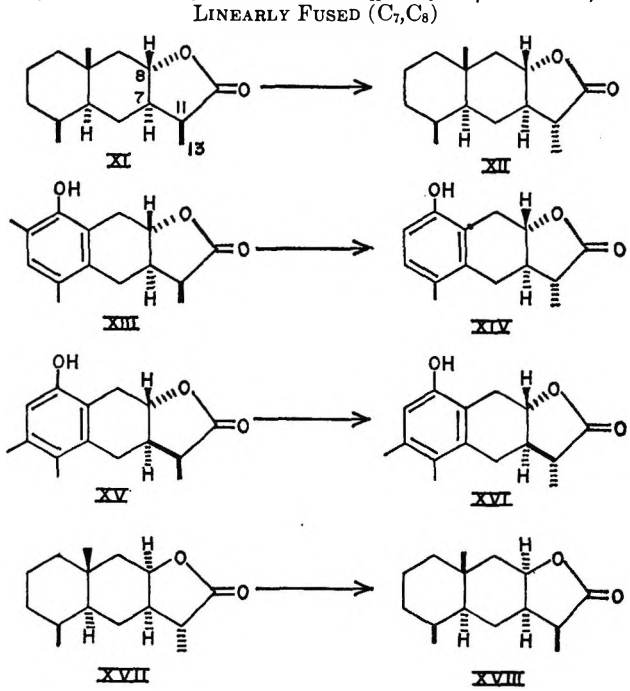
SCHEME I

STABLE CONFIGURATION OF THE C_{11}–CH_3 IN γ-LACTONES, ANGULARLY FUSED (C_6,C_7)



SCHEME II

STABLE CONFIGURATION OF THE C_{11}–CH_3 IN γ-LACTONES, LINEARLY FUSED (C_7,C_8)



It follows that the stereochemical changes involved in the isomerizations, and the order of stabilities as-

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TABLE I

MEASUREMENTS OF THE HEAT OF COMBUSTION AND THE HEAT OF SOLUTION OF α- AND β-SANTONINS AND DESMOTROPOSANTONINS[a]

Compound[b]	$-H_c$[c]	$-H_f$ (s)[c]	E (soln)[c,d]	$-H_f$ (soln)[c]
α-Santonin (II)	1884.40 ± 0.54	141.22 ± 0.54	+0.44	140.78 ± 0.5
β-Santonin (I)	1885.23 ± 0.43	141.39 ± 0.43	+0.01	140.38 ± 0.4
6-Epi-α-santonin (V)	1885.80 ± 0.36	139.82 ± 0.36	−1.09	140.91 ± 0.4
6-Epi-β-santonin (VI)	1881.47 ± 0.56	144.15 ± 0.56	+0.09	144.06 ± 0.6
(−)α-DTS* (VII)	2073.95 ± 0.64	208.08 ± 0.64	−0.36	208.44 ± 0.6
(+)α-DTS* (X)	2071.88 ± 0.43	210.15 ± 0.43	−1.06	211.21 ± 0.4
(−)α-DTS$^+$ (VII)	2031.24 ± 0.52	156.74 ± 0.52	+1.54	155.20 ± 0.5
(+)α-DTS$^+$ (X)	2028.27 ± 0.45	159.71 ± 0.45	+0.33	159.38 ± 0.5

[a] Enthalpy data measure thermochemical rather than thermodynamic stability, but it is unlikely that the standard molar entropies of each pair of isomers differ significantly.[23] [b] *, acetate; $^+$, methyl ether. [c] Kilocalories per mole. [d] E (soln) refers to measurements made on 0.01 M solutions in $CHCl_3$ at 25°.

sumed before, have also now to be reversed. These developments, in the light of the present knowledge of the correct stereochemistry of these sesquiterpene lactones at C_{11}, can now be summarized as follows.

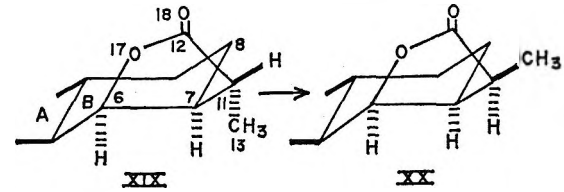
β-Santonin I and tetrahydro-β-santonin III, which have a *trans*-lactone system, isomerize to α-santonin II and tetrahydro-α-santonin IV, respectively,[13,14] showing thereby that the C_{11}–CH_3 is more stable in the α configuration in these systems, but in 6-epi-α-santonin V, 6-epi-β-santonin VI, (−)-α-desmotroposantonin VII, and (−)-β-desmotroposantonin VIII (DTS), which have the lactone ring 6,7-β-*cis*, the C_{11}–CH_3 prefers the β configuration.[15,16] In (+)-β-desmotroposantonin IX and (+)-α-desmotroposantonin X, which have a C_6,C_7 α-*cis*-lactone fusion, the C_{11} side chain is seen to be more stable[16] in the α configuration (Scheme I). Similarly in the case of the linear *trans*-lactone, tetrahydroepialantolactone[17] XI or the desmotropopseudosantonins[8,18] XIII to XVI, the C_{11}-methyl group is found to be more stable in the α configuration, but in the C_7,C_8 β-*cis*-lactone XVII, derived from alantolactone, it is the β configuration of the C_{11}–CH_3 (XVIII) that is found to be preferred[19] (Scheme II).

Some of the isomerization procedures leading to the above conclusions have been criticized,[20] but these criticisms have subsequently been met,[21,22] these and other experiments have been repeated, and the original conclusion, that (−)-β-desmotroposantonins are more stable than (−)-α-desmotroposantonins, has been confirmed. Accurate measurements of the heat of combustion and the heat of solution of α-santonin II, β-santonin I, 6-epi-α-santonin V, 6-epi-β-santonin VI, and those of the acetates and methyl ethers of (−)-α- and (+)-α-desmotroposantonins VII and X have been carried out.[23] The data obtained as given in Table I clearly show that the thermodynamic stabilities arrived at earlier[24] are indeed correct.

The authors of the above measurements,[22,23] however, conclude from these results that the order of stabilities arrived at is difficult to reconcile with the configurations presently assigned to the *cis*-lactones from X-ray studies. We, however, find that a detailed study of these systems fully justifies the above order of stabilities.

Nmr spectral studies of the lactones (section A) show that ring B in santonin and derivatives exists in the chairlike conformation in both the *cis*- and *trans*-lactones.[2] Solvent shift studies of the C_{11}-methyl group (section A) in the lactones independently confirm the stereochemistry assigned to them after the X-ray studies on 2-bromodihydroisophoto-α-santonic lactone acetate[9] and 2-bromo-a-santonin.[10] Hence an explanation for the present stability orders is called for. For this it becomes essential to go into some detail about the reasons why certain stereochemical relations in the stability orders were considered correct before,[5,6] and whether adequate grounds can be found at present to reverse these stereochemical relationships to fit the experimental facts now obtained.

The stability relationship now found for the *cis*-lactones can be represented by XIX, which isomerizes to the more stable form XX, whether ring A is aromatic or nonaromatic, whereas it was originally considered[5,6] that XIX should be the more stable form and that on equilibration XX should isomerize to XIX. (It will be



shown in section A that ring B retains the same chair or half-chair conformation in the *cis*-lactones with ring A aromatic or not as was present in the original *trans*-lactone of the ring-A nonaromatized santonin derivative, from which the *cis*-lactone is made.) This led to the wrong assignment of stereochemistry for santonin at C_{11}, and subsequently for all the related lactones.[24] The reasons why XIX should be more stable than XX have not been spelled out. It is only stated that "it may scarcely be doubted that XIX will be

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(15) D. H. R. Barton, J. E. D. Levisalles, and J. T. Pinhey, *J. Chem. Soc.*, 3472 (1962).
(16) N. M. Chopra, W. Cocker, and J. T. Edward, *Chem. Ind.* (London), 41 (1955).
(17) W. Cocker, T. B. H. McMurry, and L. U. Hopkins, *J. Chem. Soc.*, 1998 (1959).
(18) W. Cocker, B. E. Cross, and C. Lipman, *ibid.*, 959 (1949).
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(20) J. W. Huffman, *J. Org. Chem.*, **28**, 601 (1963).
(21) N. K. Venkatasubramanian, Ph.D. Thesis, Poona University, 1966.
(22) A. J. N. Bolt, M. S. Carson, W. Cocker, L. O. Hopkins, T. B. H. McMurry, M. A. Nisbet, and S. J. Shaw, *J. Chem. Soc., Sect.* C, 261 (1967).
(23) W. Cocker, T. B. H. McMurry, M. A. Frisch, T. McAllister, and H. Mackle, *Tetrahedron Lett.*, 2233 (1964).
(24) See, for a review, W. Cocker and T. B. H. McMurry, *Tetrahedron*, **8**, 181 (1960).

strongly favored in stability to XX, on obvious steric reasons" [5] and "clearly XX is the unstable and XIX, the stable arrangement." [6]

The instability attributed to XX should apparently be due to the nearly eclipsed interaction between the C_{11}-β-CH_3 and the methylene at 8, since they are on the same side of the C_7,C_{11} bond, whereas, in XIX, they are on opposite sides. Although this apparently looks very reasonable, a consideration of all the possible interactions on the methyl group in the two alternate configurations and the actual conformation of the lactone ring may show that this need not necessarily be true. Those factors that reduce the instability of XX but increase that of XIX are given below.

i.—Recent X-ray studies[9,10,25,26] have shown that in γ-lactones resonance structure XXII makes an important contribution with the result that the O_{17},C_{12} bond acquires considerable double-bond character. As

XXI XXII

a consequence, the lactone group consisting of C_6, C_{11}, C_{12}, O_{17}, and O_{18} [C—O—C(=O)—C] becomes planar, with C_7 out of the plane. It is now recognized that a carbanion,[27] or the lone pair of electrons on the nitrogen[28,29] or the oxygen[30,31] atom, can exert an appreciable steric effect. In XIX, the lone pair of electrons on the oxygen atom or the π electrons, which are in a plane perpendicular to the lactone ring, could be expected to exert a steric effect on the pseudo-axial, α-methyl group at C_{11}, besides the strong nonbonded interaction on this methyl group by the α-hydrogen atoms at C_6 and C_5. These are absent in XX.

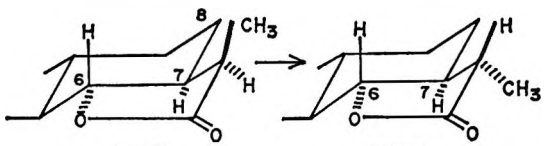
ii.—Models indicate that, in XX, the double-bond character of the O_{17},C_{12} bond, with buckling at C_7, increases the dihedral angle between the planes made by $C_{13}C_{11}C_7$ and $C_{11}C_7C_8$. This will move C_{13} a little further away from C_8.

iii.—X-Ray work on 2-bromo-α-santonin[10] shows that the $C_6C_7C_{11}$ and $C_7C_{11}C_{12}$ angles are much smaller (99 and 102°, respectively) and the $C_8C_7C_{11}$ and $C_7C_{11}C_{13}$ angles are much larger (122 and 115°, respectively) than normal, and the C_{11},C_{13} bond longer (1.63 Å) than usual. These angle distortions are largely brought about by the fusion of the five-membered lactone ring to the rigid cyclohexane ring B. Distortions of bond angles and bond lengths are also found to take place to accommodate steric strain, as in the case of ring A of the normal triterpenes with a *gem*-dimethyl group at C_4.[32] Hence, if we make the reasonable assumption that these distortions take place at least to the same extent in the *cis*-lactones as well, all these factors will help to move C_{13} away from C_8.

iv.—If the angles at C_6 are also distorted as is true at C_8, in the case of the *cis*-lactone in the guaianolide bromogeigerin acetate,[25] the plane of the lactone ring in the *cis*-lactone will be so bent and twisted from the plane of ring B, that C_{13} is quite away from 8 (further support for this is given at the end of section B).

This would minimize the interaction between C_{11}-β-CH_3 on the one hand, and the carbon atom 8 and the protons on it on the other. At the same time the change in the plane of the lactone ring brings C_{11}-α-CH_3 closer to C_6 and C_7-α-H in XIX, thus increasing its instability. These factors thus appear to tilt the equilibrium in the *cis*-lactones in favor of the pseudo-equatorial β-methyl group of XX over the pseudo-axial one in XIX.

In the *trans*-lactones, the pseudo-axial methyl group at C_{11} in XXIII, being destabilized by the axial hy-



XXIII XXIV

drogen atoms at C_6 and C_8 and the lone pair of electrons on the oxygen or the π electrons of the lactone ring as mentioned before, would readily isomerize to the pseudo-equatorial conformation as in XXIV. Thus the side-chain C_{11}-CH_3 prefers the pseudo-equatorial orientation over the pseudo-axial one in the *trans*- as well as the *cis*-fused γ-lactones.

Two Simple Methods to Find the Stereochemistry at C_{11}.—Two simple methods are now presented by which the stereochemistry of the side chain of sesquiterpene lactones can be directly and independently determined.

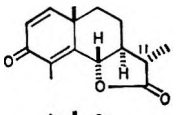
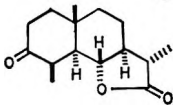
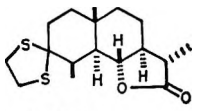
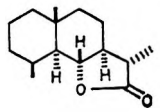
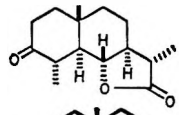
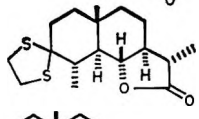
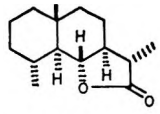
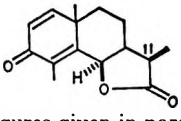
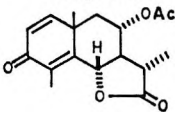
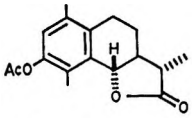
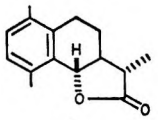
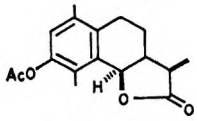
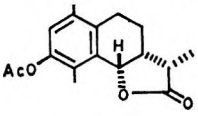
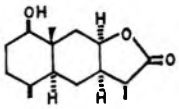
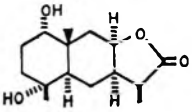
A.—In *trans*-lactones like α- or β-santonins (XXV, XL, Tables II and III) or their hydrogenation products (XXVI, XXIX, XLI, XLII), the B ring has no flexibility and is rigidly held owing to the *trans* fusion of the lactone ring. In 6-epi-α-santonin (XLIV) and its hydrogenation products (XLV, XLVI) the B ring is capable of existing in a boat conformation, but, if it were so, models show that the lactone carbonyl should strongly shield the C_{10}-angular methyl group. However, the angular methyl group shows virtually the same chemical shifts of about 1.33 ppm in α- and 6-epi-α-santonin (XXV, XLIV) and of about 1.20 ppm in tetrahydro-α- and tetrahydro-6-epi-α-santonin (XXIX, XLVI). This shows that the B ring is in the chair conformation in the *cis*-lactones as well as in the *trans*-lactones. Hence in the *trans* angular (XXV to XXXI, XXXIII to XXXV, XL to XLIII) or linear (XLVIII) lactones, the C_{11}-β-CH_3 would be pseudo-axial and C_{11}-α-CH_3 pseudo-equatorial. In the *cis* angular (XXXII, XXXVI, XLIV to XLVII) and linear lactones (XXXVIII, XXXIX) the opposite relations would hold; *viz.*, C_{11}-β-CH_3 would be pseudo-equatorial and the C_{11}-α-CH_3 pseudo-axial. Lactone XXXVII is the optical antipode of XXXVI.

It has recently been observed that axial and equatorial methyl groups adjacent to ester carbonyl groups show different types of solvent shifts in benzene, when compared with those in chloroform.[33] This difference should be much more prominent with respect to the

(25) J. A. Hamilton, A. T. McPhail, and G. A. Sim, *J. Chem. Soc.*, 708 (1962).
(26) I. C. Paul, G. A. Sim, T. A. Hamor, and J. M. Robertson, *ibid.*, 4133 (1962).
(27) D. H. R. Barton and R. C. Cookson, *Quart. Rev.* (London), **10**, 44 (1956).
(28) K. Brown, A. R. Katrizky, and J. A. Waring, *Proc. Chem. Soc.*, 257 (1964).
(29) J. B. Lambert and R. G. Keske, *J. Amer. Chem. Soc.*, **88**, 620 (1966).
(30) R. J. Abraham and W. A. Thomas, *J. Chem. Soc.*, 335 (1965).
(31) E. L. Eliel and M. C. Knober, *J. Amer. Chem. Soc.*, **88**, 5347 (1966).
(32) S. R. Hall and E. N. Masler, *Acta Cryst.*, **18**, 265 (1965).
(33) C. R. Narayanan and N. K. Venkatasubramanian, *Tetrahedron Lett.*, 3639 (1965).

TABLE II

PSEUDO-EQUATORIAL METHYL GROUP

No.	Compound	Chemical shift of C_{11}–CH_3 in $CDCl_3$	Chemical shift of C_{11}–CH_3 in Benzene (pyridine)[a]	$\delta_{CDCl_3} - \delta_{C_6H_6}$ ($\delta_{CDCl_3} - \delta_{C_5H_5N}$)[b]	Ref
XXV		1.28	0.99 (1.23)	+0.29 (+0.05)	4
XXVI		1.25	1.05 (1.19)	+0.20 (+0.06)	c
XXVII		1.18	0.97 (1.15)	+0.21 (+0.03)	d
XXVIII		1.21	1.04 (1.18)	+0.17 (+0.03)	d
XXIX		1.24	1.03 (1.16)	+0.21 (+0.08)	d
XXX		1.18	0.96 (1.13)	+0.22 (+0.05)	d
XXXI		1.19	1.02 (1.16)	+0.17 (+0.03)	d
XXXII		1.26	0.98 (1.21)	+0.28 (+0.05)	15
XXXIII		1.28	1.06 (1.34)	+0.22 (−0.06)	e
XXXIV		1.28	1.03 (1.23)	+0.05 (+0.05)	13
XXXV		1.26	1.01 (1.21)	+0.05 (+0.25)	4
XXXVI		1.27	1.02 ...	+0.25 ...	4
XXXVII		1.27	1.02 ...	+0.25 ...	4
XXXVIII		1.21	1.03 (1.19)	+0.18 (+0.02)	f
XXXIX		1.23	... (1.18)	... (+0.25)	g

[a] The figures given in parentheses are the chemical shifts in pyridine solution. [b] The figures in parentheses are the chemical shifts in $CDCl_3$ minus those in pyridine solution. [c] J. B. Hendrickson and T. L. Bogard, *J. Chem. Soc.*, 1678 (1962). [d] O. Kovacs, V. Herout, M. Horak, and F. Šorm, *Coll. Czech. Chem. Commun.*, **21**, 225 (1956). [e] M. Sumi, *J. Amer. Chem. Soc.*, **80**, 4869 (1958). [f] W. Herz and N. V. Viswanathan, *J. Org. Chem.*, **29**, 1022 (1964). [g] W. Herz, G. Högenauer, and A. Romo de Vivar, *ibid.*, **29**, 1700 (1964).

side-chain methyl of γ-lactones, wherein both the carbonyl and the methyl groups are held rigidly in a cyclic structure. To determine this, 24 γ-lactones of different types were prepared and their nmr spectra scanned in chloroform, benzene, and pyridine solutions. The chemical shifts of C_{11}–CH_3 in these compounds are tabulated in Tables II and III.

The tables show that the signals of the pseudo-equatorial methyl groups exhibit an upfield shift of about 0.23 ± 0.06 ppm in benzene relative to chloroform solution (Table II), whereas the pseudo-axial ones exhibit a very large upfield shift of 0.46 ± 0.06 ppm (Table III). The difference between the solvent shifts of the two categories is so large that the conformation of this methyl group could not be mistaken. Interestingly, these shifts are somewhat different in magnitude and direction from those observed for methyl groups adjacent to ketones.[34]

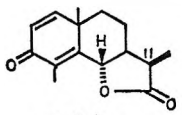
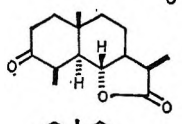
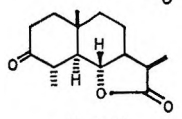
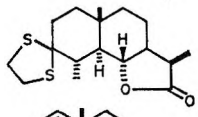
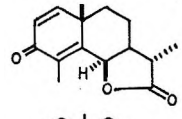
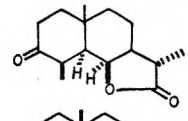
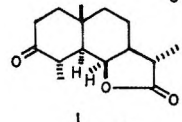
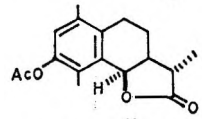
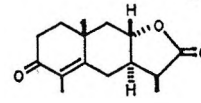
The tables show that chemical shifts of the C_{13} protons (in $CDCl_3$) are affected by the carbonyl group and double bonds in ring A (compare XXV with XXXI in column 3). The C_3 carbonyl group alone deshields the C_{13} protons by 0.05 ppm, although they are seven bonds (six carbon–carbon and one carbon–hydrogen single bonds) away (compare XXVI with XXVIII, or XXIX with XXXI, in column 3). When this distant methyl group comes a little closer in space to the C_3 carbonyl, by becoming pseudo-axial, the deshielding is more, *ca.* 0.10 ppm (compare XLIII with XLI or XLII, column 3), and when it is still nearer the deshielding rises to +0.16 ppm (compare XLIII with XLV or XLVI). Since in these cases the separation of seven single bonds is maintained, the downfield shift of these distant protons is probably to be attributed to the field effect of the carbonyl, rather than to its inductive effect. It is interesting to note that in XXIX the distance between the two groups on Dreiding models is over 7 Å. Similarly an aromatized ring A deshields the pseudo-equatorial C_{11}–CH_3 by about 0.08 ppm (compare XXXI, column 3, with XXXIV to XXXVII, column 9) and pseudo-axial C_{11}–CH_3 by about 0.18 ppm (compare XXXI, column 3, with XLVII, column 3).

The solvent shifts (columns 5 and 11) do not seem to be very much affected by the presence of a C_3 ketone or double bonds. Thus between XLIII and XLIV which show the largest difference of 0.23 ppm in their chemical shifts in chloroform (column 3) the difference in $\delta_{CHCl_3} - \delta_{C_6H_6}$ is only 0.03 ppm (column 5) and between XXVI and XXVII or XXIX and XXX having

(34) D. H. Williams and N. S. Bhacca, *Tetrahedron*, **21**, 2021 (1965).

TABLE III

PSEUDO-AXIAL METHYL GROUP

No.	Compound	Chemical shift of —the C_{11}–CH_3 in— $CDCl_3$	Benzene (pyridine)[a]	$\delta_{CDCl_3} - \delta_{C_6H_6}$ ($\delta_{CDCl_3} - \delta_{C_5H_5N}$)[b]	Ref
XL		1.26	0.71 (1.16)	+0.55 (+0.10)	4
XLI		1.27	0.79 (1.14)	+0.48 (+0.13)	14
XLII		1.26	0.78 (1.10)	+0.48 (+0.16)	14
XLIII		1.16	0.76 ...	+0.40 ...	3
XLIV		1.39	0.96 (1.29)	+0.43 (+0.10)	*c*
XLV		1.31	0.84 (1.18)	+0.47 (+0.13)	*d*
XLVI		1.32	0.88 (1.23)	+0.44 (+0.09)	*d*
XLVII		1.37	1.00 (1.28)	+0.37 (+0.09)	4
XLVIII		1.26	0.81 (1.18)	+0.45 (+0.08)	*e*

[a] The figures in parentheses are the chemical shifts in pyridine solution. [b] The figures in parentheses are the chemical shifts in $CDCl_3$ minus those in pyridine solution. [c] H. Ishikawa, *J. Pharm. Soc. Jap.*, **76**, 504 (1956). [d] W. Cocker, B. Donnelly, H. Gobinsingh, T. B. H. McMurry, and M. A. Nisbet, *J. Chem. Soc.*, 1262 (1963). [e] W. Cocker and M. A. Nisbet, *ibid.*, 534 (1963).

a difference of 0.06–0.07 ppm in chloroform (column 3) there is practically no difference in $\delta_{CDCl_3} - \delta_{C_6H_6}$ (column 5). Thus these large shifts appear to be mostly brought about by the lactone group alone.

Pseudo-equatorial methyl groups seem to be too far away from the benzenoid A ring to be seriously affected by it (*e.g.*, XXXIV to XXXVII), but a pseudo-axial methyl group appears to be affected; *e.g.*, in compound XLVII the signal of the C_{13} protons is slightly brought down from its normal value of 0.46 ± 0.06 ppm (column 5).

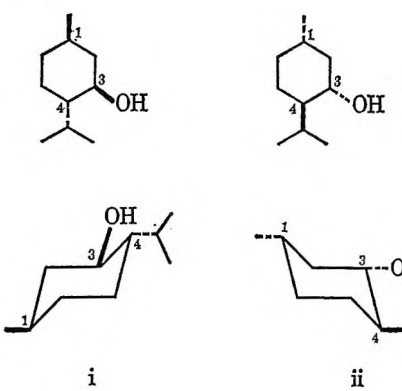
Since the *cis* or *trans* nature of the lactone will be easily revealed from the J values of C_6– or C_8–H, as the case may be,[35,36] determination of these solvent shifts would directly lead to the stereochemistry of the C_{11}–CH_3. Spectra in pyridine solution also show similar shifts, though of small magnitude (about +0.05 ppm for pseudo-equatorial and about +0.10 ppm for pseudo-axial ones), and could be used when the compound is insoluble in benzene, as is the case with XXXIX.

These results clearly show that C_{11}–CH_3, in either of the two possible configurations in any of the γ-lactone rings, assumes a pseudo-axial or pseudo-equatorial position, as the case may be, with respect to the lactone ring. If the methyl group were equally inclined to the plane of the lactone ring as in simple methylcyclopetenes or -pentanes (which have an average planar form), a marked solvent shift in the two different configurations would not be expected. Comparable solvent shifts have recently been observed for similarly located methyl groups in axial and equatorial conformations of fused δ-lactones.[37]

The present results also show that ring B in all desmotroposantonins except XXXVII retains the same chair or half-chair conformation as that of its parent santonin, since the C_{11}–CH_3 has the corresponding conformation in both. Since XXXVII also displays the solvent shift characteristic of a pseudo-equatorial C_{11}–CH_3 as XXXVI, models would show that ring B in XXXVII should exist in the alternate half-chair conformation to that in XXXVI (or the parent santonin). This is to be expected since the two have enantiomeric structures.[38]

B.—Another approach can also be made in suitable cases to determine the stereochemistry of C_{11}–CH_3. This depends on finding the C_{11}–H—C_7–H coupling constant. As the γ-lactones can be fused *cis* or *trans*, and in each case the C_{11}–H can have an α or β orientation, there are four possible situations that can arise. When these four different situations and the coupling pattern of the C_{11}–H in each of them are examined, the following results are obtained.

i.—***trans*-Lactones, Pseudo-Axial C_{11}–H.**—The C_{11}–β-H in α-santonin[36] (XXV) and 6-epidesmotroposantonin acetate (XXXIV) is found split into a doublet of



quartets. Double irradiation at the signal of the C_{11}–CH_3 on a 100-Mc nmr spectrometer shows the C_{11}–H as a doublet centered at δ 2.47 in XXV and at δ 2.43 in XXXIV, $J_{11\beta,7\alpha}$ being 12.5 cps.

ii.—***trans*-Lactones, Pseudo-Equatorial C_{11}–H.**—The C_{11}–α-H in β-santonin (XL) on the other hand is split into a quintet, J = 7.5 cps, showing thereby that the

(35) C. R. Narayanan and N. K. Venkatasubramanian, *Indian J. Chem.*, **2**, 274 (1964).

(36) J. T. Pinhey and S. Sternhell, *Aust. J. Chem.*, **18**, 543 (1965).

(37) G. Di Maio, P. A. Tardella, and C. Iavarone, *Tetrahedron Lett.*, 2825 (1966).

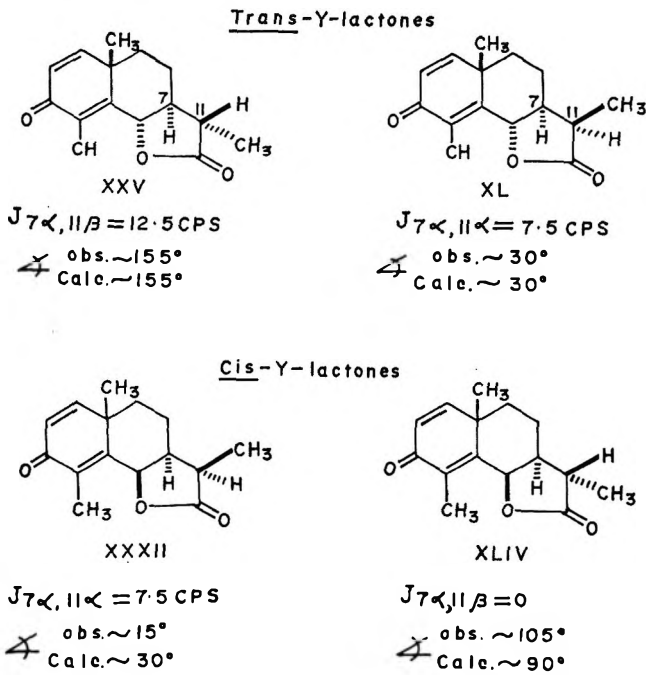
(38) See for example the enantiomeric menthols i and ii. The chair form of i has to be flipped to form the alternate chair in the case of ii so as to retain the conformations of the substituents which are the same in both.

C_{11}–H in this case makes equal coupling with the C_7–H and the C_{11}–CH_3.

iii.—*cis*-Lactones, Pseudo-Axial C_{11}–H.—In 6-epi-β-santonin (XXXII) and (−)-β-desmotroposantonin acetate (XXXVI), the C_{11}–α-H again shows up as a quintet, J = 7.5 cps, the C_{11}–H having in this case also equal coupling with the C_{11}–CH_3 and the C_7–H.

iv.—*cis*-Lactones, Pseudo-Equatorial C_{11}–H.—In 6-epi-α-santonin (XLIV) and (−)-α-desmotroposantonin acetate (XLVII) the C_{11}–β-H shows up as a quartet, J = 7 cps, showing thereby that the C_7–α-H has no appreciable coupling with the C_{11}–β-H. This is confirmed by spin decoupling of the C_{11}–CH_3, which shows the C_{11}–β-H as a sharp singlet at δ 2.57 in XLIV and at δ 2.52 in XLVII.

These distinctive coupling patterns of the C_{11}–H, wherever they are identifiable, can also be used to find the stereochemistry of the C_{11}–CH_3 and also that of the lactone fusion. In ii and iii where the pattern is the same, the coupling constant of the C_6–H (in the case of angular lactones) or C_8–H (in the case of linear lactones) as the case may be, with the 7-H, can show whether the lactone is *trans* or *cis* fused, and the coupling pattern of the C_{11}–H would then give the configuration of the C_{11}–CH_3.



The J values of 12.5 cps in α-santonin (XXV) and 7.5 cps in β-santonin (XL) which have the *trans*-lactone system (i and ii) would require a dihedral angle of about 155° in the former and about 30° in the latter.[39] Models show that these are nearly as required, but with the *cis*-lactones (iii and iv) the situation is somewhat different. In the case of 6-epi-β-santonin (XXXII), where there is a coupling constant of about 7.5 cps, one expects a dihedral angle of about 30° between 11α-H and 7α-H, but Dreiding models of the molecule show a dihedral angle of about 15° only. Similarly in the case of 6-epi-α-santonin (XLIV) there is no observable coupling between H_7 and H_{11}. This would indicate a dihedral angle of about 90° between them. However, models show only a dihedral angle of 105°. A bending and twisting of the lactone plane, away from ring B, at C_7–C_{11} (and probably at C_6–O_{17}), by about 15° or more so as to move C_{11}–CH_3 further away from C_8 would be needed in the case of both the *cis*-lactones to give the dihedral angles corresponding to the J values observed. This thus gives strong support to the argument advanced in the earlier section that in the case of the *cis*-lactones the plane of the lactone ring is so bent and twisted that the α- and β-C_{11}–CH_3 is considerably farther away from the C_8 protons than would be expected from models.

Making a rough energy calculation, a dihedral angle of 30° in (XXXII) between the 7α-H and 11α-H would mean that the angle between the planes $C_8C_7C_{11}$ and $C_7C_{11}C_{13}$ is 30°, *i.e.*, midway between an eclipsed and skew interaction[27,40] between C_8 and C_{13}. Making allowance for the larger angles $C_7C_{11}C_{13}$ (115°), $C_8C_7C_{11}$ (122°), and longer bond length of C_{11}–C_{13} (1.63 Å)[10] the energy of the interaction between C_8 and C_{13} should be expected to be less than 2 kcal (eclipsed, 4.4–6.1, and skew, 0.8 kcal/mol). Similarly in XLIV whose lactone is found to make the same angle as XXXII with ring B, the C_{11}–α-CH_3 is much closer to the two α-hydrogen atoms at C_6 and C_7 than 2.55 Å, the normal distance between an axial methyl group and the 1,3-*cis*-diaxial hydrogen atoms in a cyclohexane ring[41] ($C_8C_7C_{11}$ angle is 99° and $C_7C_{11}C_{12}$ angle 102°).[10] This alone would considerably raise the energy of XLIV.[42] Added to this is also the small interaction of the lone pair of electrons on O_{17}. All of these together may therefore be expected to give an energy of over 2 kcal (two normal axial CH_3–H interactions alone, 1.8 kcal/mol)[43] for the C_{11}–αCH_3, thus giving XLIV a significantly higher energy than XXXII, as observed by actual measurements,[23] and thus leading to the isomerization of this methyl group[15,24] from the pseudo-axial to the pseudo-equatorial conformation in the *cis*-lactones. As this is largely brought about by angle distortions needed for the fusion of the five-membered lactone ring to a rigid cyclohexane ring, such a ready isomerization of a methyl group or bond from a pseudo-axial to a pseudo-equatorial conformation should be expected as a general feature of such systems, although this might appear to involve an eclipsed butane interaction.

Experimental Section

Melting points are uncorrected and were taken on a Gallenkamp melting point apparatus. Optical rotations were determined in 1% chloroform solution in a Perkin-Elmer spectrophotometer or a Carl Zeiss polarimeter. Nmr spectra were recorded on a Varian A-60 spectrometer in 10% solution in the solvents given. The signals were recorded in δ (parts per million) using TMS as an internal standard. Infrared spectra were recorded on a Perkin-Elmer Model 221 spectrometer. Chromato-

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

(40) K. S. Pitzer, *Discussions Faraday Soc.*, **10**, 66 (1951).

(41) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, Inc., New York, N. Y., 1965, p 43.

(42) Some idea of the energy involved in nonbonded interactions between two hydrogen atoms when they come too close can be gained from the following data [the internuclear distance is given in angstroms and the potential energy (in parentheses) is given in kilocalories per mole]: 2.6 (0.7), 2.4 (1.4), 2.2 (2.7), 2.0 (5.0), 1.8 (9.1). In the present case, the energy involved would be about three times those given, since the interaction involved is that between one hydrogen atom and the three hydrogen atoms on a methyl group: E. A. Mason and M. M. Kreevoy, *J. Amer. Chem. Soc.*, **77**, 5808 (1955); L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p 825.

(43) C. W. Beckett, K. S. Pitzer, and R. Spitzer, *J. Amer. Chem. Soc.*, **69**, 2488 (1947).

grams were run on neutral Brockmann grade II alumina. Thin layer chromatography was carried out on silica gel mixed with plaster of Paris (15%) as binder. The plates were sprayed with concentrated H_2SO_4. Petroleum ether refers to fraction boiling between 60 and 80°.

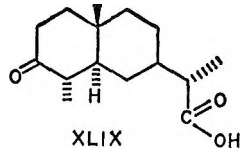
All known compounds were prepared according to the procedures given in the literature as cited in the references and identified by their melting points, specific rotations, and infrared spectra. The homogeneity of the compounds was often checked by thin layer chromatography on silica gel.

Thio Ketal of 4 α-Methyltetrahydro-β-santonin (XLIII).—To a solution of 100 mg of 4α-methyltetrahydro-β-santonin in 3 ml of acetic acid was added 0.1 ml of ethanedithiol and 0.2 ml of BF_3 etherate and kept at room temperature for 5 hr. The solution was poured into water and worked up. The product was crystallized from alcohol and recrystallized from the same solvent to yield 90 mg of XLIII: mp 155°; $[\alpha]D$ +75° (c 1.2); ν_{max} 1754 cm^{-1} (γ-lactone). *Anal.* Calcd for $C_{17}H_{26}O_2S_2$: C, 62.56; H, 8.03. Found: C, 62.50; H, 8.16.

4β-Methyltetrahydro-6-epi-α-santonin (XLV).—Considerable difficulty was experienced in preparing this compound. Hydrogenation of 6-epi-α-santonin on 10% Pd–$CaCO_3$, 2% Pd–$SrCO_3$, or 5% Pd–C gave almost exclusively an acid, by the hydrogenolysis of the 6β-ether oxygen function. In α-santonin, where the C_6–O bond is quasi-equatorial, practically no hydrogenolysis was encountered under these conditions, showing thereby that the quasi-axial alcoholic oxygen is more prone to hydrogenolysis. The title compound was, however, prepared in about 20% yield by the following procedure.

6-Epi-α-santonin (1 g) in 30 ml of ethyl acetate was hydrogenated over 200 mg of 10% Pd–C[44,45] until no more hydrogen was absorbed (2 hr). The solution was filtered and extracted with 5% sodium bicarbonate solution. The ethyl acetate solution was further washed with water, dried over sodium sulfate, and evaporated. The solid was crystallized from ethyl acetate to give 225 mg of the compound: mp 196° (lit.[46] mp 196–197°); $[\alpha]D$ −133° (c 1.4) (lit.[46] −135°); ν_{max} 1770 (lactone) and 1710 cm^{-1} (cyclohexanone).

The bicarbonate extract was acidified and extracted with ether to give 700 mg of an acid. It was esterified with diazomethane to give a liquid which was chromatographed over 30 g of alumina grade II. Elution with 25% petroleum ether–75% benzene (250 ml) and removal of solvent gave 650 mg of a viscous liquid. It was distilled under vacuum: bath temperature, 160–165° (0.2 mm); $[\alpha]D$ +44° (c 1.5); ν_{max} (liquid film) 1750 (ester) and 1725 cm^{-1} (cyclohexanone). *Anal.* Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.20; H, 9.32. The nmr spectrum showed signals at δ 0.92 (3 H, doublet, J = 7 cps, C_4–CH_3), 1.06 (3 H, singlet, C_{10}–CH_3), 1.07 (3 H, doublet, J = 7 cps, C_{11}–CH_3), and 3.63 (3 H, singlet, $COOCH_3$). The signal of the C_4–CH_3 shifts from 0.92 in chloroform to 0.99 in benzene, the small downfield shift showing that the methyl group is equatorial. The C_{11}–CH_3 shows, on the other hand, a small upfield shift of 0.05 ppm. Although the C_4–CH_3 originally produced should have been β axial, by the *cis* addition of hydrogen at C_4,C_5, epimerization must have taken place during the acidification process and work-up. That the A/B rings are *trans* locked was confirmed by the CD spectrum of the compound which gave a positive Cotton effect,[47] ΔE at 292 mμ = +0.78 (solvent dioxane). The same acid was produced by hydrogenolysis and hydrogenation with other catalysts as well. It should thus have structure XLIX.



XLIX

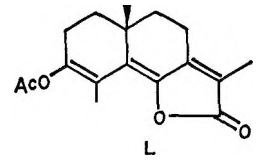
(44) This catalyst in its preparation had to be finally reduced by hydrogen.[45] That prepared by reduction with formaldehyde in the final stage completely hydrogenolyzed the lactone.

(45) A. I. Vogel, "A Textbook of Practical Organic Chemistry," Longmans, Green and Co., London, 1964, p 950.

(46) See Table III, footnote *d*.

(47) We are indebted to Professor G. Snatzke, University of Bonn, for the CD measurements.

6-Epidesmotroposantonin acetate (XXXIV) could be prepared only twice.[48] Treatment of α-santonin with acetyl chloride and acetic anhydride gave a 20% yield of this substance,[13] a reaction which was able to be repeated only once. Purification of the reagents or addition of small amounts of aqueous hydrochloric acid did not improve the situation. The product invariably obtained, either as the main product or as the sole product, was the enol lactone for which structure L has been proposed.[13]



L

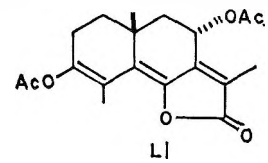
The nmr spectrum of this compound confirmed the proposed structure. It showed the acetate methyl at δ 2.23, C_4-vinyl methyl at 1.89, C_{10}–CH_3 at 1.17, and C_{11}–CH_3 as a clear triplet (J = 1.5 cps) centered at 2.00 (probably due to long-range coupling with the two protons at C_8, or an axial proton at C_8 and another axial proton at C_2[49,50]), and no vinyl proton signal.

Registry No.—I, 13927-50-9; II, 481-06-1; III, 13902-55-1; IV, 13902-54-0; V, 1618-78-6; VI, 1618-77-5; VII, 13743-88-9; acetate of VII, 14794-71-9; methyl ether of VII, 13743-90-3; VIII, 13743-89-0; IX, 13743-96-9; X, 16963-59-0; acetate of X, 16963-60-3; methyl ether of X, 16963-61-4; XI, 16963-62-5; XII, 16963-63-6; XIII, 16963-64-7; XIV, 16963-65-8; XV, 16963-66-9; XVI, 16963-31-8; XVII, 16963-32-9; XVIII, 15797-9-30; XXVI, 14804-46-7; XXVII, 16963-35-2; XXVIII, 2221-83-2; XXX, 14804-50-3; XXXI, 14804-52-5; XXXIII, 1618-76-4; XXXIV, 16963-40-9; XXXV, 14794-97-9; XXXVI, 6339-71-5; XXXVIII, 16963-43-2; XXXIX, 14794-72-0; XLI, 14804-47-8; XLIII, 16963-46-5; XLV, 14987-66-7; XLVI, 14794-68-4; XLVIII, 10208-52-3; methyl ester of XLIX ($C_{16}H_{26}O_3$), 3717-63-3.

Acknowledgment.—We are indebted to Professor W. Cocker for samples XXXII, XXXIII, and XL, Professor Werner Herz for samples XXXVIII and XX, Shri N. R. Bhadane for the data on XXVII, and Dr. U. Scheidegger of Varian AG, Switzerland, for the decoupling experiments.

(48) We are indebted to Professor W. Cocker for kindly informing us that he also could prepare this compound only twice or thrice.

(49) To ascertain which of these two possibilities was the correct one, an enol lactone was prepared under the same conditions from artemisin acetate XXXIII. This compound, after chromatography on silica gel in benzene, showed a single spot in thin layer chromatography (solvent 5% ethyl acetate, 95% benzene) and had $[\alpha]D$ −132° (c 1.2), but could not be induced to crystallize. Its infrared spectrum was similar to that of L and hence should have the structure LI. Its nmr spectrum showed signals at δ 2.20



LI

(singlet, C_3 and C_8 acetate methyl signals), 1.27 (singlet, C_{10}–CH_3), 1.97 (singlet, C_4–CH_3), and at 2.05 (doublet, J = 1 cps, C_{11}–CH_3). Hence the triplet signal of the C_{11}–CH_3 in L is due to long-range coupling of the C_{11}–CH_3 with the C_8 α and β protons. (Such biallylic couplings[35] between both the protons of the allylic ring methylene group on the one side, and the protons of the vinyl methyl group on the other side, has recently been reported.[50]

(50) M. D. Nair and R. Mehta, *Indian J. Chem.*, **5**, 123 (1967).

Synthesis of an Analog of the Aminoglycoside Antibiotics[1]

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Received March 22, 1968

Synthetic routes to 1D-4-*O*-(6-amino-6-deoxy-β-D-glucopyranosyl)-3-*O*-methyl-*chiro*-inositol (**6**) are described. The key intermediate, 1D-1,2:5,6-di-*O*-isopropylidene-3-*O*-methyl-4-*O*-(2,3,4-tri-*O*-acetyl-6-*O*-*p*-tolylsulfonyl-β-D-glucopyranosyl)-*chiro*-inositol (**4**), was obtained by deacetylation, tosylation, and reacetylation of the known 1D-1,2:5,6-di-*O*-isopropylidene-3-*O*-methyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-*chiro*-inositol (**1**, 57%), or directly by coupling 2,3,4-tri-*O*-acetyl-6-*O*-*p*-tolylsulfonyl-α-D-glucopyranosyl bromide (**2**) with 1D-1,2:5,6-di-*O*-isopropylidene-3-*O*-methyl-*chiro*-inositol (**3**, 52%). The ammonolysis and deacetonation of **4** gave **6** (73%). Alternatively **4** with sodium azide gave the crystalline 1D-1,2:5,6-di-*O*-isopropylidene-3-*O*-methyl-4-*O*-(2,3,4-tri-*O*-acetyl-6-azido-6-deoxy-β-D-glucopyranosyl)-*chiro*-inositol (**5**), which was converted into **6** (70% from **4**) by deacetylation, reduction, and deacetonation. The aminoglucoside **6** did not show antibiotic activity or cause code "misreading" in *in vitro* protein synthesis.

The synthesis of analogs of the aminoglycoside (pseudo-oligosaccharide) antibiotics, which include the streptomycins, neomycins, paromomycins, and kanamycins, is of substantial interest in view of the clinical usefulness of some members of the group and the finding that these antibiotics cause the "misreading" of messenger RNA during protein synthesis.[2] A few of the desired structures, consisting of sugars linked glycosidically to cyclitols, usually with amino groups in both moieties, have been obtained by direct coupling of the suitably blocked and activated components.[3] However, the effectiveness of this approach is restricted by the limited availability of suitably blocked aminocyclitols and the low reactivity of these toward acylglycosyl halides. An alternate route, the coupling of an ordinary sugar to an ordinary cyclitol followed by introduction of the amino group(s) into the resulting glycoside, is illustrated in this paper.

Scheme I summarizes the synthesis, which proceeded *via* the tosylated glucoside **4** to 1D-4-*O*-(6-amino-6-deoxy-β-D-glucopyranosyl)-3-*O*-methyl-*chiro*-inositol[4] (**6**). The key intermediate **4** was obtained in two ways. In one preparation the previously known 1D-1,2:5,6-di-*O*-isopropylidene-3-*O*-methyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-*chiro*-inositol (**1**),[5] made by coupling 1D-1,2:5,6-di-*O*-isopropylidene-3-*O*-methyl-*chiro*-inositol (diisopropylidene-D-pinitol, **3**) and tetra-*O*-acetyl-α-D-glucopyranosyl bromide, was deacetylated, tosylated, and reacetylated to give crystalline **4** in 32% over-all yield from diisopropylidenepinitol. The second method was to couple diisopropylidene-D-pinitol with 2,3,4-tri-*O*-acetyl-6-*O*-*p*-tolylsulfonyl-α-D-glucopyranosyl bromide (**2**) by the Koenigs–Knorr procedure. In this reaction the yield, based on diisopropylidene-D-pinitol, was 52%, unusually high for a coupling involving a secondary ring hydroxyl on a blocked sugar.

For the conversion of **4** into the aminoglucoside **6**, two methods were again used. Treatment of **4** with methanolic ammonia at 110° followed by deacetonation and chromatography of the crude product gave **6** as a colorless glass in 73% yield. Alternatively, **4** was converted into the crystalline azidoglucoside **5**. The azido compound was then deacetylated, reduced, and deacetonated, and the crude product was chromatographed. The yield of pure aminoglucoside (**6**), based on intermediate **4**, was 70%. Samples of **6** prepared by the two methods had identical chemical and spectroscopic properties, which fully substantiated the assigned stereoformula (see Experimental Section).

The good yield in the coupling step, which is one of the attractive features of the present synthesis, is probably due to the favorable conformational and electronic properties of the specific cyclitol derivative used. Suitably blocked halides of the several aminodeoxyglucoses (perhaps not the 2 isomer) could no doubt be coupled directly with diisopropylidenepinitol in good yield. However, deblocking the coupling products would be more difficult than the simple deblocking–reduction of our azidoglucoside (**5**). Also, the over-all syntheses would require several more steps than the procedure of coupling first, then aminating. This procedure should be capable of considerable extension, hopefully to the preparation of glycosides with both the cyclitol portion and the sugar aminated.

The aminoglucoside **6** showed no antibiotic activity against several bacteria and fungi, and a yeast, when it was included in the culture media at 1000 ppm.[6] It caused no misreading at 200 μg/ml in an *in vitro* protein-synthesizing system sensitive to natural aminoglycoside antibiotics.[7]

Experimental Section

Nuclear magnetic resonance spectra were taken on a Varian A-60 spectrometer. Tetramethylsilane and sodium dimethylsilapentanesulfonate (DSS) were used as internal standards. Infrared spectra were taken on a Beckman IR-5 instrument. Melting points were determined in Pyrex capillaries immersed in a heated oil bath equipped with a calibrated thermometer.

1D-1,2:5,6-Di-*O*-isopropylidene-3-*O*-methyl-4-*O*-(2,3,4-tri-*O*-acetyl-6-*O*-*p*-tolylsulfonyl-β-D-glucopyranosyl)-*chiro*-inositol (4).

(1) Presented at the 149th National Meeting of the American Chemical Society, Detroit, Mich., April 1965.

(2) (a) J. Davies, W. Gilbert, and L. Gorini, *Proc. Natl. Acad. Sci. U. S.*, **51**, 883 (1964); (b) J. Davies, L. Gorini, and B. D. Davis, *Mol. Pharmacol.*, **1**, 93 (1965).

(3) (a) S. Umezawa and Y. Ito, *Bull. Chem. Soc. Jap.*, **34**, 1540 (1961); (b) S. Koto, Y. Ito, and S. Umezawa, *ibid.*, **38**, 1447 (1965); (c) S. Umezawa and S. Koto, *ibid.*, **39**, 2014 (1966); (d) S. Umezawa, S. Koto, K. Tatsuta, and T. Tsumura, *J. Antibiot.* (Tokyo), **21**, 162 (1968); (e) M. Nakajima, A. Hasegawa, N. Kurihara, H. Shibata, T. Ueno, and D. Nishimura, *Tetrahedron Lett.*, 623 (1968).

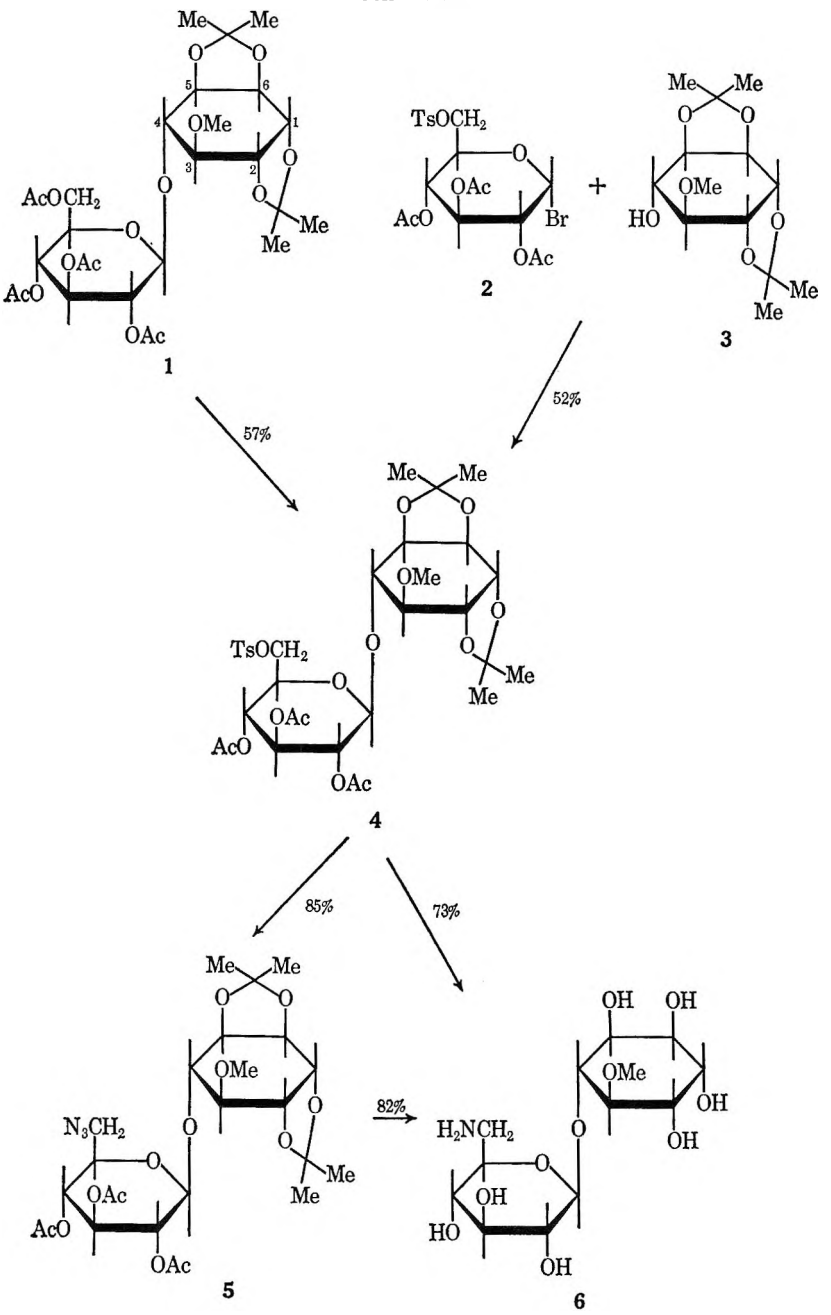
(4) The compounds described here are named as substituted cyclitols. For the cyclitol moieties, the recently adopted IUPAC/IUB Tentative Rules for Cyclitol Nomenclature (soon to be published) are used. Under these rules the parent inositol of the series, formerly known as *d*-inositol, (+)-inositol, or D-inositol, is now designated D- (or 1D-) *chiro*-inositol. The naturally occurring D-pinitol, which has been called 5-*O*-methyl-D-inositol in most recent American literature, is 1D-3-*O*-methyl-*chiro*-inositol.

(5) K. A. Caldwell, S. P. Raman, and L. Anderson, *Nature*, **199**, 373 (1963); the compound is there named 1,2:3,4-di-*O*-isopropylidene-5-*O*-methyl-6-*O*-(tetra-*O*-acetyl-β-D-glucopyranosyl)-D-inositol.

(6) The authors are grateful to Mr. Donald M. Murphy of the Wisconsin Alumni Research Foundation for carrying out these tests.

(7) This test was by Professor Julian Davies of this department.

SCHEME I



A. From 1D-1,2:5,6-Di-*O*-isopropylidene-3-*O*-methyl-4-*O*-(2,3,-4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-*chiro*-inositol (1).—The deacetylation,[8] then tosylation, and reacetylation[9] of 1 (1.0 g) were accomplished without isolation of intermediates. The crude **4** obtained by crystallization from absolute ethanol melted at 139–142°: yield 0.67 g (57%). Recrystallization from ethanol–water gave colorless needles: mp 145.0–145.5°; $[\alpha]^{25}D$ +6° (*c* 6, $CHCl_3$); nmr ($CDCl_3$), τ 2.19 (d, 2, *J* = 8 Hz, tosyl ring H), 2.63 (d, 2, *J* = 8 Hz, tosyl ring H), 6.49 (s, 3, OCH_3), 7.54 (s, 3, tosyl CH_3), 7.96 (s, 3, acetyl CH_3), 8.01 (s, 6, acetyl CH_3), 8.50 (s, 6, isopropylidene CH_3), 8.66 ppm (s, 6, isopropylidene CH_3); ir (KBr), 2950 (C–H), 1750 cm^{-1} (C=O).

B. From 1D-1,2:5,6-Di-*O*-isopropylidene-3-*O*-methyl-*chiro*-inositol (3) and 2,3,4-Tri-*O*-acetyl-6-*O*-*p*-tolylsulfonyl-α-D-glucopyranosyl Bromide (2).—Silver oxide[10] (2.5 g), powdered Drierite (2.5 g), and **3**[11] (1.0 g, 3.6 mmol) were stirred (magnetic bar) with 8 ml of anhydrous, alcohol-free chloroform in a 125-ml erlenmeyer which was wrapped with black tape and protected from moisture. After 30 min 0.1 g of iodine was added, and then, dropwise over a 3-hr period, a solution of 4.0 g (7.2 mmol) of the 6-tosyltriacetylglucopyranosyl bromide **2**[12] in 10 ml of anhydrous, alcohol-free chloroform. Stirring was continued overnight. Water (*ca.* 0.5 ml) was then added to destroy any excess glycosyl halide and the mixture was filtered and concentrated.

The resulting syrup was chromatographed on a column of 60–200 mesh silica gel (200 g, 57 × 2.5 cm) with acetone–benzene (7:93, v/v as developer). Peaks were detected by the sulfuric acid char method.[13] The product, identified by thin layer chromatography (silica gel G, acetone–benzene, 30:70, v/v), emerged in the lead peak. After concentration and crystallization from ethanol the yield was 1.37 g (52%), mp 144.5–145.5°. Recrystallization from methanol–water gave pure **4**, mp 146–147°, identical

(8) A. Thompson, M. L. Wolfrom, and E. Pacsu in "Methods in Carbohydrate Chemistry," Vol. II, R. L. Whistler and M. L. Wolfrom, Ed., Academic Press Inc., New York, N. Y., 1963, p 216.

(9) E. Hardegger and R. M. Montavon, *Helv. Chim. Acta*, **29**, 1199 (1946).

(10) Prepared as described by E. L. Hirst and E. Percival [*Methods Carbohyd. Chem.*, **2**, 146 (1963)]; sodium hydroxide was used in place of barium hydroxide.

(11) Prepared from D-pinitol by the method of S. J. Angyal and R. M. Hoskinson, *J. Chem. Soc.*, 2985 (1962), with dimethoxypropane instead of diethoxypropane as the acetonating agent.

(12) B. Helferich and S. Grünler, *J. Prakt. Chem.*, [2] **148**, 107 (1937). These authors give mp 89–90° and $[\alpha]^{20}D$ +165°; our preparations agreed in rotation but were lower melting (65–69°).

(13) P. Ways, *J. Lipid Res.*, **4**, 101 (1963).

in all respects (mixture melting point, ir, specific rotation) with the product of method A.

Anal. Calcd for $C_{32}H_{44}O_{16}S$ (716.74): C, 53.61; H, 6.19. Found: C, 53.93; H, 6.26.

1D-1,2:5,6-Di-*O*-isopropylidene-3-*O*-methyl-4-*O*-(2,3,4-tri-*O*-acetyl-6-azido-6-deoxy-β-D-glucopyranosyl)-*chiro*-inositol (5).—Sodium azide (2.5 g, 38 mmol) was stirred with **4** (4.0 g, 5.6 mmol) in 50 ml of dimethylformamide for 1 hr at 100–105°. The mixture was then concentrated under reduced pressure, the residue was dissolved in hot methanol–water, and crystallization was induced by adding more water, dropwise, to the hot solution. The pure **5** thus obtained weighed 2.8 g (85%), melted at 140–140.5°, and had $[\alpha]^{24}D$ −13.5° (c 7, DMF), and nmr ($CDCl_3$), τ 6.46 (s, 3, OCH_3), 7.96 (s, 3, acetyl CH_3), 7.98 (s, 6, acetyl CH_3), 8.48 (s, 6, isopropylidene CH_3), 8.66 ppm (s, 6, isopropylidene CH_3); ir (KBr), 2950 (C–H), 2090 (N_3), 1740 cm^{-1} (C=O).

Anal. Calcd for $C_{25}H_{37}O_{13}N_3$ (587.37): C, 51.10; H, 6.35. Found: C, 51.03; H, 6.27.

1D-4-*O*-(6-Amino-6-deoxy-β-D-glucopyranosyl)-3-*O*-methyl-*chiro*-inositol (6). A. From 1D-1,2:5,6-Di-*O*-isopropylidene-3-*O*-methyl-4-*O*-(2,3,4-tri-*O*-acetyl-6-*O*-*p*-tolylsulfonyl-β-D-glucopyranosyl)-*chiro*-inositol (4) by Ammonolysis.—A solution of **4** (4.0 g, 5.6 mmol) in 60 ml of methanol saturated with ammonia at 0° was sealed in a glass-lined steel bomb and heated at 110° for 12 hr. The pale yellow reaction mixture was decolorized with Darco G-60 and concentrated to a syrup under reduced pressure.

For deacetonation the syrup was dissolved in 10 ml of acetic acid–water (1:1, v/v) and heated 8 hr in an oil bath at 100–105°. The resulting brown solution was chromatographed on a column of Bio-Rad AG 1-X2 anion-exchange resin (OH^- form, 200–400 mesh, 65 × 2.5 cm), by development with distilled water at 0.5 ml/min. Peaks were again detected by the sulfuric acid char method.[13] The components were identified on thin layer plates of cellulose (without binder). These were developed with pyridine–ethyl acetate–acetic acid–water (5:5:1:3 by volume), and spots were visualized with silver nitrate–alkali.[14]

The first product to be eluted was pinitol, 0.16 g; the eluate volume was 430–470 ml.[15] The following peak, eluate volume 700–2000 ml, was basic and contained the desired pinitol 6-aminoglucoside **6**. The product (1.45 g, 73%) was obtained as a colorless glass by removal of the solvent: $[\alpha]^{18}D$ +27° (c 1, H_2O); nmr (D_2O), τ 6.40 (s, 3, OCH_3), 5.24 ppm (d, 1, J = 8 Hz, anomeric H); ir (KBr), 3320 cm^{-1} (O—H), no band for ester C=O.

Anal. Calcd for $C_{13}H_{25}O_{10}N$ (355.34): C, 43.93; H, 7.09; N, 3.94. Found: C, 43.55; H, 7.15; N, 3.89.

The 8-Hz spacing of the doublet for the anomeric proton in the nmr spectrum indicates a β configuration for the glucoside bond, as previously deduced for compound **1** on other grounds.[5] Compound **6** did not reduce Fehling's solution, but treating it with 8 *N* hydrochloric acid for 15 min at 100°, followed by removal of the chloride ion with Dowex-1 (OH^-) resin, gave a hydrolysate with reducing properties. When the hydrolysate was chromatographed on cellulose thin layer plates, it gave reduced silver spots at R_f 0.24 (w), 0.34 (w), and 0.56 (s). Control spots showed R_f 0.24 for the unhydrolyzed glycoside and R_f 0.56 for authentic pinitol. Approximately 1 molar equiv of nitrogen was evolved when **6** reacted with nitrous acid in a Van Slyke apparatus.

B. From 1D-1,2:5,6-Di-*O*-isopropylidene-3-*O*-methyl-4-*O*-(2,3,4-tri-*O*-acetyl-6-azido-6-deoxy-β-D-glucopyranosyl)-*chiro*-inositol (5).—The azidoglucoside **5** (4.0 g, 6.8 mmol) was deacetylated,[8] and the deacetylated product was concentrated to a syrup. This was dissolved in *ca.* 100 ml of ethanol and added to a suspension of palladium-on-carbon catalyst (0.7 g, 5% Pd) in *ca.* 50 ml of ethanol. The mixture was stirred magnetically for 3 hr under hydrogen at 1 atm of pressure with frequent exchange of the gas for fresh hydrogen. The catalyst was then filtered off and the filtrate was concentrated to a glassy solid. The infrared spectrum of the solid showed no absorption in the ester carbonyl or azide regions.

The solid was deacetonated and chromatographed as described under A. The product was in eluate volume of 1050–2050 ml from the resin column. Concentration of this gave 2.0 g of colorless glass, thus a yield of 82% based on **5**, or 70% over-all from compound **4**. This product was identical in all respects with **6** prepared by method A.

Registry No.—**4**, 16802-83-8; **5**, 16802-81-6; **6**, 16802-82-7.

Acknowledgment.—This investigation was supported in part by the Graduate School of the University of Wisconsin from funds supplied by the Wisconsin Alumni Research Foundation. The authors are grateful to the Department of Chemistry for the use of their nmr spectrometer, purchased with funds granted by the National Science Foundation.

(14) L. Hough and J. K. N. Jones, *Methods Carbohyd. Chem.*, **1**, 28 (1962).

(15) The appearance of free pinitol in the eluate was probably due to the hydrolysis of pinitol 3,6-anhydroglucoside, an expected side product of the ammonolysis reaction. The 3,6-anhydroglucoside would be very acid labile, whereas the glucoside bond of **4** is stable to the deacetonation conditions.

Selective Reactions of Sulfonic Esters of Carbohydrates on Alumina[1]

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Selective hydrolysis of primary sulfonic ester groups of carbohydrates occurs on basic or neutral alumina. In the presence of aliphatic alcohols, hydrolysis is accompanied by selective alcoholysis of a sulfonic ester group at a primary position.

Hydrolysis of carboxylic[2,3] and sulfonic[4] esters of steroids on basic alumina has long been known, and more recently selective hydrolysis of a primary acetate group in the presence of a secondary acetate group has been demonstrated[5] with several steroidal esters.

In carbohydrate chemistry, acetylation is frequently employed to protect hydroxyl functions but migration[6] of acetate groups can be a source of difficulty during a definitive synthetic procedure. Few examples have been reported[7,8] of migration of sulfonic ester groups of carbohydrates, and the usefulness of these esters in synthetic work is well documented.[9] Our studies on the hydrolysis of sulfonic esters of carbohydrates stemmed from our observations on deacetylation of sugar acetates on basic alumina. The sulfonic ester derivatives examined in detail in this study are readily

(1) This work was supported in part by the Army Research Office, Durham, N. C.

(2) A. Butenandt and L. Poschmann, *Chem. Ber.*, **77**, 392 (1944).

(3) R. H. Levin, A. V. McIntosh, Jr., G. B. Spero, D. E. Rayman, and E. M. Meinzer, *J. Amer. Chem. Soc.*, **70**, 511 (1948).

(4) R. J. W. Cremlyn and C. W. Shoppee, *J. Chem. Soc.*, 3515 (1954).

(5) W. F. Johns and D. M. Jerina, *J. Org. Chem.*, **28**, 2922 (1963).

(6) W. A. Bonner, *J. Amer. Chem. Soc.*, **80**, 3697 (1958).

(7) A. C. Cope and T. Y. Shen, *ibid.*, **78**, 5912 (1956).

(8) J. S. Brimacombe and L. C. N. Tucker, *Chem. Commun.*, 903 (1966).

(9) R. S. Tipson, *Advan. Carbohyd. Chem.*, **8**, 107 (1953).

available by partial methanesulfonylation[10] of the corresponding methyl D-aldohexopyranoside followed by methylation of unesterified hydroxyl groups.

When a slurry of methyl 3,4-di-*O*-methyl-2,6-di-*O*(methylsulfonyl)-α-D-glucopyranoside[11] (**1**) with basic alumina of Brockmann activity I in benzene is kept at 50°, then eluted with ether–methanol (19:1), a product (**2**) is obtained in 66% yield accompanied by unchanged **1** (33%). The mixture can be resolved by silica gel chromatography, and nuclear magnetic resonance and infrared spectral data for **2** indicate the presence of hydroxyl and methylsulfonyl groups. This indication was confirmed by formation of a crystalline triphenylmethyl(trityl) ether derivative (**3**) having an elemental analysis consistent with its being a mono-*O*-(methylsulfonyl)mono-*O*-trityl derivative. Formation of trityl ether derivatives is often employed[12] with primary alcohol groups, but trityl ethers of secondary alcohol groups have also been obtained;[13] consequently, formation of a trityl ether does not establish unequivocally which hydroxyl group is unsubstituted in **2**.

Thin layer chromatographic examination of the course of hydrolysis of **1**, methyl 3,4,6-tri-*O*-methyl-2-*O*-(methylsulfonyl)-α-D-glucopyranoside[11] (**4**), or methyl 2,3,4-tri-*O*-methyl-6-*O*-(methylsulfonyl)-α-D-glucopyranoside (0.03 *M* solution in 1.25 *M* aqueous sodium hydroxide) revealed no difference in the ease of hydrolysis of the primary *vs.* the secondary *O*-(methylsulfonyl) group under these conditions. However, methylation[14] of **2** afforded a crystalline derivative indistinguishable from **4**, and this establishes that selective hydrolysis of the primary sulfonic ester group of **1** had occurred on basic alumina.

Hydrolysis of **1** was extremely slow on activity I basic alumina at room temperature (27°); at 50° little hydrolysis occurred on activity III alumina, and none occurred on activity V alumina.

We then examined the reaction on basic alumina at 50° of methyl 4-*O*-methyl-2,3,6-tri-*O*-(methylsulfonyl)-α-D-mannopyranoside[10] (**5**) which in the favored *C1* (D) conformation possesses an axial methylsulfonyl group at C-2. A single crystalline product (**6**) was obtained in 98% yield which, from elemental analysis and spectral data, was shown to be a monohydroxy compound derived from **5** by hydrolysis of a single *O*-methylsulfonyl group. By analogy with the formation of **2** from **1**, we expected **6** to possess an unsubstituted hydroxyl group at C-6, and this was confirmed by comparison of the trityl ether of **6** with that prepared by the following unequivocal synthetic route. Methanesulfonylation of methyl 4,6-*O*-ethylidene-α-D-mannopyranoside[15] followed by deacetalation afforded crystalline methyl 2,3-di-*O*-(methylsulfonyl)-α-D-mannopyranoside in 40% over-all yield. The latter compound on tritylation was converted into a single, crystalline product (60% yield) which was methylated[14] to give methyl 4-*O*-methyl-2-3-di-*O*-(methylsulfonyl)-6-*O*-trityl-α-D-mannopyranoside (**7**) identical with the trityl ether derivative of **6**.

Methanesulfonic ester groups at C-4 in some methyl D-aldohexopyranosides exhibited similar reactivity to corresponding groups situated at C-6.[16] For this reason we investigated the reaction on basic alumina at 50° of methyl 2,3-di-*O*-methyl-4,6-di-*O*-(methylsulfonyl)-β-D-glucopyranoside (**8**), and obtained a single product (**9**) in 63% yield, derived from **8** by hydrolysis of a methylsulfonyl group. Compound **9** was shown to be methyl 2,3-di-*O*-methyl-4-*O*-(methylsulfonyl)-β-D-glucopyranoside which was synthesized by the following route. Methyl β-D-glucopyranoside was treated with 2,2-dimethoxypropane to give crystalline methyl 4,6-*O*-isopropylidene-β-D-glucopyranoside, which has not previously been described, in 51% yield. Methylation of the latter compound, in 87% yield, followed by deacetalation, gave the known crystalline methyl 2,3-di-*O*-methyl-β-D-glucopyranoside in 86% yield. This compound, when treated with trityl chloride, afforded a single derivative in 33% yield which from elemental analysis and nmr data was shown to be a mono-*O*-trityl ether; as tritylation would be expected to occur at the primary hydroxyl group of C-6 in preference to the secondary hydroxyl group at C-4,[12] we consider that the product is methyl 2,3-di-*O*-methyl-6-*O*-trityl-β-D-glucopyranoside (**10**). Support for this structural assignment was obtained by a comparison of the nmr spectra of **10** and of the product (**11**) obtained from **10** in 74% yield by methanesulfonylation. Esterification of a hydroxyl group causes the adjacent ring hydrogen to resonate at a lower field. The nmr spectrum of **11** showed this downfield shift to the region of the anomeric proton (τ 5.5) for one proton only. If methanesulfonylation had occurred at the primary position, the shift of two protons would have been observed. Detritylation of **11** afforded a crystalline product in 66% yield identical with **9**.

Little or no reaction occurred in benzene on basic alumina at 50° during 24 hr with 1,2-*O*-isopropylidene-3-*O*-(methylsulfonyl)-D-threose, methyl 2,3-di-*O*-benzyl-6-deoxy-4-*O*-(methylsulfonyl)-α-D-glucopyranoside, methyl 2,3-di-*O*-benzyl-6-deoxy-4-*O*-(methylsulfonyl)-α-D-galactopyranoside, 4,6-*O*-ethylidene-1,2-*O*-isopropylidene-3-*O*-*p*-tolylsulfonyl-D-galactose, 1,6-anhydro-3,4-*O*-isopropylidene-2-*O*-(methylsulfonyl)-D-galactose, or **4**. Under the same conditions, hydrolysis of 1,2:3,4-di-*O*-isopropylidene-6-*O*-*p*-tolylsulfonyl-D-galactose to 1,2:3,4-di-*O*-isopropylidene-D-galactose was slow requiring 100 hr for complete reaction.

When chloroform was used in place of benzene in the reaction of **1** with basic alumina, elution of the alumina with chloroform, after 15 hr of reaction at 50°, gave a syrupy product, in 21% yield, identical with that obtained by ethylation of **2**. The ethyl ether group in the above product from the reaction on alumina is derived from the 0.75% of ethanol used as a preservative in chloroform. Further elution of the alumina with chloroform afforded a mixture of **1** (1%) and **2** (67%) which was resolved by silica gel column chromatography.

(10) R. C. Chalk, D. H. Ball, and L. Long, Jr., *J. Org. Chem.*, **31**, 1509 (1966).
(11) A. K. Mitra, D. H. Ball, and L. Long, Jr., *ibid.*, **27**, 160 (1962).
(12) G. R. Baker, "Methods in Carbohydrate Chemistry," Vol. II, Academic Press Inc., New York, N. Y., 1963, p 168.
(13) R. C. Hockett and C. S. Hudson, *J. Amer. Chem. Soc.*, **53**, 4456 (1931).
(14) R. Kuhn, H. Trischmann, and I. Löw, *Angew. Chem.*, **67**, 32 (1955).
(15) G. O. Aspinall and G. Zweifel, *J. Chem. Soc.*, 2271 (1957).
(16) J. Hill, L. Hough, and A. C. Richardson, *Proc. Chem. Soc.*, 346 (1963).

Subsequently, we performed reactions of **1** on basic alumina in mixtures of benzene or ethanol-free chloroform with up to 3% methanol, and obtained **4** in 38% yield together with **2** (58%) and unchanged **1** (4%). Similarly, compound **5** gave methyl 4,6-di-*O*-methyl-2,3-di-*O*-(methylsulfonyl)-α-D-mannopyranoside (**12**) in 38% yield, identical with the methylation product from **6**, together with **6** (59%) and unchanged **5** (3%). The use of solvent mixtures containing more than 3% methanol caused inactivation of the alumina, and starting material was recovered quantitatively.

In attempts to increase the yields of 6-*O*-methyl derivatives, by generation of methanol *in situ*, we performed reactions of **1** or **5** on basic alumina at 50° in mixtures of benzene or ethanol-free chloroform with up to 3% methyl acetate. However, yields of **4** or **12** were not improved over those obtained with solvent mixtures containing methanol.

Similarly, reaction of **1** on basic alumina in benzene containing 2% benzyl alcohol or 2% benzaldehyde[17] afforded unchanged **1** (45%), **2** (44%), and methyl 6-*O*-benzyl-3,4-di-*O*-methyl-2-*O*-(methylsufolnyl)-α-D-glucopyranoside (11%).

Identical hydrolysis and alcoholysis reactions of methanesulfonic esters of aldohexopyranosides occur on neutral alumina of Brockmann activity I. For example, reaction of **5** at 50° for 20 hr on neutral alumina in chloroform containing 2% methanol gave **12** in 36% yield together with **6** (50% yield) and unchanged **5** (6% yield).

Experimental Section[18]

Methyl 3,4-Di-*O*-methyl-2-*O*-(methylsulfonyl)-α-D-glucopyranoside (2).—A slurry of methyl 3,4-di-*O*-methyl-2,6-di-*O*-(methylsulfonyl)-α-D-glucopyranoside (**1**) (1 g) and Woelm basic alumina (50 g) in benzene was placed in a jacketed column and heated at 50° for 41 hr. After being cooled to room temperature the column was eluted with ether–methanol (19:1), and the solvent was removed by evaporation. The residue was chromatographed on silica gel (120 g) with ethyl acetate as eluent to give 332 mg (33%) of **1**, 47 mg of a mixture of two unidentified materials, and 521 mg (66%) of syrupy **2** having $[\alpha]^{22}D$ +119° (*c* 2.8, chloroform).

Anal. Calcd for $C_{10}H_{20}O_8S$: C, 40.00; H, 6.71; S, 10.68. Found: C, 40.04; H, 6.73; S, 10.72.

Methyl 3,4-Di-*O*-methyl-2-*O*-(methylsulfonyl)-6-*O*-trityl-α-D-glucopyranoside (3).—A mixture of **2** (475 mg), trityl chloride (2.4 g), and dry pyridine (20 ml) was kept 16 hr at 25° and then 4 hr at 70°. Water (3 ml) was added, and the solution was evaporated. The residue was treated with chloroform (4 ml), filtered to remove some triphenylmethanol, and chromatographed on silica gel (150 g) with chloroform (containing 0.5% triethylamine to minimize hydrolysis) as eluent to give **3** (896 mg, 74%) with mp 63–64° and $[\alpha]^{22}D$ +84° (*c* 0.5, chloroform) after recrystallization from hexane.

Anal. Calcd for $C_{29}H_{34}O_8S$: C, 64.19; H, 6.32; S, 5.91. Found: C, 64.30; H, 6.38; S, 6.04.

Methyl 3,4,6-Tri-*O*-methyl-2-*O*-(methylsulfonyl)-α-D-glucopyranoside (4). A. From 2.—Compound **2** (100 mg) was dissolved in anhydrous *N*,*N*-dimethylformamide (5 ml) and methyl iodide (5 ml). Silver oxide (1 g) was added, and the mixture was shaken in the dark for 24 hr. Solids were removed by filtration and washed with *N*,*N*-dimethylformamide, then with chloroform. The filtrate and washings were combined and concentrated to a syrup which was redissolved in chloroform. Residual silver salts were removed by filtration, and the chloroform solution was concentrated to a syrup which crystallized. After recrystallization from ethanol, **4** (58 mg, 56%) was obtained having a melting point and mixture melting point with authentic material of 86° and $[\alpha]^{22}D$ +116° (*c* 1.0, chloroform).

B. From 1.—A slurry of **1** (1 g) and Woelm basic alumina (80 g) in benzene containing 2% methanol was kept 18 hr at 50°. After being cooled to room temperature, elution with ether (1 l.) gave **4** (404 mg) containing small amounts of **1** and **2** (mixture A); elution with ether–methanol (19:1) then gave **2** (463 mg, 58%). Fractionation of mixture A on silica gel (60 g) with ether as eluent gave **1** (40 mg, 4%), **2** (3 mg), and **4** (314 mg, 38%); the latter compound when crystallized from ethanol had mp 86° and $[\alpha]^{22}D$ +116° (*c* 1.0, chloroform).

Anal. Calcd for $C_{11}H_{22}O_8S$: C, 42.03; H, 7.05; S, 10.20. Found: C, 42.09; H, 7.13; S, 10.35.

Methyl 4-*O*-Methyl-2,3-di-*O*-(methylsulfonyl)-α-D-mannopyranoside (6).—Methyl 4-*O*-methyl-2,3,6-tri-*O*-(methylsulfonyl)-α-D-mannopyranoside (**5**) (1.04 g) and Woelm basic alumina (50 g) in benzene were kept 41 hr at 50°. After being cooled to room temperature, elution with ether–methanol (19:1) gave **6** (835 mg, 98%) which crystallized on removing solvent. Recrystallization from ether gave **6** having mp 131–132° and $[\alpha]^{22}D$ +19° (*c* 1.0, chloroform).

Anal. Calcd for $C_{10}H_{20}O_{10}S_2$: C, 32.96; H, 5.53; S, 17.60. Found: C, 33.01; H, 5.55; S, 17.84.

Methyl 4-*O*-Methyl-2,3-di-*O*-(methylsulfonyl)-6-*O*-trityl-α-D-mannopyranoside (7). A. From Methyl 4,6-*O*-Ethylidene-α-D-mannopyranoside.[15]—Methyl 4,6-*O*-ethylidene-α-D-mannopyranoside (1.1 g) in anhydrous pyridine (10 ml) at −30° was treated dropwise with stirring with methanesulfonyl chloride (1 ml). The reaction mixture was kept at −20° for 24 hr and at 25° for 24 hr. The syrup obtained on concentrating the pyridine solution was dissolved in water, and the aqueous solution was extracted with chloroform to give syrupy methyl 4,6-*O*-ethylidene-2,3-di-*O*-(methylsulfonyl)-α-D-mannopyranoside (1.5 g), homogeneous by tlc in ether or ethyl acetate.

The syrup was dissolved in hot methanol (100 ml), Dowex 50 W (H^+) resin (30 g) was added, and the mixture was stirred 12 hr at 50°. The resin was removed by filtration, and washed with warm methanol. On removing solvent and crystallizing from chloroform–heptane, methyl 2,3-di-*O*-(methylsulfonyl)-α-D-mannopyranoside (0.57 g, 40% yield) was obtained having mp 113–114.5° and $[\alpha]^{20}D$ +22° (*c* 1.3, acetone).

Anal. Calcd for $C_9H_{18}O_{10}S_2$: C, 30.85; H, 5.14; S, 18.28. Found: C, 30.80; H, 4.97; S, 17.98.

Methyl 2,3-di-*O*-(methylsulfonyl)-α-D-mannopyranoside (0.30 g) in anhydrous pyridine (8 ml) was treated with trityl chloride (0.26 g) at 25° for 24 hr then at 60° for 5 hr, when tlc in ether indicated reaction was complete. After removing pyridine, the product was chromatographed on silica gel with ether as eluent. Methyl 2,3-di-*O*-(methylsulfonyl)-6-*O*-trityl-α-D-mannopyranoside (0.30 g, 60% yield) was obtained on crystallization from ethanol and had mp 119–120° and $[\alpha]^{20}D$ +7.7° (*c* 1.0, chloroform).

Anal. Calcd for $C_{28}H_{32}O_{10}S_2$: C, 56.75; H, 5.40; S, 10.80. Found: C, 56.40; H, 5.57; S, 10.48.

Methyl 2,3-di-*O*-(methylsulfonyl)-6-*O*-trityl-α-D-mannopyranoside (0.09 g) in anhydrous N,N-dimethylformamide (2 ml) and methyl iodide (0.2 ml) at 0° was stirred with silver oxide (0.2 g) for 5.5 hr. After this time, methyl iodide (0.2 ml) and silver oxide (0.2 g) were added, and the reaction mixture was stirred for an additional 5.5 hr. The reaction mixture was worked up as previously described for the preparation of **4** to give **7** (0.05 g, 53% yield), on crystallization from ethanol, having mp 212.5–214° and $[\alpha]^{22}D$ +27° (*c* 1.0, chloroform).

Anal. Calcd for $C_{29}H_{34}O_{10}S_2$: C, 57.41; H, 5.65; S, 10.57. Found: C, 57.27; H, 5.41; S, 10.84.

B. From 6.—A mixture of **6** (400 mg), dry pyridine (8.5 ml), and trityl chloride (1.2 g) was kept 4 hr at 70°. Water (3 ml) was added, and the solution was evaporated. The residue was treated with chloroform (4 ml), filtered to remove some triphenylmethanol, and chromatographed on silica gel (100 g) with chloroform containing 0.5% triethylamine as eluent to give **7** (665 mg,

(17) V. J. Hruby, *Proc. N. Dakota Acad. Sci.*, **16**, 12 (1962).

(18) Solutions were concentrated under reduced pressure. Melting points were determined with a Thomas–Hoover capillary melting point apparatus and optical rotations were measured using an ETL-NPL automatic polarimeter. Infrared spectra were recorded on a Perkin-Elmer Infracord spectrophotometer and nmr spectra were recorded on a Varian Model A-60 spectrometer. Ascending thin layer chromatography (tlc) was performed on 0.25-mm layers of silica gel G (distributed by Brinkmann Instruments, Inc., Great Neck, Long Island, N. Y.). For the detection of spots, the plates were sprayed successively with a 1% solution of α-naphthol in ethanol and with 10% sulfuric acid and were then heated. Column chromatography was performed on 0.05–0.20-mm silica gel (distributed by Brinkmann Instruments, Inc.). The microanalyses were performed by C. DiPietro and nmr spectra were obtained by F. H. Bissett.

83%) having mp 213° on crystallization from hexane, $[\alpha]^{22}D$ +27° (*c* 1.0, chloroform).

This product was identical with that obtained on tritylation of **6** by mixture melting point determination and comparison of infrared and nmr spectra.

Anal. Calcd for $C_{29}H_{34}O_{10}S_2$: C, 57.41; H, 5.65; S, 10.57. Found: C, 57.60; H, 5.67; S, 10.80.

Methyl 4,6-Di-*O*-methyl-2,3-di-*O*-(methylsulfonyl)-α-D-mannopyranoside (12). A. From 6.—A mixture of **6** (105 mg), anhydrous *N*,*N*-dimethylformamide (2 ml), silver oxide (0.6 g), and methyl iodide (0.6 ml) was stirred for 6 hr at room temperature. The mixture was filtered, and the filtrate was concentrated to dryness. The residue was dissolved in chloroform, filtered to remove some silver salts, and concentrated to give **12** (96 mg, 88%) which on crystallization from ethanol had mp 128° and $[\alpha]^{22}D$ +30.5° (*c* 2.5, chloroform).

Anal. Calcd for $C_{11}H_{22}O_{10}S_2$: C, 34.91; H, 5.86; S, 16.94. Found: C, 35.19; H, 5.89; S, 16.83.

B. From 5.—A slurry of **5** (1.04 g) and Woelm basic alumina (80 g) in a mixture of benzene or ethanol-free chloroform containing 2% methanol was kept 18 hr at 50°, cooled to room temperature, then eluted with ether (1 l.) followed by ether–methanol (19:1, 250 ml). Evaporation of the ether eluate afforded a mixture which was fractionated on silica gel with ether as eluent to give unchanged **5** (31 mg, 3%) and **12** (350 mg, 38%): mp 128°; $[\alpha]^{22}D$ +30.5° (*c* 2.4, chloroform).

Anal. Calcd for $C_{11}H_{22}O_{10}S_2$: C, 34.91; H, 5.86; S, 16.94. Found: C, 35.08; H, 5.87; S, 16.85.

Concentration of the ether–methanol (19:1) eluate gave **6** (500 mg, 59%) having mp 132° (ether) and $[\alpha]^{22}D$ +19.5° (*c* 1.0, chloroform).

Anal. Calcd for $C_{10}H_{20}O_{10}S_2$: C, 32.96; H, 5.53; S, 17.60. Found: C, 33.05; H, 5.56; S, 17.80.

Methyl 2,3-Di-*O*-methyl-4-*O*-(methylsulfonyl)-β-D-glucopyranoside (9).—A slurry of methyl 2,3-di-*O*-methyl-4,6-di-*O*-(methylsulfonyl)-β-D-glucopyranoside (**8**, 300 mg) with Woelm basic alumina (30 g) in benzene was kept 24 hr at 50°, cooled to room temperature, and eluted with ether to give unchanged **8** (84 mg, 28%) then with ether–methanol (19:1) to give **9** (150 mg, 63%): mp 86°; ½(ether); $[\alpha]^{22}D$ −29° (*c* 1.0, chloroform).

Anal. Calcd for $C_{10}H_{20}O_8S$: C, 40.00; H, 6.71; S, 10.68. Found: C, 40.08; H, 6.74; S, 10.75.

Synthesis of Methyl 2,3-Di-*O*-methyl-4-*O*-(methylsulfonyl)-β-D-glucopyranoside (9). A. Methyl 4,6-*O*-Isopropylidene-β-D-glucopyranoside.—Methyl β-D-glucopyranoside (6 g) was treated with 2,2-dimethoxypropane (7 g) in *N*,*N*-dimethylformamide (35 ml) using *p*-toluenesulfonic acid (0.05 g) as catalyst according to the method of Evans, Parrish, and Long.[19] The product, methyl 4,6-*O*-isopropylidene-β-D-glucopyranoside, crystallized and was recrystallized twice from 1-propanol: yield 2.6 g; mp 128–128.5°; $[\alpha]^{25}D$ −72° (*c* 1.4, water). A second crop of crystals (1.1 g) obtained from the mother liquors had mp 123–125°. The nmr spectrum of this compound was consistent with the proposed structure.

Anal. Calcd for $C_{10}H_{18}O_6$: C, 51.28; H, 7.69. Found: C, 51.45; H, 7.70.

B. Methyl 4,6-*O*-Isopropylidene-2,3-di-*O*-methyl-β-D-glucopyranoside.—Methyl 4,6-*O*-isopropylidene-β-D-glucopyranoside (1.0 g) in *N*,*N*-dimethylformamide was treated with methyl iodide (3 ml) and silver oxide (3 g) for 20 hr. Tlc (ethyl acetate) showed mainly one product. The product was purified on a silica gel column using ethyl acetate containing 1% triethylamine as solvent. The yield of syrupy product was 0.97 g, $[\alpha]^{23}D$ −43° (*c* 1.0, chloroform). The nmr spectrum was consistent with the proposed structure.

Anal. Calcd for $C_{12}H_{22}O_6$: C, 52.80; H, 8.80. Found: C, 52.45; H, 8.63.

C. Methyl 2,3-Di-*O*-methyl-β-D-glucopyranoside.—Methyl 4,6-*O*-isopropylidene-2,3-di-*O*-methyl-β-D-glucopyranoside (0.97 g) was stirred and heated at 50° in 95% methanol (45 ml) with Dowex 50 W (H^+) ion-exchange resin (10 g) for 5 hr. The resin was removed by filtration and the filtrate was concentrated to a syrup which crystallized. Recrystallization of the product from benzene gave 0.72 g of methyl 2,3-di-*O*-methyl-β-D-glucopyranoside: mp 61.5–63.5°; $[\alpha]^{21}D$ −45° (c 1.5, chloroform). Oldham[20] quotes mp 62–64° and $[\alpha]D$ −47.8° (*c* 4.4, chloroform) for this compound.

(19) M. E. Evans, F. W. Parrish, and L. Long, Jr., *Carbohyd. Res.*, **3**, 453 (1967).

(20) J. W. H. Oldham, *J. Amer. Chem. Soc.*, **56**, 1360 (1934).

D. Methyl 2,3-Di-*O*-methyl-6-*O*-trityl-β-D-glucopyranoside (10).—Methyl 2,3-di-*O*-methyl-β-D-glucopyranoside (0.32 g) and trityl chloride (0.26 g) were dissolved in pyridine (8 ml). The solution was left at room temperature for 20 hr and heated under reflux at 75° for 2 hr. Tlc (ether and isopropyl ether) indicated complete reaction. The mixture was concentrated to a syrup and the product was purified using silica gel chromatography with isopropyl ether containing 1% triethylamine as eluent. The product was obtained as a syrup in a yield of 0.228 g, $[\alpha]^{25}D$ −35° (*c* 2.0, chloroform). The nmr spectrum was consistent with the proposed structure.

E. Methyl 2,3-Di-*O*-methyl-4-*O*-(methylsulfonyl)-6-*O*-trityl-β-D-glucopyranoside (11).—Methyl 2,3-di-*O*-methyl-6-*O*-trityl-β-D-glucopyranoside (0.152 g) was dissolved in pyridine (8 ml) and cooled to −40°. Methanesulfonyl chloride (0.3 ml) was added and the mixture left at −20° for 16 hr and at room temperature for 24 hr. The pyridine was removed on the evaporator and the resultant syrup was dissolved in water and extracted into chloroform. The chloroform extracts were combined and dried (anhydrous magnesium sulfate); the solids were removed by filtration; and the filtrate was concentrated to a syrup. The 4-*O*-mesyl derivative moved slightly slower than the starting material on tlc in ether, isopropyl ether, or chloroform–ethyl acetate (1:1). The product was obtained as a syrup by purification on a silica gel column using hexane–ether (1:2) as solvent: yield 0.119 g; $[\alpha]^{25}D$ −12° (*c* 1.5, chloroform).

Anal. Calcd for $C_{29}H_{34}O_8S$: C, 64.2; H, 6.3; S, 5.9. Found: C, 64.5; H, 6.5; S, 6.0.

F. Methyl 2,3-Di-*O*-methyl-4-*O*-(methylsulfonyl)-β-D-glucopyranoside (9).—Methyl 2,3-di-*O*-methyl-4-*O*-(methylsulfonyl)-6-*O*-trityl-β-D-glucopyranoside (0.8 g) was dissolved in 80% aqueous acetic acid (20 ml) and heated at 50° for 45 min. Tlc in ether indicated complete removal of the trityl group. The product was purified by passage down a silica gel column using ether as solvent. The product crystallized and was recrystallized from ether: yield 0.292 g; mp 85.5–86.5°; $[\alpha]^{22}D$ −28° (*c* 0.9, chloroform).

Anal. Calcd for $C_{10}H_{20}O_8S$: C, 40.00; H, 6.67; S, 10.67. Found: C, 40.07; H, 6.39; S, 10.4.

Methyl 6-*O*-Benzyl-3,4-di-*O*-methyl-2-*O*-(methylsulfonyl)-α-D-glucopyranoside (13).—A slurry of **1** (1 g) and Woelm basic alumina in benzene containing 2% benzyl alcohol was kept 24 hr at 50°, cooled to room temperature, and eluted with ether–methanol (19:1). The concentrated eluate was fractionated on silica gel (100 g) with ethyl acetate to give unchanged **1** (450 mg, 45%), **2** (345 mg, 44%), and a syrupy product (113 mg, 11%) having $[\alpha]^{22}D$ +102° (*c* 2.4, chloroform) designated as **13** by analogy with the other products from **1** described above. The structure proposed as **13** was supported by spectral data and elemental analysis.

Anal. Calcd for $C_{17}H_{26}O_8S$: C, 52.29; H, 6.71; S, 8.21. Found: C, 52.50; H, 6.68; S, 8.00.

Similarly, **1** (300 mg) and Woelm basic alumina (30 g) in benzene containing 2% benzaldehyde[17] afforded unchanged **1** (120 mg, 40%), **2** (99 mg, 42%), and **13** (55 mg, 17%) having $[\alpha]^{22}D$ +100° (c 2.4, chloroform).

Methyl 2,3,4-Tri-*O*-methyl-6-*O*-(methylsulfonyl)-α-D-glucopyranoside.—Methyl 6-*O*-(methylsulfonyl)-α-D-glucopyranoside[10] (3 g) in anhydrous *N*,*N*-dimethylformamide (50 ml) was treated with methyl iodide (10 ml) and silver oxide (10 g) according to the procedure of Kuhn, *et al.*[14] The product was shown by tlc in hexane–methyl ethyl ketone (6:4) to consist of two components which were separated with this solvent by silica gel chromatography. The faster moving compound was shown by comparison of infrared and nmr spectra to be methyl 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranoside.

The second component, obtained as a syrup (0.73 g), had $[\alpha]^{23}D$ +106° (*c* 1.0, chloroform).

Anal. Calcd for $C_{11}H_{22}O_8S$: C, 42.05; H, 7.01; S, 10.21. Found: C, 42.05; H, 7.05; S, 10.18.

Hydrolysis of 1, 4, and Methyl 2,3,4-Tri-*O*-methyl-6-*O*-(methylsulfonyl)-α-D-glucopyranoside.—A solution of methyl 2,3,4-tri-*O*-methyl-6-*O*-(methylsulfonyl)-α-D-glucopyranoside, **1**, or **4** (0.3 mmol) in boiling 1.25 *M* sodium hydroxide (10 ml) was examined at 15-min intervals by tlc on silica gel with ether as solvent. All three compounds were completely hydrolyzed after 90 min with no apparent differences in rate.

Methyl 6-*O*-Ethyl-3,4-di-*O*-methyl-2-*O*-(methylsulfonyl)-α-D-glucopyranoside. A. From 1.—A slurry of **1** (7.0 g) and Woelm basic alumina (500 g) in chloroform (containing 0.75% ethanol

as preservative) was kept 15 hr at 50°. After cooling to room temperature, elution with chloroform afforded methyl 6-*O*-ethyl-3,4-di-*O*-methyl-2-*O*-(methylsulfonyl)-α-D-glucopyranoside (1.266 g, 21% yield) having $[\alpha]^{26}D$ +120° (*c* 2.0, chloroform).

Anal. Calcd for $C_{12}H_{24}O_8S$: C, 43.89; H, 7.37; S, 9.76. Found: C, 44.09; H, 7.30; S, 9.52.

Further elution with chloroform afforded a mixture of **1** (99 mg, 1%) and **2** (4.71 g, 67%) which was resolved by silica gel column chromatography.

B. From 2.—Compound **2** (0.104 g) in N,N-dimethylformamide (2 ml) with ethyl iodide (0.5 ml) and silver oxide (0.5 g) was stirred 3.5 hr when reaction was complete as judged by tlc using ether as solvent. The reaction mixture was worked up as described above for methylation reactions to give methyl 6-*O*-ethyl-3,4-di-*O*-methyl-2-*O*-(methylsulfonyl)-α-D-glucopyranoside (0.094 g, 83%) having $[\alpha]^{26}D$ +119° (*c* 2.4, chloroform). The infrared and nmr spectra were identical with those of the product from **1** described in A.

Anal. Calcd for $C_{12}H_{24}O_8S$: C, 43.89; H, 7.37; S, 9.76. Found: C, 43.87; H, 7.48; S, 9.62.

Registry No.—**2**, 16802-84-9; **3**, 16802-85-0; **4**, 7045-36-5; **6**, 16802-87-2; **7**, 16853-03-5; methyl 2,3-di-*O*-(methylsulfonyl)-α-D-mannopyranoside, 16802-88-3; methyl 2,3-di-*O*-(methylsulfonyl)-6-*O*-trityl-α-D-mannopyranoside, 16802-89-4; **9**, 16802-90-7; methyl 4,6-*O*-isopropylidene-β-D-glucopyranoside, 16802-97-4; methyl 4,6-*O*-isopropylidene-2,3-di-*O*-methyl-β-D-glucopyranoside, 16802-91-8; **11**, 16802-92-9; **12**, 16802-93-0; **13**, 16802-94-1; methyl 2,3,4-tri-*O*-methyl-6-*O*-(methylsulfonyl)-α-D-glucopyranoside 16802-95-2; methyl 6-*O*-ethyl-3,4-di-*O*-methyl-2-*O*-(methylsulfonyl)-α-D-glucopyranoside, 16802-96-3.

Stereochemistry of the Anomers of Methyl 2-Deoxy-D-ribofuranoside. Synthesis of Methyl 5-(6-Aminopurin-9-yl)-2,5-dideoxy-α-D-ribofuranoside, a "Reversed" Nucleoside[1]

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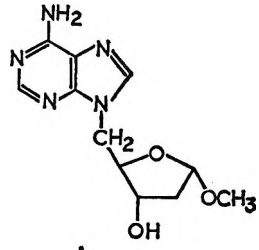
Methyl 2-deoxy-5-*O*-triphenylmethyl-α-D-ribofuranoside (**2**) and methyl 2-deoxy-5-*O*-triphenylmethyl-β-D-ribofuranoside (**3**) were synthesized and the stereochemistry of their anomeric centers was established unambiguously by chemical means and by complete analysis of their nmr spectra. The results are in agreement with those predicted by the Hudson isorotation rules. The syntheses of related ribofuranosides and of methyl 5-(6-aminopurin-9-yl)-2,5-dideoxy-α-D-ribofuranoside (**1**) are also described.

A route to the synthesis of ribose derivatives of adenine bonded at C-5 of the sugar moiety ("reversed" nucleosides) has been described[2] as part of a cooperative program with Professor Skoog at the University of Wisconsin[3] to determine the cytokinin activity[4,5] and chemical properties of compounds closely related to kinetin.[6,7] In providing a synthetic route to 2-deoxyribose derivatives of "reversed" nucleoside type, as exemplified by methyl 5′-(6-aminopurin-9-yl)-2′,5′-dideoxy-α-D-ribofuranoside (**1**), we found it desirable and also necessary to establish the stereochemistry of the anomeric centers for a series of useful intermediates.



1

A mixture of the α and β forms of methyl 2-deoxy-D-ribofuranosides[8] was treated with 1 equiv of triphenylmethyl chloride. Chromatography on silica gel afforded a separation of methyl 2-deoxy-5-*O*-triphenylmethyl-α-D-ribofuranoside (**2**) (28%), $[\alpha]^{26}D$ 64.4° (*c* 1.2, $CHCl_3$), and methyl 2-deoxy-5-*O*-triphenylmethyl-β-D-ribofuranoside (**3**) (24%), $[\alpha]D^{26}$ −43.8° (*c* 1.3, $CHCl_3$). The stereochemistry of the anomeric centers was temporarily assigned on the basis of Hudson's rules of isorotation[9] which correlate optical rotation and anomeric configuration. However, it has recently been discovered that several pyrimidine[10−12] and purine[13] 2-deoxy-D-ribonucleosides constitute exceptions to Hudson's rules. Although there is consistency among the rotations of a wide variety of 2-deoxy-D-ribofuranose esters and glycosides and there is no evidence currently available that Hudson's rules are not applicable to such substances,[14] it was desirable to confirm the assignments by further physical and chemical means. Accordingly, the configuraton of the anomeric center in **2** and **3** was rigorously established by an unambiguous chemical synthesis and by a complete analysis of their nmr spectra.

(1) The support of this work by a research grant (USPHS-GM-05829) from the National Institutes of Health, U. S. Public Health Service, is gratefully acknowledged.

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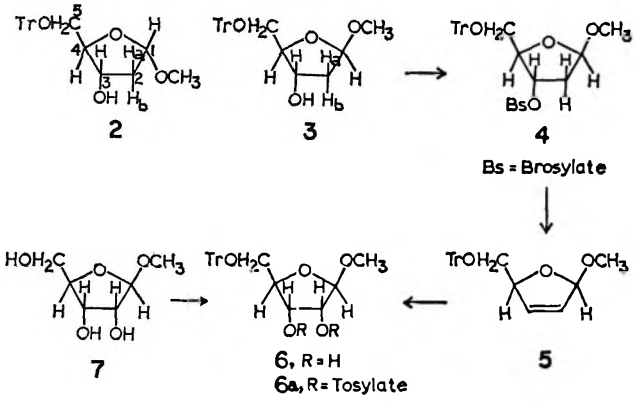
The chemical determination of the stereochemistry of the anomeric center consisted in the conversion of methyl 2-deoxy-5-*O*-triphenylmethyl-β-D-ribofuranoside (**3**) into a substance of known anomeric configuration, methyl di-2,3-*O*-*p*-toluenesulfonyl-5-*O*-triphenylmethyl-β-D-ribofuranoside (**6a**). Thus, treatment of **3** with *p*-bromobenzenesulfonyl chloride in pyridine provided the *p*-bromobenzenesulfonate **4**, which was transformed into the olefin **5** in 63% yield by means of excess sodium methoxide in anhydrous DMF (Scheme I).[15,16]

SCHEME I



Osmylation of **5** followed by alkali–mannitol hydrolysis afforded the diol **6** in 74% yield. It was predicted that the diol would have the ribose configuration since osmium tetroxide should attack the double bond of **5** from the less hindered side, *i.e.*, from the side opposite the trityl and methoxyl groups. The diol was converted into its crystalline ditosylate derivative **6a**. That **6** and consequently **6a** did have the ribose configuration was shown by the intersecting conversion of methyl β-D ribofuranoside (**7**),[17] of known configuration, into the 5-*O*-trityl compound **6** and thence to the ditosylate derivative **6a**. Identity of the samples of **6a** prepared by the separate routes was established by melting point and mixture melting point, infrared and nmr spectra, and optical rotation. Since the stereochemistry at the anomeric center of **7** was known,[17] the methyl 2-deoxy-5-*O*-triphenylmethyl-D-ribofuranoside with the negative specific rotation necessarily had the β configuration (**3**) and the dextrorotatory isomer had the α configuration (**2**).[18,19]

The configuration at C-1 of the α and β anomers of methyl 2-deoxy-5-*O*-triphenylmethyl-D-ribofuranoside (**2** and **3**), predicted first on optical rotation and then based firmly on chemical interconversion, was correlated with the nmr spectra of these anomers by a full analysis for the C-1, C-2, and C-3 protons, which is in itself of interest. This study is relevant to correlations between nmr spectra and configuration of the anomeric proton reported by Jardetzky,[20] Lemieux,[11,21] Leonard and Laursen,[22] and Robins and Robins.[23] In particular, Jardetzky[20] and Robins and Robins[23] have suggested a correlation for a series of α and β anomers of 2′-deoxyribofuranosyl nucleosides based purely on the appearance of the resonance due to the anomeric proton, its peak width, and vicinal coupling constants abstracted on a first-order basis from these signals. Our purpose in presenting the full nmr analysis of this part of the molecule is to establish accurate values of vicinal coupling constants of the anomeric proton and to emphasize the variation, with configuration, of the chemical-shift difference between the C-2 protons in **2** and **3**.

Chemical-shifts and coupling constants of the furan ring protons are tabulated (see below). The chemical shift of the C-5 protons and the overlapping methyl signals of the methoxyls are included. Assignments of multiplets to protons on C-1, C-2, C-3, and C-5 were obvious from the relative chemical shifts, integrated areas, and amount of fine structure. Difficulties with the C-3 and C-4 protons included considerable overlapping in the case of the α anomer and complexity of splitting patterns in the β anomer.

The two compounds gave an ABMX system[24] for H_{2a}, H_{2b} (AB part), H_1 (X), and H_3 (M), the M multiplet being further split by H_4. As usual, A is defined as the downfield part of the AB multiplet. The ABMX patterns can be analyzed by the general treatment of Pople and Schaefer[24] or by the procedure of Abraham and McLauchlan.[25] We chose to use the latter but with slight modifications. The AB part (showing 16 lines in the 100-Mc spectrum) was simplified by double irradiation at the position of the X resonance, which reduced this to an 8-line pattern (AB of ABM) which was analyzed by the general procedure for ABX analysis.[26] The 16-line AB part can be treated as the 8-line ABX pattern with each line doubled by M. The doublings, "d_{AM}" and "d_{BM}" (due to but not equal to J_{AM} and J_{BM} obtained in above analysis) are line separations in the M doublet of doublets. Subtraction of these doublings from the full AB part left the AB of ABX. The X part in both anomers appeared as a multiplet of four lines which gave $|J_{AX} + J_{BX}|$ for comparison with AB analysis. The parameters obtained from the analysis were used for the calculation of splitting patterns and intensities. In every case, excellent agreement was obtained between the calculated and the observed spectrum.

(15) This substance is crystalline and stable at room temperature, and the method offers a convenient route for the introduction of 2,3 double bonds into the pentofuranosides; *cf.* J. Hildesheim, J. Cléophax, and S. D. Géro, *Tetrahedron Lett.*, 1685 (1967).

(16) Compound **6** may be of related biochemical interest in view of the recent investigations on 2′,3′-unsaturated nucleosides: (a) DHFUDR, see T. A. Khwaja and C. Heidelberger, *J. Med. Chem.*, **10**, 1066 (1967); (b) blasticidin S, see N. Otake, S. Takeuchi, T. Endo, and H. Yonehara, *Tetrahedron Lett.*, 1411 (1965); (c) J. R. McCarthy, Jr., M. J. Robins, L. B. Townsend, and R. K. Robins, *J. Amer. Chem. Soc.*, **88**, 1549 (1966); (d) J. P. Horwitz, J. Chua, M. Noel, and J. T. Donatti, *J. Org. Chem.*, **32**, 817 (1967); (e) J. P. Horwitz, J. Chua, M. A. DaRooge, M. Noel, and I. L. Klundt, *ibid.*, **31**, 205 (1966); (f) J. P. Horwitz, J. Chua, J. A. Urbanski, and M. Noel, *ibid.*, **28**, 942 (1963); (g) J. P. Horwitz, J. Chua, I. L. Klundt, M. A. DaRooge, and M. Noel, *J. Amer. Chem. Soc.*, **86**, 1896 (1964); (h) J. J. Fox and N. C. Miller, *J. Org. Chem.*, **28**, 936 (1963); (i) P. Reichard, *J. Biol. Chem.*, **237**, 3513 (1962).

(17) R. Barker and H. G. Fletcher, Jr., *J. Org. Chem.*, **26**, 4605 (1961).

(18) Catalytic reduction of 2,3-didehydro-2,3-dideoxy compounds leads to dideoxyribose derivatives, which are of interest particularly in purine nucleoside combination.[19]

(19) (a) M. J. Robins and R. K. Robins, *J. Amer. Chem. Soc.*, **86**, 3585 (1964); (b) M. J. Robins, J. R. McCarthy, Jr., and R. K. Robins, *Biochemistry*, **5**, 224 (1966); (c) G. L. Tong, W. W. Lee, and L. Goodman, *J. Org. Chem.*, **30**, 2854 (1965).

(20) C. D. Jardetzky, *J. Amer. Chem. Soc.*, **83**, 2919 (1961).

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

(22) N. J. Leonard and R. A. Laursen, *Biochemistry*, **4**, 354 (1965).

(23) M. J. Robins and R. K. Robins, *J. Amer. Chem. Soc.*, **87**, 4934 (1965).

(24) J. A. Pople and T. Schaefer, *Mol. Phys.*, **3**, 547 (1960).

(25) R. J. Abraham and K. A. McLauchlan, *ibid.*, **5**, 195 (1962).

(26) 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, pp 132–135.

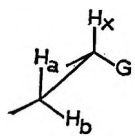
TABLE I

CHEMICAL-SHIFT AND COUPLING CONSTANT DATA FOR METHYL 2-DEOXY-5-O-TRIPHENYLMETHYL-D-RIBOFURANOSIDES

		Chemical shifts[a] δ scale, ppm									Splitting patterns for H_1,	Coupling constants, cps					
Compound	Solvent	X H_1	A[b] H_{2a}	B[b] H_{2b}	M H_3	H_4	H_5	Me	OH	δ_{AB}, cps	H_2, H_3	J_{AB}	J_{AX}	J_{BX}	J_{AM}	J_{BM}	J_{AX}/J_{BX}
α anomer 2	$CDCl_3$ TMS	5.12	2.17	1.98	4.15	4.21	3.17	3.35	2.84	19.2	ABMX	13.4	4.8	0.7	5.8	1.3	6.85
β anomer 3	$CDCl_3$ TMS	5.01	2.10	1.96	3.82–4.40		3.25[c]	3.25	2.10	13.6	ABMX	13.0	1.9	5.5	6.4	6.4	0.34

[a] Aromatic protons absorbed between δ 7.08 and 7.54. [b] Assignment of A and B between H_{2a} and H_{2b} discussed in text. [c] Approximate value.

Parameters were obtained above in terms of A, B, M, and X, and the problem that remained was the assignment of A and B to H_{2a} and H_{2b} or *vice versa*. We resorted to empirical analogy using rigid cyclic molecules containing the monosubstituted ethane fragment **8**. There are several examples of this where the proton



8

H_b, *cis* to and eclipsed by the substituent group G (such as Cl, Br, OH, CN, N_3), is upfield from H_a, *trans* to G.[27,28] Chemical-shift theory is at present inadequate to make such predictions with confidence. Chemical shifts for H_{2a} and H_{2b} in these two compounds have been assigned by selecting the upfield component as the proton *cis* to the hydroxyl group after consideration of possible conformations. In the α anomer this shielding will occur both from the hydroxyl group and the methoxyl group but in the β anomer the shielding effects from these groups are in opposition. Recourse had to be taken then in the values of the coupling J_{AX} and J_{BX} and an approach in terms of small and large J_{vic} and the general Karplus equations.[29,30] Internal support for our assignment is discussed below (see Table I).

In the α anomer (**2**), the resonance of the C-1 proton was a clear doublet of doublets with $J_{AX} + J_{BX} = 5.5$ cps. The resonance of the C-3 proton was partly obscured by that of the C-4 proton but its splitting pattern was easily recognized in the overlapping sets of multiplets. The absorption of H_4 was a ragged doublet of doublets. Protons on C-5 were found to be magnetically equivalent and appeared as a clean doublet. The absorption of the C-2 protons (AB) appeared as a multiplet of 16 lines with some transitional degeneracies in the higher field part. The coupling constants $J_{AX} > J_{BX}$ and $J_{AM} > J_{BM}$ are of sufficient magnitude to use the ideas mentioned above on *cis* shielding by the hydroxyl and methoxyl groups and to assign H_{2a} as A and H_{2b} as B. An internal cross-check for self-consistency is provided by the larger observed value of δ_{AB} in this compound compared with that in the β anomer **3**.

In the spectrum of the β anomer the resonance of the C-1 proton appeared as a quartet with $J_{AX} + J_{BX} = 7.4$ cps. The signals due to H_3 and H_4 were a complex set of multiplets and were not analyzed. Analysis of the resonance of the C-5 protons was not possible because the methylene signal was obscured by the methoxyl group, but the former appeared to be magnetically nonequivalent. This is also the situation in the 2,3-didehydro compound **5**. The absorption of the methylene protons (H_{2a}, H_{2b}) appeared as a multiplet of 16 lines with little overlapping. The assignment of A and B as H_{2a} and H_{2b} was again made on the basis of the value of δ_{AB} and J_{vic}. The observation that $J_{AM} = J_{BM}$ is merely a reflection that changes in the conformation of the ring and orientation of substituents can produce gross changes in coupling constants.[31] In the two compounds the observed values of geminal coupling constants (J_{AB}) fit well their environment on both theoretical[32] and empirical grounds.[33] No sign determinations have been carried out but these values are presumed to be negative. The many factors which influence the magnitude of vicinal coupling constants in molecules of such complexity (in relation to their nmr spectra) cannot be dissected out in any quantitative fashion. Finally, the observed correlations between nmr spectra and configurations are as follows: (1) in the α anomer $J_{AX} > J_{BX}$, whereas in the β anomer $J_{AX} < J_{BX}$; (2) the value of δ_{AB} is larger in the α anomer.

Returning to the original goal, a series of five transformations converted the α anomer **2**, now of established configuration, into the "reversed" deoxynucleoside **1**. On treatment with *p*-bromobenzoyl chloride in pyridine, methyl 2-deoxy-5-*O*-triphenylmethyl-α-D-ribofuranoside was converted into methyl 3-*p*-bromobenzoyl-2-deoxy-5-*O*-triphenylmethyl-α-D-ribofuranoside (**9**). Aqueous acetic acid brought about detritylation. The resulting alcohol **10** was transformed by the action of *p*-bromobenzenesulfonyl chloride in pyridine into methyl 5-*p*-bromobenzenesulfonyl-3-*p*-bromobenzoyl-2-deoxy-α-D-ribofuranoside (**11**). The brosylate **11** reacted smoothly with sodium adenide in anhydrous DMF to give the blocked nucleoside, methyl 5-(6-aminopurin-9-yl)-3-*p*-bromobenzoyl-2,5-dideoxy-α-D-ribofuranoside (**12**), and methanolic ammonia transformed this into the "reversed" deoxynucleoside, methyl 5-(6-aminopurin-9-yl)-2,5-dideoxy-α-D-ribofuranoside (**1**) (Scheme II).

(27) (a) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, London, in press, Chapter 2-2; (b) A. D. Broom, M. P. Schweizer, and P. O. P. Ts'o, *J. Amer. Chem. Soc.*, **89**, 3612 (1967).

(28) For a full discussion of this point, see R. H. Andreatta, V. Nair, and A. V. Robertson, *Aust. J. Chem.*, **20**, 2701 (1967).

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

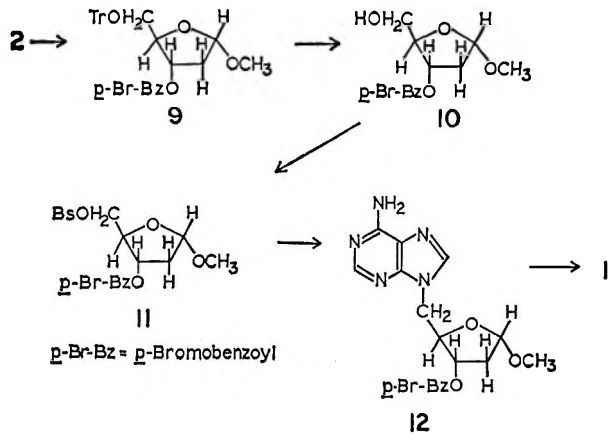
(30) M. Karplus, *J. Amer. Chem. Soc.*, **85**, 2870 (1963).

(31) It is of interest to note that no long range coupling was evident in the two spectra.

(32) A. A. Bothner-By, *Advan. Magnetic Resonance*, **1**, 195 (1965).

(33) R. C. Cookson, T. A. Crabb, J. J. Frankel, and J. Hudec, *Tetrahedron, Suppl.*, No. 7, 355 (1966).

SCHEME II



Experimental Section[34]

Methyl 2-Deoxy-5-*O*-triphenylmethyl-α- and -β-D-ribofuranosides (2 and 3).—To a solution of 9.60 g (67.5 mmol) of 2-deoxy-D-ribose in 200 ml of dry methanol was added 4.0 ml of saturated methanolic hydrochloric acid. After standing at room temperature for 30 min, the pale yellow solution was neutralized with Dowex-1 (HCO_3^-), filtered, and evaporated to dryness *in vacuo*. The residual oil was dissolved in 50 ml of dry pyridine and evaporated to dryness under high vacuum. This process was repeated once and the residue was dissolved in 200 ml of dry pyridine and treated with 19.0 g (68.0 mmol) of triphenylmethyl chloride. The solution was stirred at room temperature for 3 days and then poured into 2 l. of ice-cold 5% hydrochloric acid. The pH was adjusted to 3 by the further addition of ice-cold 10% hydrochloric acid. The mixture ws extracted with 700 ml of ether, and the aqueous phase was separated and extracted again with 300 ml of ether. The combined organic layers were shaken with three 100-ml portions of 5% potassium bisulfate, three 100-ml portions of water, and two 100-ml portions of saturated sodium chloride solution and were dried over anhydrous sodium sulfate. The ether was evaporated under reduced pressure. The residue was dissolved in 25 ml of methanol and this was placed in the icebox for 3 days. The precipitated triphenylcarbinol was removed by filtration (3.10 g) and washed thoroughly with cold methanol, and the methanol solution was evaporated *in vacuo*. The residue (23.0 g) was dissolved in ether, 15 g of silica gel was added, and the mixture was evaporated to dryness. The solid was applied to the top of a column of 400 g of silica gel packed in pentane–ether (9:1). The progress of the column was conveniently followed by tlc using the solvent system with which the column was being eluted. Elution was continued with pentane–ether (9:1) until all the triphenylcarbinol was removed. Polarity was gradually increased to pentane–ether (6:4), and 7.3 g (28%) of methyl 2-deoxy-5-*O*-triphenylmethyl-α-D-ribofuranoside (**2**) was eluted, $[\alpha]^{26}D$ 64.4° (*c* 1.3, $CHCl_3$), as a colorless gum. The material was homogeneous by tlc but could not be induced to crystallize. Continued elution of the column with pentane–ether (6:4) afforded 6.3 g (24%) of methyl 2-deoxy-5-*O*-triphenylmethyl-β-D-ribofuranoside (**3**), $[\alpha]^{26}D$ −43.8° (*c* 1.2, $CHCl_3$). This material was also homogeneous by tlc but could not be induced to crystallize. Separation of the two anomers was practically quantitative; only three of the fractions contained mixtures and these were discarded.

Methyl 3-*p*-Bromobenzenesulfonyl-2-deoxy-5-*O*-triphenylmethyl-β-D-ribofuranoside (4).—A solution of 1.10 g (2.80 mmol) of methyl 2-deoxy-5-*O*-triphenylmethyl-β-D-ribofuranoside (**3**) in 25 ml of anhydrous pyridine was treated with 1.07 g (4.20 mmol) of *p*-bromobenzenesulfonyl chloride in one portion and the solution was stirred at room temperature for 24 hr. It was poured into 150 ml of 5% sodium bicarbonate solution and extracted with 300 ml of ether. The ether was washed with four 100-ml portions of 5% potassium bisulfate solution, water to neutrality, and saturated sodium chloride solution. The ethereal solution was dried over anhydrous sodium sulfate; then the ether was evaporated under reduced pressure. The residue crystallized from methyl alcohol–ethyl acetate (10:2) to give 1.65 g of crude product. Recrystallization from methanol gave 425 mg, mp 94–95°, of a first crop and 350 mg, mp 93–95°, of a second crop (45%) of **4**: $[\alpha]^{23}D$ −8.0° (*c* 1.3, $CHCl_3$); ν_{max}^{Nujol} 1580, 1555 cm^{-1} (phenyl nuclei); nmr δ 7.76–7.15 (19 H, multiplet, aromatic protons), 5.16–4.88 (2 H, multiplet, H_1 and H_3), 4.30–4.05 (1 H, multiplet, H_4), 3.24 (3 H, singlet, CH_3O–), 3.10 (2 H, doublet, J = 6 cps, $2H_5$) and 2.31–2.15 (2 H, multiplet, $2H_2$)

Anal. Calcd for $C_{31}H_{29}BrO_6S$: C, 61.08; H, 4.79; S, 5.25. Found: C, 61.18; H, 5.01; S, 5.57.

Methyl 2,3-Didehydro-2,3-dideoxy-5-*O*-triphenylmethyl-β-D-ribofuranoside (5).—A solution of 230 mg (0.01 g-atom) of sodium in 25 ml of anhydrous methanol was evaporated to a small volume under reduced pressure. The solution was diluted with 20 ml of anhydrous dimethylformamide and evaporation was continued for 30 min to ensure complete removal of the methanol. A solution of 1.00 g (1.65 mmol) of methyl 3-*p*-bromobenzenesulfonyl-2-deoxy-5-*O*-triphenylmethyl-β-D-ribofuranoside (**4**) in 10 ml of dry dimethylformamide was added dropwise during 5 min at room temperature. The solution was stirred for 45 min and poured into a two-phase mixture of 400 ml of water and 200 ml of ether. The aqueous phase was separated and extracted again with 100 ml of ether. The combined organic extracts were washed with water and saturated sodium chloride solution and dried over anhydrous sodium sulfate. Evaporation under reduced pressure afforded 500 mg of a colorless gum which was applied to the top of a column of 20 g of silica gel packed in pentane–ether (9:1). The column was eluted with pentane–ether (8:2) and 20 ml fractions were collected. Fractions 3–7 were combined, evaporated, and recrystallized from ether–pentane to give 386 mg (63%) of **5** as colorless needles: mp 82–83°; $[\alpha]^{23}D$ −72.2° (*c* 1.1, $CHCl_3$); ν_{max}^{Nujol} 1625 (C=C) and 1590 cm^{-1} (phenyl nuclei); nmr δ 7.61–7.30 (15 H, multiplet, aromatic protons), 6.20–5.70 (3 H, multiplet, H_1, H_2, H_3), 5.01 (1 H, multiplet, H_4), 3.40 (3 H, singlet, CH_3O), and 3.20 (2 H, multiplet, $2H_5$).

Anal. Calcd for $C_{25}H_{24}O_3$: C, 80.61; H, 6.49. Found: C, 80.48; H, 6.49.

Methyl 5-*O*-Triphenylmethyl-β-D-ribofuranoside (6). A. From Olefin 5.—A solution of 1.46 g (3.93 mmol) of methyl 2,3-didehydro-2,3-dideoxy-5-*O*-triphenylmethyl-β-D-ribofuranoside (**5**) in 35 ml of anhydrous ether was treated with a solution of 1.00 g (3.93 mmol) of osmium tetroxide in 35 ml of the same solvent. A solution of 0.62 g (7.86 mmol) of anhydrous pyridine in 30 ml of dry ether was added, and the resulting solution was allowed to stand at room temperature for 24 hr. The light brown precipitate was collected by filtration, washed with ether, and dissolved in 50 ml of methylene chloride. A solution of 7.5 g of mannitol in 75 ml of 1% aqueous potassium hydroxide was added, and the two-phase system was stirred vigorously until the organic layer became colorless (*ca.* 5 hr). The methylene chloride layer was separated, washed with water, dried over anhydrous sodium sulfate, and evaporated. The resulting gum was filtered through a column of 20 g of silica gel with ether–pentane (4:1) and the eluate was evaporated under reduced pressure to give 1.18 g (74%) of **6** as a colorless glass: $[\alpha]^{23}D$ −18.8° (*c* 1.8, $CHCl_3$), homogeneous on tlc plates in solvent systems A, B, C, and D. It was characterized as the 2,3-ditosylate derivative.

A solution of 250 mg (0.61 mmol) of the compound described above in 10 ml of anhydrous pyridine, together with 285 mg (1.50 mmol) of *p*-toluenesulfonyl chloride, was stirred at room temperature for 5 days. The solution was poured into 100 ml of ice-cold 5% sodium bicarbonate, and the crystals were collected by filtration and washed well with water. One recrystallization from methanol–ethyl acetate gave 200 mg (46%) of methyl 2,3-di-*O*-*p*-toluenesulfonyl-5-*O*-triphenylmethyl-β-D-ribofuranoside (**6a**) as colorless needles: mp 140–141°; $[\alpha]^{23}D$ 63.8° (*c* 0.76' $CHCl_3$); ν_{max}^{Nujol} 1600 cm^{-1} (phenyl nuclei); nmr δ 7.96–7.03 (23 H, multiplet, aromatic protons), 5.15–4.91 (3 H, multiplet,

(34) Melting points were determined on a Thomas–Hoover capillary melting point apparatus and are corrected. The infrared spectra were recorded on a Perkin-Elmer Model 337 grating spectrophotometer. The ultraviolet spectra were recorded on a Cary Model 15 spectrophotometer. Thin layer chromatography was performed on Eastman silica gel strips with a fluorescent indicator. Solvent system A refers to pentane–ether (1:1); B, to pentane–ether (1:4); C, to pentane–ethyl acetate (7:3); and D, to 4% methanol in chloroform. Routine nmr spectra were recorded on a Varian Associates A-60A or A-56/60 spectrometer at ordinary probe temperatures. Unless otherwise noted nmr spectra were run in $CDCl_3$. Nmr analyses were carried out on expanded traces of the decoupled and undecoupled spectra recorded on a Varian HA-100 instrument. Experimental errors are estimated at ±0.1 cps for coupling constants and ±0.01 ppm for chemical shifts. We are indebted to Mr. J. Nemeth and his associates at the University of Illinois for the microanalyses.

H_1, H_2, H_3), 4.46–4.16 (1 H, multiplet, H_4), 3.33 (3 H, singlet, CH_3O), and 2.45 and 2.36 (3 H each, singlets, *p*-CH_3).

Anal. Calcd for $C_{39}H_{38}O_9S_2$: C, 65.52; H, 5.35; S, 8.97. Found: C, 65.63; H, 5.38; S, 9.04.

B. From Methyl β-D-Ribofuranoside (7).[17]—A solution of 5.0 g (33 mmol) of D-ribose in 100 ml of anhydrous methanol was cooled to 0° and treated with 0.5 ml of concentrated sulfuric acid. The colorless solution was allowed to stand at 4° for 16 hr and was passed through a column of Amberlite IR-45 (OH^-). The filtrate was evaporated to a pale yellow oil under reduced pressure. The nmr spectrum of this oil in D_2O showed the anomeric proton as a singlet at δ 4.90, indicating the β orientation of the methoxyl group at that center. The crude oil (4.5 g, 27.4 mmol) was dissolved in 25 ml of anhydrous pyridine and evaporated to dryness under reduced pressure. The process was repeated once, the residue was dissolved in 50 ml of anhydrous pyridine and treated with 7.6 g (27.4 mmol) of triphenylmethyl chloride, and the solution was stirred at room temperature for 3 days. It was poured into 500 ml of ice-cold water, and the aqueous solution was extracted with three 200-ml portions of ether. The ether was washed with four 100-ml portions of 5% potassium bisulfate, water to neutrality, and a saturated solution of sodium chloride. The ethereal solution was dried over anhydrous sodium sulfate; the ether was evaporated under reduced pressure to give 11.2 g of colorless gum. It was dissolved in ether, 5 g of silica gel was added, and the suspension was evaporated to dryness. The solid was applied to the top of a column of 100 g of silica gel packed in pentane–ether (9:1). Elution with the same solvent system removed the triphenylcarbinol present and increasing the polarity to pentane–ether (2:8) afforded 8.6 g (77%) of **6** as a colorless foam, $[\alpha]^{23}D$ −7.5° (*c* 1.9, $CHCl_3$). The material was homogeneous in solvent systems A, B, and C, but showed the presence of a very slight contaminant in system D. It was characterized as the 2,3-ditosylate derivative.

A solution of 500 mg (1.23 mmol) of the foam in 20 ml of anhydrous pyridine was treated with 570 mg (3.0 mmol) of *p*-toluenesulfonyl chloride and stirred at room temperature for 5 days. The solution was poured into 200 ml of ice-cold 5% sodium bicarbonate solution, and the crystals were collected by filtration and washed well with water. One recrystallization from methanol–ethyl acetate gave 425 mg (48%) of **6a** as colorless needles: mp 140–141°; $[\alpha]^{23}D$ 61.4° (*c* 0.64, $CHCl_3$). The infrared and nmr spectra were identical with the material prepared in section A. On admixture with a specimen from that section the mixture melted at 140–141°.

Anal. Calcd for $C_{39}H_{38}O_9S_2$: C, 65.52; H, 5.35; S, 8.97. Found: C, 65.38; H, 5.51; S, 9.25.

Methyl 3-*p*-Bromobenzoyl-2-deoxy-5-*O*-triphenylmethyl-α-D-ribofuranoside (9).—A solution of 3.1 g (7.95 mmol) of methyl of 2-deoxy-5-*O*-triphenylmethyl-α-D-ribofuranoside (**2**) in 25 ml of anhydrous pyridine was evaporated to dryness under reduced pressure. This process was repeated twice, and the resulting residue was dissolved in 25 ml of anhydrous pyridine, treated with 5.75 g (26.75 mmol) of freshly prepared *p*-bromobenzoyl chloride, and another 10-ml portion of anhydrous pyridine was added. The solution was stirred at room temperature for 18 hr, and the resulting pink suspension was poured into 200 ml of ice-cold 5% sodium bicarbonate solution. The precipitate was suspended in 200 ml of water, stirred for 1 hr, and filtered. The resulting light tan powder was suspended in 150 ml of ether, stirred for 1 hr, and filtered. The residue was extracted in the same manner with a second 150-ml portion of ether and filtered again. The combined ether extracts were washed with water and a saturated sodium chloride solution, dried over anhydrous sodium sulfate, and evaporated. The yellow semisolid was recrystallized from methanol–ethyl acetate (3:1) to give 3.9 g of **9** contaminated with a second component. The material was dissolved in 100 ml of ether, 10 g of silica gel was added, and the suspensions were evaporated to dryness and applied to the top of a column of 200 g of silica gel. Elution with pentane–ether (8.5:1.5) gave 3.5 g (77%) of **9** as a white crystalline solid, mp 123–126°, sufficiently pure for use in the preparation of **10**. An analytical specimen was recrystallized from methanol as colorless prisms: mp 125–126°; $[\alpha]^{26}D$ 101.3° (*c* 1.05, $CHCl_3$); ν_{max}^{KBr} 1720 (C=O) and 1595 cm^{-1} (phenyl nuclei); nmr δ 8.01–7.10 (19 H, multiplet, aromatic protons), 5.55–5.15 (2 H, multiplet, H_1 and H_3), 4.53–4.25 (1 H, multiplet, H_4), 3.50–3.28 (5 H, multiplet, CH_3O and $2H_5$), and 2.63–1.93 (2 H, multiplet, $2H_2$).

Anal. Calcd for $C_{32}H_{29}BrO_5$: C, 67.01; H, 5.09; Br, 13.93. Found: C, 66.98; H, 5.28; Br, 13.63.

Methyl 5-*p*-Bromobenzenesulfonyl-3-*p*-bromobenzoyl-2-deoxy-α-D-ribofuranoside (11).—A suspension of 10.25 g (0.018 mol) of methyl 3-*p*-bromobenzoyl-2-deoxy-5-*O*-triphenylmethyl-α-D-ribofuranoside (**9**) in 160 ml of glacial acetic acid was warmed on a steam bath until solution was complete, *ca.* 5 min. Water (25 ml) was added, and the solution was warmed for an additional 5 min. Water (15 ml) was added, and the warming was continued for 10 min. The colorless solution was cooled, and the solvents were evaporated *in vacuo*. The white crystalline residue was dissolved in 300 ml of ether, extracted with two 100-ml portions of 5% sodium bicarbonate solution, water, and saturated sodium chloride solution, and was then dried over anhydrous sodium sulfate. Evaporation of the ether under reduced pressure gave 12.5 g of semisolid residue which was suspended on 15 g of silica gel and applied to the top of a column of 225 g of silica gel packed in pentane–ether (9:1). Elution with pentane–ether (8:2) gave 6.10 g of triphenylcarbinol. The polarity was gradually increased to pentane–ether (2:8), and 2.85, g (48%) of **10** was obtained as a pale yellow syrup. The syrup (2.75 g, 8.30 mmol) was dissolved in 25 ml of anhydrous pyridine and the solution was evaporated to dryness *in vacuo*. This process was repeated once again, and the residue was dissolved in 50 ml of dry pyridine and treated with 3.18 g (12.15 mmol) of *p*-bromobenzenesulfonyl chloride in one portion. The solution was stirred at room temperature for 24 hr, poured into 400 ml of ice-cold 5% sodium bicarbonate solution, and stirred for 15 min, and the precipitate was collected by filtration. One recrystallization from methanol–ethyl acetate (1:1) gave 3.2 g (70%) of **11**, sufficiently pure for use in the preparation of **12**. An analytical specimen crystallized from methanol–ethyl acetate (1:1) as long colorless rods: mp 137–138° dec (insertion at 135°); $[\alpha]^{23}D$ 99.7° (*c* 0.71, $CHCl_3$); ν_{max}^{KBr} 1720 (C=O), 1600 and 1585 cm^{-1} (phenyl nuclei); nmr δ 7.96–7.45 (8 H, multiplet, aromatic protons), 5.28–4.98 (2 H, multiplet, H_1 and H_3), 4.43–4.20 (3 H, multiplet, H_4 and $2H_5$), 3.33 (3 H, singlet, CH_3O), and 2.41–2.11 (2 H, multiplet, $2H_2$).

Anal. Calcd for $C_{19}H_{18}Br_2O_7S$: C, 41.47; H, 3.29; Br, 29.04. Found: C, 41.33; H, 3.46; Br, 28.67.

Methyl 5-(6-Aminopurin-9-yl)-3-*p*-bromobenzoyl-2,5-dideoxy-α-D-ribofuranoside (12).—A suspension of 162 mg (1.20 mmol) of adenine in 5 ml of anhydrous dimethylformamide was treated with 60 mg (*ca.* 1.20 mmol) of a 50% oil dispersion of sodium hydride, and the mixture was stirred at room temperature for 1 hr. It was warmed to 50°, maintained there for 30 min, and cooled to room temperature. A solution of 550 mg (1.00 mmol) of methyl 5-*p*-bromobenzenesulfonyl-3-*p*-bromobenzoyl-2-deoxy-α-D-ribofuranoside (**11**) in 15 ml of anhydrous dimethylformamide was added over a 10-min period, and the suspension was stirred at room temperature for 90 min. It was warmed to 50° and maintained at that temperature for 3 hr. After cooling to room temperature, the dimethylformamide was evaporated under high vacuum at a bath temperature of 40°. The white solid residue was extracted with two 25-ml portions of warm chloroform and the filtered chloroform extracts were combined, shaken with water, and dried over anhydrous sodium sulfate. Evaporation of the chloroform afforded 225 mg (42%) of **12**, mp 219–220°. Two recrystallizations from methanol afforded an analytical sample of **12** as small colorless rods: mp 221.5–222°; $[\alpha]^{23}D$ 142.9° (*c* 0.70, $CHCl_3$); ν_{max}^{KBr} 1715 (C=O), 1670 (purine nucleus), 1610 and 1575 cm^{-1} (purine and phenyl nuclei); nmr δ 8.18 and 7.21 (1 H each, singlets, purine H_2 and H_8), 7.76 (4 H, broad singlet, phenyl protons), 5.41–5.06 (2 H, multiplet, H_1 and H_3), 4.76–4.38 (2.7 H, multiplet, H_4 and $-NH_2$), 3.32 (3 H, singlet, CH_3O), 3.28 (2 H, singlet, $2H_5$). The $2H_2$ protons are obscured by DMSO-d_6.

Anal. Calcd for $C_{18}H_{18}BrN_5O_4$: C, 48.22; H, 4.04; Br, 17.82; N, 15.62. Found: C, 48.50; H, 4.21; Br, 18.11; N, 15.36.

Methyl 5-(6-Aminopurin-9-yl)-2,5-dideoxy-α-D-ribofuranoside (1).—Methyl 5-(6-aminopurin-9-yl)-3-*p*-bromobenzoyl-2,5-dideoxy-D-ribofuranoside (**12**) (700 mg, 1.56 mmol) was dissolved in 600 ml of anhydrous methanol at room temperature, and ammonia was bubbled through the solution for 30 min. After 36 hr at room temperature, the solution was evaporated to dryness under reduced pressure. The solid was triturated with ether to remove the methyl *p*-bromobenzoate and was collected by filtration. One recrystallization from a small volume of methanol afforded 386 mg (93%) of **1** as a white microcrystalline solid: mp 200–201°; $[\alpha]^{23}D$ 97.6° (*c* 1.09, *CHCl*$_3$); $\lambda_{max}^{H_2O}$ 260 mμ (ε 14,600), λ_{min} 227 (2200), $\lambda_{max}^{0.1\ N\ HCl}$ 258 (14,100), λ_{min} 230 (2900), $\lambda_{max}^{0.1\ N\ NaOH}$ 260 (14,500), λ_{min} 227 (2200); ν_{max}^{KBr} 1660,

1600, and 1585 cm^{-1} (purine nucleus); nmr δ (D_2O)[34] (2 H, singlet, purine H_2 and H_8), 5.34 (1 H, quartet, $J_{AX} + J_{BX} = 7.5$ cps, H_1), 4.50–4.21 (3 H, multiplet, H_4 and $2H_5$), 3.45 (3 H, singlet, CH_3O), and 2.16–1.97 (2 H, multiplet, $2H_2$). The ultraviolet spectra confirmed 9 substitution on the adenine nucleus.[35]

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Anal. Calcd for $C_{11}H_{15}N_5O_3$: C, 49.80; H, 5.69; N, 26.40. Found: C, 49.46; H, 5.77; N, 26.10.

Registry No.—**1**, 16803-00-2; **2**, 16801-99-3; **3**, 16802-00-9; **4**, 16802-01-0; **5**, 16802-02-1; **6a**, 16802-03-2; **9**, 16802-04-3; **11**, 16802-05-4; **12**, 16802-06-5.

A Kinetic Study of the Acid-Catalyzed Hydrolysis of Some Indolyl-β-D-glucopyranosides[1]

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First-order rate coefficients have been determined along with energies (E_a), enthalpies ($\Delta H^{\pm}$), and entropies ($\Delta S^{\pm}$) of activation for the acid-catalyzed hydrolyses of 3-indolyl- (**1a**), 5-bromo-3-indolyl- (**1b**), and 5-bromo-4-chloro-3-indolyl-β-D-glucopyranoside (**1c**). It was demonstrated that the rate of oxidation of the intermediate indoxyl (**2**) to indigo (**3**) was not rate determining. No significant difference in E_a is observed over a range of hydronium ion concentration. The relatively good agreement between the observed rate coefficients (k') and the corresponding theoretical values (k) supports the conclusion that the hydrolysis step and not the oxidation of the intermediate indoxyl (**2**) to an indigo (**3**) is rate determining. The solvent isotope effect ($k'_{D_2O}/k'_{H_2O} \geq 2$) indicates rapid preequilibrium protonation of the glucosides. The dependence of rate on acidity (Hammett–Zucker relationship and the Bunnett w parameter) provides evidence for the unimolecularity of these hydrolyses. On the other hand, the values of $\Delta S^{\pm}$, which are narrowly positive, are consistent with several mechanistic possibilities which include the A1 mechanism.

Recent reports[3,4] from this laboratory described the syntheses of a number of indolyl-β-D-glycopyranosides (**1**) which have found application as agents for the histochemical localization of corresponding β-glycosidases in mammalian tissue.[4-6] The chromogenic reaction sequence underlying what has come to be known as "indigogenic staining" [7,8] is initiated by enzymic release of an intermediate indol-3-ol (indoxyl, **2**). The latter (*cf.* Scheme I) is rapidly and irreversibly transformed on air oxidation to an essentially insoluble (and highly colored) indigo (**3**) which is deposited at the sites of the activity.

The *O*-indoxyl derivatives, by virtue of the indigogenic principle, constitute a potentially useful group of substrates for kinetic studies of acid and base catalyzed, as well as enzymatic hydrolyses. The present study was undertaken to ascertain whether indolyl-β-D-glucopyranosides, as a consequence of a unique aglycon moiety, exhibit any unusual features when judged on the basis of the usual criteria (*vide infra*) employed in deciding the mechanism of the acid-catalyzed hydrolysis of relatively simple glycosides.

Experimental Section

Materials.—3-Indolyl-β-D-glucopyranoside {mp 178–180° dec $[\alpha]^{27}D$ −65° (*c* 1.0, 50% aqueous DMF)} was purchased from the J. T. Baker Co. 5-Bromo-3-indolyl-β-D-glucopyranoside [mp 260–261° dec, $[\alpha]^{25}D$ −59° (*c* 1.0, 50% aqueous DMF)] and 5-bromo-4-chloro-3-indolyl-β-D-glucopyranoside {mp 240–243°, $[\alpha]^{23}D$ −89° (*c* 1.0, 50% aqueous DMF)} were prepared according to methods outlined in previous reports.[3,4] The purity of these pyranosides was checked by tlc on silica gel in butanol–water (86:14).

Spectrophotometry.—Spectrophotometric rates were determined using a Cary Model 11 recording spectrophotometer which was equipped with cell jackets thermostated by a Haake Type F constant-temperature bath. Both the jackets and the bath were joined in a series to a Thermo-Cool heat exchanger. This arrangement provided a temperature regulation of ± 0.02° over the desired range (47–65°). Rates were followed by observing the formation of **3a**, **b**, and **c** at 670, 600, and 660 mμ, respectively.

Beer–Lambert plots were utilized to ascertain the quantity of indigo (**3**) formed in the oxidation step. These plots, in turn, afforded a measure of the intermediate indoxyl (**2**) generated in the hydrolysis step. The procedure of Cotson and Holt[9] was adopted for the preparation of the plots which is based on the spectrophotometric measurement of the rate of appearance of the dyes. When such oxidations are carried out in aqueous solutions, the dyes initially form colloidal suspensions, the stabilities of which are not suitable for making reliable optical measurements. The dye sols can be stabilized by inclusion of 0.5% polyvinyl alcohol so that their optical properties do not vary over several hours, and certainly not for the duration of the kinetic measurements. It was found that the Beer–Lambert laws were obeyed by the polyvinyl alcohol stabilized sols of the indigo dyes over the concentration range encountered. Accordingly, it was possible to utilize optical densities directly in calculating velocity constants of the oxidation reactions.

(1) (a) This investigation was supported in part by Public Health Service Research Grant No. CA-02624 from the National Cancer Institute and in part by an institutional grant to the Detroit Institute of Cancer Research Division of the Michigan Cancer Foundation from the United Foundation of Greater Detroit. (b) Presented in part at the 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1967. (c) Taken in part from a dissertation submitted by C. V. Easwaran to the Graduate School of The University of Detroit in partial fulfillment of the degree of Doctor of Philosophy.

(2) To whom all correspondence should be addressed at the Detroit Institute of Cancer Research Division of the Michigan Cancer Foundation.

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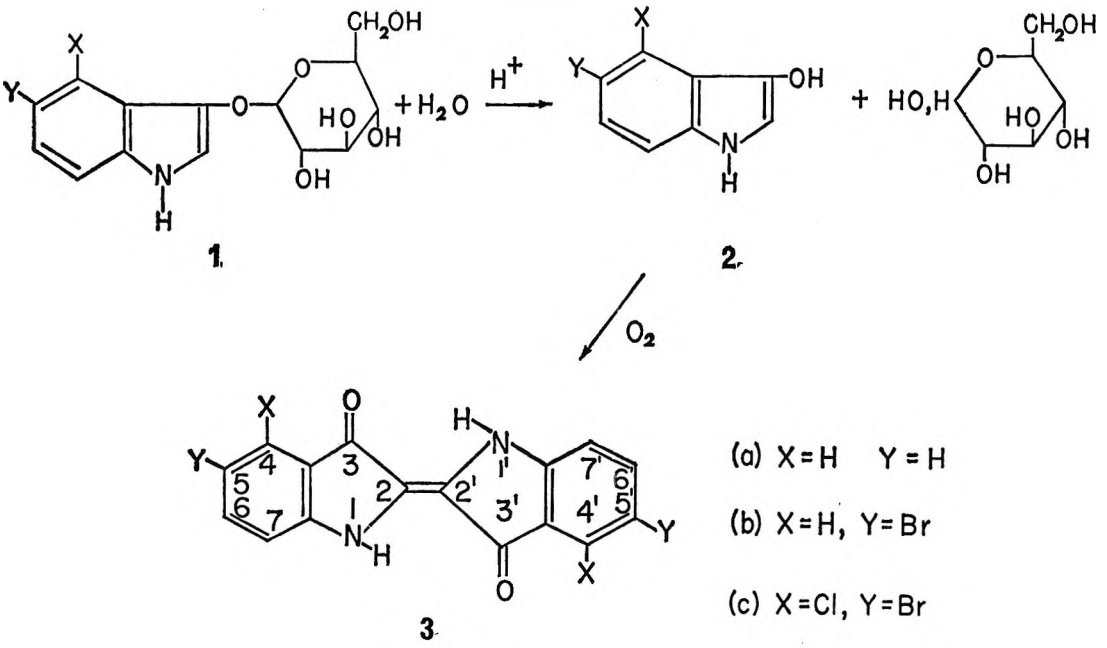
SCHEME I



The following procedure is considered typical. 5-Bromo-4-chloro-3-indolyl-β-D-glucopyranoside (1c, 17.5 mg) in 2 ml of ethanol was diluted to 100 ml by the addition of a deoxygenated solution of 0.5% aqueous polyvinyl alcohol. To 3 ml of 1.16 *M* hydrochloric acid, which had previously been swept with (99.9%) nitrogen, was added 3 ml of the stock solution of substrate (1c). The reaction mixture was maintained under a positive pressure of highly purified nitrogen[10] until the hydrolysis of 1c was complete (*ca.* ten half-life periods). Only in this manner was it possible to prepare solutions of 2c of known strength, *i.e.*, free of the product (3c) of oxidation.

Shortly before spectrophotometric measurements were to be made (as described below), 3 ml of the indoxyl solution was withdrawn using a nitrogen-filled pipet and emptied rapidly into 1 ml of oxygenated 0.5% polyvinyl alcohol. The reaction mixture was then quickly transferred to a 3.5-ml cuvette (10-mm path), the mixing and transfer requiring less than 30 sec. The cuvette, after shaking, was inserted in the thermostated block of the spectrophotometer to initiate the recording of the absorbance change. It was found that the Beer–Lambert laws were obeyed by the polyvinyl alcohol stabilized sols of the indigo dyes over the concentration ranges encountered.

Hydrolysis Procedure.—Solutions of 1 in aqueous hydrochloric acid were prepared as described in the previous section. The reactants consisting, for example, of 3 ml of 2.54 *M* hydrochloric acid and 3 ml of the stock solution of substrate (3.43×10^{-4} *M*) were elevated (individually) to the desired temperature by incubation in the constant-temperature bath, then mixed, and immediately transferred to the spectrophotometer. The procedure, in essence, was identical with that described above for the oxidation of 2 to 3 with exception that the hydrolysis was effected under aerobic conditions.

From a knowledge of the concentration of 3 and the initial concentration of 1, the fraction of unreacted substrate could be calculated. Plots of the natural logarithm of the concentration of unreacted 1 *vs.* time were constructed and first-order rate constants were calculated by least-square straight-line fits. Duplicate rate constant determination agreed within ±2.5%.

Calculation of Activation Parameters.—Energies of activation were obtained from a minimum of five rate constants determined at 47, 50, 55, and 65°. When log *k* was plotted against 1/T, straight lines were obtained throughout. Entropies of activation were calculated from the relationship

$$T\Delta S^{\ddagger} = E - RT - RT \ln (kT/h) + RT \ln (k'/h_0),$$

where T = temperature of the hydrolysis, °K; $k = 1.3805 \times 10^{-16}$ erg deg^{-1} molecule^{-1}; $h = 6.6252 \times 10^{-27}$ erg sec^{-1}; k' = first-order rate coefficient, sec^{-1}; $h_0 = e^{-H_0}$ (at T, °C).

Results

The selection of the particular 3-indolyl-β-D-glucopyranosides was based on the earlier observation that 5-bromo (1b) and 5-bromo-4-chloro (1c) derivatives afford the most precise histochemical results.[5,6] The unsubstituted derivative (1a) was utilized to evaluate, as a first approximation, the effect of the halogen(s).

The aerial oxidation of a number of haloindol-3-ols (2) to the corresponding indigo (3) has been studied kinetically over a pH range of 6–8.5 by Cotson and Holt.[9] The velocity constant for the oxidation of 5-bromo-4-chloroindol-3-ol (2c), for example, which was generated from the hydrolysis of the 3-*O*-acetyl derivative was found to be 4×10^{-3} sec^{-1} at pH 8.0. However, the rate of oxidation was observed to decrease sharply below pH 7.4. Accordingly, it was first necessary to demonstrate that the oxidation step in aqueous hydrochloric acid is not rate controlling in the conversion of 1 into 3. The methods of the English group[9] were applied to the oxidation of 2c to 3c, which served as a model. The rate coefficients, compiled in Table I, were determined as a function of temperature at several concentrations of hydrochloric acid. The rate values, as will be shown in a succeeding section, were found to be significantly greater (*cf.* Tables I and

TABLE I
RATE COEFFICIENTS FOR THE AIR OXIDATION OF 5-BROMO-4-CHLOROINDOL-3-OL TO 5,5′-DIBROMO-4,4′-DICHLOROINDIGO

Acid molarity	Temp, °C	Rate coefficient $k' \times 10^5$, sec^{-1}
1.16	47.2	10.65
2.95	47.2	8.65
3.70	47.2	7.82
3.70	49.5	9.30
3.70	55	14.70
3.70	60	22.00

(10) Matheson high purity grade nitrogen (99.9%) was further purified by passing the gas through a train consisting of copper oxide (400°), soda lime, magnesium perchlorate, and manganese oxide (150°), according to the procedure of K. E. Francis and N. Hodge, *At. Energy Research Establ., G. Brit.*, Rept. R-3710, 12 (1961); *Chem. Abstr.*, **56**, 12703 (1962).

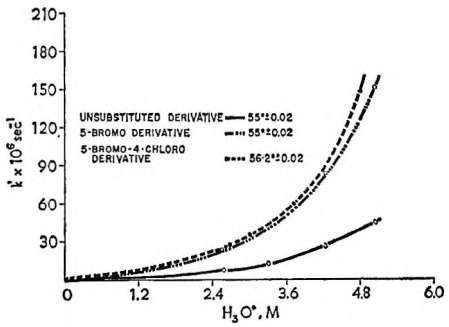


Figure 1.—Effect of hydronium ion concentration on the rate of hydrolysis of some indolyl-β-D-glucopyranosides (Scheme I).

II) than the rate constant for the hydrolysis of **1c** at a corresponding acid molarity. An apparent energy of activation (E_a) of 17.5 kcal for the oxidation step was derived from a plot of ln k *vs.* $1/T$.

TABLE II
RATE COEFFICIENTS FOR THE HYDROLYSIS OF SOME 3-INDOLYL-β-D-GLUCOPYRANOSIDES (1) IN HYDROCHLORIC ACID

Glucoside	Temp, °C	k' × 10⁵ sec⁻¹ 2.54 *M*	3.28 *M*	4.26 *M*	5.04 *M*	
1a	55	0.71	1.11	2.57	4.48	
	56.2	0.89	1.26	2.78	6.05	
	60	1.35	2.5	5.5	10.6	
	65	2.51	4.36	10.4	18.2	
1b	47.2	0.75	1.12	3.02	5.5	
	50	1.15	2.04	4.57	8.42	
	55	2.31	3.20	8.42	15.14	
	60	4.57	5.75	15.97	27.80	
		2.67 *M*	2.95 *M*	3.70 *M*	4.80 *M*	5.40 *M*
1c	47.2	0.84	1.13	2.10	5.0	8.45
	50	1.21	1.31	2.81	7.25	14.80
	56.2	2.54	3.02	5.50	14.75	23.65
	60	4.65	5.31	7.95	22.90	35.40

The observed first-order rate coefficients for the hydrolysis of **1**, at several different concentrations of hydrochloric acid and at various temperatures, are shown in Table II. The rate constants for the halogen substituted derivatives (**1b** and **1c**) are only slightly greater than those for the unsubstituted compound (**1a**). Apparently, these substituents are too distant from the site of bond fission to be of any serious consequence in the rate-determining step.

Figure 1 shows plots of these same constants *vs.* hydronium ion concentration. The latter were calculated from the ionization of aqueous hydrochloric acid, according to the methods of Young, *et al.*,[11a] and Leininger.[11b] It is apparent that the rate constants are nearly proportional to the hydronium ion concentration at low concentrations but increase rapidly above approximately 1.5 *M*.

The activation energies and their estimated standard deviations (Table III) were calculated from least-squares straight-line fits of Arrhenius plots. No significant difference in activation energies was detected over a range of hydronium ion concentrations. The relatively good agreement (*cf.* Table IV) between the observed rate coefficients (k') and the corresponding theoretical values (k), calculated from the relationship

$$k = AT^n e^{-E/RT}$$

supports the conclusion that the hydrolysis, and not the oxidation step, is rate determining.

TABLE III
KINETIC AND THERMODYNAMIC PARAMETERS FOR THE HYDROLYSIS OF SOME 3-INDOLYL-β-D-GLUCOPYRANOSIDES IN HYDROCHLORIC ACID[a,b]

Glucoside	E_a kcal mol⁻¹	$\Delta S^{\ddagger}$ cal deg⁻¹ mol⁻¹	$\Delta H^{\ddagger}$ kcal mol⁻¹	$\Delta F^{\ddagger}$ kcal mol⁻¹
1a	28.4 ± 0.5	2.2 ± 0.2	27.7 ± 1.0	27.0 ± 1.0
1b	27.8 ± 0.15	0.6 ± 0.01	26.75 ± 0.75	26.5 ± 0.5
1c	26.4 ± 0.4	0.4 ± 0.01	27.1 ± 1.0	26.9 ± 1.0

[a] Concentration of HCl ranged from 2.54 to 5.04 *M*. [b] Reaction examined over the temperature range of 47–60°.

TABLE IV
THEORETICAL AND EXPERIMENTAL RATE COEFFICIENTS FOR THE HYDROLYSIS OF SOME 3-INDOLYL-β-D-GLUCOPYRANOSIDES IN HYDROCHLORIC ACID

Glucoside	HCl, *M*	Temp, °C	Rate constant, × 10⁻⁵, sec⁻¹ Theoretical k	Observed k'
1a	2.54	55	0.74	0.71
		56.2	0.87	0.89
		60	1.41	1.35
		65	2.57	2.51
1b	2.54	47.2	0.93	0.75
		50	1.29	1.15
		55	2.37	2.31
		60	4.93	4.57
1c	3.70	47.2	2.65	2.10
		50	2.95	2.81
		55	5.58	5.50
		60	8.15	7.95

A solvent isotope effect was observed (*cf.* Table V) in the hydrolysis of **1** by measuring the reaction rates in normal and heavy water. The ratios of these constants

TABLE V
RATE COEFFICIENTS FOR THE HYDROLYSIS OF SOME 3-INDOLYL-β-D-GLUCOPYRANOSIDES IN D_2O AND H_2O

Glucoside	Temp, °C	Rate constants × 10⁵, sec⁻¹ k'_{H_2O}	k'_{D_2O}	k'_{D_2O}/k'_{H_2O}
1a	55	0.704	1.35	1.92
	60	1.30	2.44	1.88
1b	50	1.10	2.84	2.58
	60	4.36	11.10	2.54
1c	50	1.13	3.04	2.70
	60	4.45	11.75	2.63

(k'_{D_2O}/k'_{H_2O}) are in a range (1.9–2.7) indicative of rapid pre-equilibrium protonation of the glucosides and of specific acid catalysis.[12,13] Evidence for the molecularity of the slow step was derived from examination of the dependence of rate on acidity. Plots of log k'_{obsd} *vs.* H_0 are straight lines (Figure 2) of virtually unit negative slopes (Table VI). This implies, according to the Hammett–Zucker hypothesis,[14] that the rate-determining step in-

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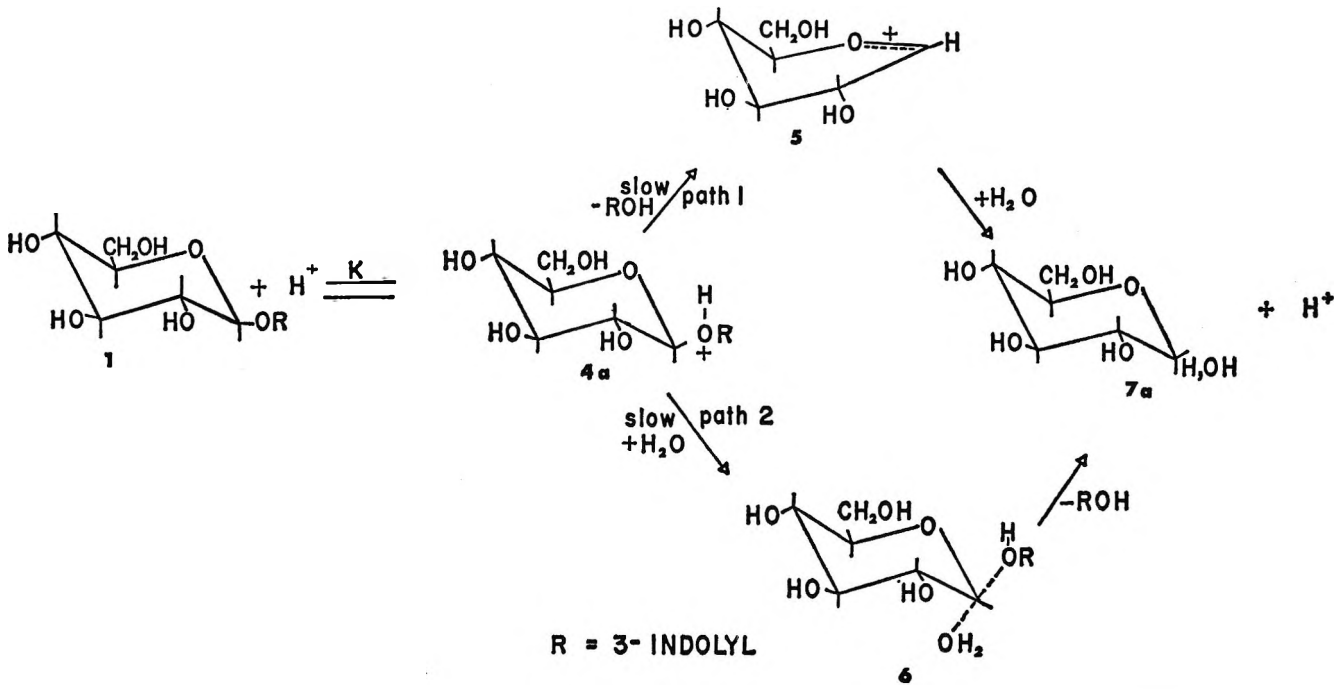
(14) (a) L. Zucker and L. P. Hammett, *J. Amer. Chem. Soc.*, **61**, 2791 (1939); (b) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p 273.

SCHEME II



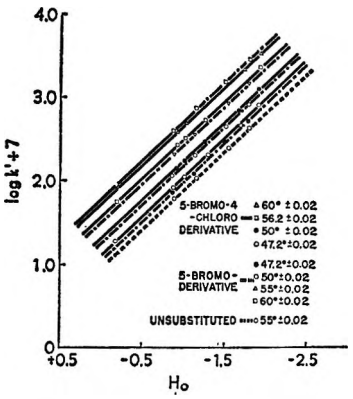


Figure 2.—Hammett–Zucker plot (log k *vs.* H_0) for the hydrolysis of 1 in hydrochloric acid.

TABLE VI

SLOPES DERIVED FROM PLOTS OF HAMMETT–ZUCKER AND BUNNETT PARAMETERS

Glucoside	Temp Range, °C	Hammett–Zucker slope values	Bunnett (w) slope values
1a	55–65	-0.970 ± 0.03	$+0.2 \pm 0.02$
1b	47.2–60	-0.970 ± 0.005	$+0.25 \pm 0.03$
1c	47.2–60	-0.950 ± 0.003	$+0.33 \pm 0.01$

volves unimolecular decomposition of the conjugate acid without participation of water (A1). However, Timell[15] has recently shown that, in the hydrolysis of methyl α-D-glucopyranoside, the requirement of unit slope is only approximately fulfilled in three of four mineral acids examined. For this reason, acidity dependence was investigated by the method of Bunnett.[16] Plots of log $k'_{obsd} + H_0$ *vs.* a_{H_2O} for the three glucosides were straight lines (Figure 3) with slopes ("w" parameter) in the range of +0.2 to +0.4 (*cf.* Table VI). These slopes are narrowly within the range of w values (+0.4 to −5.0) for the acid-catalyzed hydrolysis of glycopyranosides which are classified by Bunnett as proceeding by the unimolecular mechanism. It is pertinent to note, however, that a distinction in mechanism in the case of certain glycosides, made on the basis of this criterion, is not in accord with conclusions reached from interpretation of entropy data.[17]

In view of the doubts associated with rate–acidity correlations as a basis for predicting molecularity, additional evidence was deemed necessary to decide the mechanism of hydrolysis of 1. Accordingly, the thermodynamic activation parameters of the three glucosides were calculated on the basis of the theory of absolute reaction rates.[18] The method of determination of specific rates utilized in the calculation of the free energies of activation was described above. The activation energies used, in turn, to calculate the enthalpies of activation were average values taken over the range of hydronium ion concentration examined. The results are listed in Table III. It is apparent that the enthalpies of activation for the three glucosides are essentially the same and the small differences in the rate constant are, accordingly, a consequence of the entropy function.

Discussion

The mechanism generally accepted for the acid-catalyzed hydrolysis of simple alkyl glycopyranosides is that first suggested by Edward.[19] It involves a rapid, equilibrium-controlled protonation of the glycosidic oxygen to give the corresponding conjugate acid (Scheme II, **4a**). In the rate-determining step, **4a** decomposes in a unimolecular heterolysis (A1 mechanism) to form an alcohol and a carbonium–oxonium ion (**5**), which reacts with water to form glucose (**7a**). However, the suggestion has been made that some glycopyranosides hydrolyze by the A2 mechanism[16] which is characterized by the presence of a molecule of water in the transition state (**6**). If the reaction were bimolecular, then the

(15) T. E. Timell, *Can. J. Chem.*, **42**, 1456 (1964).
(16) J. F. Bunnett, *J. Amer. Chem. Soc.*, **83**, 4956, 4968, 4973, 4978 (1961).
(17) L. L. Schaleger and F. A. Long, *Advan. Phys. Org. Chem.*, **1**, 1 (1963).
(18) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," John Wiley and Sons, Inc., New York, N. Y., 1963, p 77.
(19) J. T. Edward, *Chem. Ind.* (London), 1102 (1955).

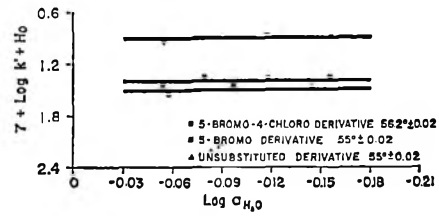


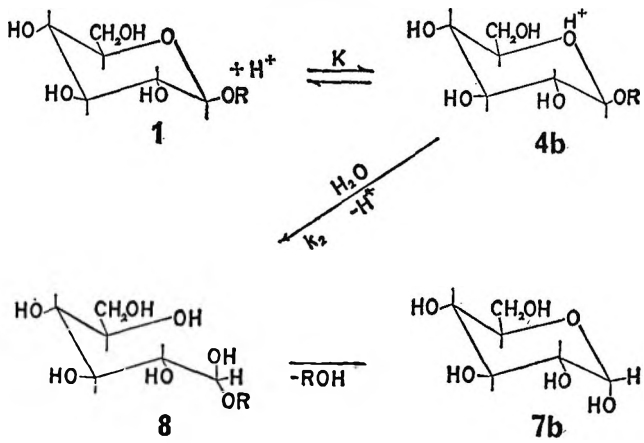
Figure 3.—Bunnett plot (log k + H_0 *vs.* log a_{H_2O}) for the hydrolysis of **1** in hydrochloric acid.

transition step would constitute a more highly ordered structure than the ground state (**4a**). This would result in a decrease in entropy and $\Delta S^{\pm}$ would tend to be negative. The unimolecular reaction, on the other hand, presents a less ordered transition state relative to **4a** and, $\Delta S^{\pm}$ should be positive.

The $\Delta S^{\pm}$ values for **1** are all narrowly positive (*cf.* Table III) and, as such, are in accord with the fact that unimolecular acid-catalyzed hydrolyses usually exhibit entropies of activation near zero, though exceptions are known.[17,20] Moreover, the entropy data, when viewed in context with other criteria of molecularity that have been examined in this study, constitute convincing evidence for the A1 mechanism. On the other hand, the observed entropies of activation are considerably lower than the mean of +13.7 eu reported by Overend and coworkers[21] for 24 glycosides for which the A1 mechanism has also been suggested. It might be argued that this difference indicates a change of mechanism, possibly some participation by water in the transition state, *i.e.*, partial A2 character. However, the incursion of the A2 mechanism in the case of pyranosides encounters the objection that nucleophilic attack on a six-membered ring is a slow process.[22]

An alternative explanation of the low entropy values can be derived by assuming that the 3-indolyl-β-D-glucopyranosides, unlike the simple alkyl derivatives, react with ring opening; that is, the reactive conjugate acid (**4b**) is the ring-protonated species, shown in Scheme III. Obviously, the requirement of rapid proton transfer, indicated by the solvent isotope effect, is satisfied by either conjugate acid (**4a** or **b**). Attack by water concerted with ring opening would lead to an acyclic hemiacetal (**8**) and ultimately to glucose (**7b**) in a manner analogous to that suggested by Capon[23] for furanosides. The observed rate constant would be given by $k'_{obsd} = k_2K$ where

SCHEME III



K is the equilibrium constant for the initial proton transfer reaction. The observed entropy of activation would then be $\Delta S^{\pm} = \Delta S^0 + \Delta S_2^{\pm}$ where ΔS^0 is the standard entropy of proton-transfer. The latter is normally positive and, in addition, usually large.[24] While $\Delta S_2^{\pm}$ is negative, since it is the entropy of activation of the bimolecular reaction (k_2) between the ring-protonated conjugate acid and water, the observed entropy of activation ($\Delta S^{\pm}$) might still be positive if ΔS^0 is dominant.[25]

The possibility of an acyclic ion was considered along with a carbonium–oxonium ion by Vernon and coworkers[26] in connection with the unimolecular mechanism. There remains the problem of distinguishing experimentally between these possibilities and consequently the argument still rages. One objection to the "open-chain" mechanism is that it would lead to extensive anomerization unless recyclization of the carbonium ion is much faster than rotation about the C_1–C_2 bond. No effort was made to resolve this question in the present study, but it should be noted that attack by water concerted with ring opening overcomes this objection. However, this interpretation, while it perhaps provides a more satisfactory explanation of the observed entropy data, stands in contradiction to the molecularity of the slow step as established on the basis of rate *vs.* acidity studies.

It is apparent that the present data precludes a firm choice between the several mechanistic possibilities. However, the bulk of the evidence favors an A1 mechanism for the acid-catalyzed hydrolysis of **1**.

Registry No.—**1a**, 16934-10-4; **1b**, 16934-09-1; **1c**, 15548-60-4.

(20) R. K. Chaturvedi and E. H. Cordes, *J. Amer. Chem. Soc.*, **89**, 4631 (1967).

(21) W. G. Overend, C. W. Rees, and J. S. Sequeiva, *J. Chem. Soc.*, 3429 (1962).

(22) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., New York, N. Y., 1962, p 265.

(23) B. Capon and D. Thacker, *J. Chem. Soc.*, 185 (1967).

(24) E. Whalley, *Trans. Faraday Soc.*, **55**, 799 (1959).

(25) Because of the high values of ΔS^0 that can occur, an observed entropy of activation of +10 eu, according to Whalley (see ref 24), cannot be considered to prove or even to suggest strongly an A1 mechanism.

(26) C. A. Bunton, T. A. Lewis, R. Llewellyn, and C. A. Vernon, *J. Chem. Soc.*, 4419 (1955).

Kinetics of the Nitric Acid Oxidation of Nitrosophenol to Nitrophenol[1]

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Received February 13, 1968

The oxidation of nitrosophenol to nitrophenol with dilute nitric acid (0.40 *M*) in 20% dioxane–80% water has been studied kinetically by following the rate by ultraviolet spectrophotometry. The rate was much faster than that of nitrosobenzenes[2] and, hence, the enhancement of the rate could not be explained by means of the ordinary substituent effect by a hydroxyl group. The rate is expressed as $v = k'$[nitrosophenol][HNO_3], the rate being increased with acidity of the solution. The rate is independent of nitrous acid concentration. A possible mechanism is discussed on the basis of these observations, and it is suggested that the rate-determining step for oxidation of nitrosophenol is different from that for other nitrosobenzenes.

In our previous report[2] on the nitric acid oxidation of nitrosobenzenes to nitrobenzenes, *p*-nitrosoanisole was eliminated from the measurement of substituent effect because of its susceptibility to hydrolysis giving *p*-nitrosophenol. Afterward, *p*-nitrosoanisole was found to yield *p*-nitrophenol. Since *p*-nitroanisole was not hydrolyzed under these conditions, the main reaction should go by way of *p*-nitrosophenol (eq 1).

$$CH_3OC_6H_4NO \xrightarrow{H_2O} HOC_6H_4NO \xrightarrow{HNO_3} HOC_6H_4NO_2 \quad (1)$$

Nitrosophenol is more rapidly oxidized than nitrosobenzene by nitric acid; the oxidation is rapid and quantitative even in 20% dioxane at 40°, whereas nitrosobenzene is hardly oxidized under these conditions. Hence, the rate of nitrosophenol is difficult to compare with those of other nitrosobenzenes.

In the present paper, nitrosophenol was oxidized by 0.4 *M* nitric acid in 20% dioxane at 40°, and the rate was followed by means of ultraviolet spectrophotometry to elucidate the mechanism.

Results and Discussion

Effect of Nitrous Acid and Other Added Compounds.—The removal of nitrous acid by the addition of urea results in the appearance of a long induction period (Table I), and, hence, the remarkable enhancement of the oxidation by introducing hydroxyl group into nitrosobenzene could not be explained by assuming nitric acid or nitrate ion as attacking species, in addition to nitrogen dioxide proposed for the nitric acid oxidation of nitrosobenzene. Nitrous acid is an effective initiator of the present reaction. It is of interest to note that the rate constant is independent of the concentration of added nitrous acid (Table I); this behavior was not observed with the other nitrosobenzenes.

TABLE I

EFFECT OF VARIOUS ADDED COMPOUNDS IN THE NITRIC ACID OXIDATION OF NITROSOPHENOL IN 20% DIOXANE AT 40° (INITIAL CONCENTRATION: [NITROSOPHENOL] = 0.0535 *M*, [HNO_3] = 0.40 *M*)

Compd added	*M*	Induction period, min	First-order rate constant, 10^4k, sec^{-1}
None	...	>100	...
$CO(NH_2)_2$	0.1	>100	...
$NaNO_2$	0.005	...	2.40
$NaNO_2$	0.007	...	2.22
$NaNO_2$	0.01	...	2.62
$NaNO_2$	0.005[a]	...	3.72
$NaNO_2$ + BPO[b]	0.005 + 0.005[a]	...	3.49
BPO[b]	0.005[a]	>65	...
AIBN[c]	0.005[a]	>65	...

[a] Experiments in 40% dioxane. [b] Benzoyl peroxide. [c] Azobisisobutyronitrile.

Ordinary initiators in radical reactions such as benzoyl peroxide (BPO) and azobisisobutyronitrile (AIBN) neither initiate the reaction nor affect the oxidation rate, probably because such initiators decompose hardly at their low temperature such as 40° (Table I).

The Rate Equation.—A typical first-order rate equation with respect to nitrosophenol was obtained in excess nitric acid. The rate constants do not vary with changing initial concentration of nitrosophenol (Table II). Hence, the rate, with an excess of nitric acid, is expressed as $v = k$[nitrosophenol].

TABLE II

FIRST-ORDER RATE CONSTANTS FOR THE NITRIC ACID OXIDATION OF NITROSOPHENOL AT VARIOUS INITIAL CONCENTRATIONS OF REACTANTS IN 20% DIOXANE AT 40°

[Nitrosophenol], *M*	[HNO_3], *M*	10^4k, sec^{-1}
0.0527	0.40	2.46
0.0436	0.40	2.69
0.0316	0.40	2.38
0.0202	0.40	2.46
0.0538	0.10	4.72[a]
0.0538	0.20	12.3[a]
0.0546	0.30	14.8[a]
0.0546	0.40	21.4[a]
0.0573	0.50	26.9[a]

[a] Values obtained in the presence of 0.20 *M* sulfuric acid. These values were corrected to those at $H_0 = 0$.

The rate increased with nitric acid concentration, the plot of log *k vs.* log [HNO_3] giving a straight line with a slope of *ca.* unity, if the *k* values are corrected to those at $H_0 = 0$ to eliminate the acidity effect (Table II). Hence, the rate is expressed as $v = k'$[nitrosophenol][HNO_3]. The rate is independent of the concentration of nitrous acid, and this behavior was not observed with other nitrosobenzenes.

Effect of Acidity of Solution.—On addition of sulfuric acid, the reaction was accelerated. The plot of log *k vs.* H_0 gave a straight line with a slope of −1.2 (Figure 1). It was confirmed spectrophotometrically that the tautomerism between nitrosophenol and benzoquinone oxime, or their dimerization (see later), was not affected by the acidity of media; *i.e.*, absorption spectra at *ca.* 700 mμ varied little by changing acidity in the present reaction.

(1) Contribution No. 109.
(2) Y. Ogata and H. Tezuka, *J. Amer. Chem. Soc.*, **89**, 5428 (1967).

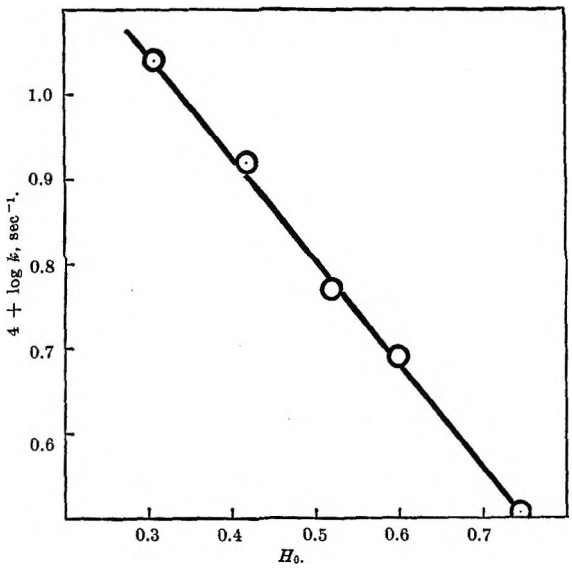


Figure 1.—Plots of log k *vs.* acidity function for the nitric acid oxidation of nitrosophenol in the presence of sulfuric acid in 20% dioxane at 40°.

The Solvent Effect.—The rate constant k increases with an increase of the dioxane content in the solvent in spite of decreasing acidity. This phenomenon has been observed in nitric acid oxidations of some organic compounds,[2-4] and it has been explained in terms of the increasing concentration of attacking species, probably nitrogen dioxide, with the rise of dioxane content.[2-4] This solvent effect is much larger than that for nitrosobenzene, and this fact suggests that the effect is due not only to changes in nitrogen dioxide concentration but also to other factors.

TABLE III

EFFECT OF SOLVENT COMPOSITION ON THE FIRST-ORDER RATE CONSTANTS FOR THE NITRIC ACID OXIDATION OF NITROSOPHENOL AT 40°

(INITIAL CONCENTRATION: $[HNO_3] = 0.40\ M$, $[NaNO_2] = 0.005\ M$, [NITROSOPHENOL] = $0.0560\ M$)

Dioxane, %	ϵ	10^4k, sec^{-1}	H_0
20	2.0[a] (—)[b]	2.40 (0.15)[c]	0.76
40	3.7[a] (38)[b]	3.72 (1)[c]	1.29
60	6.6[a] (44)[b]	12.5 (19)[c]	1.91

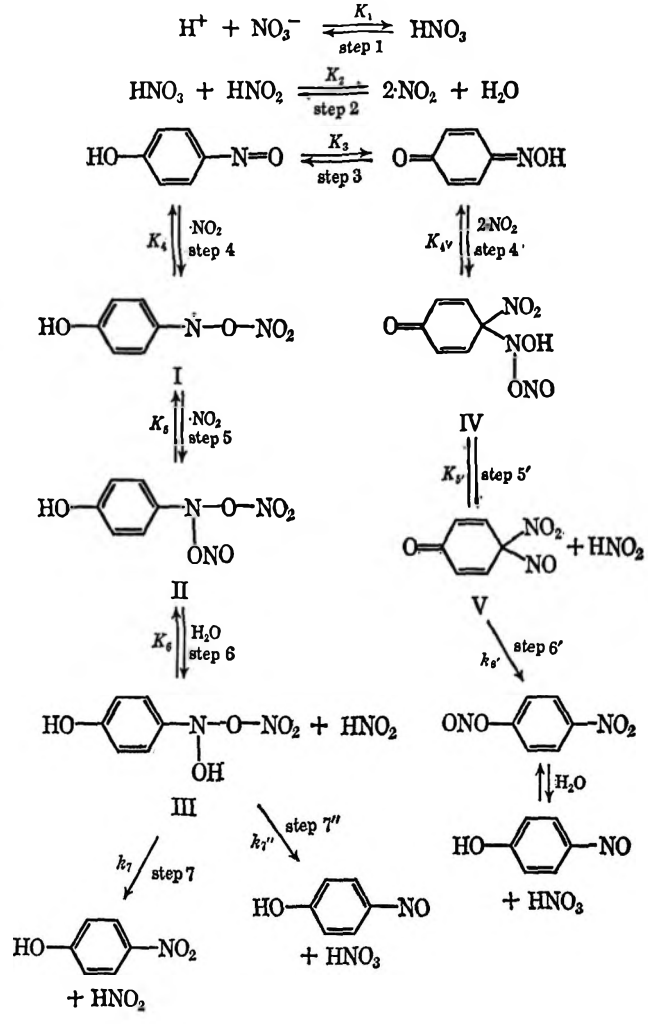
[a] Molar extinction coefficient of nitrosophenol at *ca.* 700 mμ. [b] Molar extinction coefficient of nitrosobenzene at *ca.* 750 mμ. [c] Relative rate constants compared at constant acidity.

Light absorption at about 700–750 mμ is characteristic of the nitroso group.[5] The molar extinction of nitrosophenol is very small at this wavelength because of the dimerization of nitrosophenol and/or the tautomerism of nitrosophenol to benzoquinone oxime.[5] The absorption of nitrosophenol in dioxane–water at *ca.* 700 mμ increases with increasing dioxane content in the solvent in parallel with an increase of the rate constant (Table III). Hence, the rate may depend on the extent of dimerization and/or tautomerization. The observed degree of dimerization of nitrosobenzene also depends on the content of water in water–organic solvent and it is small (Table III). Similarly the dimerization of nitrosophenol seems to occur to a fairly small extent. The observed solvent effect on the ϵ values probably is not due to the change in the extent of tautomerization but to change in the extent of dimerization because the variation of ϵ values with varying solvent composition is nearly comparable with that of nitrosobenzene, which dimerizes but does not tautomerize (Table III). However, the fact that the solvent effect on oxidation of nitrosophenol is larger than that of nitrosobenzene may be explained by assuming a rate-determining homolytic formation of nitrophenol as will be discussed below.

Effect of Temperature.—The first-order rate constants (10^{-4} sec^{-1}) were 0.772, 1.41, 2.40, and 5.68 at 30, 35, 40, and 45°, respectively. An Arrhenius plot afforded a straight line, which gave the values of 25 kcal/mol and 4.6 eu for the apparent energy and entropy of activation, respectively.

The Mechanism.—The oxidation of nitrosophenol is much more rapid than that of nitrosobenzene, and its rate is independent of nitrous acid concentration. A possible mechanism is given in Scheme I.

SCHEME I



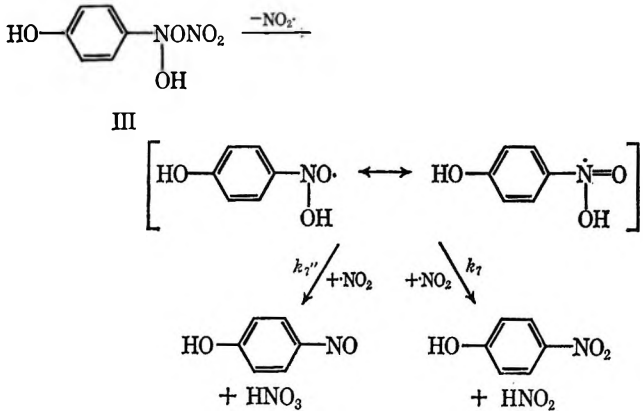
Nitrosophenol is in equilibrium with benzoquinone oxime,[5,6] and both species may be attacked. The most probable pathway involves an attack of nitrogen dioxide on the nitroso group in the same way as on

(3) Y. Ogata, H. Tezuka, and Y. Sawaki, *Tetrahedron*, **23**, 1007 (1967).
(4) Y. Ogata and Y. Sawaki, *J. Amer. Chem. Soc.*, **88**, 5832 (1966).
(5) A. Schors, A. Kraaijeveld, and E. Havinga, *Rec. Trav. Chim. Pays-Bas*, **74**, 1243 (1955).
(6) L. C. Anderson and M. B. Geiger, *J. Amer. Chem. Soc.*, **54**, 3064 (1932).

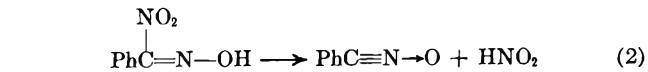
nitrosobenzene. The rate-determining step for nitrosobenzene is step 4,[2] but in the present reaction, the rate should be determined by step 7 instead of step 4 because the rate is independent of nitrous acid concentration. The two nitrogen dioxide radicals in steps 4 and 5 are equivalent to a nitrous acid in step 2 and thus cancel in the rate equation yielding the relation given in eq 4. Since the slow step for nitrosobenzene is not slow in the present reaction, nitrosophenol may be much more rapidly oxidized than nitrosobenzene. In the present reaction, step 4 may probably be rapid because of the stable intermediate of the semiquinone-type radical I.

Generally, alkyl nitrites are easily hydrolyzed,[7] but it is obscure whether nitrate II is decomposed *via* hydrolysis or directly as in nitric acid oxidation of nitrosobenzenes. The reversibility of the hydrolysis (6) is required for the explanation of the independence of rate on the nitrous acid concentration. Therefore, the preliminary hydrolysis of the nitrite may occur also with other nitrosobenzenes. According to the ordinary β elimination, nitrosophenol should be formed instead of nitrophenol but γ elimination to form nitrophenol also may occur as in Scheme II.

SCHEME II



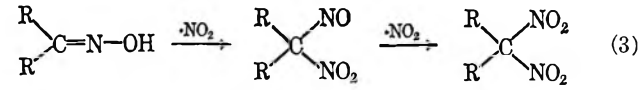
The elimination of nitrous or nitric acid from intermediate III may occur by a polar mechanism as H^+ plus NO_2^- or NO_3^-, but it seems less probable, since the oxidation is more retarded in more polar solvents such as water-rich dioxane (Table III). Therefore, intermediate III probably decomposes homolytically rather than heterolytically in analogy to the dissociation of dinitrogen tetroxide. Even if nitrosophenol and nitric acid may be formed from III, the products are the original reactants. Hence, the rate of the formation of nitrophenol depends on Scheme II; *i.e.*, k_7 is independent of the rate of reproduction of nitrosophenol, $k_{7''}$. The similar homolytic γ elimination is expected for the formation of nitrile oxide from nitrolic acid, *i.e.*, eq 2.[8]



(2)

Since oximes can be oxidized by nitrogen dioxide as shown in eq 3[8,9] benzoquinone oxime may be oxidized

(7) A. D. Allen, *J. Chem. Soc.*, 1968 (1954).
(8) J. H. Boyer and H. Alul, *J. Amer. Chem. Soc.*, **81**, 4237 (1959).
(9) J. L. Riebsomer, *Chem. Rev.*, **36**, 183 (1945).



(3)

to intermediate IV and then V. The nitroso group may naturally rearrange homolytically to the oxygen atom of carbonyl group, because of the formation of a stable benzene ring by the elimination of either nitro or nitroso group from V. The rearrangement of nitro group gives rise to the initial state. No further oxidation of the nitroso group in V is likely, since the rearrangement should be faster than the oxidation because of the retarding effect on oxidation exerted by the electron-attracting *gem*-nitro group as in the oxidation of *m*-nitronitrosobenzene.[2]

The mechanism in eq 3 leads to a rate law (eq 4)

$$v = k_7[\mathrm{III}] + k_6'[\mathrm{V}] = \{K_2K_1(k_7K_6K_5 + k_6'K_5'K_4'K_3)/(1 + K_3)\} \times [\mathrm{H}^+][\mathrm{NO}_3^-](a - x) \quad (4)$$

where a = initial concentration of nitrosophenol. The rate equation is consistent with the observed rate expression. The initial attack on the nitrogen atom of benzoquinone oxime by nitrogen dioxide seems to be preferred to that on the carbon atom. In spite of a large equilibrium constant, K_3, in organic solvents,[6] the electrophilic radical attack of nitrogen dioxide on the oxygen atom of nitrosophenol is probably more favorable than that on the nitrogen atom of the oxime because of the more electronegative nature of oxygen atom. Hence, it is impossible to decide here if the main pathway is *via* nitroso or *via* oxime.

The fact that the slope of a line obtained from the plot of log k *vs.* H_0 is -1.2 instead of -1 suggests that protonated nitrogen dioxide ($HNO_2 \cdot^+$) may participate a little as an attacking species in a parallel reaction,[2-4] although nitrosophenol is so reactive that it needs almost no highly reactive species such as $HNO_2 \cdot^+$ for the present reaction and hence, $NO_2 \cdot$ is the principal attacking species.

Side reactions may occur, but their rates are extremely slow and hence they are hardly detectable, unless the reaction mixture is treated for several hours with nitric acid from which nitrous acid has been removed by addition of urea.

Experimental Section

Materials.—*p*-Nitrosophenol was prepared by nitrosation of phenol[10] and recrystallization from methanol: mp 135–136° dec (lit.[11] mp 135–136°); λ_{max} 300 mμ (ε 18,500). *p*-Nitrophenol had mp 113° (lit.[12] mp 113–114°); uv bands at λ_{max} 312 mμ (ε 10,000).

Kinetic Procedure.—The rate was measured by the same method as that in the previous report[2] except that the extract was washed with saturated aqueous sodium chloride instead of aqueous sodium bicarbonate. *p*-Nitrosophenol was not always extracted completely and the content of *p*-nitrophenol was measured by means of a simultaneous equation at the following wavelengths: *p*-nitrosophenol, 290 mμ (ε 16,600), 312 (16,700); *p*-nitrophenol, 290 (6590), 312 (10,000).

Registry No.—*p*-Nitrosophenol, 104-91-6; *p*-nitrophenol, 100-02-7; nitric acid, 7697-37-2.

(10) C. S. Marvel and P. K. Porter, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1956, p 411.
(11) J. T. Hays, E. H. de Butts, and H. L. Young, *J. Org. Chem.*, **32**, 153 (1967).
(12) N. V. Sidgwick, W. J. Spurrell, and T. E. Davies, *J. Chem. Soc.*, **107**, 1202 (1915).

Microbiological Oxygenation of Alicyclic Amides

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Continuing our broad study of the microbiological oxygenation of simple monocyclic systems, a series of N-cycloalkylamides and N,N-dicycloalkylamides was subjected to fermentation by *Sporotrichum sulfurescens*. Consonant with the hypothetical enzyme–substrate model proposed earlier, N-cyclododecylacetamide was monooxygenated at the 5, 6, and 7 positions, while a variety of N-cyclohexylamides and N-cycloheptylamides underwent oxygenation at the 4 position. N-Cyclooctylamides gave two products, thought to be monoxygenated at the 4 and 5 positions. When confronted with two alicyclic rings of different sizes in the same N,N-dicycloalkylacetamide molecule, the organism seemed to prefer the cycloheptyl to the cyclohexyl ring, and showed little tendency to attack a cyclopentyl ring.

The hypothetical enzyme–substrate model proposed[1] for the microbiological oxygenation of monoalicyclic alcohols such as cyclododecanol suggested as an additional line of investigation the microbiological oxygenation of cycloalkylamines. When cyclododecylamine was exposed to *Sporotrichum sulfurescens* ATCC 7159 in a complex nutrient medium a mixture of N-(hydroxycyclododecyl)acetamides was obtained that was oxidized to a mixture of N-(oxocyclododecyl)-acetamides with Jones chromic acid reagent.[2] Appropriate chromatography and crystallization afforded N-(6-oxocyclododecyl)acetamide as the preponderant product, a lesser amount of N-(7-oxocyclododecyl)-acetamide, and a very small amount of N-(5-oxocyclododecyl)acetamide. The same products were obtained when N-cyclododecylacetamide was used as the substrate. Evidently N-acetylation (either microbial or chemical) is a necessary prerequisite to ring hydroxylation, since a variety of other microorganisms failed to acetylate or hydroxylate cyclododecylamine, but readily hydroxylated N-cyclododecylacetamide. Even *S. sulfurescens* failed to bring about hydroxylation of cyclododecylamine when the fermentation was conducted in Czapek–Dox medium, under which conditions N-acetylation did not take place.

Unequivocal structure proofs were carried out for the isomeric N-(5-, 6-, and 7-oxocyclododecyl)acetamides, wherein each compound was reduced with sodium borohydride to the corresponding N-(hydroxycyclododecyl)acetamide, which was acetylated. Treatment of the N-(acetoxycyclododecyl)acetamide with dinitrogen tetraoxide by the method of White[3] gave the N-nitroso product, with subsequent elimination of nitrogen and rearrangement to the diacetate. Hydrolysis and subsequent chromic acid oxidation led to the previously described cyclododecanediones.[1,4]

Attempted microbial hydroxylation of N-cyclohexylacetamide was not successful, perhaps for the same reasons presented in the earlier[1] discussion of experiments with cyclohexanol. When the microorganism was presented with the more lipophilic N-cyclohexylbenzamide, hydroxylation to N-(4-hydroxycyclohexyl)-benzamide took place. The structure of this product was established by oxidizing it to the keto derivative, which was identical with N-(4-oxocyclohexyl)benzamide synthesized from 4-hydroxycyclohexylamine.[5]

Similarly, microbial hydroxylation of benzyl cyclohexylcarbamate[6] gave benzyl 4-hydroxycyclohexylcarbamate, identical with material synthesized by N-acylation of 4-hydroxycyclohexylamine with carbobenzoxy chloride. Microbial hydroxylation of N-cyclohexyl-*p*-toluenesulfonamide gave, after Jones reagent oxidation, N-(4-oxocyclohexyl)-*p*-toluenesulfonamide identical with synthetic material obtained by N-acylation of 4-hydroxycyclohexylamine with *p*-toluenesulfonyl chloride followed by Jones reagent oxidation.

Microbial hydroxylation of N-cycloheptylbenzamide,[7] N-cycloheptyl-*p*-toluenesulfonamide, and benzyl cycloheptylcarbamate gave (in each case after Jones reagent oxidation to convert alcohol–ketone mixtures entirely into ketone) the corresponding 4-oxo compounds. The structures for these compounds were established by synthesis, using diazomethane ring expansion of the corresponding 4-oxocyclohexyl compounds.

Interestingly, although the N-(4-oxocycloheptyl)-benzamides obtained by bioconversion and by synthesis had identical infrared and nmr spectra, the bioconversion product was optically active whereas the synthetic product was a racemate. The same racemate was obtained by reduction of microbially produced N-(4-oxocycloheptyl)-*p*-toluenesulfonamide to 4-hydroxycycloheptylamine, followed by benzoylation, and oxidation. Thus the microorganism apparently attacks stereoselectively at one of the 4-methylene groups when the nitrogen bears the benzoyl group, but not when it bears the *p*-toluenesulfonyl group. In the case of the benzyl cycloheptylcarbamate bioconversion, the optical activity of the product was of such a low order that it is impossible to assess possible stereospecificity with the present data.

Microbial hydroxylation of N-cyclooctyl-*p*-toluenesulfonamide gave two keto amides whose structures have not been established unequivocally. The higher melting compound is tentatively assigned the structure N-(5-oxocyclooctyl)-*p*-toluenesulfonamide on the basis of its anomalous nmr spectrum, which suggests that the material exists as an equilibrium internal redox mixture of keto amide and N-(5-hydroxycyclooctylidene)-*p*-toluenesulfonamide. The transannular redox reaction would be consistent with a 1,5 relationship of the

(1) G. S. Fonken, M. E. Herr, H. C. Murray, and L. M. Reineke, *J. Amer. Chem.*, **89**, 672 (1967).
(2) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).
(3) E. H. White, *J. Amer. Chem. Soc.*, **77**, 6008, 6011 (1955).
(4) E. T. Niles and H. R. Snyder, *J. Org. Chem.*, **26**, 330 (1961).
(5) E. Ferber and H. Bruckner, *Ber.*, **72**, 995 (1939).
(6) A. B. Foster, M. Stacy, and S. V. Vardheim, *Acta Chem. Scand.*, **13**, 281 (1959).
(7) M. Mousseron, R. Jacquier, and H. Christol, *Bull. Soc. Chim. Fr.*, **24**, 346 (1957).

functional groups. The lower melting compound is tentatively assigned the structure N-(4-oxocyclooctyl)-*p*-toluenesulfonamide by elimination of alternatives *via* consideration of the nmr spectrum.

By melting point analogy to the N-cyclooctyl-*p*-toluenesulfonamide compounds, the higher melting keto amide from microbial hydroxylation of N-cyclooctylbenzamide is tentatively considered to be N-(5-oxocyclooctyl)benzamide, and the lower melting compound N-(4-oxocyclooctyl)benzamide.

N,N-Dicycloalkylacetamides should also fulfill the polarity (lipophilicity) and geometry requirements of the enzyme–substrate model. The dicycloalkyl amide system would be expected to be particularly useful for measuring the relative effects of ring conformations and sizes on the tendency to hydroxylate. N,N-Dicyclopentylacetamide, when subjected to *S. sulfurescens*, afforded only a very low yield of impure material that was not characterized but is believed to be a hydroxylated derivative. On the other hand, bioconversion of N,N-dicyclohexylacetamide by *S. sulfurescens* gave a good yield of N-cyclohexyl-N-(4-hydroxycyclohexyl)-acetamide. The structure was established by comparison with an authentic sample, synthesized by condensing 4-hydroxycyclohexylamine with cyclohexanone in a Leuckart reaction[8] to give cyclohexyl-(4-hydroxycyclohexyl)amine, which was acetylated to the O,N-diacetyl derivative and then saponified to the desired compound. N-Cyclohexyl-N-cyclopentylacetamide was hydroxylated in modest yield to N-cyclopentyl-N-(4-hydroxycyclohexyl)acetamide, whose structure was established by synthesis from 4-hydroxycyclohexylamine and cyclopentanone *via* the Leuckart reaction, followed by acylation. N-Cyclohexyl-N-cycloheptylacetamide, prepared *via* a Leuckart reaction using cycloheptanone and cyclohexylamine, gave a hydroxylated product that was most readily isolated as the corresponding ketone. This was shown not to be N-(4-hydroxycyclohexyl)-N-cycloheptylacetamide by synthesizing this compound from 4-hydroxycyclohexylamine, following the route outlined above for the N-cyclohexyl-N-(4-hydroxycyclohexyl)acetamide synthesis. Assuming that the microbially introduced hydroxyl group was probably in the cycloheptyl ring, its position was readily established by oxidizing N-cyclohexyl-N-(4-hydroxycyclohexyl)acetamide to the corresponding ketone and then subjecting the latter to ring expansion with diazomethane. The resulting N-cyclohexyl-N-(4-oxocycloheptyl)acetamide was identical with that obtained by oxidation of the bioconversion product, which may then be formulated as N-cyclohexyl-N-(4-hydroxycycloheptyl)acetamide.

N,N-Dicycloheptylacetamide underwent microbial oxygenation at the 4 position to give N-cycloheptyl-N-(4-oxocycloheptyl)acetamide (after Jones reagent oxidation), whose structure was established by synthesis *via* diazomethane ring expansion of N-cycloheptyl-N-(4-oxocyclohexyl)acetamide.

The organism may prefer the seven-membered over the six-membered ring because of the greater number of 5.5-Å spacings possible from the carbonyl oxygen to the two equivalent methylene groups in the conformationally less rigid seven-membered ring.

(8) As a leading reference, see M. L. Moore, *Org. Reactions*, **5**, 301 (1949).

Experimental Section[9]

Bioconversion of N-Cyclododecylacetamide.—The fermentation procedure with *Sporotrichum sulfurescens* ATCC 7159 and the subsequent beer extraction procedure have been described previously.[1] The crude extract residue from bioconversion of 25 g of N-cyclododecylacetamide contained a mixture of N-(oxocyclododecyl)acetamides and N-(hydroxycyclododecyl)acetamides, with the former preponderant. Chromatography on Florisil gave N-(6-oxocyclododecyl)acetamide and N-(7-oxocyclododecyl)acetamide in the 25% acetone–petroleum ether and 50% acetone–petroleum ether eluates, respectively. The appropriate fractions were combined and rechromatographed, and the eluted materials were recrystallized from acetone to give two crops of N-(6-oxocyclododecyl)acetamide (5.06 g, mp 143–148° and 3.23 g, mp 145–147°) and two crops of N-(7-oxocyclododecyl)acetamide (1.53 g, mp 195–197° and 0.50 g, mp 191–193°). For analysis, a sample of N-(6-oxocyclododecyl)acetamide was rerecrystallized from acetone to mp 150.5–151.5°.

Anal. Calcd for $C_{14}H_{25}NO_2$: C, 70.25; H, 10.53; N, 5.85. Found: C, 70.26; H, 10.49; N, 6.14.

For analysis, a sample of N-(7-oxocyclododecyl)acetamide was recrystallized from acetone to mp 196.5–198°.

Anal. Calcd for $C_{14}H_{25}NO_2$: C, 70.25; H, 10.53; N, 5.85. Found: C, 70.51; H, 10.45; N, 5.81.

Bioconversion of Cyclododecylamine.—Bioconversion of 25 g of cyclododecylamine afforded a mixture of N-(oxocyclododecyl)-acetamides and N-(hydroxycyclododecyl)acetamides. Repeated chromatography as described above, with pooling and recrystallization of appropriate fractions as indicated by paper chromatographic assay, gave three crops of N-(6-oxocyclododecyl)-acetamide (7.92 g, mp 147–148°, 3.20 g, mp 143–145°, and 1.96 g, mp 135–139°), two crops of N-(7-oxocyclododecyl)acetamide (1.43 g, mp 200–201°, and 1.12 g, mp 194.5–198°), as well as about 3.69 g of mixed N-(hydroxycyclododecyl)acetamides. This last was oxidized in acetone with Jones chromic acid reagent to a mixture of N-(oxocyclododecyl)acetamides that was separated by chromatography, to give N-(5-oxocyclododecyl)acetamide in the early 20% acetone–Skellysolve B eluate fractions. Recrystallization from acetone–petroleum ether and finally from ether gave 0.17 g, mp 128–129°.

Anal. Calcd for $C_{14}H_{25}NO_2$: C, 70.25; H, 10.53; N, 5.85. Found: C, 70.60; H, 10.75; N, 6.19.

N-(6-Acetoxycyclododecyl)acetamide.—The reduction of 7.17 g of N-(6-oxocyclododecyl)acetamide in 250 ml of 95% ethanol with a solution of 6.0 g of sodium borohydride in 60 ml of 0.1 *N* sodium hydroxide solution at room temperature for 2 hr gave, after appropriate work-up, 6.80 g of crude solid hydroxy amide, whose infrared spectrum showed the disappearance of carbonyl and introduction of hydroxyl, with amide still intact. Acetylation of 4 g of the crude hydroxy amide with acetic anhydride in pyridine gave 4.65 g of crude product that was recrystallized from ether–petroleum ether to give 3.57 g of N-(6-acetoxycyclododecyl)acetamide, mp 96–100°.

Anal. Calcd for $C_{16}H_{29}NO_3$: C, 67.81; H, 10.31; N, 4.94. Found: C, 67.98; H, 10.48; N, 4.83.

Cyclododecane-1,6-dione from N-(6-Acetoxycyclododecyl)-acetamide.—Liquid dinitrogen tetraoxide (1.0 ml) was transferred to a cold (10°) solution of 10 ml of acetic acid and 10 ml of methylene chloride. Freshly fused sodium acetate (1.97 g) and N-(6-acetoxycyclododecyl)acetamide (1.42 g) were added and the mixture was stirred in an ice water bath for 15 min. It was poured into ice water, stirred, and adjusted to pH 6 with sodium hydroxide solution. The mixture was extracted with methylene chloride, and the extract was washed with 5% sodium bicarbonate solution and dried (sodium sulfate). The filtered solution was made up to 200 ml of methylene chloride. One-half of this solution was taken to dryness under reduced pressure (cold) to give a yellow oil of unstable N-nitroso compound. A vacuum was applied to this material while warming on a steam bath. In

(9) All melting points were determined using a Fisher-Johns block. "Petroleum ether" refers to a product, bp 60–70°, of the Skelly Corp. called Skellysolve B. Florisil is a synthetic magnesium silicate product of the Florida Co. Gas–liquid partition chromatograms were carried out on a 3-ft, stainless steel column of 2.6% SE-30 silicone oil on 100–200 mesh Gas Chrom Z (W/W). Thin layer chromatograms were run on E. Merck silica gel GF plates (250 μ) with 20% methanol in benzene. Detection was with Dragendorff reagent [E. Roberts and C. C. Delwicke, *J. Biol. Chem.*, **205**, 565 (1953)]. Contrast was enhanced by overspray with 1:1 methanolic sulfuric acid followed by 0.1 *N* iodine–potassium iodide reagent.

a few seconds a violent reaction occurred and nitrogen gas was eliminated, leaving an oily residue that was heated at reflux in petroleum ether for 30 min and the solvent was then distilled off. The residue was heated at reflux for 30 min with 10 ml of methanol and 2 ml of 10% sodium hydroxide solution. The cooled mixture was diluted with water, extracted with ether, washed with water, dried (sodium sulfate), and evaporated. The residue of crude diol was chromatographed on Florisil, using gradient elution with 5–30% acetone–petroleum ether. The diol, found in the 14–18% acetone eluate fractions, was oxidized with Jones reagent. Crystallization of the crude product from acetone–petroleum ether gave cyclododecane-1,6-dione, mp 89–91° (lit.[4] mp 94–95°), whose infrared spectrum and thin layer chromatographic mobility were identical with those of an authentic specimen.

N-(7-Oxocyclododecyl)acetamide and N-(5-Oxocyclododecyl)-acetamide Degradation.—The degradative procedure described above was applied to 1.0 g of N-(7-oxocyclododecyl)acetamide. The crude diol, eluted from Florisil with petroleum ether containing 14–18% acetone, was oxidized with Jones reagent to give cyclododecane-1,7-dione, mp 134–135° (lit.[1] mp 134–136°). The infrared spectrum and paper chromatographic mobility were identical with those of an authentic specimen.

Because of the extreme paucity of N-(5-oxocyclododecyl)acetamide, degradation could be undertaken only on 125 mg of material, which yielded only enough cyclododecane-1,5-dione for characterization by thin layer chromatography and gas–liquid partition chromatography, where it showed mobilities identical with those of an authentic sample.[1]

N-(4-Hydroxycyclohexyl)benzamide.—The extract residue from the bioconversion of 2.0 g of N-cyclohexylbenzamide was taken up in methylene chloride and filtered to give 0.46 g of crude product, and the filtrate was chromatographed on Florisil. The product was eluted slowly by 25% acetone–petroleum ether and readily by acetone. Appropriate fractions were combined with the crude material from the initial filtration and recrystallized from acetone–petroleum ether to give 0.64 g of N-(4-hydroxycyclohexyl)benzamide, mp 213.5–214°. The analytical sample was recrystallized from acetone to mp 212.5–213.5°.

Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.82; N, 6.39. Found: C, 70.83; H, 7.91; N, 6.47.

N-(4-Oxocyclohexyl)benzamide. A. From Bioconversion Product.—N-(4-Hydroxycyclohexyl)benzamide (100 mg) was oxidized with Jones reagent to give, after recrystallization from acetone–petroleum ether, 80 mg of N-(4-oxocyclohexyl)benzamide, mp 174–175°.

Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 72.00; H, 6.97; N, 6.85.

B. Synthesis.—Diacylation of 1.4 g of 4-hydroxycyclohexylamine with 3 ml of benzoyl chloride in pyridine gave crude N-(4-hydroxycyclohexyl)benzamide benzoate, which was hydrolyzed to the crude free alcohol by heating with 6 *N* methanolic potassium hydroxide on a steam bath. Oxidation with Jones reagent gave the crude keto amide (0.23 g, mp 152–170°), which was chromatographed on Florisil. The product was eluted with 10% acetone–methylene chloride, giving N-(4-oxocyclohexyl)-benzamide, mp 172–173.5°, whose infrared spectrum was identical with that of the bioconversion-derived keto amide. The mixture melting point was undepressed.

Benzyl 4-Hydroxycyclohexylcarbamate. A. Bioconversion.—The extract residue from the bioconversion of 20 g of benzyl cyclohexylcarbamate was dissolved in 250 ml of hot acetone and treated with 20 g of Nuchar C-190N; the mixture was filtered through Celite, and the filter cake was washed with hot acetone. The product was precipitated by concentrating the combined acetone filtrate and wash, and diluting with petroleum ether: yield 5.03 g.; mp 159–161°. The analytical sample, recrystallized from acetone–petroleum ether, had mp 161°.

Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.44; H, 7.68; N, 5.62. Found: C, 67.38; H, 7.51; N, 5.94.

B. Synthesis.—A mixture of 2.3 g of 4-hydroxycyclohexylamine, 10 ml of tetrahydrofuran, and 5 ml of 2 *N* sodium hydroxide was stirred and chilled in an ice bath while adding, alternately in small portions, 10 ml of 2 *N* sodium hydroxide and 5.0 ml of carbobenzoxy chloride during 25 min. The mixture was diluted with water and stirred; the solid was recovered by filtration and washed with water and a little ether. This was taken up in acetone and filtered to remove insoluble material. The filtrate was concentrated and diluted with petroleum ether to precipitate the product, mp 161°, whose infrared spectrum was the same as that of the bioconversion product. The mixture melting point was undepressed.

Oxidation of benzyl 4-hydroxycyclohexylcarbamate from either preparation with Jones reagent afforded the same **benzyl 4-oxocyclohexylcarbamate**, mp 82–83°.

Anal. Calcd for $C_{14}H_{17}NO_3$: C, 67.99; H, 6.93; N, 5.67. Found: C, 67.74; H, 6.86; N, 5.61.

N-(4-Oxocyclohexyl)-*p*-toluenesulfonamide. A. Bioconversion.—The extract residue from the bioconversion of 2.0 g of N-cyclohexyl-*p*-toluenesulfonamide was chromatographed on Florisil. The product, eluted as an oil with 22–30% acetone–petroleum ether, was oxidized with Jones reagent to give 0.627 g of N-(4-oxocyclohexyl)-*p*-toluenesulfonamide, mp 111–112°. The analytical sample crystallized from ether melted at 116–117°.

Anal. Calcd for $C_{13}H_{17}NO_3S$: C, 58.40; H, 6.41; N, 5.24; S, 12.00. Found: C, 58.53; H, 6.63; N, 5.00; S, 12.06.

B. Synthesis.—A mixture of 5.0 g of 4-hydroxycyclohexylamine, 50 ml of 2 *N* sodium hydroxide, and 8.0 g of *p*-toluenesulfonyl chloride was shaken vigorously for 10 min and allowed to stand for 30 min. A gummy residue extracted from the acidified mixture with methylene chloride was oxidized with Jones reagent and the resulting product was crystallized from methylene chloride–ether to give N-(4-oxocyclohexyl)-*p*-toluenesulfonamide, mp 108–109°, whose infrared spectrum and thin layer chromatographic and gas–liquid chromatographic mobility were identical with that of the bioconversion product.

N-(4-Oxocycloheptyl)benzamide. A. Bioconversion.—The extract residue from the bioconversion of 2.0 g of N-cycloheptylbenzamide was chromatographed on Florisil. About 0.9 g of substrate was found in the 10% acetone–petroleum ether eluate, about 0.6 g of crude N-(4-oxocycloheptyl)benzamide in the early 25% acetone–petroleum ether eluate, and about 0.3 g of N-(4-hydroxycycloheptyl)benzamide in the later 25% acetone–petroleum ether eluate. All product fractions were combined and oxidized with Jones reagent, and the resultant ketoamide was chromatographed on Florisil. Recrystallization of the early 25% acetone–petroleum ether eluate fraction from acetone–petroleum ether gave 0.82 g of N-(4-oxocycloheptyl)benzamide, mp 143–145°. The analytical sample had mp 144–146° and $[\alpha]_D$ +65° (c 1, $CHCl_3$).

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.42; H, 7.61; N, 6.05.

B. Synthesis. 1. From N-(4-Oxocycloheptyl)-*p*-toluenesulfonamide.—To a mixture of 6.0 g of lithium aluminum hydride in 150 ml of anhydrous tetrahydrofuran was added with stirring a solution of 6.0 g of N-(4-oxocycloheptyl)-*p*-toluenesulfonamide in 75 ml of anhydrou stetrahydrofuran. The mixture was heated at reflux for 18 hr, chilled in an ice bath, and carefully treated dropwise with 25 ml of water. Ether (300 ml) was added and, after stirring for 30 min, the solids were removed by filtration and washed well with ether. The combined filtrate and wash solution was tried (sodium sulfate) and the solvent was evaporated. The residue was well stirred with 25 ml of 10% hydrochloric acid and the insoluble residue of N-(4-hydroxycycloheptyl)-*p*-toluenesulfonamide was separated from the aqueous acid phase. The acid solution was made strongly basic by the addition of 10 ml of 50% sodium hydroxide solution. The alkaline solution was chilled and shaken with 2.0 ml of benzoyl chloride for 30 min. The insoluble product was recovered by filtration, washed with water and ether, and dried. This material was taken up in acetone and oxidized with Jones reagent. The resulting product was recrystallized from acetone–hexane: yield 0.356 g; mp 137–138°; mixture melting point with biosynthetic N-(4-oxocycloheptyl)benzamide, 132–135°; $[\alpha]_D$ −1° (*c* 1, $CHCl_3$). The infrared spectrum in chloroform and the nmr spectrum in deuteriochloroform were identical with those of the optically active biosynthetic material.

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41. Found: C, 72.64; H, 7.40.

2. From N-(4-Oxocyclohexyl)benzamide.—A suspension of 0.5 g of N-(4-oxocyclohexyl)benzamide in 10 ml of methanol was chilled in an ice bath and treated with 10 ml of a cold ether solution containing excess diazomethane. The mixture was removed from the ice bath and allowed to stand in an open beaker in the hood until the solvent was evaporated. The residue was again subjected to the same procedure. This product was chromatographed over Florisil. Gradient elution with acetone (0–25%) in petroleum ether, followed by recrystallization from acetone–hexane, gave 260 mg of N-(4-oxocycloheptyl)benzamide, mp 137–139°, from the 21–25% acetone eluate fractions.

Recrystallization (from acetone–hexane) of material eluted from the column by 17–20% acetone gave a small amount of **6-benzamido-1-oxaspiro[2.5]octane**, mp 178–179°. The nmr spectrum in deuteriochloroform showed a sharp signal at 2.70 ppm (δ) for the isolated methylene of the oxaspiro ring.

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.64; H, 7.51; N, 6.27.

Benzyl Cycloheptylcarbamate.—A solution of 33.9 g of cycloheptylamine in 150 ml of pyridine was chilled and stirred in an ice–methanol bath while adding 56.3 g of carbobenzoxy chloride. The mixture was stirred for 15 min in the cold bath and 30 min with no temperature control, diluted with 350 ml of water, and allowed to stand for 18 hr in an open beaker. Concentrated hydrochloric acid (100 ml) was added and the mixture was extracted with ether. N,N'-Dicycloheptylurea crystals (6.78 g) were separated at the interface. The ether extract was washed with dilute hydrochloric acid, water, and 5% sodium bicarbonate, and dried (sodium sulfate) and the solvent was removed. The residue was chromatographed over Florisil, using gradient elution with petroleum ether containing increasing proportions of acetone from 0 to 30%. The benzyl cycloheptylcarbamate was eluted with 10–14% acetone–petroleum ether to give 19.0 g, mp 56°.

Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 73.43; H, 8.52; N, 5.50.

Benzyl-4-Oxocycloheptylcarbamate. A. Bioconversion.—The residue from the bioconversion of 56.36 g of benzyl cycloheptylcarbamate was oxidized with Jones reagent to give 42.0 g, of dark oil, 35 g of which was chromatographed over Florisil, using gradient elution with petroleum ether containing increasing proportions of acetone from 0 to 30%. The benzyl 4-oxcycloheptylcarbamate was eluted as an oil by 20–30% acetone–petroleum ether: yield 15.1 g; $[\alpha]_D$ +9° (c 1, $CHCl_3$). This compound finally crystallized to a low melting solid after prolonged storage in a desiccator.

Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 69.16; H, 7.49; N, 5.28.

The semicarbazone, prepared in the usual way, was recrystallized from methylene chloride–ether and then from aqueous methanol: mp 188–191°.

Anal. Calcd for $C_{16}H_{22}N_4O_3$: C, 60.36; H, 6.97; N, 17.60. Found: C, 59.94; H, 7.31; N, 17.52.

B. Synthesis.—Treatment of benzyl 4-oxocyclohexylcarbamate with diazomethane as described above gave an oily product whose infrared spectrum and gas–liquid partition chromatographic mobility were identical with those of the benzyl 4-oxocycloheptylcarbamate from the bioconversion.

Benzyl 4-Hydroxycycloheptylcarbamate.—The reduction of 5.0 g of benzyl 4-oxocycloheptylcarbamate in 50 ml of methanol with a solution of 5.0 g of sodium borohydride in 30 ml of 0.1 *N* sodium hydroxide gave a yellow oil. Chromatography on Florisil, using gradient elution, gave the desired compound in the 15–22% acetone–petroleum ether eluate fractions. Recrystallization from ether–petroleum ether gave 2.98 g of benzyl 4-hydroxycycloheptylcarbamate, mp 63–68°.

Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.41; H, 8.04; N, 5.32. Found: C, 68.36; H, 8.00; N, 5.28.

N-Cycloheptyl-*p*-toluenesulfonamide.—Shaking a mixture of 25.0 ml of cycloheptylamine, 40.0 g of *p*-toluenesulfonylchloride, and 200 ml of 8% sodium hydroxide solution and crystallizing the isolated crude product from methanol–water gave 84.05 g of product, mp 63–64°.

Anal. Calcd for $C_{14}H_{21}NO_2S$: C, 62.88; H, 7.99; N, 5.24; S, 11.99. Found: C, 62.46; H, 8.04; N, 5.10; S, 12.21.

N-(4-Oxocycloheptyl)-*p*-toluenesulfonamide. A. Bioconversion.—The extract residue from the bioconversion of 25.0 g of N-cycloheptyl-*p*-toluenesulfonamide was oxidized with Jones reagent. The neutral residue obtained by methylene chloride extraction was triturated with 150 ml of ether to give 14.77 g of solid material, which was chromatographed on Florisil. Elution with 20% acetone–petroleum ether, followed by recrystallization from ether, gave 11.58 g of N-(4-oxocycloheptyl)-*p*-toluenesulfonamide, mp 109–111°. The analytical sample, recrystallized from ether, had mp 110–112°.

Anal. Calcd for $C_{14}H_{19}NO_3S$: C, 59.76; H, 6.81; N, 4.98; S, 11.40. Found: C, 59.80; H, 6.94; N, 4.80; S, 11.36.

B. Synthesis.—Treatment of N-(4-oxocyclohexyl)-*p*-toluenesulfonamide with diazomethane as described above gave a residue that was chromatographed over Florisil, using gradient elution. N-(4-Oxocycloheptyl)-*p*-toluenesulfonamide was eluted with 12–15% acetone–petroleum ether and then recrystallized from ether to mp 109–110°. The mixture melting point with the bioconversion product was not depressed, and the infrared spectrum was identical with that of the bioconversion product.

N-Cyclooctylbenzamide.—Benzoylation of 25.5 g of cyclooctylamine by the Schotten–Baumann procedure gave 44.0 g of N-cyclooctylbenzamide, mp 110–111°. A sample recrystallized from acetone–water melted at 112–113°.

Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.06. Found: C, 78.20; H, 9.26; N, 6.03.

Bioconversion of N-Cyclooctylbenzamide.—The dried extract residue from the bioconversion of 20.0 g of N-cyclooctylbenzamide was chromatographed on Florisil. Elution with 20% acetone–petroleum ether, followed by recrystallization from methylene chloride–ether, gave 3.02 g of (presumably) N-(4-oxocyclooctyl)-benzamide, mp 136–139°.

Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.43; H, 7.81; N, 5.71. Found: C, 73.11; H, 7.71; N, 5.59.

Elution with 25% acetone–petroleum ether, followed by recrystallization from acetone–petroleum ether, gave 9.20 g of (presumably) N-(5-oxocyclooctyl)benzamide, mp 164–166°.

Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.43; H, 7.81; N, 5.71. Found: C, 73.51; H, 7.85; N, 5.84.

N-Cyclooctyl-*p*-toluenesulfonamide was prepared from 12.7 g of cyclooctylamine by the Schotten–Baumann procedure and crystallized from aqueous methanol to give 23.6 g of N-cyclooctyl-*p*-toluenesulfonamide, mp 66–67°.

Anal. Calcd for $C_{15}H_{23}NO_2S$: N, 4.98; S, 11.38. Found: N, 4.68; S, 11.49.

Bioconversion of N-Cyclooctyl-*p*-toluenesulfonamide.—The extract residue from the bioconversion of 20.0 g of N-cyclooctyl-*p*-toluenesulfonamide was chromatographed on Florisil. Gradient elution with petroleum ether plus increasing proportions of acetone from 0–30% afforded (presumably) N-(5-oxocyclooctyl)-*p*-toluenesulfonamide in the 10–15% acetone–petroleum ether eluates. Recrystallization from ether gave 2.23 g, mp 163–164°.

Anal. Calcd for $C_{15}H_{21}NSO_3$: C, 60.99; H, 7.17; N, 4.74; S, 10.86. Found: C, 61.04; H, 7.17; N, 5.09; S, 10.84.

The (presumed) N-(4-oxocyclooctyl)-*p*-toluenesulfonamide was eluted with 18–21% acetone–petroleum ether, and was recrystallized from ether to give 6.04 g, mp 107–108°.

Anal. Calcd for $C_{15}H_{21}NSO_3$: C, 60.99; H, 7.17; N, 4.74; S, 10.86. Found: C, 60.93; H, 7.40; N, 4.69; S, 10.73.

General Procedure for Conducting Leuckart Reductive Amination[9] of Ketones.—In general the amine was added to 98+% formic acid with cooling; the ketone was then added directly to the still warm mixture. Boiling pellets were added to control the evolution of generated carbon dioxide and the mixture was heated at reflux for 5 hr. Dilution with water, acidification of the cooled mixture with hydrochloric acid, and extraction with ether removed unreacted ketone. The aqueous acid solution was boiled to remove dissolved ether and then heated at reflux for 1–4 hr to hydrolyze formates of unreacted starting materials or products. In some cases hydrochloride salts separated directly from the cooled mixture; otherwise the mixture was made basic with 50% sodium hydroxide and the product was extracted with ether.

Cyclohexylcyclopentylamine Hydrochloride.—The Leuckart reaction of cyclohexylamine (57 ml), cyclopentanone (67 ml), and formic acid (24 ml) produced 50.38 g of amine hydrochloride, mp 271°. The preparation of the free base has been reported.[10]

Anal. Calcd for $C_{11}H_{22}NCl$: C, 64.84; H, 10.89; Cl, 17.40. Found: C, 64.83; H, 11.03; Cl, 17.40.

N-Cyclohexyl-N-cyclopentylacetamide.—Acetylation of 41 g of cyclohexylcyclopentylamine (generated from the hydrochloride by sodium hydroxide treatment) with acetic anhydride in pyridine gave, after recrystallization from acetone–petroleum ether, 37.5 g of N-cyclohexyl-N-cyclopentylacetamide, mp 53–54°.

Anal. Calcd for $C_{13}H_{23}NO$: C, 74.59; H, 11.07; N, 6.69. Found: C, 74.70; H, 11.18; N, 6.66.

N-Cyclopentyl-N-(4-hydroxycyclohexyl)acetamide. A. Bioconversion.—The extract residue from the bioconversion of 15.0 g of N-cyclohexyl-N-cyclopentylacetamide was chromatographed on Florisil using gradient elution with 0–30% acetone–petroleum ether. The yield of N-cyclopentyl-N-(4-hydroxycyclohexyl)-acetamide, eluted with 15–30% acetone–petroleum ether, and

(10) K. Jewers and J. McKenna, *J. Chem. Soc.*, 2209 (1958).

crystallized from methylene chloride–ether, was 5.99 g, mp 144–146°.

Anal. Calcd for $C_{13}H_{23}NO_2$: C, 69.29; H, 10.29; N, 6.22. Found: C, 69.21; H, 10.18; N, 6.37.

B. Synthesis.—The Leuckart reaction of 11.5 g of 4-hydroxycyclohexylamine, 13.2 ml of cyclopentanone, and 7.5 ml of formic acid afforded 3.05 g of cyclopentyl-(4-hydroxycyclohexyl)amine, mp 160–162°. The analytical sample was recrystallized from acetone to mp 165–167°.

Anal. Calcd for $C_{11}H_{21}NO$: C, 72.08; H, 11.55; N, 7.64. Found: C, 71.95; H, 11.47; N, 7.58.

Acetylation of cyclopentyl-(4-hydroxycyclohexyl)amine with acetic anhydride in pyridine, followed by hydrolysis of the ester with methanolic sodium hydroxide gave N-cyclopentyl-N-(4-hydroxycyclohexyl)acetamide, mp 145–147° (from aqueous methanol), identical with material from the bioconversion.

N-Cyclopentyl-N-(4-oxocyclohexyl)acetamide.—Oxidation of 2 g of N-cyclopentyl-N-(4-hydroxycyclohexyl)acetamide with Jones reagent gave a quantitative yield of crude N-cyclopentyl-N-(4-oxocyclohexyl)acetamide that was recrystallized from aqueous acetone to mp 144–145°.

Anal. Calcd for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27. Found: C, 70.22; H, 9.50; N, 6.55.

N-Cyclohexyl-6-(4-hydroxycyclohexyl)acetamide. A. Bioconversion.—The extract residue from the bioconversion of 25 g of N,N-dicyclohexylacetamide was recrystallized twice from acetone to give 7.85 g of N-cyclohexyl-N-(4-hydroxycyclohexyl)acetamide, mp 172–173.5°. A second crop (7.5 g, mp 167–169°), was obtained by chromatography of mother liquor solids on Florisil (elution with 25% acetone–petroleum ether), followed by recrystallization from acetone. The analytical sample (from acetone) had mp 177–178°.

Anal. Calcd for $C_{14}H_{25}NO_2$: C, 70.25; H, 10.53; N, 5.85. Found: C, 70.19; H, 10.27; N, 5.52.

B. Synthesis.—The Leuckart reaction of 23 g of 4-hydroxycyclohexylamine, 10.4 ml of cyclohexanone and 15 ml of formic acid afforded 2.25 g of cyclohexyl-(4-hydroxycyclohexyl)amine, mp 181° from acetone.

Anal. Calcd for $C_{12}H_{23}NO$: C, 73.04; H, 11.75; N, 7.10. Found: C, 73.13; H, 11.54; N, 7.13.

4-(Cyclohexylamino)cyclohexanol (1.0 g) was acetylated with acetic anhydride in pyridine. After hydrolysis of the ester with methanolic sodium hydroxide 0.335 g of N-cyclohexyl-N-(4-hydroxycyclohexyl)acetamide, mp 167–169°, crystallized from the neutralized (acetic acid) and partially evaporated mixture. The infrared spectrum was identical with that of the bioconversion product.

N-Cyclohexyl-N-(4-oxocyclohexyl)acetamide.—Oxidation of 0.20 g of N-cyclohexyl-N-(4-hydroxycyclohexyl)acetamide with Jones reagent and recrystallization of the crude product from acetone–petroleum ether gave 0.13 g of N-cyclohexyl-N-(4-oxocyclohexyl)acetamide, mp 142–146°. The analytical sample, recrystallized from the same solvent, had mp 142–144.5°.

Anal. Calcd for $C_{14}H_{23}NO_2$: C, 70.85; H, 9.77; N, 5.90. Found: C, 71.07; H, 9.76; N, 6.15.

The **oxime**, prepared in ethanol–pyridine at reflux, was recrystallized from aqueous methanol to mp 179–183°.

Anal. Calcd for $C_{14}H_{24}N_2O_2$: C, 66.63; H, 9.59; N, 11.10. Found: C, 66.96; H, 9.60; N, 11.33.

N-Cycloheptylcyclohexylamine Hydrochloride.—The Leuckart reaction was carried out with 37.7 ml of formic acid, 112 ml of cyclohexylamine, and 59.0 ml of cycloheptanone. When the reaction mixture was diluted with 500 ml of water and acidified with 100 ml of concentrated hydrochloric acid, the hydrochloride salt precipitated. After chilling, this was recovered by filtration, washed with a little cold water and with ether, and dried to yield 76 g of N-cycloheptylcyclohexylamine hydrochloride, mp 264°. For analysis a sample was recrystallized from methanol–ether.

Anal. Calcd for $C_{13}H_{26}NCl$: C, 67.35; H, 11.31; Cl, 15.30. Found: C, 66.99; H, 11.08; Cl, 15.41.

N-Cycloheptyl-N-cyclohexylacetamide.—The acetylation of 50 g of N-cycloheptylcyclohexylamine hydrochloride was carried out as described above for N-cyclohexylcyclopentylamine. The product, obtained as an oil, solidified upon standing under reduced pressure for 3 days to give 43.16 g of N-cycloheptyl-N-cyclohexylacetamide, mp 48–49°. The analytical sample, recrystallized from acetone–water had mp 48–49°.

Anal. Calcd for $C_{15}H_{27}NO$: C, 75.89; H, 11.47; N, 5.90. Found: C, 75.92; H, 11.46; N, 5.90.

Bioconversion of N-Cycloheptyl-N-cyclohexylacetamide.—A standard bioconversion of 2 g of N-cycloheptyl-N-cyclohexylacetamide in 10 l. of beer afforded an extract residue that contained N-cyclohexyl-N-(4-hydroxycycloheptyl)acetamide but that was, for convenience, oxidized with Jones reagent to the keto amide by methods described above. Chromatography on Florisil (elution with 16% acetone–petroleum ether) gave an oil that soon crystallized, mp 76–79°. For analysis the N-cyclohexyl-N-(4-oxocycloheptyl)acetamide was recrystallized from petroleu mether to mp 80–82°.

Anal. Calcd for $C_{15}H_{25}NO_2$: C, 71.67; H, 10.03; N, 5.57. Found: C, 71.90; H, 10.04; N, 5.76.

When the bioconversion of N-cycloheptyl-N-cyclohexylacetamide was carried out on a 20-g scale, it afforded 8 g of N-cyclohexyl-N-(4-oxocycloheptyl)acetamide, mp 73–76°.

The **2,4-dinitrophenylhydrazone**, mp 221–223°, was prepared in the standard fashion and recrystallized from ethanol.

Anal. Calcd for $C_{21}H_{29}N_5O_5$: C, 58.45; H, 6.77; N, 16.23. Found: C, 58.25; H, 6.39; N, 16.49.

N-Cycloheptyl-N-(4-oxocyclohexyl)acetamide.—The Leuckart reaction of 23.0 g of 4-hydroxycyclohexylamine, 11.8 ml of cycloheptanone, and 15 ml of formic acid gave 1.34 g of crude product,[11] mp 150° (from acetone).

Anal. Calcd for $C_{13}H_{25}NO$: C, 73.88; H, 11.92; N, 6.63. Found: C, 72.38; H, 12.17; N, 6.85.

Acetylation of this material with acetic anhydride in pyridine, followed by alkaline hydrolysis of the ester as described above and oxidation with Jones reagent, gave N-cycloheptyl-N-(4-oxocyclohexyl)acetamide, mp 121° (from acetone–water).

Anal. Calcd for $C_{15}H_{25}NO_2$: C, 71.67; H, 10.03; N, 5.57. Found: C, 71.48; H, 9.90; N, 5.65.

N-Cyclohexyl-N-(4-oxocycloheptyl)acetamide.—Treatment of N-cyclohexyl-N-(4-oxocyclohexyl)acetamide with diazomethane as described above gave an oil whose thin layer chromatographic and gas chromatographic mobility was the same as that of the N-cyclohexyl-N-(4-oxocycloheptyl)acetamide described above, and which afforded a 2,4-dinitrophenylhydrazone, mp 221–223°, identical with that derived from the bioconversion product.

N,N-Dicycloheptylamine Hydrochloride.—The Leuckart reaction of 64 ml of cycloheptylamine, 89 ml of cycloheptanone, and 18.8 ml of formic acid gave 80.8 g of N,N-dicycloheptylamine hydrochloride, mp 230° (from methanol–ether).

Anal. Calcd for $C_{14}H_{28}NCl$: C, 68.40; H, 11.48; Cl, 14.42. Found: C, 68.53; H, 11.13; Cl, 14.52.

N,N-Dicycloheptylacetamide was prepared by the acetylation procedure described above. From 73.6 g of dicycloheptylamine hydrochloride there was obtained 72.3 g of N,N-dicycloheptylacetamide, mp 61–64°. The analytical sample from acetone melted at 63–64°.

Anal. Calcd for $C_{16}H_{29}NO$: C, 76.44; H, 11.63; N, 5.57. Found: C, 76.19; H, 11.67; N, 5.75.

N-Cycloheptyl-N-(4-oxocycloheptyl)acetamide. A. Bioconversion.—The extract residue from the bioconversion of 2.5 g of N,N-dicycloheptylacetamide was chromatographed on Florisil. Gradient elution with petroleum containing increasing proportions of acetone from 0 to 30% afforded crude N-cycloheptyl-N-(4-hydroxycycloheptyl)acetamide in the 25–30% acetone eluates. Oxidation with Jones reagent gave 0.43 g of N-cycloheptyl-N-(4-oxocycloheptyl)acetamide, mp 99–101°. The analytical sample was recrystallized from acetone–petroleum ether to mp 106–108°.

Anal. Calcd for $C_{16}H_{22}NO_2$: C, 72.41; H, 10.26. Found: C, 72.29; H, 10.49.

B. Synthesis.—Treatment of N-cycloheptyl-N-(4-oxocyclohexyl)acetamide with diazomethane as described above gave N-cycloheptyl-N-(4-oxocycloheptyl)acetamide, mp 94–96° from acetone–petroleum ether. Although thin layer chromatographic and gas–liquid partition chromatographic analysis showed the presence of a small amount of residual N-cycloheptyl-N-(4-oxocyclohexyl)acetamide, the major component was chromatographically and spectrally (infrared) identical with the N-cycloheptyl-N-(4-oxocycloheptyl)acetamide from the bioconversion.

Registry No.—N-(6-Oxocyclododecyl)acetamide, 16801-59-5; N-(7-oxocyclododecyl)acetamide, 16801-60-8; N-(5-oxocyclododecyl)acetamide, 16801-61-9; N-

(11) Cycloheptyl(4-hydroxycyclohexyl)amine is the crude product.

(6-acetoxycyclododecyl)acetamide, 16853-01-3; N-(4-hydroxycyclohexyl)benzamide, 13941-93-0; N-(4-oxocyclohexyl)benzamide, 13942-05-7; benzyl 4-hydroxycyclohexylcarbamate, 16801-62-0; benzyl 4-oxocyclohexylcarbamate, 16801-63-1; N-(4-oxocyclohexyl)-*p*-toluenesulfonamide, 16801-64-2; N-(4-oxocycloheptyl)-benzamide, 14156-24-2; 6-benzamido-1-oxaspiro[2.5]-octane, 16801-78-8; benzyl cycloheptylcarbamate, 16801-66-4; benzyl 4-oxocycloheptylcarbamate, 16801-67-5; semicarbazone of benzyl 4-oxocycloheptylcarbamate, 16801-68-6; benzyl 4-hydroxycycloheptylcarbamate, 16801-69-7; N-cycloheptyl-*p*-toluenesulfonamide, 16801-70-0; N-(4-oxocycloheptyl)-*p*-toluenesulfonamide, 16801-71-1; N-cyclooctylbenzamide, 13364-13-1; N-(4-oxocyclooctyl)benzamide, 16801-73-3; N-(5-oxocyclooctyl)benzamide, 16853-02-4; N-cyclooctyl-*p*-toluenesulfonamide, 16801-74-4; N-(5-oxocyclooctyl)-*p*-toluenesulfonamide, 16801-75-5; N-(4-oxocycloacetyl)-*p*-toluenesulfonamide, 16801-76-6; cyclohexylcyclopentylamine hydrochloride, 16801-77-7; N-cyclohexyl-N-cyclopentylacetamide, 16803-22-8; N-cyclopentyl-N-(4-hydroxycyclohexyl)acetamide, 16803-23-9; cyclopentyl-(4-hydroxycyclohexyl)amine, 16803-24-0; N-cyclopentyl-N-(4-oxocyclohexyl)acetamide, 16803-25-1; N-cyclohexyl-N-(4-hydroxycyclohexyl)acetamide, 16803-26-2; cyclohexyl(4-hydroxycyclohexyl)amine, 16803-27-3; N-cyclohexyl-N-(4-oxocyclohexyl)acetamide, 16803-28-4; oxime of N-cyclohexyl-N-(4-oxocyclohexyl)acetamide, 16803-29-5; N-cycloheptylcyclohexylamine hydrochloride, 16803-30-8; N-cycloheptyl-N-cyclohexylacetamide, 16803-31-9; N-cyclohexyl-N-(4-oxocycloheptyl)acetamide, 16803-32-0; 2,4-dinitrophenylhydrazone of compound preceding, 16803-33-1; cycloheptyl(4-hydroxycyclohexyl)amine, 16803-34-2; N-cycloheptyl-N-(4-oxocyclohexyl)acetamide, 16803-35-3; N,N-dicycloheptylamine hydrochloride, 16803-36-4; N,N-dicycloheptylacetamide, 16803-37-5; N-cycloheptyl-N-(4-oxocycloheptyl)acetamide, 16803-38-6.

The Microbiological Oxygenation of Azacycloalkanes. Structural Determinations and Some Chemical Modifications Leading to Transannular Reactions

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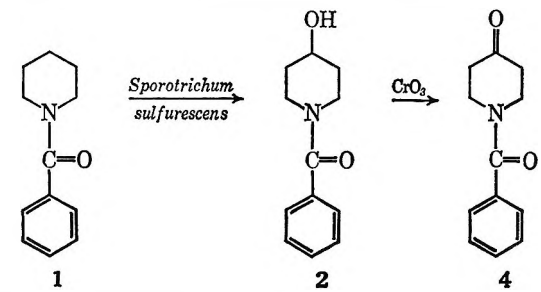
Microbiological oxygenation with *Sporotrichum sulfurescens* has been shown to occur at C-4 of 1-benzoylpiperidine (**1**), at C-3 and C-4 of 1-benzoylhexamethylenimine (**6**), at C-4 of 1-*p*-toluenesulfonylhexamethylenimine (**7**), and at C-4 and C-5 of 1-benzoylheptamethylenimine (**15**) and 1-benzoyloctamethylenimine (**34**). Further chemical modifications in the hepta- and octamethylenimine series have led to a number of transannular reactions. Included in these reactions is the conversion of 1-benzoylhexahydro-5(2H)-azocinone (**18**) into the iminium salt (**26**) *via* 9-benzoyl-1,4-dioxa-9-azaspiro[4.7]dodecane (**20**), 9-benzyl-1,4-dioxa-9-azaspiro[4.7]dodecane (**21**), and 1,4-dioxa-9-azaspiro[4.7]dodecane (**25**). A similar reaction series converted 1-benzoyloctamethylenimine (**34**) into the iminium salt (**41**).

The microbiological oxygenation of organic molecules recently has been extended to include macrocyclic alcohols[1a] and the acyl derivatives of cyclic and macrocyclic amines.[1b] Included in the study of the oxygenation of macrocyclic alcohols with *Sporotrichum sulfurescens* was a consideration of the molecular geometry of the substrate, which led to the formulation of a hypothetical enzyme–substrate model. Among the features proposed in this model was an optimal spacing of 5.5 Å between an electron-rich center of the substrate and the point of enzymatic oxygenation.[1a] We now describe the microbiological oxygenation of a series of heterocyclic compounds, which includes piperidine and hexa-, hepta-, and octamethylenimine as their benzoyl derivatives as well as the *p*-toluenesulfonyl derivative of hexamethylenimine, with *S. sulfurescens*. In these substrates, the electron-rich group is considered to be the oxygen of the carbonyl or sulfonyl groups. The structures of the products have been determined by chemical means with the aid of spectroscopic techniques. The oxygenation of this series of compounds follows that proposed by the enzyme–substrate model outlined previously[1a] and provides a new method of inserting oxygen functions at positions accessible with difficulty by chemical means. These new compounds therefore became available for further chemical studies which are included in the following discussion.

In general, the biotransformation products were extracted from the filtered beer of the fermentations with methylene chloride. A typical fermentation and workup is described in detail in the Experimental Section. The concentrated methylene chloride extracts were either chromatographed on Florisil columns or were oxidized with Jones reagent[2] and chromatographed. This latter procedure converts the hydroxylic products into ketonic products and simplifies the purification of the biotransformation products in this heterocyclic series. The yields of oxygenated products are generally in the range of 25–60%.

Piperidine Series.—The structure of the product from the biotransformation of 1-benzoylpiperidine (**1**) with



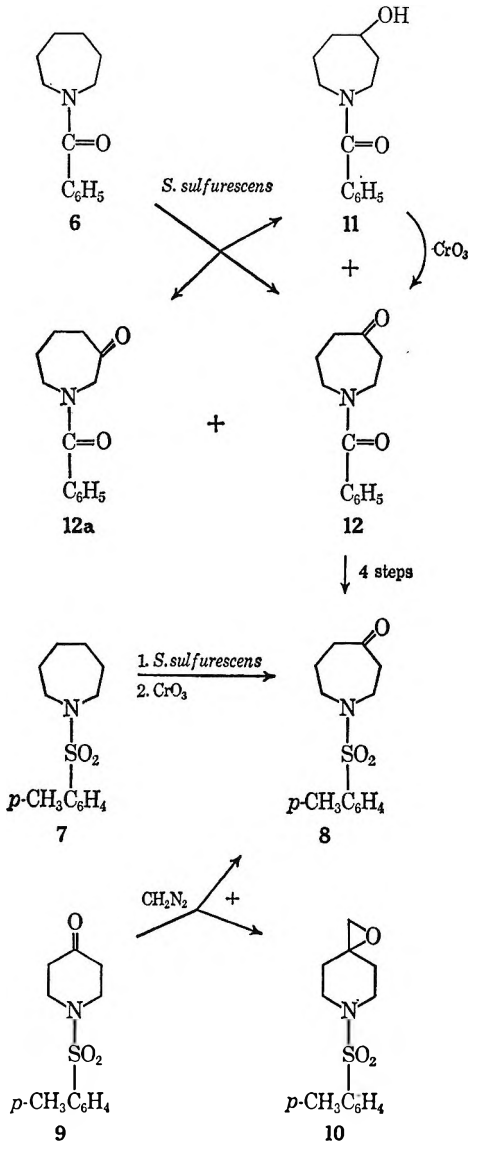
(1) (a) G. S. Fonken, M. E. Herr, H. C. Murray, and L. M. Reineke, *J. Amer. Chem. Soc.*, **89**, 672 (1967); (b) G. S. Fonken, M. E. Herr, H. C. Murray, and L. M. Reineke, *J. Org. Chem.*, **33**, 3182 (1968).

(2) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

Sporotrichum sulfurescens was shown to be 1-benzoyl-4-piperidinol (**2**) by comparison of derivatives. The phenylurethan (**3**) of **2** has the reported melting point 184.5–186.5°.[3] Oxidation of **2** with Jones reagent[2] gave the oily 1-benzoyl-4-piperidone (**4**), whose 2,4-dinitrophenylhydrazone (**5**) has the reported mp 196–198°.[3]

Hexamethylenimine Series.—Both the benzoyl (**6**) and *p*-toluenesulfonyl (**7**) derivatives of hexamethylenimine (see Scheme 1) were used as substrate for bio-

SCHEME I



conversion with *S. sulfurescens*. The nature of the acyl function had little effect on this conversion since in each case a similar mixture of hydroxy and ketonic products was isolated. The presence of the two types of products was shown by partial chromatographic separation followed by inspection of infrared spectra. To facilitate purification and identification of the products, which may include stereoisomers, the product mixture was oxidized,[2] giving entirely ketonic material. Thus a single ketone (**8**), having dimorphic crystalline forms, mp 81 and 90°, was obtained from the bioconversion of **7**. The probable position of the ketone in **8** is at C-4 of the saturated ring. This was proved by synthesis of **8** from 1-*p*-toluenesulfonyl-4-piperidone[4] (**9**) *via* a diazomethane ring expansion.[5] In addition to **8**, the ring expansion gave the oxide (**10**), resulting from insertion of a methylene group into the carbonyl double bond. While such insertions are not uncommon,[5] of interest in this case is the nmr spectrum of **10**. Sharp signals are found at δ 2.62 ppm and 2.43 ppm, corresponding to the isolated methylene and the aromatic methyl protons, respectively, and, in addition, the remaining spectrum in the methylene proton region consists of a series of at least 26 signals, suggesting nonequivalence of the ring methylene protons.

The microbiological oxygenation of 1-benzoylhexamethylenimine (**6**) occurred primarily at the 4 position as it did for 1-*p*-toluenesulfonylhexamethylenimine (**7**). This was proved by interrelating the two series in the following manner. (See Scheme I.) The amide–ketone (**12**), obtained by oxidation of the biotransformation products from **6**, was converted into the amide–ketal, which was reduced to the amine–ketal (**13**) with lithium aluminum hydride. The benzyl group of **13** was removed readily by hydrogenolysis over palladium-on-carbon catalyst, giving the secondary amine (**14**). The *p*-toluenesulfonate was prepared before removal of the ketal with dilute acidic acetone. The ketone obtained in this manner was identical with the ketone (**8**) obtained from the bioconversion of **7** in crystalline form, mp 90°. A second product (**12a**) was isolated in addition to **12** during the work-up[6] of a large-scale, oxidized bioconversion of **6**. This crystalline ketone (**12a**) was shown by the nmr spectrum (see Table I) to be the result of oxygenation at the 3 position.

TABLE I

CHEMICAL SHIFTS OF PROTONS OF KETONIC PRODUCTS IN DEUTERIOCHLOROFORM[a]

Compd	$-CH_2CH_2CH_2-$	$-CH_2CH_2\overset{O}{\overset{\|}{C}}-$	$-CH_2CH_2\overset{|}{N}-$	$-\overset{O}{\overset{\|}{C}}CH_2\overset{|}{N}-$
8	1.89 (2)	2.63 (4)	3.43 (4)	
12	1.79 (2)	2.68 (4)	3.72 (4)	
12a	1.77 (4)	2.60 (2)	3.61 (2)	4.16 (2)[b]
12a[c]	1.77 (4)	2.58 (2)	3.64 (2)	4.14 (2)[b]
18	2.19 (4)[d]	2.39 (4)[d]	3.47 (4)[e]	
19	1.95 (4)	2.58 (4)	3.42 (4)[f]	
35	1.82 (6)	2.48 (4)	3.42 (4)	
36	1.52 and 2.03 (6)	2.47 (2) and 2.8 (2)	3.38 (2) and 3.73 (2)	

[a] Chemical shifts were measured as δ values in parts per million (number of protons), multiplets unless indicated otherwise. [b] Singlet. [c] In d_7-DMF at 95°. [d] Broad signals at 2.19 and 2.39 overlap. [e] Triplet (J = 4.5 cps). [f] Triplet (J = 5.5 cps).

The significant signal in this spectrum is the sharp singlet seen at δ 4.14 ppm, resulting from the methylene adjacent to both the ketone carbonyl and the nitrogen.

Heptamethylenimine Series.—The bioconversion of 1-benzoylheptamethylenimine (**15**) (see Scheme II) with *S. sulfurescens* gave an oily mixture of products, which were shown by infrared spectra following chromatography to be hydroxylic and ketonic in nature.

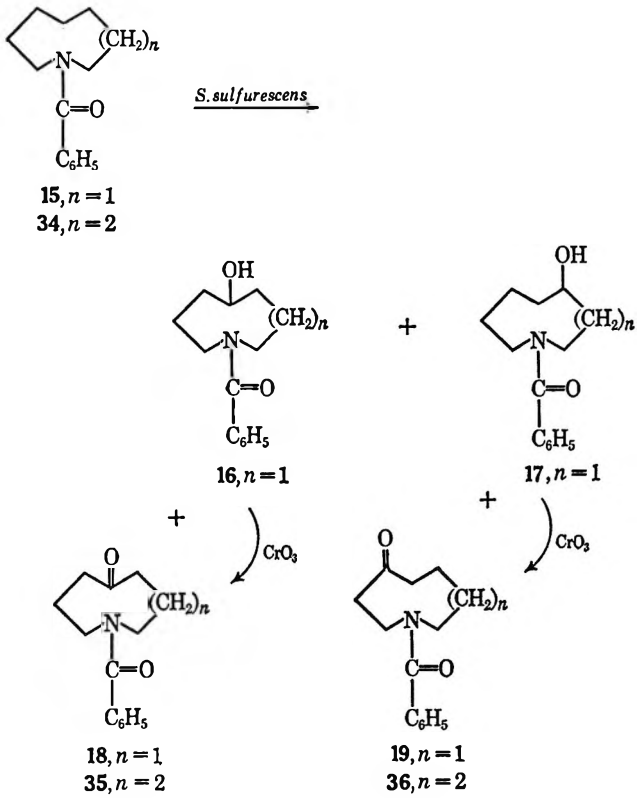
(3) S. M. McElvain and R. E. McMahon, *J. Amer. Chem. Soc.*, **71**, 901 (1949).

(4) F. Arndt and A. Kalischek, *Chem. Ber.*, **63**, 587 (1930).

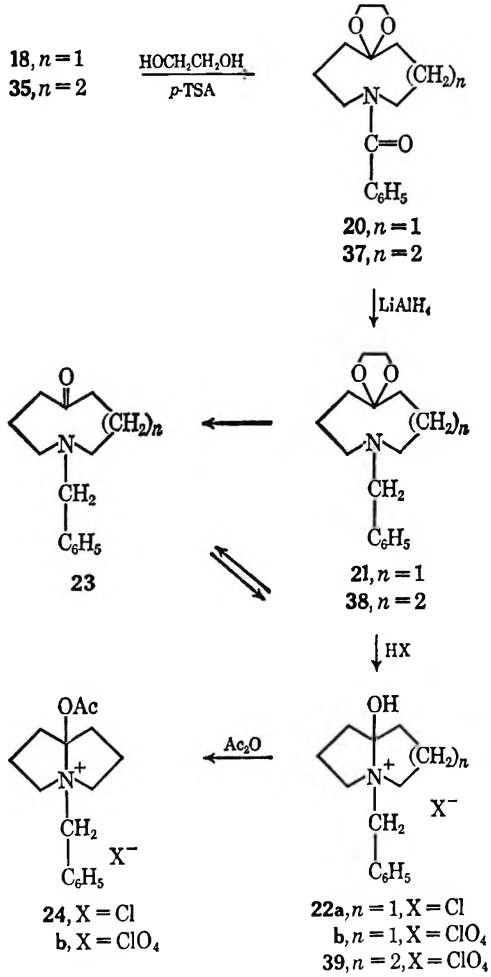
(5) (a) E. Muller and M. Bauer, *Ann. Chem.*, **654**, 92 (1962); (b) E. Mosettig and A. Burger, *J. Amer. Chem., Soc.*, **52**, 3456 (1930).

(6) We thank Dr. Jackson B. Hester, Jr., and Mr. J. R. Greene for these experimental results.

SCHEME II



SCHEME III



Although a crystalline alcohol (**16**) was obtained from this mixture, the work-up was simplified if the entire crude reaction product was oxidized.[2] Using this technique, a more polar major ketonic product (**18**) and a less polar minor ketonic product (**19**) were separated upon chromatography on a Florisil column. The crystalline alcohol (**16**) was oxidized separately to the major ketonic product (**18**); therefore the structure of **16** follows from the evidence presented below in support of the structure of ketone (**18**). In the light of past experience with the microbiological oxygenation of cyclic compounds,[1a] it was felt that oxygenation of **15** had occurred in the 4 and 5 positions of the eight-membered heptamethylenimine ring, with the latter considered the most probable. If this were true, it can be seen that the major ketonic product (**18**) would be a molecule having the needed requirements for undergoing transannular interactions and reactions,[7] provided that the appropriate chemical modifications were carried out. With this in mind, it was apparent that the benzamide function of **18** must be changed in a way such that the nitrogen became basic. This was achieved by protecting the ketone in the form of its ethylene ketal (**20**) and then reducing the amide carbonyl with lithium aluminum hydride (Scheme III). This gave the ketal–benzyl amine (**21**), potentially an amino ketone of the type first studied in detail by Leonard and coworkers in their work on transannular interactions in eight-membered-ring systems.[8] Hydrolysis of **21** with aqueous hydrochloric or aqueous perchloric acid gave the hexahydropyrrolizinium salts **22a** and **b**, respectively, in which regeneration of the ketone has been followed immediately by transannular reaction. The intermediate ketone (**23**) was obtained by making the reaction mixture alkaline following hydrolysis of the ketal. Upon reaction with acid, **23** was converted into the hexahydropyrrolizinium salt (**22**). The infrared spectra of **23**, **22a**, and **22b** are consistent with the requirements of these molecules and with the observations of Leonard,[8] with one exception in the case of the hydroxyl absorption of the hydrochloride (**22a**). The carbonyl band of the ketone (**23**) is shifted to 1675 cm^{-1} (in chloroform), which agrees with the value (1683 cm^{-1}) observed by Leonard.[8] Absorption in the infrared due to a carbonyl is absent in both salts. A hydroxyl band is seen at 3290 cm^{-1} in the hexahydropyrrolizinium perchlorate (**22b**); however, no typical hydroxyl absorption is present in the infrared of the hydrochloride (**22a**). Instead the spectrum of **22a** shows a series of weak bands at 3000, 2760, 2720, 2620, and 2560 cm^{-1} in Nujol. This shift is apparently the result of hydrogen bonding, because the hydroxyl group in **22a** has been shown to be intact by the regeneration of the ketone (**23**) in alkaline solution. Reaction of the pyrrolizinium perchlorate (**22b**) with acetic anhydride gave the acetylated compound (**24b**). The infrared spectrum of **24b** supports the structure in that it has a typical ester carbonyl absorption band at 1750 cm^{-1}. Similarly, the hydrochloride (**22a**) formed an acetate (**24a**, carbonyl band at 1750 cm^{-1}) in acetic anhydride, which, because of its hygroscopic nature, was not further purified. Similar acetylations of

(7) N. J. Leonard, *Rec. Chem. Progr.*, **17**, 243 (1956); an appropriate distinction has been made between interactions and reactions, "the former signifying either partial orbital overlap or a field effect, and the latter, the generation of a full bond."

(8) N. J. Leonard, M. Ōki, and S. Chiavarelli, *J. Amer. Chem. Soc.*, **77**, 6234 (1955).

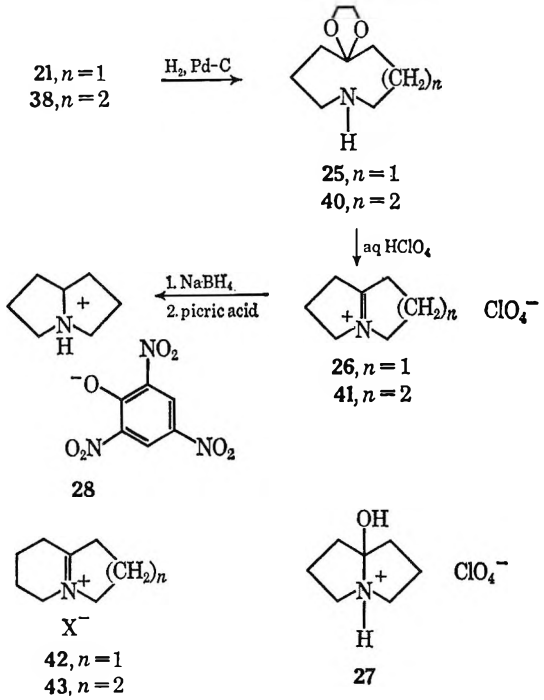
transannular carbinol–ammonium salts do not appear to have been reported. This reaction also served to support the conclusion that the hydroxyl group is present in the hydrochloride (**22a**). The above results provide proof that the major ketonic product from the bioconversion of **15** is 1-benzoylhexahydro-5(2H)-azocinone (**18**) as was anticipated.

It was of interest to continue with this series of compounds since removal of the benzyl group of **21** would provide a potential secondary amino ketone. Previous studies[7,9] of transannular interactions have dealt exclusively with tertiary amines. The hydrogenolysis of the benzyl group of **21** proceeded smoothly over palladium-on-charcoal catalyst, giving the ketal–amine (**25**) (Scheme IV). Reaction of **25** with aqueous perchloric acid gave a salt (**26**), which had a strong, sharp infrared absorption band at 1690 cm^{-1} while lacking any OH or NH absorption. The product (**26**) was found to contain a mole less of water than is required by the expected transannular salt (**27**). Dehydration of structure **27**, possibly formed as an intermediate, would explain the loss of water and suggested an iminium salt structure for **26**. The infrared absorption band at 1690 cm^{-1} in the spectrum of **26** is analogous to bands observed for a number of iminium salts.[10,11] The nmr spectrum of **26** confirms this structure. The spectrum has three multiplets, each integrating for four protons. Bands centered at δ 3.92, 2.95, and 2.55 ppm are assigned to the methylene groups $-CH_2-N^+(=)-CH_2-$, $-CH_2-C(=)-CH_2-$, and $2(-CH_2-CH_2-CH_2-)$, respectively. The nmr spectra of a series of 2,3,5,6,7,8-hexahydro-1H-indolizinium salts (**42**) and 1,2,3,4,6,7,8,9-octahydroquinolizinium salts (**43**) have been tabulated.[11] The signals for the $-CH_2-N^+(=)-$ and $-CH_2-C(=)-$ methylene groups were found in the ranges δ 4.12–4.30 and 3.18–3.20 ppm, respectively, when in the five-membered ring, and between 3.70–3.94 ppm and 2.74–2.90 ppm, respectively, when in the six-membered ring. Hydride reduction of iminium salts is a well-known reaction.[12] When **26** was reduced with sodium borohydride, hexahydro-1H-pyrrolizine (pyrrolizidine) was obtained and isolated as the picrate (**28**), mp 260–263° dec. Hexahydro-1H-pyrrolizine picrate (**28**) has been reported by several groups,[13] mp 260–262° dec. The pathway **18** → **20** → **21** → **25** → **26** described above provides a new synthetic route to iminium salts *via* transannular reactions.

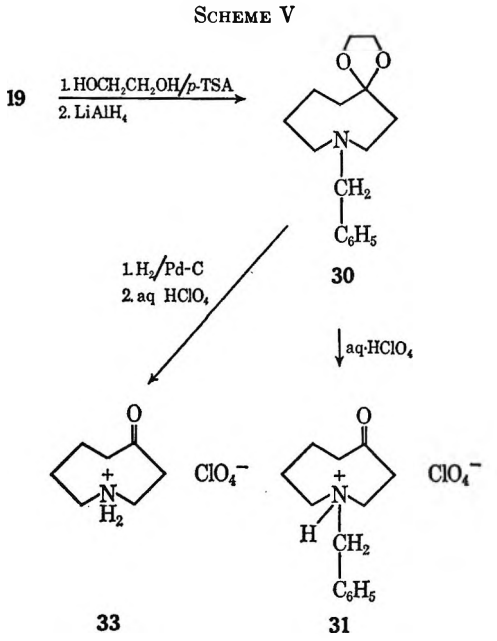
With the position of the ketone in the major bioconversion product (**18**) established at C-5, three possibilities remain for the position of the ketone in the minor product (**19**). The nmr spectrum of **19** (see Table I) bears out the prediction that this ketone will be found at C-4 of the heptamethylenimine ring. This spectrum has multiplet signals, corresponding to four protons each, centered at δ 3.42, 2.58, and 1.95 ppm, which are assigned to the methylene groups $-CH_2-N-CH_2-$, $-CH_2-C(=O)-CH_2-$, and $-CH_2-CH_2-$, respectively.

For comparative purposes, we carried out a sequence of chemical modifications of **19** (Scheme V) similar to those which were applied to the 5 ketone (**18**). In this series, transannular interactions[7] are expected to be reduced greatly while transannular reactions are not expected to occur. Consequently, **19** was converted into the ketal–amide (**29**), which was reduced, without purification, to the ketal–amine (**30**). Reaction of **30** with aqueous perchloric acid gave the perchlorate salt (**31**), in which the presence of a ketone was demonstrated by an absorption band at 1700 cm^{-1} in the infrared spectrum. Hydrogenolysis removed the benzyl group of **30**, giving **32**, which showed NH absorption at 3360 cm^{-1} in the infrared spectrum. The

SCHEME IV



SCHEME V



(9) M. G. Reineke, L. R. Kray, and R. F. Francis, *Tetrahedron Lett.*, 3549 (1965).
(10) N. J. Leonard and V. W. Gash, *J. Amer. Chem. Soc.*, **76**, 278 (1954).
(11) M. G. Reineke and L. R. Kray, *J. Org. Chem.*, **31**, 4215 (1966).
(12) N. J. Leonard, A. S. Hay, R. W. Fulmer, and V. W. Gash, *J. Amer. Chem. Soc.*, **77**, 439 (1955).
(13) (a) E. E. Schweizer and K. K. Light, *ibid.*, **86**, 2963 (1964); *J. Org. Chem.*, **31**, 870 (1966); (b) N. J. Leonard and W. E. Goode, *J. Amer. Chem. Soc.*, **72**, 5404 (1950).

final step in this sequence gave the ketone–amine salt (**33**, carbonyl absorption at 1695 cm^{-1}) when **32** was treated with aqueous perchloric acid. The infrared carbonyl absorptions of the two ketone–amine salts (**31** and **33**) in this series are found at the lower limits (with respect to wave numbers) usually given for normal ketones.[14] This may reflect a slight transannular interaction shifting the carbonyl bands in these molecules.

Octamethylenimine Series.—The bioconversion of 1-benzoyloctamethylenimine (**34**) with *S. sulfurescens* proceeded in a manner very similar to that of the heptamethylenimine series. Following oxidation of the isolated products, major (**35**) and minor (**36**) ketonic products (see Scheme II) were separated by chromatography. In view of recent results[1a] and now with the analogy of the heptamethylenimine series, the positions of oxygenation of the nine-membered ring (**34**) are predicted to be at C-5 (major product) and at C-4. The use of transannular reactions as a method of structure proof was applicable in this series also and the appropriate transformations which were carried out are described briefly below.

The ketal (**37**) of the major ketonic product (**35**) was first prepared and then was reduced to the ketal–amine (**38**) with lithium aluminum hydride. Transannular reaction followed the treatment of **38** with aqueous perchloric acid, giving **39** (no carbonyl absorption, OH absorption at 3420 cm^{-1} in the infrared spectrum). Hydrogenolysis of **38** gave the secondary amine–ketal (**40**). Reaction of **40** with aqueous perchloric acid resulted in ketal hydrolysis, transannular reaction, and dehydration of the molecule, giving the hexahydroindolizinium perchlorate (**41**), mp 227–228°, with an iminium salt absorption band at 1690 cm^{-1} in the infrared spectrum. The compound **41** has been prepared previously from the reaction of the product of mercuric acetate dehydrogenation of octahydroindolizine with perchloric acid and is reported[15] to have mp 218–219° dec while having an absorption band at 1689 cm^{-1} in its infrared spectrum. These results prove that the major product (**35**) from oxygenation of **34** is 1-benzoyloctahydro-5H-azonin-5-one. The minor ketonic product (**36**) was shown by its nmr spectrum (see Table I) to be the result of oxygenation of **34** at C-4. The important feature of this spectrum is the lack of a resonance signal which could be attributed to a methylene adjacent to both the nitrogen and the ketone group.

Experimental Section[16]

Biotransformation Process.—The culture used in these experiments was *Sporotrichum sulfurescens* V. Beyma (ATCC 7159). A medium of commercial dextrose (10 g/l.) and cornsteep liquor (20 g/l.) was prepared with tap water (to 1 l.) and adjusted to pH 5.0 with sodium hydroxide. Flasks of the sterilized medium were inoculated with spores of *S. sulfurescens*, which were grown on malt (wort) agar slants. The flasks were shaken for 48 hr (until heavy growth was apparent) and then used for seeding other flasks or tanks. The tanks used in this work were inoculated with five parts of the vegetative culture to 100 parts of fresh medium. On any scale the culture is aerated and agitated for the growth period. In stirred vessels, with good agitation, aeration with five to ten volumes of air per minute per 100 volumes of culture was satisfactory. The substance to be oxygenated was dissolved in dimethylformamide or acetone and was added after 24 hr of growth. The amount of solvent used for the substance was kept to a minimum (or less than one part solvent to 100 parts culture). The level of substrate was 0.2 to 0.3 g per liter. A conversion time of 72 hr was used. The products and residual substrate were removed from the "beer" by extraction with methylene chloride, using a volume of solvent one-fourth that of the "beer." The solvent was evaporated under reduced pressure.

1-Benzoyl-4-piperidinol (**2**).—The dry extract from the 10 l. bioconversion of 1-benzoylpiperidine (2.0 g) was dissolved in a minimum of methylene chloride and placed on a Florisil (200 g) column packed with Skellysolve B. Elution with 25% (v/v) acetone–Skellysolve B gave the product (0.407 g) as an oil: ν_{OH} 3420, $\nu_{C=O}$ 1620 cm^{-1} (neat).

Reaction with phenylisocyanate followed by chromatography on Florisil gave the phenylurethan, mp 184.5–186.5° (lit.[3] mp 184–185°).

1-Benzoyl-4-piperidone (**4**).—Jones reagent[2] was added until present in excess to a cold (ice bath) solution of 1-benzoyl-4-piperidinol (0.151 g, 0.000737 mol) in acetone. The excess oxidant was destroyed by addition of isopropyl alcohol and the mixture was allowed to evaporate to dryness. Water was added to the residue and the mixture was extracted with methylene chloride. After drying over sodium sulfate, the methylene chloride solution was concentrated to an oil: 0.137 g; $\nu_{C=O}$ 1715, 1625 cm^{-1} (neat).

Reaction with 2,4-dinitrophenylhydrazine gave the 2,4-dinitrophenylhydrazone (0.089 g). Recrystallization from ethanol gave the product, mp 196–198° (lit.[3] mp 196–198°).

1-*p*-Toluenesulfonylhexahydro-4H-azepin-4-one (**8**). **A. From the Fermentation Beer Extracts.**—The dry extract from the 2-l. bioconversion of 1-*p*-toluenesulfonylhexamethylenimine[17] (2.0 g) fermentation beer was chromatographed on Florisil by a gradient elution method. The residue was placed on a Florisil column with methylene chloride (75 ml). The column was eluted with Skellysolve B (4 l.) containing increasing proportions (from 0 to 30%) of acetone. Fractions of 105-ml volume were collected. Fractions 19–25, containing the product, were combined in acetone and oxidized with an excess of Jones reagent.[2] The resulting mixture was extracted with methylene chloride, and the extract was washed with water, dried over sodium sulfate, and concentrated by distillation of the solvent. Crystallization from ether gave 0.33 g of colorless product: mp 81°; $\nu_{C=O}$ 1700 cm^{-1} (in Nujol).

Anal. Calcd for $C_{13}H_{17}NO_3S$ (267.29): C, 58.41; H, 6.41; N, 5.24; S, 11.98. Found: C, 58.40; H, 6.47; N, 5.26; S, 12.24.

When the product was recrystallized from acetone–hexane a crystalline modification, mp 89–90°, was obtained. The infrared spectra of the two forms are identical when taken in chloroform solution. This latter form also is identical with 1-*p*-toluenesulfonylhexahydro-4H-azepin-4-one prepared synthetically as described below (part C).

B. From Ring Expansion of 1-*p*-Toluenesulfonyl-4-piperidone. Together with 6-*p*-Toluenesulfonyl-1-oxa-6-azaspiro[2.5]octane (**10**).—A solution of 1-*p*-toluenesulfonyl-4-piperidone[4] (4.41 g, 0.0174 mol) in methylene chloride (20 ml) and methanol (50 ml) was chilled in an ice–acetone bath and was treated with an ether solution (100 ml) containing an excess of diazomethane. The mixture was removed from the cold bath and left at room temperature for 20 min. The solvent was removed on a steam bath, applying reduced pressure during the latter stage. The treatment with diazomethane was repeated as just described. The residue was chromatographed on Florisil (200 g) by the gradient elution method, eluting with 8 l. of solvent. The solvent used was Skellysolve B plus an increasing proportion (0–30%) of acetone. Fractions of 225-ml volume were collected. By infrared spectroscopic examination, the fractions were pooled as follows: (A) fractions 9–11, (B) fractions 12–13, (C) fractions 14–16, (D) fraction 17, and (E) fractions 18–23.

Fraction A was recrystallized from acetone–Skellysolve B, giving 0.773 g (0.00289 mol, 16%) of 6-*p*-toluenesulfonyl-1-oxa-6-

(14) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, pp 132–160.

(15) N. J. Leonard, W. J. Middleton, P. D. Thomas, and D. Choudhury, *J. Org. Chem.*, **21**, 344 (1956).

(16) Melting points were determined on a calibrated Fisher-Johns hot stage and are corrected. Magnesium sulfate was used as the drying agent unless indicated otherwise. Infrared spectra were determined with either a Perkin-Elmer Infracord or Model 421 spectrophotometer. The nmr spectra were determined at 60 Mc with a Varian Model A-60 spectrometer, using tetramethylsilane as an internal standard.

(17) A. Muller and A. Sauerwald, *Monatsh. Chem.*, **48**, 727 (1927).

azaspiro[2.5]octane (10) as colorless crystals, mp 152–154°; no carbonyl bands were present in their spectrum in Nujol.

Anal. Calcd for $C_{13}H_{17}NO_3S$ (267.29): C, 58.41; H, 6.41; N, 5.24; S, 11.98. Found: C, 58.46; H, 6.22; N, 5.31; S; 12.19.

Fraction B was a mixture (1.10 g) of **10** and unchanged starting material. Fraction C was 0.97 g of unchanged starting material. Fraction D was a mixture of unchanged starting material and **8**. Fraction E contained **1-*p*-toluenesulfonylhexahydro-4H-azepin-4-one (8)** (1.36 g, 0.00509 mol, 29%), mp 89–90°. The infrared spectrum in Nujol is identical with that of the product obtained below.

C. From 1,4-Dioxa-8-azaspiro[4.6]undecane (14).—A solution of 1,4-dioxa-8-azaspiro[4.6]undecane (0.622 g, 0.00396 mol) in 16% aqueous sodium hydroxide was mixed with *p*-toluenesulfonyl chloride (0.786 g, 0.00413 mol). The mixture was shaken vigorously for several minutes, then warmed, and shaken more. The mixture was left at room temperature overnight and then was extracted with two 20-ml portions of ether. The ether solution was dried and concentrated to an oil. The oil was mixed with 2 *N* hydrochloric acid (10 ml) and acetone was added until solution was obtained. The acetone was removed on the steam bath, giving an oil, which was extracted with two 50-ml portions of ether. It was necessary to add some methylene chloride to the ether to prevent crystallization of the product. After drying the solution it was concentrated to an oil, which crystallized. Recrystallization from ether gave two crops of colorless needles, 0.506 g and 0.114 g (total 0.00232 mol, 58%), mp 91–92°. The mixture melting point with the sample obtained from diazomethane ring expansion of 1-*p*-toluenesulfonyl-4-piperidone was undepressed and their infrared spectra in Nujol are identical.

Isolation of 1-Benzoylhexahydro-4H-azepin-4-ol (11) and 1-Benzoylhexahydo-4H-azepin-4-one (12) from Bioconversion of 1-Benzoylhexamethylenimine.—The extract from the bioconversion of 1-benzoylhexamethylenimine[17,18] (2.0 g) with *Sporotrichum sulfurescens* was chromatographed on a Florisil (200 g) column packed with Skellysolve B. Elution with 25% (v/v) acetone–Skellysolve B gave unchanged starting material (0.25 g) and **1-benzoylhexahydro-4H-azepin-4-one (12)**: 0.25 g; $\nu_{C=O}$ 1700, 1625 cm^{-1} (on the oil). Elution with acetone gave a mixture of **12** and **1-benzoylhexahydro-4H-azepin-4-ol (11)**: ν_{OH} 3400, $\nu_{C=O}$ 1660 broad cm^{-1} (on the oil).

Oxidation of **11** with Jones reagent[2] gave an oil giving an infrared spectrum identical with that of **12**.

Oxidation and Isolation of Products from the Bioconversion of 1-Benzoylhexamethylenimine. 1-Benzoylhexahydro-4H-azepin-4-one (12).—The oily extract residue from the 125-l. bioconversion of 1-benzoylhexamethylenimine[17,18] (54.0 g, 0.266 mol) was dissolved in acetone (1 l.) and oxidized with an excess (cloudy mixture remained reddish brown) of Jones reagent.[2] The excess of oxidizing agent was consumed with isopropyl alcohol. The mixture was evaporated to dryness, the residue was diluted with water, and the mixture was extracted six times with methylene chloride. The methylene chloride solution was dried over sodium sulfate and concentrated to an oil. The oil was chromatographed on a Florisil column (2.5 kg) packed with Skellysolve B. The column was eluted with two fractions of Skellysolve B, three fractions of 10% (v/v) acetone–Skellysolve B, eleven fractions of 25% acetone–Skellysolve B, and two fractions of acetone. Fractions 11–17 contained one material as detected by thin layer chromatography and were pooled, giving 32.1 g (0.148 mol, 55%) of oily product. Attempted crystallization from acetone–Skellysolve B was unsuccessful; however, the oil partially crystallized after standing at room temperature for 2 months. A sample of the oil was distilled: bp 170–174° (0.3 mm) (a center cut of bp 173° was used for analysis); $\nu_{C=O}$ 1700, 1630, $\nu_{C=C}$ 1600, 1575, 1495, $\nu_{C_6H_5}$ 780, 730, 700 cm^{-1} (on the oil).

Anal. Calcd for $C_{13}H_{15}NO_2$ (217.26): C, 71.86; H, 6.96; N, 6.45. Found: C, 71.51; H, 7.25; N, 6.46.

1-Benzoylhexahydro-3H-azepin-3-one (12a).[6]—Chromatography of the oxidized products (200 g) obtained from a large-scale bioconversion of 1-benzoylhexamethylenimine on a Florisil (7 in. × 36 in.) column gave in addition to **12** (96.9 g), a second, crystalline ketonic product (12.57 g), mp 111.5–113°. Three recrystallizations from ethyl acetate–Skellysolve B gave 1-benzoylhexahydro-3H-azepin-3-one (12a) as colorless crystals: mp 113–114°; $\nu_{C=O}$ 1705, 1655, $\nu_{C=C}$ 1600, 1575, 1495, $\nu_{C_6H_5}$ 785, 750, 705 cm^{-1} (in Nujol).

Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.48; H, 6.75; N, 6.49.

8-Benzyl-1,4-dioxa-8-azaspiro[4.6]undecane (13) *via* the Ketal-Amide.—A mixture of 1-benzoylhexahydro-4H-azepin-4-one (11.957 g, 0.0551 mol) in benzene (200 ml) and *p*-toluenesulfonic acid hydrate (1.020 g, 0.00537 mol) in ethylene glycol (28 ml) was stirred and heated to the reflux temperature of benzene for 24 hr. The condensate was passed through a calcium carbide trap to remove water. Pyridine (3 ml) was added at the end of the reflux period and the mixture was cooled. The mixture was extracted with 5% aqueous sodium bicarbonate (100 ml) and with two 100-ml portions of water. The benzene layer was dried and concentrated under reduced pressure to a brownish yellow oil, $\nu_{C=O}$ 1630 cm^{-1} (on the oil).

After the above oil failed to crystallize, it was dissolved in ether (75 ml) and added to a mixture of lithium aluminum hydride (2.0 g) and ether (200 ml). The mixture was stirred and heated to reflux for 3 hr, stirred at room temperature over a weekend, and again heated to reflux for 2 hr before the excess lithium aluminum hydride was decomposed by the addition of ethyl acetate and water. The solids were removed by filtration and were washed with ether. The combined pale yellow ether solutions were dried and concentrated to a yellow oil. Simple distillation of the oil gave the product (9.696 g, 0.0392 mol, 71%) as a pale yellow oil: bp 120–121° (0.13 mm); $n^{25}D$ 1.5312; $\nu_{C=C}$ 1600, 1580, 1490, $\nu_{C_6H_5}$ 730, 695 cm^{-1} (neat).

Anal. Calcd for $C_{16}H_{21}NO_2$ (247.33): C, 72.84; H, 8.56; N, 5.66. Found: C, 73.22; H, 8.98; N, 6.11.

1,4-Dioxa-8-azaspiro[4.6]undecane (14).—A solution of 8-benzyl-1,4-dioxa-8-azaspiro[4.6]undecane (8.692 g, 0.0352 mol) in methanol (130 ml) was shaken with hydrogen and 5% palladium-on-carbon (2.50 g) in a Parr apparatus until the uptake of hydrogen ceased. The catalyst was removed by filtration and washed with methanol. The combined methanol solution was concentrated under reduced pressure to an oil. Simple distillation of the oil in a semimicro apparatus gave the product (5.047 g, 0.0321 mol, 91%) as a colorless oil: bp 58–60° (0.05 mm); $n^{25}D$ 1.4885; ν_{NH} 3330 cm^{-1} (neat).

Anal. Calcd for $C_8H_{15}NO_2$ (157.21): C, 61.12; H, 9.62; N, 8.91. Found: C, 61.17; H, 9.86; N, 8.85.

1-Benzoylhexahydro-5(2H)-azocinol (16) from the Bioconversion of 1-Benzoylheptamethylenimine.—The dry extract from the 125 l. of bioconversion of 1-benzoylheptamethylenimine[19] (25.0 g) was dissolved in a minimum of methylene chloride and placed on a Florisil column (2.5 kg) packed with Skellysolve B. Fractions (2 l.) were collected, beginning by elution with one fraction of Skellysolve B, followed by five fractions of 10% (v/v) acetone–Skellysolve B, six fractions of 25% acetone–Skellysolve B, nine fractions of 50% acetone–Skellysolve B, and four fractions of acetone. Fractions 11–13 (6.6 g) consisted of an oil: ν_{OH} 3450, $\nu_{C=O}$ 1710, 1650 cm^{-1} (on the oil). Fractions 15–18 (12.4 g) consisted of oily crystals: ν_{OH} 3460, $\nu_{C=O}$ 1710, 1625 cm^{-1} (on the oil). Crystals (1.5 g), mp 118–120°, were obtained from fraction 16 by washing with acetone. Two recrystallizations from acetone–Skellysolve B gave colorless crystals: mp 119–120°; ν_{OH} 3430, $\nu_{C=O}$ 1610, $\nu_{C=C}$ 1560, 1500, $\nu_{C_6H_5}$ 796, 737, 707 cm^{-1} (in Nujol).

Anal. Calcd for $C_{14}H_{19}NO_2$ (233.30): C, 72.07; H, 8.21; N, 6.00. Found: C, 71.98; H, 8.41; N, 5.84.

Oxidation and Isolation of the Products from Bioconversion of 1-Benzoylheptmethylenimine. 1-Benzoylhexahydro-4(1H)-azocinone (19) and 1-Benzoylhexahydro-5(2H)-azocinone (18).—The dry extract from the 125 l. bioconversion of 1-benzoylheptamethylenimine[19] (23.0 g) was dissolved in acetone (750 ml) and oxidized with Jones reagent as described above for **12**. The oily solid product was combined with crude ketone (7.2 g) from a previous run and was dissolved in methylene chloride (100 ml) and placed on a Florisil column (2.5 kg) packed with Skellysolve B. Fractions (2 l.) were collected, beginning by elution with two fractions of Skellysolve B, followed by three fractions of 10% (v/v) acetone–Skellysolve B, ten fractions of 25% acetone–Skellysolve B, and five fractions of acetone. Fractions 9, 10, and 11 contained 4.75 g of a brownish yellow

(18) (a) A. Muller, *Chem. Ber.*, **61**, 568 (1928). (b) G. S. Kolesnikov, T. V. Smirnova, L. I. Mizrakh, N. N. Mikhailovskaya, and L. I. Shcherbo, *Zh. Obshch. Khim.*, **27**, 3005 (1957); *J. Gen. Chem. USSR*, **27**, 3034 (1957).

(19) (a) R. Takamoto, *Yakugaku Zasshi*, **48**, 686 (1928); *Chem. Abstr.*, **23**, 387 (1929). (b) A. Muller, E. Srepel, E. Funder-Fritzsche, and F. Dicher, *Monatsh. Chem.*, **83**, 386 (1952).

crystalline material. Following decolorization with activated charcoal from an acetone solution, crystallization occurred from methylene chloride–Skellysolve B in the freezer. Colorless, slightly sticky crystals were obtained, mp 59–62°. Two recrystallizations from cold methylene chloride–Skellysolve B gave colorless crystals of **1-benzoylhexahydro-4(1H)-azocinone** (19): mp 64–65°; $\nu_{C=O}$ 1700 ms, 1640 s, $\nu_{C_6H_5}$ 792 m, 754 mw, 716 m cm^{-1} (in Nujol).

Anal. Calcd for $C_{14}H_{17}NO_2$ (231.28): 72.70; H, 7.41; N, 6.06. Found: C, 72.75; H, 7.21; N, 6.39.

Fractions 15 through 18 gave 14.50 g of brownish oily crystals. Decolorization with activated charcoal and crystallization from acetone–Skellysolve B gave **1-benzoylhexahydro-5(2H)-azocinone** (18) as colorless crystals: mp 124–126°; $\nu_{C=O}$ 1685 ms, 1630 s, $\nu_{C_6H_5}$ 796 m, 748 m, 718 cm^{-1} (in Nujol).

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.63; H, 7.59; N, 6.31.

1-Benzoylhexahydro-5(2H)-azocinone (18) from 1-Benzoylhexahydro-5(2H)-azocinol.—A solution of 1-benzoylhexahydro-5(2H)-azocinol (1.163 g, 0.00500 mol) in acetone was oxidized with Jones reagent[2] as described above except that the acetone solution of the product was filtered and concentrated. Addition of Skellysolve B resulted in crystallization of the product. Colorless crystals (0.594 g, 0.00257 mol, 51%) were collected, mp 126–129°. There was no depression in the mixture melting point with the sample obtained from the oxidized bioconversion products and their infrared spectra in Nujol are identical.

9-Benzoyl-1,4-dioxa-9-azaspiro[4.7]dodecane (20).—A mixture of 1-benzoylhexahydro-5(2H)-azocinone (39.883 g, 0.172 mol), *p*-toluenesulfonic acid hydrate (2.96 g, 0.0155 mol), ethylene glycol (75 ml, 83 g, 1.34 mol), and benzene (500 ml) was heated to reflux. The condensate was dried by passing it through a calcium carbide trap. The mixture was refluxed 30 hr. Pyridine (6 ml) was added to the cooled mixture; the benzene layer was extracted with three 100-ml 5% aqueous sodium bicarbonate and dried. Concentration of the benzene solution gave a viscous oil. An attempted distillation of this oil was stopped after the pot temperature reached 180° and the oil did not appear about to distil. As the cooled oil (42.95 g, 0.156 mol, 90%) was being transferred in ether, it crystallized, mp 72–74°. Two recrystallizations from ether–Skellysolve B gave colorless crystals: mp 72–73°; $\nu_{C=O}$ 1630 s cm^{-1} (in Nujol).

Anal. Calcd for $C_{16}H_{21}NO_3$ (275.34): C, 69.79; H, 7.69; N, 5.09. Found: C, 69.99; H, 7.84; N, 5.20.

9-Benzyl-1,4-dioxa-9-azaspiro[4.7]dodecane (21).—A solution of 9-benzoyl-1,4-dioxa-9-azaspiro[4.7]dodecane (40.9 g, 0.148 mol) in ether (300 ml) was added slowly to a stirred mixture of lithium aluminum hydride (6.0 g, 0.158 mol) and ether (200 ml). The resulting mixture was stirred at room temperature for 16 hr and at reflux temperature for 5 hr. The excess lithium aluminum hydride was decomposed with 1:1 acetone–water and with water. The inorganic solids were collected on a pad of Celite in a sintered glass funnel. The solids were washed three times with ether and the combined ether solution was dried and concentrated to an oil (38.26 g). Simiple distillation gave a colorless oil (33.72 g, 0.129 mol, 87%): bp 125–127° (0.3 mm); ν_{C-O} 1115 s cm^{-1} (on the liquid).

Anal. Calcd for $C_{16}H_{23}NO_2$ (261.35): C, 73.53; H, 8.87; N, 5.36. Found: C, 73.39; H, 8.31; N, 5.34.

1-Benzylhexahydro-5(2H)-azocinone (23). **A. From Hydrolysis of 9-Benzyl-1,4-dioxa-9-azaspiro[4.7]dodecane.**—A solution of 9-benzyl-1,4-dioxa-9-azspiro[4.7]dodecane (6.734 g, 0.0258 mol) in 0.75 *M* hydrochloric acid (40 ml) was stirred at room temperature for 3 hr. The solution was made alkaline with 1 *M* sodium hydroxide solution, causing an oil to precipitate. The oil was extracted with ether and the ether solution was dried and concentrated to a nearly colorless oil. Distillation of the oil in a semimicro still gave the following fractions: (1) colorless oil (1.00 ml), bp 110–112° (0.1 mm); (2) colorless oil, bp 112–115° (0.1 mm); and (3) colorless oil (1.15 ml), bp 115–117° (0.1 mm); total weight 6.293 g (0.0290 mol, 112%). A sample of fraction 2 was used for analysis: $\nu_{C=O}$ 1685 cm^{-1} (on the liquid), 1675 cm^{-1} (in chloroform solution).

Anal. Calcd for $C_{14}H_{19}NO$ (217.30): C, 77.38; H, 8.81; N, 6.45. Found: C, 77.21; H, 8.63; N, 6.49.

B. From Basification of 4-Benzylhexahydro-7a-hydroxy-1H-pyrrolizinium Chloride.—A solution of 4-benzoylhexahydro-7a-hydroxy-1H-pyrrolizinium chloride (0.146 g) in water (10 ml) was made alkaline (pH 10) with the addition of 1 *M* sodium hydroxide solution. The solution was extracted with three 15-ml portions of ether; the ether was dried and concentrated to an oil. The infrared spectrum of the oil is identical with that of the oil obtained by reduction of 9-benzoyl-1,4-dioxa-9-azaspiro[4.7]dodecane with lithium aluminum hydride.

4-Benzylhexahydro-7a-hydroxy-1H-pyrrolizinium Chloride (22a).—Addition of concentrated aqueous hydrochloric acid (4 ml) to a solution of 1-benzylhexahydro-5(2H)-azocinone (2.729 g, 0.0125 mol) in absolute ethanol (15 ml) caused an exothermic reaction. After 5 min ether was added to the solution until it became cloudy. Ethanol was added until a clear solution was obtained. Crystallization occurred slowly and gave 2.157 g (0.00850 mol, 68%) of colorless crystals, mp 205–212°. Three recrystallizations from ethanol–ether gave colorless crystals: mp 212–214°; ν_{OH}? 3000, 2760 w, 2720 w, 2620 w, 2560 w, $\nu_{C=C}$ 1565 w, 1495, 1490, $\nu_{C_6H_5}$ 735, 705 cm^{-1} (in Nujol).

Anal. Calcd for $C_{14}H_{20}NOCl$ (253.77): C, 66.26; H, 7.94; N, 5.52. Found: C, 66.13; H, 8.28; N, 5.60.

4-Benzylhexahydro-7a-acetoxy-1H-pyrrolizinium Chloride (24a).—A mixture of 4-benzylhexahydro-7a-hydroxy-1H-pyrrolizinium chloride (0.190 g, 0.000750 mol) and acetic anhydride (6 ml) was heated on a steam bath for 1.5 hr. Complete solution was obtained after 0.5 hr and the solution became yellow after 1 hr. Ether was added to the cooled solution causing precipitation of a crystalline solid. The solid was collected by filtration and was immediately placed in a desiccator when it was found to be hygroscopic. The infrared spectrum had bands at $\nu_{C=O}$ 1750 s, $\nu_{C_6H_5}$ 763 s, 708 s cm^{-1} (in Nujol).

4-Benzylhexahydro-7a-hydroxy-1H-pyrrolizinium Perchlorate (22b). **A. From 9-Benzyl-1,4-dioxa-9-azaspiro[4.7]dodecane.**—Aqueous (70%) perchloric acid (1 ml) was added dropwise to a solution of 9-benzyl-1,4-dioxa-9-azaspiro[4.7]dodecane (0.2 ml) in absolute ethanol (3 ml). A cloudy and warm solution was formed. Addition of ether gave a clear solution in which crystals began to form. Colorless needles were obtained, mp 144–145°. Two recrystallizations from ethanol–ether gave colorless crystals: mp 144–145°; ν_{OH} 3290 m, $\nu_{C_6H_5}$ 760 m, 715 ms, 705 ms cm^{-1} (in Nujol).

Anal. Calcd for $C_{14}H_{20}NO_5Cl$ (317.77): C, 52.91; H, 6.34; N, 4.41. Found: C, 52.78; H, 6.44; N, 4.62.

B. From 1-Benzylhexahydro-5(2H)-azocinone.—Aqueous (70%) perchloric acid (ten drops) was added to a solution of 1-benzylhexahydro-5(2H)-azocinone (0.298 g, 0.00137 mol) in absolute ethanol (3 ml). The soluion became warm and crystals began to form after several minutes. Ether (6 ml) was added and the product (0.347 g, 0.00109 mol, 80%), mp 142–144°, was collected after 1 hr. The infrared spectrum in Nujol is identical with that of the compound obtained from reaction of 9-benzyl-1,4-dioxa-9-azaspiro[4.7]dodecane with aqueous perchloric acid.

4-Benzylhexahydro-7a-acetoxy-1H-pyrrolizinium Perchlorate (24b).—A mixture of 4-benzylhexahydro-7a-hydroxy-1H-pyrrolizinium perchlorate (0.342 g, 0.00108 mol) and acetic anhydride (6 ml, 0.065 mol) was warmed on a steam bath for 0.5 hr, giving a light yellow solution. Addition of ether to the cooled solution gave an oily precipitate which rapidly crystallized (0.281 g, 0.000781 mol, 72%). Recrystallization from acetone–ether gave nearly colorless crystals, mp 190–195°. Two more recrystallizations from acetone–ether gave colorless crystals: mp 203–204°; $\nu_{C=O}$ 1750 s, $\nu_{C=C}$ 1580, 1495, $\nu_{C_6H_5}$ 760, 700 cm^{-1} (in Nujol).

Anal. Calcd for $C_{16}H_{22}NO_6Cl$ (359.81): C, 53.41; H, 6.16; N, 3.89. Found: C, 53.62; H, 6.18; N, 4.04.

1,4-Dioxa-9-azaspiro[4.7]dodecane (25).—A solution of 9-benzyl-1,4-dioxa-9-azaspiro[4.7]dodecane (24.642 g, 0.0945 mol) in absolute ethanol (150 ml) was shaken with 5% palladium on carbon (5.88 g) and hydrogen in a Parr hydrogenation apparatus. After 30 min the hydrogen uptake had stopped and totaled 28 lb (calculated, 27.4 lb). The catalyst was removed by a first filtration through Celite on a coarse porosity sintered-glass funnel and then by filtration through a medium porosity sintered-glass funnel. The catalyst was washed twice in each case with ethanol. The ethanol was removed by distillation through a 30-cm Vigreux column. The residual oil was purified by a simple distillation which gave a colorless oil (14.447 g, 0.0844 mol, 89%): bp 70–75° (0.2 mm); $n^{25}D$ 1.4835; ν_{NH} 3360 cm^{-1} (on the oil).

Anal. Calcd for $C_9H_{17}NO_2$ (171.23): C, 63.13; H, 10.00; N, 8.18. Found: C, 63.31; H, 10.02; N, 8.17.

The oil gives a white solid when left in contact with the atmosphere, presumably from reaction with carbon dioxide.

1,2,3,5,6,7-Hexahydropyrrolizinium Perchlorate (26).—Aqueous 70% perchloric acid (3 ml) was added to a solution of 1,4-dioxa-9-azaspiro[4.7]dodecane (1.070 g, 0.00625 mol) in ethanol (5 ml). The solution became hot. After cooling, ether was added, causing formation of colorless crystals (1.032 g, 0.00493 mol, 78%). Recrystallization from ethanol gave colorless crystals, mp 239–241° dec. A second recrystallization gave colorless plates: mp 238–240° slight dec; $\nu_{C=N^+}$ 1690 s cm^{-1} (in Nujol).

Anal. Calcd for $C_7H_{12}NO_4Cl$ (209.64): C, 40.10; H, 5.77; N, 6.68. Found: C, 40.23; H, 5.82; N, 6.87.

Hexahydro-1H-pyrrolizine Picrate (28).—A mixture of 1,2,3,-5,6,7-hexahydropyrrolizinium perchlorate (0.353 g, 0.00168 mol) and sodium borohydride (0.9 g) in absolute ethanol was heated on a steam bath for 3 hr. Water (10 ml) and 1 *M* aqueous sodium hydroxide solution (20 ml) were added and the mixture was filtered. The filtrate was extracted with three 50-ml portions of ether; the ether was dried and concentrated to a small quantity of oil. The oil was dissolved in ethanol (5 ml) and ethanolic picric acid (3–5 ml) was added in small portions. The solution became dark red in color. Cooling in the freezer gave dark red crystals, mp 145–160°, with some crystals remaining to 225°. Recrystallization gave olive-yellow crystals, mp 260–263° dec (lit.[13] mp 260–262° dec).

8-Benzoyl-1,4-dioxa-8-azaspiro[4.7]dodecane (29).—A mixture of 1-benzoylhexahydro-4(1H)-azocinone (16.487 g, 0.0712 mol), *p*-toluenesulfonic acid hydrate (1.35 g, 0.00710 mol), ethylene glycol (25 ml), and benzene (200 ml) was heated to reflux for 24 hr. The condensate was passed through a calcium carbide drying trap during this time. Pyridine (2 ml) was added and the mixture was cooled. The mixture was extracted with aqueous sodium bicarbonate solution and with three 100-ml portions of water. The benzene layer was dried and concentrated to a viscous oil which did not crystallize. This oil was used in the next reaction without further purification.

8-Benzyl-1,4-dioxa-8-azaspiro[4.7]dodecane (30).—The oily 8-benzoyl-1,4-dioxa-8-azaspiro[4.7]dodecane from the preceding reaction was partially dissolved in ether (2 l.) and slowly added to a stirred mixture of lithium aluminum hydride (3.0 g, 0.0790 mole) and ether (200 ml). The excess ether was allowed to boil off. The remaining oil, insoluble in ether, was dissolved in tetrahydrofuran and added to the reaction mixture. The mixture was stirred and refluxed 7 hr and then kept at room temperature overnight. The excess lithium aluminum hydride was destroyed by addition of ethyl acetate and water. The inorganic solids were removed by filtration through Celite and were washed with ether. The combined ether filtrates were dried and concentrated to a yellow oil. Distillation of the oil gave 8-benzyl-1,4-dioxa-8-azaspiro[4.7]dodecane (**30**) (5.700 g, 0.0218 mol, 30%) as a colorless oil: bp 140–150° (0.2 mm); $n^{26}D$ 1.5284; $\nu_{C=C}$ 1600 mw, 1580 w, 1490 s, $\nu_{C_6H_5}$ 725 s, 695 s cm^{-1} (on the oil).

Anal. Calcd for $C_{16}H_{23}NO_2$ (261.35): C, 73.53; H, 8.87; N, 5.36. Found: C, 73.33; H, 8.91; N, 5.14.

Distillation also gave a light yellow oil (4.768 g), bp 190–205° (0.2 mm), obtained by heating the distillation flask with a small flame.

1-Benzylhexahydro-4(1H)-azocinone Perchlorate (31).—Aqueous 70% perchloric acid (0.5 ml) was added to a solution of 8-benzyl-1,4-dioxa-8-azaspiro[4.7]dodecane (0.357 g, 0.00137 mol) in absolute ethanol (2 ml). Ether was added to the point of cloudiness and the mixture was allowed to cool. Oil drops precipitated and crystallized after cooling in the freezer, giving colorless crystals (0.301 g, 0.000949 mol, 69%), mp 103–142° dec. Three recrystallizations from ethanol–ether gave colorless crystals: mp 151–153°; ν_{NH^+} 3080 ms, $\nu_{C=O}$ 1700 s, $\nu_{C=C}$ 1495 m, $\nu_{C_6H_5}$ 745 ms, 700 ms cm^{-1} (in Nujol).

Anal. Calcd for $C_{14}H_{20}NO_5Cl$ (317.77): C, 52.91; H, 6.34; N, 4.41. Found: C, 52.91; H, 6.58; N, 4.17.

1,4-Dioxa-8-azaspiro[4.7]dodecane (32).—A solution of 8-benzyl-1,4-dioxo-8-azaspiro[4.7]dodecane (5.152 g, 0.0197 mol) in absolute ethanol (75 ml) was shaken with 5% palladium on carbon (1.5 g) and hydrogen in a Parr apparatus for 3 hr. Hydrogen uptake was complete after 1 hr. The catalyst was removed by filtration and was washed twice with methanol. The excess solvent was removed by distillation through a 30-cm Vigreux column under reduced pressure. Distillation of the residual oil gave a colorless oil (2.771 g, 0.0162 mol, 82%): bp 68–69° (0.1 mm); $n^{26}D$ 1.4853; ν_{NH} 3360 mw cm^{-1} (on the oil).

Anal. Calcd for $C_9H_{17}NO_2$ (171.23): C, 63.13; H, 10.00; N, 8.18. Found: C, 63.16; H, 10.04; N, 7.88.

Hexahydro-4(1H)-azocinone Perchlorate (33).—Aqueous (70%) perchloric acid (1.0 ml) was added to a solution of 1,4-dioxa-8-azaspiro[4.7]dodecane (0.269 g, 0.00157 mol) in absolute ethanol (2 ml). The reaction was exothermic. After the solution cooled, ether was added and the solution placed in the freezer. Crystals formed overnight and were recrystallized from ethanol–ether, giving colorless crystals: mp 55, 75–85°; $\nu_{OH,NH}$ 3600 m, 3150 ms, $\nu_{C=O}$ 1695 s cm^{-1} in Nujol. The crystals were dissolved in ethanol and the solution was refluxed for 45 min. Addition of ether gave colorless crystals, mp 87–89°. Recrystallization from ethanol–ether gave colorless flakes: mp 87–89°; ν_{NH} 3150 s, $\nu_{C=O}$ 1695 s cm^{-1} (in Nujol).

Anal. Calcd for $C_7H_{14}NO_5Cl$ (227.65): C, 36.93; H, 6.20; N, 6.15. Found: C, 37.04; H, 6.28; N, 6.40.

Oxidation and Isolation of the Products from the Bioconversion of 1-Benzoyloctamethylenimine. 1-Benzoyloctahydro-4H-azonin-4-one (36) and 1-Benzoyloctahydro-5H-azonin-5-one (35).—The dry extract from the bioconversion of 1-benzoyloctamethyleneimine (25.0 g) was dissolved in acetone (500 ml) and oxidized with excess Jones reagent[2] as described previously. The residual oily material was dissolved in methylene chloride (100 ml) and the solution was placed on a column of Florisil (2.5 kg) packed in Skellysolve B. The following 2-l. fractions were collected: 2 of Skellysolve B, 10 of 10% (v/v) acetone in Skellysolve B, 8 of 20% acetone in Skellysolve B, 5 of 50% acetone-Skellysolve B, and 3 of acetone. Fractions 15 through 18 gave 4.80 g of **1-benzoyloctahydro-4H-azonin-4-one (36)** as a yellow crystalline material and fractions 20 through 23 gave 11.62 g of **1-benzoyloctahydro-5H-azonin-5-one (35)** as a yellowish crystalline solid. Removal of color from these products with activated charcoal renders them sufficiently pure for most uses; however, for preparation of analytical samples, portions were rechromatographed on Florisil. A sample (1.60 g) of the less polar material was dissolved in methylene chloride and placed on a column of Florisil (80 g) packed with Skellysolve B. Elution with 10% (v/v) acetone in Skellysolve B gave colorless crystals. Two recrystallizations from cold methylene chloride–Skellysolve B gave **36** as colorless plates: mp 87–88°; $\nu_{C=O}$ 1700 ms, 1625 s, $\nu_{C_6H_5}$ 787 ms, 744, ms, 705 ms cm^{-1} (in Nujol).

Anal. Calcd for $C_{15}H_{19}NO_2$ (245.31): C, 73.44; H, 7.81; N, 5.71. Found: C, 73.30; H, 8.03; N, 5.80.

A sample (11.40 g) of the more polar material dissolved in methylene chloride was placed on a column of Florisil (600 g) packed with Skellysolve B. Elution with 25% (v/v) acetone in Skellysolve B gave colorless crystals. Recrystallization from acetone–Skellysolve B was achieved by placing the solution in the freezer and gave colorless crystals, mp 69–71°. A final recrystallization from acetone–Skellysolve B gave **35** as colorless crystals: mp 70–72°; $\nu_{C=O}$ 1700 ms, 1625 s, ν 800 m, 748 ms, 717 s cm^{-1} (in Nujol).

Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.54; H, 7.72; N, 5.94.

9-Benzoyl-1,4-dioxa-9-azaspiro[4.8]tridecane (37).—A solution of 1-benzoyloctahydro-5H-azonin-5-one (18.819 g, 0.0768 mol) and *p*-toluenesulfonic acid hydrate (1.46 g) in benzene (200 ml) was stirred with ethylene glycol (30 ml). The mixture was heated to the reflux temperature of benzene for 22 hr and the condensate was passed through a calcium carbide drying trap. Pyridine (3 ml) was added at the end of the reflux period; the mixture was cooled and then extracted with 5% aqueous sodium bicarbonate (100 ml) and with two 100-ml portions of water. The benzene layer was dried and was concentrated under reduced pressure, giving a viscous yellow oil. The infrared spectrum of the oil showed the presence of a carbonyl function (1730 w cm^{-1}) and so the oil was again dissolved in benzene (200 ml) and mixed with ethylene glycol (30 ml) and *p*-toluenesulfonic acid hydrate (3 g). The mixture was heated to reflux for 24 hr after which the work-up used above was repeated. The oil product retained the unusual carbonyl absorption in its infrared spectrum. A sample of the oil kept from the first work-up partially crystallized and when the oil product was mixed with these crystals, crystallization occurred. Recrystallization from ether–Skellysolve B gave two crops (13.682 g, 0.0473 mol, 61%) of light yellow crystals, mp 90–95°. Recrystallization from ether–Skellysolve B gave crystals, mp 98–100°. A final recrystallization preceded by decolorization with activated charcoal gave colorless needles: mp 99–101°; $\nu_{C=O}$ 1630 s, $\nu_{C_6H_5}$ 798 m, 737 m, 704 ms cm^{-1} (in Nujol).

Anal. Calcd for $C_{17}H_{23}NO_3$ (289.36): C, 70.56; H, 8.01; N, 4.84. Found: C, 70.50; H, 8.08; N, 5.16.

9-Benzyl-1,4-dioxa-9-azaspiro[4.8]tridecane (38).—A solution of 9-benzoyl-1,4-dioxa-9-azaspiro[4.8]tridecane (13.331 g, 0.0462 mole in ether (250 ml) was dribbled into a mixture of lithium aluminum hydride (2.0 g) in ether (100 ml). The mixture was stirred at room temperature for 16 hr and at reflux temperature for 4 hr. The excess hydride was decomposed by the cautious addition of water. The inorganic solids were removed by filtration and washed with ether. The combined ether solution was dried and concentrated to an oil. A simple distillation of the oil gave the product (10.779 g, 0.0392 mol, 85%) as a colorless oil: bp 145–147° (1.5 mm); $n^{26}D$ 1.5302; $\nu_{C=C}$ 1600 w, 1498 m, $\nu_{C_6H_5}$ 750 m, 715 ms, 701 ms cm^{-1} (on the oil).

Anal. Calcd for $C_{17}H_{25}NO_2$ (275.38): C, 74.14; H, 9.15; N, 5.09. Found: C, 74.77; H, 9.66; N, 5.04.

The oil crystallized when kept overnight in the refrigerator, mp 44–46°.

4-Benzyloctahydro-8a-hydroxyindolizinium Perchlorate (39).—Aqueous (70%) perchloric acid (2 ml) was added to a solution of 9-benzyl-1,4-dioxa-9-azaspiro[4.8]tridecane (0.491 g, 0.00178 mole) in ethanol (3 ml). The solution became hot After cooling, ether was added to the point of forming two phases. Crystals formed slowly. The mixture was cooled in the freezer. Colorless crystals (0.456 g, 0.00137 mol, 73%) were obtained, mp 143–145°. Two recrystallizations from ethanol–ether gave colorless crystals: mp 152–153°; ν_{OH} 3420 s, $\nu_{C_6H_5}$ 768 s, 710 s cm^{-1} (in Nujol).

Anal. Calcd for $C_{15}H_{22}NO_5Cl$ (331.80): C, 54.29; H, 6.68; N, 4.22. Found: C, 54.16; H, 6.85; N, 4.48.

1,4-Dioxa-9-azaspiro[4.8]tridecane (40).—A solution of 9-benzyl-1,4-dioxa-9-azaspiro[4.8]tridecane (9.451 g, 0.0344 mol) in methanol (150 ml) was shaken with 5% palladium on carbon (2.5 g) in hydrogen for 45 min at which time uptake of hydrogen appeared complete. The catalyst was removed by filtration and the colorless filtrate was stored overnight in the refrigerator. The solution, now yellow, was concentrated under reduced pressure. The yellow oil product crystallized as it cooled. The solid was dissolved in ether, decolorized with activated charcoal, filtered, and crystallized by addition of Skellysolve B to the ether and by cooling in the freezer. Colorless crystals (4.649 g, 0.0251 mole, 73%) were obtained, mp 55–57°. Recrystallization from ether–Skellysolve B gave colorless, chunky crystals: mp 55–57°; ν_{NH} 3400 mw cm^{-1} (in Nujol).

Anal. Calcd for $C_{10}H_{19}NO_2$ (185.26): C, 64.83; H, 10.34; N, 7.56. Found: C, 64.66; H, 10.40; N, 7.62.

2,3,5,6,7,8-Hexahydro-1H-indolizinium Perchlorate (41).—Aqueous (70%) perchloric acid (2 ml) was added to a solution of 1,4-dioxa-9-azaspiro[4.8]tridecane (0.483 g, 0.00261 mol) in absolute ethanol. The solution became hot and, after cooling, ether was added to the point of separation of two phases. The solution was placed in the freezer and crystals slowly formed. Colorless crystals (0.350 g, 0.00157 mol, 60%) were collected by filtration, mp 212–220°. Three recrystallizations from ethanol–ether gave colorless flakes: mp 227–228° dec (lit.[15] mp 218–219° dec); $\nu_{C=N^+}$ 1690 cm^{-1} (in Nujol) [lit.[16] 1689 cm^{-1} (in Nujol)].

Registry No.—**8,** 16803-02-4; **10,** 16803-03-5; **12,** 15923-40-7; **12a,** 16803-05-7; **13,** 16803-06-8; **14,** 16803-07-9; **16,** 16803-08-0; **18,** 16803-09-1; **19,** 16803-10-4; **20,** 16803-11-5; **21,** 16803-12-6; **22a,** 16853-06-8; **22b,** 16853-07-9; **23,** 16853-08-0; **24b,** 16853-09-1; **25,** 16803-13-7; **26,** 16853-10-4; **30,** 16803-14-8; **31,** 16803-15-9; **32,** 16853-11-5; **33,** 16803-16-0; **35,** 16803-17-1; **36,** 16803-18-2; **37,** 16803-19-3; **38,** 16803-20-6; **39,** 16853-12-6; **40,** 16803-21-7; **41,** 14594-57-1.

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The Microbiological Oxygenation of Some Azabicycloalkanes

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The microbiological oxygenation of 3-benzoyl-3-azabicyclo[3.3.1]nonane (**1**) and 3-benzoyl-3-azabicyclo[3.2.2]nonane (**11**) with *Sporotrichum sulfurescens* has been shown to give 3-benzoyl-*endo*-3-azabicyclo[3.3.1]nonan-6-ol (**2**) in the first case and a mixture of 3-benzoyl-*endo*-3-azabicyclo[3.2.2]nonan-6-ol (**12**) and 3-benzoyl-3-azabicyclo[3.2.2]nonan-6-one (**13**) in the second case. Reduction of ketone **13** with sodium borohydride gave 3-benzoyl-*exo*-3-azabicyclo[3.2.2]nonan-6-ol (**14**), which underwent acyl migration in acidic solution. The major and minor hydroxylated products obtained from microbiological oxygenation of 2-benzoyl-2-azabicyclo[2.2.2]octane (**23**) were assigned *endo*-5-ol (**24**) and *endo*-6-ol (**25**) structures, respectively, based on the patterns of oxygenation observed in the above and in related molecules.

The oxygenation of saturated organic molecules by microorganisms is of particular importance because of the introduction of functionality at positions inaccessable to many methods of organic chemistry. Examples of interest are the numerous oxygenations of the steroid nucleus by a variety of microorganisms.[1] Recent extensions include oxygenations of macrocyclic alcohols[2] and the amide derivatives of cyclic amines[3] by the microorganism, *Sporotrichum sulfurescens*. As yet there is considerable uncertainty as to the position of oxidative attack by microorganisms. A proposal that such attack by *S. sulfurescens* will occur at a saturated carbon approximately 5.5 Å from an electron-rich center, such as a ketone or an amide carbonyl oxygen,[2,3] provides a working hypothesis with which to consider this question. Continued expansion of the varieties of molecules submitted to microbiological oxygenation aids in testing this proposal as well as in determining the limits of the reaction with respect to chemical structure. The successful microbial oxygenation of the amides of azacycloalkanes[4] suggested the further extension to the amides of azabicycloalkanes. The oxygenation of 3-benzoyl-3-azabicyclo[3.3.1]nonane (**1**), 3-benzoyl-3-azabicyclo[3.2.2]nonane (**11**), and 2-benzoyl-2-azabicyclo[2.2.2]octane

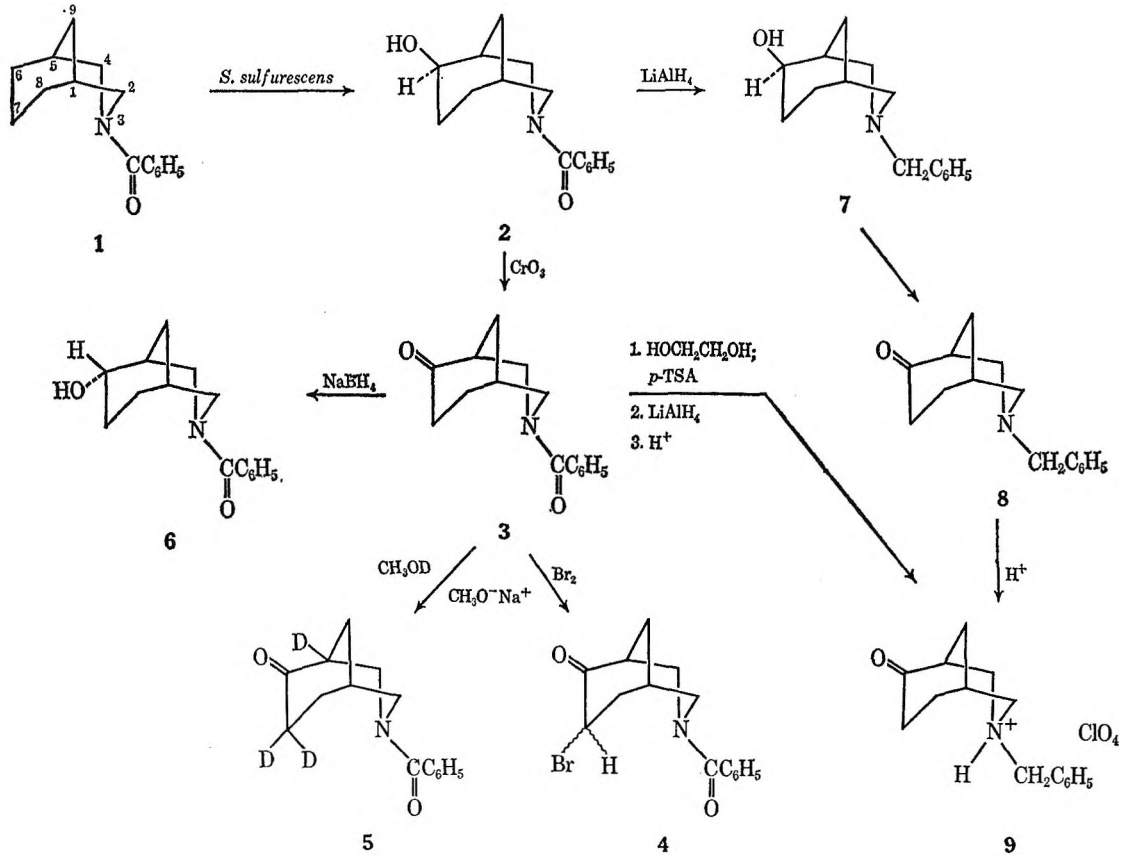
(1) *Cf.* S. H. Eppstein, P. D. Meister, H. C. Murray, and D. H. Peterson, "Vitamins and Hormones," Vol. XIV, Academic Press Inc., New York, N. Y., 1956, pp 359–432.

(2) G. S. Fonken, M. E. Herr, H. C. Murray, and L. M. Reineke, *J. Amer. Chem. Soc.*, **89**, 672 (1967).

(3) G. S. Fonken, M. E. Herr, H. C. Murray, and L. M. Reineke, *J. Org. Chem.*, **33**, 3182 (1968).

(4) R. A. Johnson, M. E. Herr, H. C. Murray, and G. S. Fonken, *ibid.*, **33**, 3187 (1968).

SCHEME I



(23) by *S. sulfurescens* and the structure determination of the products provide the subjects for this paper.

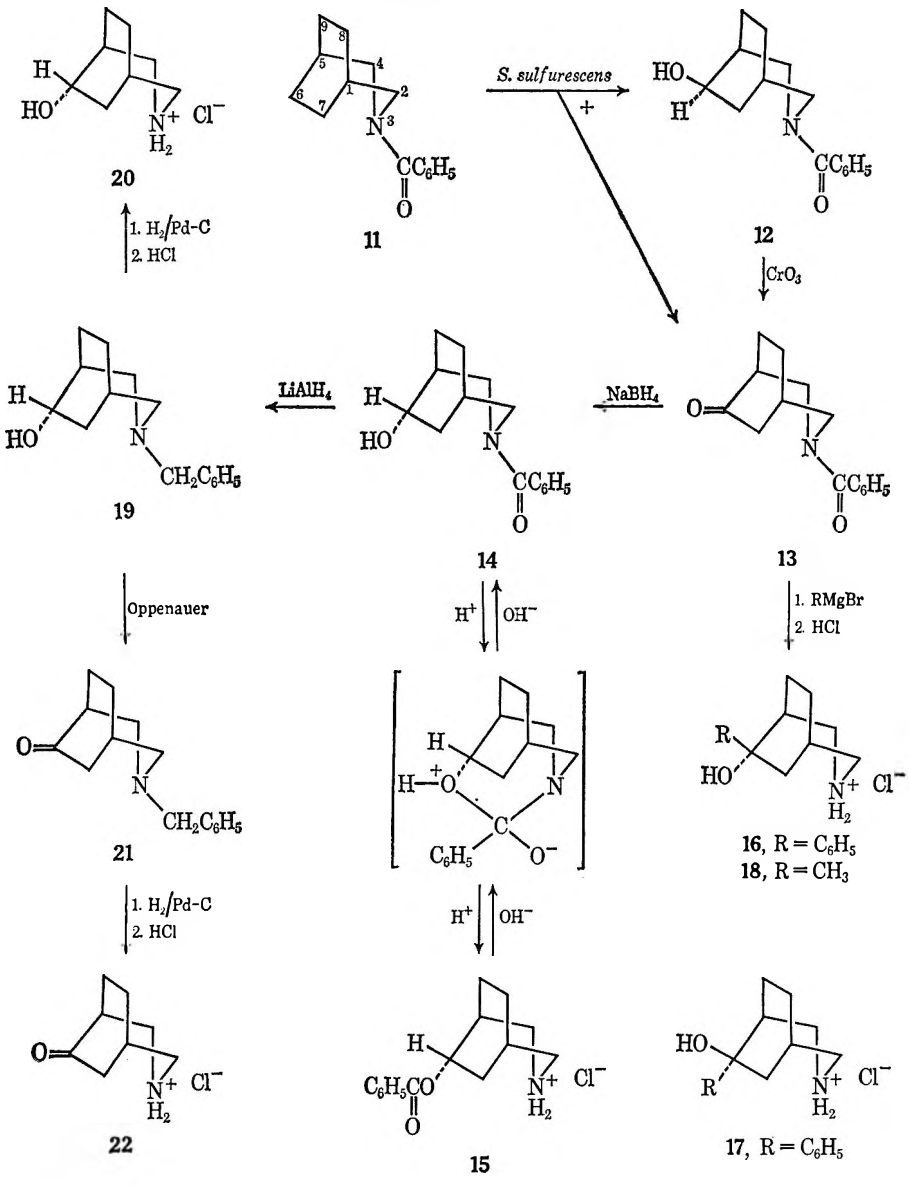
3-Benzoyl-3-azabicyclo[3.3.1]nonane (1).—The bicyclic amide **1** served as an excellent substrate, giving a single monohydroxylated product (**2**) in yields of 60–70% when oxygenated with *S. sulfurescens*. Dissimilation of the substrate (**1**) was rapid and was successful at a substrate level of 0.5 g/l. of medium (which may be compared with a level of 0.2 g/l. with the other above substrates). There are five chemically different saturated carbon atoms[5] in the substrate molecule (**1**) at which hydroxylation could occur. These are C-1 (equivalent[5] to C-5), C-2 (equivalent to C-4), C-6 (equivalent to C-8), C-7, and C-9. Formation of a ketone (**3**) (Scheme I) when **2** is oxidized with chromic acid eliminated the possible sites at C-1 and C-2 since a hydroxyl group at the former position would be tertiary and not oxidizable and at the latter position would give an imide rather than a ketone if oxidized. An imide would have characteristic reactions and spectral properties, which were not observed. Position C-9 may be eliminated by the observation that ketone **3** is rapidly brominated at room temperature in chloroform solution, giving a monobromo ketone (**4**). A ketone at C-9 in **3** would be flanked by two bridgehead carbons and bromination under such mild conditions is improbable. This conclusion was supported, and the position of the oxygen was disclosed by a deuterium exchange experiment. Exchange of the protons α to the carbonyl in **3** was catalyzed by sodium methoxide in deuteriomethanol. The resulting ketone (**5**) showed an increase of three mass units to a molecular weight of 246 as determined by mass spectrometry. Introduction of three deuterium atoms was nearly complete. A small amount of material of mass 245 was detected, which could result from incomplete exchange at a bridgehead position owing to a slower rate of exchange. No peak at 247 mass units other than that due to the natural isotopic distribution was observed. Only a ketone at the 6 position in molecule **3** has three exchangable α protons. The nmr spectrum of **3** is consistent with this assignment in that it has a triplet (J = 6.0 cps) at δ 2.53 superimposed on a second broad signal. These signals correspond to three protons, which are those on the tertiary C-5 carbon and the secondary C-7 carbon atoms. It is concluded that compound **3** contains a ketone at the 6 position and that hydroxylation of bicyclic amide **1** has occurred at the 6 position. The hydroxylating enzyme does not appear to be stereoselective, since the product has an optical rotation of only $-1°$ at the sodium D line, indicating that the product is a *dl* pair.

The configuration of the hydroxyl group[6] in **2** was determined as follows. Examination of a Dreiding model of the ketone **3**, derived from **2**, predicts that axial hydride attack on the ketone carbonyl would be less hindered sterically than would be equatorial attack. The ketone **3** therefore was reduced with sodium borohydride. A single alcohol (**6**) was isolated from the reduction and was isomeric with alcohol **2**. The hydroxy group in **6** is predicted to be equatorial and so the hy-

(5) It should be realized that the chemically equivalent positions of the bicyclic rings are not stereochemically equivalent when approached by hydroxylating enzyme.

(6) In considering the configuration of the hydroxyl group, we assume that the bicyclic molecule will prefer to be in a chair–chair conformation. Support for this assumption may be found in R. Lygo, J. McKenna, and I. O. Sutherland, *Chem. Commun.*, 356 (1965). In this conformation an axial 6-hydroxyl group will be considered *endo* and an equatorial 6-hydroxyl group will be *exo*.

SCHEME II



droxyl group in **2**, whose isomeric relationship with **6** is due only to a different alcohol conformation, can be assigned the axial configuration. A second piece of evidence supporting this conclusion is found in the nmr spectrum of the amino alcohol **7**, obtained when amido alcohol **2** is reduced with lithium aluminum hydride. Of interest here is the signal of the single C-6 proton, which is shifted downfield to δ 3.98 by the C-6 hydroxyl group. The half-band width of this signal is 8 cps, characteristic of equatorial carbinol protons.[7] It is concluded that the hydroxyl group of product **2** has an axial configuration with respect to the six-membered ring on which it is found.

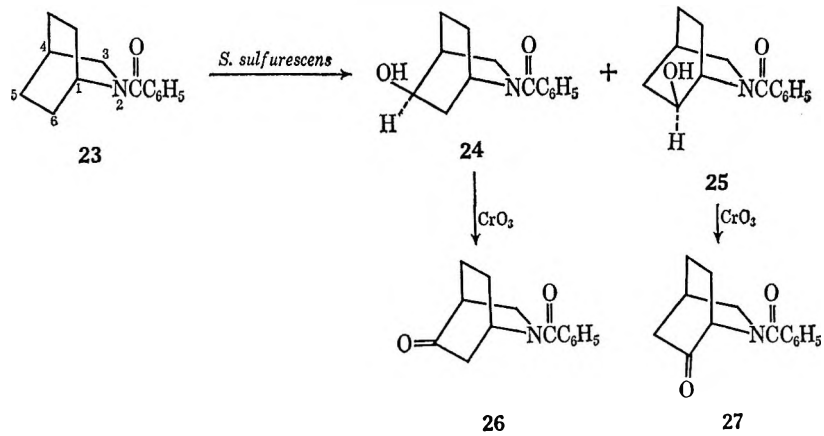
Of interest to us was the possibility of interaction between the nitrogen and either the oxygen or carbon at position 6. However, neither **2** nor **6** underwent acyl migration[8] in acidic media. Likewise, amino ketone **8**, obtained from **7** by oxidation or from **3** *via* the ketal and hydride reduction, did not exhibit transannular interactions. A keto amine salt (**9**) formed when **8** was allowed to react with acid.

(7) *Cf.* R. U. Lemieux, R. K. Kullnig, H. J. Bernstein, and W. G. Schneider, *J. Amer. Chem. Soc.*, **80**, 6098 (1958).
(8) G. Fodor and K. Nador, *J. Chem. Soc.*, 721 (1953).

3-Benzoyl-3-azabicyclo[3.2.2]nonane (11).—Two products were isolated when the bicyclic amide **11** was oxygenated with *S. sulfurenscens*. These were readily identified as an alcohol (**12**, 50%) and a ketone (**13**, 22%) and were found to be substituted at the same position when oxidation of the alcohol **12** gave ketone **13**. As in the previous series, formation of a ketone eliminates positions 1, 2, 4, and 5 of the bicyclo[3.2.2]-nonane ring as sites of oxygenation. The remaining positions are chemically equivalent[5] and therefore **12** and **13** are the 6-hydroxy and 6-keto derivatives, respectively. (See Scheme II.)

The configuration of the hydroxyl group of **12** may be *endo* or *exo* with respect to the six-membered ring and was determined as follows. Reduction of ketone **13** with sodium borohydride gave a crystalline alcohol (**14**), which was isomeric with the alcohol **12**. The individual alcohols were shown to be homogeneous by both thin layer and paper chromatography and, additionally, when in admixture, they were separated by the same chromatography systems used to determine their purity. When alcohol **14** was dissolved in a dilute solution of hydrochloric acid in tetrahydrofuran, the benzoyl group migrated from the nitrogen to the oxy-

SCHEME III



23 24 25 26 27

gen, giving the benzoate–amine hydrochloride **15** (see Scheme II) in high yield. The direction of migration was reversed by placing **15** in an alkaline solution. Analogous acyl migration reactions were first studied and discussed in detail by Fodor and coworkers.[8] In the present system migration from N to O requires that the hydroxyl group of **14** be *exo* with respect to the six-membered ring. Since **14** is isomeric with the microbiological oxygenation product **12** at the alcohol carbon, the configuration of the hydroxyl group in **12** must be *endo* with respect to the six-membered ring.

Formation of the *exo* alcohol (**14**) from reduction of the ketone must result from *endo* attack of the hydride on the carbonyl function. It may be suggested then that nucleophilic attack from the *endo* direction in general is less sterically hindered than from the *exo* direction. Examination of a Drieding model supports this idea. We have assigned structures to the products of Grignard addition to the ketone (**13**) on the basis of this reasoning. Addition of phenylmagnesium bromide to **13** gave two isomeric alcohol–amine salts. The product mixture (73% yield) was separated into a major product (**16**, 36%) and a minor product (**17**, 10%) by fractional crystallization. The phenyl group in alcohol **16** is assigned the *endo* configuration, while the phenyl group of **17** is assigned the *exo* configuration. Reaction of methyl magnesium bromide with ketone **13** gave a single alcohol–amine salt (**18**). The methyl group in **18** is assigned the *endo* configuration.

Several other reactions were carried out so that oxygenated derivatives of the unsubstituted 3-azabicyclo[3.2.2]nonane ring system could be obtained. Reduction of **14** with lithium aluminum hydride gave the amino alcohol **19**, characterized as the hydrochloride. Hydrogenolysis of the benzyl group of **19** over palladium-on-carbon catalyst proceeded readily, giving *exo*-3-azabicyclo[3.2.2]nonan-6-ol, which was characterized as the hydrochloride (**20**). Finally, Oppenauer oxidation of amino alcohol **19** gave amino ketone **21**. Hydrogenolysis of the benzyl group of **21** gave 3-azabicyclo[3.2.2]nonan-6-one, characterized as the hydrochloride (**22**).

2-Benzoyl-2-azabicyclo[2.2.2]octane (23).—Oxygenation of **23** with *S. sulfurescens* gave two alcohols, **24** (45%) and **25** (6%). Both alcohols were oxidizable with Jones reagent, giving two ketones **26** and **27**, respectively. Formation of two ketones in this manner identifies the positions of oxygenation as the 5 and 6 atoms of the bicyclic systems. Lack of ample substrate prevented complete chemical characterization of the products. However, we suggest that the alcohol (**24**) formed in higher yield is the 5-hydroxy compound (see Scheme III) since the distance between the amide carbonyl and the 5-carbon atom more nearly fits the ~5.5-Å spacing of the enzyme–substrate interaction referred to previously.[2] The position of the hydroxyl group in the minor product (**25**) will then be at the C-6 atom.

In a companion paper,[9] a number of stereochemical relationships observed in the patterns of substitution found in a variety of microbiological oxygenated products have been discussed. One set of observations suggested that the hydroxyl group and the electron-rich center of the substrate (the amide group in the present case) will be spatially oriented in opposite directions. It is therefore suggested that the hydroxyl groups in **24** and **25** will be oriented in an *endo* configuration with respect to the N-containing bridge, as shown in Scheme III.

Experimental Section[10]

Biotransformation Process.—The process used has been described previously,[4] the only exception being that substrate **1** could be used at a level of 0.5 g/l.

Isolation of the Product from the Bioconversion of 3-Benzoyl-3-azabicyclo[3.3.1]nonane (1). 3-Benzoyl-*endo*-3-azabicyclo[3.3.1]nonan-6-ol (2).—The oily methylene chloride extracts from the 125-l. bioconversion of 3-benzoyl-3-azabicyclo[3.3.1]-nonane (25 g, 0.109 mol) with *Sporotrichum sulfurescens* was chromatographed on Florisil (2.0 kg) packed with Skellysolve B. Elution with 25 and 50% (v/v) acetone–Skellysolve B gave crystalline material (19.645 g). Recrystallization from acetone preceded by decolorization with activated charcoal gave colorless crystals. From the several crops collected, a total of 16.894 g (0.0689 mol, 63%) of product was obtained, mp 137–141°. Three recrystallizations from acetone gave colorless crystals: mp 139–141°; $[\alpha]_D$ −1° (*c* 0.860, chloroform); ν_{OH} 3460, 3420 sh cm^{-1}; $\nu_{C=O}$, $_{C=C}$ 1610, 1575, 1525, 1495 cm^{-1}; $\nu_{C_6H_5}$ 785, 740, 705 cm^{-1} in Nujol.

Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.66; H, 7.96; N, 6.07.

In a similar experiment, the combined extracts from a 10-l. (5.0 g of substrate **1**) and a 125-l. (62.5 g of substrate) bioconver-

(9) R. A. Johnson, M. E. Herr, H. C. Murray, and G. S. Fonken, *J. Org. Chem.*, **33**, 3217 (1968).

(10) Melting points were determined on a calibrated Fisher-Johns hot stage and are corrected. Magnesium sulfate was used as the drying agent unless indicated otherwise. Infrared spectra were determined with either a Perkin-Elmer Infracord or Model 421 spectrophotometer. The nmr spectra were determined at 60 Mc with a Varian Model A-60 spectrometer, using tetramethylsilane as an internal standard in chloroform solution unless indicated otherwise. Mass spectra were determined on an Atlas CH14 instrument.

sion (total substrate 67.5 g, 0.293 mol) gave a total of 51.20 g (0.208 mol, 71%) of crystalline product, mp 140–143°.

3-Benzoyl-3-azabicyclo[3.3.1]nonan-6-one (3).—A solution of **2** (1.543 g, 6.30 mmol) in acetone (150 ml) was cooled on an ice bath and treated with an excess (1.8 ml) of Jones reagent.[11] After 30 min at room temperature, the excess oxidant was consumed with isopropyl alcohol. The solution was decanted, filtered through sodium sulfate, and concentrated. The green residue was dissolved in water and extracted with methylene chloride. The combined organic solutions were dried, Celite was added, and the mixture again filtered. The filtrate was concentrated under reduced pressure and cooled. Crystallization gave 0.882 g (3.63 mmol, 57%) of product, mp 158–160°. Two recrystallizations from acetone gave colorless crystals: mp 159–161°; $\nu_{C=O}$ 1705, 1620 cm^{-1}; $\nu_{C=C}$ 1600, 1580, 1570, 1490 cm^{-1}; $\nu_{C_6H_5}$ 785, 775, 735, 700 cm^{-1} in Nujol; δ 7.36 (5 H, aromatic), 4.37 (2 H, broad, equatorial N-CH), 3.18 (2 H, quartet, J_{gem} = 13 cps, J_{ae} = 3.5 cps, axial N-CH), 2.53 (3 H, triplet over broad signal, J = 6 cps, -CH-CO-CH$_2$-), 2.08 ppm (5 H, multiplet); *m/e* 243 (M$^+$), 242, 215, 214, 186, 138, 105, 77.

Anal. Calcd for $C_{16}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 74.21; H, 6.82, N, 5.74.

3-Benzoyl-7-bromo-3-azabicyclo[3.3.1]nonan-6-one (4).—A solution of bromine in chloroform was added in small portions to a cold (5–15°) solution of **3** (2.489 g, 10.2 mmol) in chloroform (50 ml) until the solution retained a light yellow color longer than 1–2 min. The solution was washed with water, 5% aqueous sodium bicarbonate (remained basic to pH paper), and again with water. The solution was dried and concentrated to an oil. The oil was crystallized from acetone–Skellysolve B, giving 2.381 g (7.40 mmol, 72%) of product, mp 141–144°. Two recrystallizations, the last preceded by decolorization with activated charcoal, from acetone–Skellysolve B gave colorless crystals: mp 147–149°; $\nu_{C=O}$ 1715, 1630 cm^{-1}; $\nu_{C=C}$ 1590, 1575, 1490 cm^{-1}; $\nu_{C_6H_5}$ 730, 715, 700 cm^{-1} in Nujol; δ 5.00 (>CHBr, doublet, J = 11.0 cps), 4.87 (>CHBr, doublet, J = 11.0 cps), 4.38 [-CH(-H)N, broad doublet, J = 13.0 cps, 2 H], 3.22 ppm [doublet (J = 14.0 cps) of doublets (J = 3.5 cps), 2 H].

Anal. Calcd for $C_{15}H_{16}BrNO_2$: C, 55.91; H, 5.01; N, 4.35; Br, 24.80. Found: C, 56.09; H, 5.28; N, 4.59; Br, 25.05.

3-Benzoyl-3-azabicyclo[3.3.1]nonan-6-one-$d_5d_7d_7$ (5).—A solution of **3** (0.035 g) and sodium (0.010 g) in methyl alcohol-*d* was kept at room temperature for 20 hr. Acetic acid-*d* in D_2O was added to neutralize the base. The solution was concentrated under reduced pressure. Water (25 ml) was added to the residue, and the mixture was extracted with three 20-ml portions of methylene chloride. The organic solution was dried and concentrated to an oil, *m/e* 246 (M$^+$).

3-Benzoyl-*exo*-3-azabicyclo[3.3.1]nonan-6-ol (6).—A solution of sodium borohydride (1.0 g, 0.0265 mol) in 0.1 *M* aqueous sodium hydroxide (10 ml) was added to a solution of **3** (1.017 g, 4.18 mmol) in methanol (40 ml). Thin layer chromatography (silica gel, 10% methanol in benzene) after 0.5 hr showed reaction to be complete. The solution was partially concentrated under reduced pressure and then was diluted to 150 ml with water. The solution was made acidic (pH 5–6) with acetic acid and was concentrated under reduced pressure over a hot water bath until crystals began to form. The mixture was extracted with three 50-ml portions of methylene chloride. From the dried extract solution, an oil was obtained following concentration. The oil crystallized and the solid was recrystallized from acetone–Skellysolve B, giving 0.695 g (2.84 mmol, 67%) of crystals, mp 135–138°. Two recrystallizations from acetone–Skellysolve B gave colorless, shiny flakes: mp 139–141°; ν_{OH} 3360 cm^{-1}; $\nu_{C=O}$ 1600 cm^{-1}; $\nu_{C=C}$ 1590, 1575, 1530, 1490 cm^{-1}; ν_{C-O} 1060 cm^{-1}; $\nu_{C_6H_5}$ 790, 780, 735, 705 cm^{-1} in Nujol.

Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.92; H, 7.95; N, 6.08.

3-Benzyl-3-*endo*-azabicyclo[3.3.1]nonan-6-ol (7).—A solution of **2** (5.0 g, 0.0204 mol) in tetrahydrofuran (100 ml) was poured into a mixture of lithium aluminum hydride (3.0 g) and tetrahydrofuran (150 ml). The whole mixture was heated at reflux temperature for 5 hr; then the excess hydride was consumed with ethyl acetate and water. The inorganic solids were removed by filtration through Celite and washed with hot tetrahydrofuran. The tetrahydrofuran solution was dried and concentrated under reduced pressure to an oil. The oil was transferred with ether to a distillation flask. After a few minutes at low pressure, the oil solidified. The solid crystallized from cold hexane, giving crystals, mp 67–69°. Three recrystallizations from cold hexane, the last preceded by decolorization with activated charcoal, resulted in colorless crystals: mp 70–71°; ν_{OH} 3320, 3220 cm^{-1}; $\nu_{C=C}$ 1600, 1495 cm^{-1}; $\nu_{C_6H_5}$ 730, 695 cm^{-1} on the oil; δ 7.29 (5 H, singlet, aromatic), 3.98 [1 H, multiplet half-band width = 8 cps, >C(-O)H], 3.38 (2 H, singlet, benzylic), 2.87 (2 H, doublet, J_{gem} = 11 cps, equatorial -N-CH), 2.18 (2 H, quadruplet, J_{gem} = 11 cps, J_{ae} = 3 cps, axial -N-CH).

Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 78.01; H, 9.54; N, 6.33.

3-Benzyl-3-azabicyclo[3.3.1]nonan-6-one (8).—A solution of 7.457 g of **7** in toluene (120 ml) and cyclohexane (30 ml) was heated to boiling and the toluene–water azeotrope distilled off. Aluminum isopropoxide (10 g) and cyclohexanone (10 ml) were added to the solution, and the mixture was heated at reflux temperature for 2 hr. The mixture was poured into ice–aqueous hydrochloric acid and stirred. The aqueous layer was separated, extracted with three 100-ml portions of ether, and made alkaline with concentrated sodium hydroxide solution. A heavy precipitate formed at the neutralization point but disappeared, and an oil formed as additional base was added. The solution and oily phase were extracted with three 100-ml portions of ether; the ether was dried and concentrated under reduced pressure to a reddish brown oil. The oil was transferred with ether to a 10-ml distillation flask and distilled, bp 126–129° (0.04 mm), giving 4.171 g (0.0182 mol, 60% from hydroxy amide) of a colorless oil: n_D 1.5499; $\nu_{C=O}$ 1700 cm^{-1}; $\nu_{C=C}$ 1600, 1580, 1490 cm^{-1}; $\nu_{C_6H_5}$ 735, 695 cm^{-1} on the oil.

Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.90; H, 8.56; N, 6.05.

3-Benzyl-3-azabicyclo[3.3.1]nonan-6-one Perchlorate (9). A. From Ketone 3 *via* the Ketal.—A mixture of **3** (0.550 g, 2.26 mmol) in benzene (100 ml), *p*-toluenesulfonic acid hydrate (0.090 g, 0.473 mmol), and ethylene glycol (10 ml) was heated to reflux for 18 hr. The condensate was dried by passing through a calcium carbide trap. A few drops of pyridine were added, and the mixture was cooled to room temperature. The mixture was extracted with 5% aqueous sodium bicarbonate solution (50 ml) and with two 25-ml portions of water. The benzene layer was dried over magnesium sulfate and concentrated under reduced pressure to an oil: $\nu_{C=O}$ 1630 cm^{-1}; $\nu_{C=C}$ 1605, 1580, 1500 cm^{-1}; $\nu_{C_6H_5}$ 708 cm^{-1} on the oil.

A solution of the above oil in ether was reduced with lithium aluminum hydride (0.5 g) in ether. After refluxing 4 hr, the excess hydride was decomposed with ethyl acetate and water, the solids were filtered off, the ether solution was dried and concentrated to an oil: ν_{CH} 2390, 2900, 2875 cm^{-1}; $\nu_{C=C}$ 1600, 1580, 1495 cm^{-1}; $\nu_{C_6H_5}$ 736, 700 cm^{-1} on the oil.

Aqueous perchloric acid (70%, 15 drops) was added to a solution of the above oil (0.25 g, 0.915 mmol) in absolute ethanol (5.0 ml). The solution was heated on the steam bath for 3 min. Addition of ether slowly precipitated an oily solid, which crystallized into colorless crystals (0.251 g, 0.763 mmol, 83%), mp 210–215°. Two recrystallizations from ethanol containing a few drops of water gave crystals: mp 213–216°; ν_{NH^+} 3080 cm^{-1}; $\nu_{C=O}$ 1695 cm^{-1}; $\nu_{C=C}$ 1500 cm^{-1}; $\nu_{C_6H_5}$ 770, 745, 705 cm^{-1} in Nujol.

Anal. Calcd for $C_{15}H_{20}NO_5Cl$: C, 54.63; H, 6.11; N, 4.25. Found: C, 54.51; H, 5.87; N, 4.33.

B. From Ketone 8.—Aqueous perchloric acid (70%, 10 drops) was added to a solution of **8** (0.236 g, 1.03 mmol) in absolute ethanol (3 ml). Crystals formed after 10 min. A first crop of 0.157 g of colorless crystals was collected by filtration. A second crop of 0.042 g (0.199 g total, 6.05 mmol, 58%) was obtained from the mother liquor. The infrared spectrum of the crystal is identical with that of the above salt.

Isolation of Products from the Bioconversion of 3-Benzoyl-3-azabicyclo[3.2.2]nonane. 3-Benzoyl-3-azabicyclo[3.2.2]nonan-6-one (13). A. From Direct Oxidation of Bioconversion Products.—The residue from the beer extract of a 25.0-g conversion of 3-benzoyl-3-azabicyclo[3.2.2]nonane with *Sporotrichum sulfurescens* was dissolved in 500 ml of acetone and oxidized by the Jones method. After 10 min, excess oxidant was destroyed by the addition of 10 ml of isopropyl alcohol. The mixture was diluted with 1 l. of water and extracted three times with 250 ml of methylene chloride. The combined extract was washed once with water and dried over sodium sulfate. The filtered solution was concentrated under reduced pressure, the residue was dis-

(11) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

tilled through a 4-in. Vigreux column, and the product was collected at 190–195° at 0.3 mm, yield 12.17 g. The infrared spectrum of this product was identical with the product obtained upon oxidation of pure alcohol (12).

B. From Oxidation of Alcohol 12.—Oxidation of pure 12 with Jones reagent[11] gave ketone 13 as colorless crystals, mp 59–62°.

Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 74.32; H, 7.13; N, 5.87.

The semicarbazone of 13 was prepared by heating at reflux a mixture of 1.0 g of ketone, 1.0 g of semicarbazide hydrochloride, 1.5 g of sodium acetate, 1.6 ml of water, and 20 ml of methanol. The analytical sample was obtained by recrystallization from aqueous methanol, mp 197–200°.

Anal. Calcd for $C_{16}H_{20}N_4O_2$: C, 63.98; H, 6.71; N, 18.65. Found: C, 64.06; H, 6.82; N, 18.29.

The oxime of 13 was prepared by heating at reflux a mixture of 0.3 g of ketone, 0.5 g of hydroxylamine hydrochloride, 5.0 ml of 5% sodium hydroxide solution, and 3 ml of methanol. The product was recrystallized from aqueous methanol, mp 156–158°.

Anal. Calcd for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.85. Found: C, 69.71; H, 7.16; N, 10.87.

2,4-Dinitrophenylhydrazone of 13 was prepared from a mixture of 2,4-dinitrophenylhydrazine, hydrochloric acid, and ethanol. The product was recrystallized from methylene chloride–ethanol, mp 198–201°.

Anal. Calcd for $C_{21}H_{21}N_5O_5$: C, 59.56; H, 5.00; N, 16.54. Found: C, 59.57; H, 4.94; N, 16.65.

3-Benzoyl-*endo*-3-azabicyclo[3.2.2]nonan-6-ol (12).—The residue from the methylene chloride extraction of the beer from a 4.0-g bioconversion of 3-benzoyl-3-azabicyclo[3.2.2]nonane was chromatographed over silica gel. The column was prepared from 200 g of silica gel (0.05–0.20 mm) and ethyl acetate–Skellysolve B hydrocarbons (5:1). The crude residue was placed on the column and eluted in 55-ml cuts with the same solvent mixture. Fractions 13–18 contained 0.950 g (22%) of ketone which was idential by comparison of infrared spectra and thin layer and paper chromatographic analysis with 3-benzoyl-3-azabicyclo-[3.3.2]nonan-6-one (13) described above. Fractions 29–50 contained 2.464 g (56%) of hydroxybenzamide (12). This product was shown by thin layer and paper chromatographic analysis to be a single entity and different than the hydroxyamide (14) described below. Treatment in acetone with activated carbon produced a colorless oil which eventually crystallized, $[\alpha]_D$ 0° (95% ethanol), mp 73–75°.

Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.08; H, 7.81; N, 6.00.

3-Benzoyl-*exo*-3-azabicyclo[3.2.2]nonan-6-ol (14).—Crude 13 (20 g) dissolved in 350 ml of methanol was treated with a solution of 16.0 g of sodium borohydride in 100 ml of 0.1 *N* sodium hydroxide for 30 min when thin layer chromatography indicated complete reaction. The mixture was diluted with 300 ml of water, allowed to stand in the hood for 18 hr, and, with chilling, adjusted to pH 6 by the cautious addition of 50% acetic acid. The solid product was recovered by filtration, washed with water, and dried: yield, 12.75 g; mp 131–135°. The analytical sample from acetone melted at 135–137°.

Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.31; H, 7.87; N, 5.89.

exo-6-Benzoyloxy-3-azabicyclo[3.2.2]nonane Hydrochloride (15).—The hydroxybenzamide (14), 2.14 g, was dissolved in 50 ml of tetrahydrofuran by warming. To the warm (50°) solution was added 4.0 ml of concentrated hydrochloric acid, and the mixture was allowed to stand at 25°. The solution was examined at intervals by thin layer chromatogaphy, and after complete reaction (23 hr) it was concentrated under reduced pressure to an oil. This was triturated twice with ether, decanting off the ether each time, and the hydrochloride salt was precipitated by adding 25 ml of acetone and 50 ml of ether: yield 2.16 g; mp 205–208°. This was recrystallized from methanol–methyl ethyl ketone: yield, 2.06 g; mp 205–208°; ν_{NH^+} 2250–2700 cm^{-1}; $\nu_{C=O}$ 1710 cm^{-1}.

Anal. Calcd for $C_{15}H_{20}NO_2Cl$: C, 63.93; H, 7.15; N, 4.97. Found: C, 63.92; H, 7.44; N, 5.24.

Reverse Reaction to Regenerate Hydroxybenzamide (14).—The salt (15) (200 mg) in 5 ml of water was treated with a few drops of 50% sodium hydroxide solution and stirred. After the resulting product had solidified, the mixture was acidified with hydrochloric acid, the product recovered, washed with water and dried: mp 135–137°. The infrared spectrum was identical with the hydroxybenzamide (14) described above. The filtrate from the above upon retreatment with base produced a second crop of the same product.

6-Phenyl-*exo*-3-azabicyclo[3.2.2]non-6-ol Hydrochloride (16).—A solution of 20 g of 13 in 400 ml of tetrahydrofuran was added to a stirred solution of 200 ml of 3 *M* phenylmagnesium bromide in ether. Solvent was removed by distillation until the boiling temperature was 60°, and the mixture was heated at reflux for 4.5 hr. After cooling, it was poured onto ice and stirred and acidified with concentrated hydrochloride while continuing to add ice. This mixture was extracted several times with ether. The neutral product from this ether extracted proved to be benzophenone. The aqueous acid solution was made basic with 50% sodium hydroxide solution, and the resulting mixture was extracted several times with ether. The extract was dried, treated with ethereal hydrogen chloride, and the insoluble salt was recovered and washed with ether: yield, 15.32 g. This was fractionally crystallized from methanol–methyl ethyl ketone to give about 7.5 g of a less soluble, higher melting isomer; mp 238–240° dec.

Anal. Calcd for $C_{14}H_{20}NOCl$: C, 66.26; H, 7.94; N, 5.52; Cl, 13.97. Found: C, 66.51; H, 8.17; N, 5.49; Cl, 13.90.

6-Phenyl-*endo*-3-azabicyclo[3.2.2]nonan-6-ol Hydrochloride (17).—From the filtrates of the above experiment 2.0 g of a more soluble, lower melting isomer were isolated, mp 218–220° dec.

Anal. Calcd for $C_{14}H_{20}NOCl$: C, 66.26; H, 7.94; N, 5.52; Cl, 13.97. Found: C, 66.09; H, 8.33; N, 5.36; Cl, 13.70.

6-Methyl-*endo*-3-azabicyclo[3.2.2]non-6-ol Hydrochloride (18).—Ketobenzamide 13 (10 g) in 200 ml of tetrahydrofuran was added to a stirred solution of 100 ml of 3 *M* methylmagnesium bromide in ether. The mixture was distilled until the vapor temperature was 60° and then heated at reflux for 4.5 hr. The stirred mixture was chilled and treated with 60 ml of water, followed by 50 ml of acetic acid, and extracted several times with ether. The ether solution, after washing with dilute HCl, water, and sodium bicarbonate solution, was dried (Na_2SO_4), and the solvent was removed to give an oil which proved to be acetophenone. The aqueous solution remaining from the ether extraction was made basic with 50% sodium hydroxide, and the resulting gelatinous mixture was continuously extracted with ether. The extract was dried (Na_2SO_4) and treated with hydrogen chloride. The resulting HCl salt was recovered and washed with ether: yield 3.29 g; mp 228–230°. Recrystallization from methanol–ether gave a product, mp 230–232°.

Anal. Calcd for $C_9H_{18}NOCl$: C, 56.38; H, 9.46; N, 7.30; Cl, 18.50. Found: C, 56.67; H, 9.97; N, 7.09; Cl, 18.63.

3-Benzyl-*exo*-3-azabicyclo[3.2.2]nonan-6-ol (19).—The hydroxy amide 14 (6.69 g) was dissolved in 80 ml of tetrahydrofuran and added with stirring to a mixture of 6.0 g of lithium aluminum hydride in 100 ml of ether. The mixture was refluxed for 1 hr, chilled in a cold bath, and carefully decomposed by the addition of 25 ml of water. After dilution with 300 ml of ether and filtering, the filtrate and ether wash was dried and the solvent removed under reduced pressure to give 5.90 g of straw-colored oil. Part of the oil (1.33 g) was dissolved in ether and treated with ethereal hydrogen chloride to precipitate the salt which was recrystallized from methanol ether: yield, 1.07 g; mp 185–187°.

Anal. Calcd for $C_{15}H_{22}NOCl$: N, 5.23; Cl, 13.24. Found: N, 5.47; Cl, 13.74.

exo-3-Azabicyclo[3.2.2]nonan-6-ol Hydrochloride (20).—The hydroxybenzylamine 19 (9.17 g) dissolved in 120 ml of ethanol was shaken with 1.0 g of 10% palladium–carbon and hydrogen (44 psig starting pressure) for 20 hr. The mixture, freed of catalyst and concentrated *in vacuo*, gave the free amine as a solid, 5.60 g. A portion of the free base was dissolved in ether and treated with ethereal hydrochloric acid to precipitate the amine hydrochloride, which was recrystallized from methanol–methyl ethyl ketone, mp 280° dec.

Anal. Calcd for $C_8H_{16}NOCl$: C, 54.07; H, 9.08; N, 7.88; Cl, 19.96. Found: C, 54.17; H, 9.05; N, 8.01; Cl, 19.99.

3-Benzyl-3-azabicyclo[3.2.2]nonan-6-one (21).—The crude benzylamine 19, resulting from the hydride reduction of 10 g of 14, dissolved in 600 ml of toluene and 150 ml of cyclohexanone was distilled to remove *ca.* 100 ml of toluene. Aluminum isopropoxide (20 g) was added; the mixture was distilled to remove *ca.* 50 ml of solvent and then heated at reflux for 60 min. After cooling it was poured onto an ice mixture containing excess hydrochloric acid and stirred, and the layers were separated. The aqueous acid layer was extracted several times with ether and then made basic with 50% sodium hydroxide solution. The

resulting emulsion was well extracted with ether, and the ether extract was washed once with water and dried. The ether solution was made up to 650 ml and 100 ml of this was treated with ethereal HCl to precipitate the salt of **21**. This was recrystallized from methanol–ethanol–ether: yield, 0.744 g; mp 222° dec.

Anal. Calcd for $C_{15}H_{20}NOCl$: C, 67.78; H, 7.59; N, 5.27; Cl, 13.34. Found: C, 68.13; H, 7.77; N, 5.42; Cl, 13.17.

3-Azabicyclo[3.2.2]nonan-6-one Hydrochloride (22).—The ether solution of free base remaining from the above experiment was taken to dryness to yield 4.55 g of oil. This was dissolved in 90 ml of ethanol and shaken with 1.0 g of 10% palladium on carbon and hydrogen (50 psig) for 180 min. The catalyst was removed by filtration; the filtrate and wash were concentrated *in vacuo* to a small volume, diluted with ether, and treated with ethereal HCl. The hydrochloride of **22** was recovered, washed with ether, and dried: yield, 3.12 g; mp 218–220° dec. A sample from methanol–ether melted at 227–229° dec.

Anal. Calcd for $C_8H_{14}NOCl$: C, 54.70; H, 8.03; N, 7.98; Cl, 20.19. Found: C, 54.22; H, 8.14; N, 7.98; Cl, 20.64.

Bioconversion of 2-Benzoyl-2-azabicyclo[2.2.2]nonane (23). 2-Benzoyl-*endo*-2-azabicyclo[2.2.2]octan-5-ol (24) and 2-Benzoyl-*endo*-2-azabicyclo[2.2.2]octan-6-ol (25).—The methylene chloride extract residue from the bioconversion of **23** (25.0 g, 0.116 mol) was chromatographed over 1000 g of Florisil. Elution with 4 l. each of Skellysolve B containing 10, 15, and 20% acetone and with 12 l. of Skellysolve B containing 25% acetone by volume was carried out with collection of 800-ml fractions. The fractions were pooled as follows on the basis of tlc. Fractions 7–11 were 3.98 g (16%) of unchanged starting material. Fractions 17, and 18 gave, after recrystallization from acetone, 1.61 g (6.97 mmol, 6% **25**, mp 200–205°).

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.03. Found: C, 72.70; H, 7.64; N, 5.82.

Fraction 19 was a mixture, 2.14 g (8%). Fractions 20–27 gave 12.16 g of solid. Recrystallization from acetone gave 10.62 g (0.0460 mol, 40%) of crystalline **24**, mp 146–148°.

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.03. Found: C, 72.52; H, 7.19; N, 6.18.

2-Benzoyl-2-azabicyclo[2.2.2]octan-6-one (26).—2-Benzoyl-*endo*-2-azabicyclo[2.2.2]octan-6-ol (2 g) in 100 ml of acetone was oxidized by the Jones method[11] to give the ketone (1.95 g) as an oil which eventually crystallized: mp 67–72°; $\nu_{C=O}$ 1740, 1610 cm^{-1} in Nujol.

Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 72.82; H, 6.94; N, 6.08.

2-Benzoyl-2-azabicyclo[2.2.2]octan-5-one (27).—2-Benzoyl-*endo*-2-azabicyclo[2.2.2]octan-5-ol (300 mg) was oxidized[11] to the ketone which was recrystallized from acetone–hexane: mp 99–101°; $\nu_{C=O}$ 1740, 1610 cm^{-1} in Nujol.

Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.15; H, 6.70; N, 5.99.

Registry No.—**2**, 16780-54-4; **3**, 16780-67-9; **4**, 16780-68-0; **6**, 16780-69-1; **7**, 16780-70-4; **8**, 16780-71-5; **9**, 16780-72-6; **12**, 16780-73-7; **13**, 16780-74-8; semicarbazone of **13**, 16780-75-9; oxime of **13**, 16808-42-7; 2,4-dinitrophenylhydrazone of **13**, 16780-76-0; **14**, 16780-77-1; **15**, 16780-78-2; **16**, 16780-79-3; **17**, 16780-80-6; **18**, 16780-81-7; **19**, 16808-43-8; **20**, 16808-44-9; **21** HCl, 16808-45-0; **22**, 16808-46-1; **24**, 16785-68-5; **25**, 16785-69-6; **26**, 16785-70-9; **27**, 16808-47-2.

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The Microbiological Oxygenation of Acylated 1-Adamantanamines. Stereochemistry and Structural Determinations

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Microbiological oxygenation of N-acetyl-1-adamantanamine with *Sporotrichum sulfurescens* produced C-4 hydroxylation as the major reaction along with a minor quantity of C-3 hydroxylation. The reaction of the same organism with N-benzoyl-N-methyl-1-adamantanamine led to C-4 and C-6 dihydroxylation as the major conversion entity with a lesser quantity of C-4 monohydroxylation. Oxygenation occurred primarily on the methylene carbons and resulted in *trans* hydroxylation with respect to the N substituent; lipophilicity led to dihydroxylation, whereas hydrophilicity led to monohydroxylation. The products obtained from the biotransformations of some other N-acetylated adamantanamines are described.

In recent papers[1] we have described the microbiological oxygenation of macrocyclic alcohols,[1a] heterocyclic ring systems,[1b] and alicylic amides.[1c] When various substrates were dispersed in the active fermentation medium of *Sporotrichum sulfurescens*, oxygenation was shown to occur at an optimal distance of about 5.5 Å from an electron-rich center to the position of attachment at an unactivated methylene site. The authors have now studied the action of *S. sulfurescens* on some N-acylated 1-adamantanamines (Charts I, II, and III). The structures of the products, including the stereochemistry, have been determined by chemical and spectroscopic methods. The proposed enzyme–substrate model described previously[1a] was helpful in predicting the most favorable position for oxygenation of this rigid cage molecule, and the products obtained were compatible with the hypothesis.

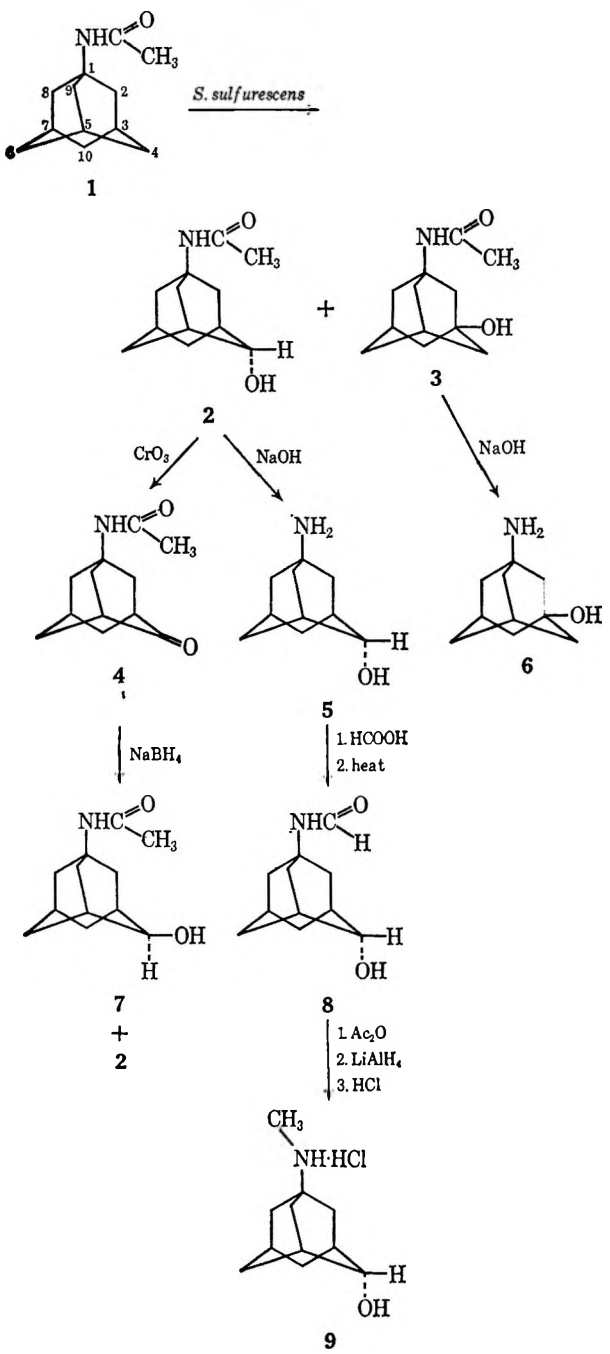
Bioconversion products of N-acetyl-1-adamantanamine[2] (**1**) (Chart I) unexpectedly were found to be quite water-soluble compounds and could not be extracted with methylene chloride. The compounds were readily absorbed on carbon from which they were recovered and further purified. Two monohydroxylated compounds were isolated from this conversion. The one produced in minor quantity could not be oxidized to ketone and was assigned a tertiary alcohol structure (**3**).[3] Heating at reflux in aqueous base produced the

(1) (a) G. S. Fonken, M. E. Herr, H. C. Murray, and L. M. Reineke, *J. Amer. Chem. Soc.*, **89**, 672 (1967); (b) R. A. Johnson, M. E. Herr, H. C. Murray, L. M. Reineke, and G. S. Fonken, *J. Org. Chem.*, **33**, 3195 (1968); (c) G. S. Fonken, M. E. Herr, H. C. Murray, and L. M. Reineke, *ibid.*, **33**, 3182 (1968).

(2) H. Stetter, M. Schwarz, and A. Hirschborn, *Chem. Ber.*, **92**, 1679 (1959).

(3) Since our isolation of this compound its chemical preparation has been reported: H. Stetter, J. Gartner, and P. Tacke, *Angew. Chem.*, **4**, 153 (1965).

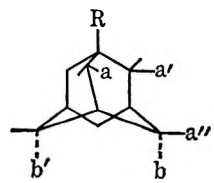
CHART I



hydroxy amine (**6**). The more important compound from this conversion on the basis of yield and uniqueness was the secondary alcohol (**2**). Oxidation of this product by the method of Jones, *et al.*,[4] readily produced a ketone (**4**); this could be expected from either a 2- or 4-hydroxy compound. Examination of the nmr spectrum of the keto amide (**4**) showed a downfield symmetrical signal centered at δ 2.60 ppm which integrated for two protons.[5] This signal could be attributed to the tertiary protons on carbon atoms 3 and 5 α to the C-4 carbonyl (compound **4**). However, it could be argued that if the ketone was at C-2 the long-range effect of the carbonyl function could cause a downfield shift of signal for the two protons on carbons 8 and 9 in closest proximity to the carbonyl. The latter possibility was ruled out by the observation that sodium borohydride reduction of the ketone gave a mixture of hydroxy amides, which was readily separated byc hromatography into two pure compounds, of mp 176–177° (**2**) and mp 206–207° (**7**), the former of which was identical with the major biotransformation product. Reduction of a C-2 ketone would have produced a racemic mixture of hydroxy amides on an asymmetric carbon which would not have been resolvable by chromatography. It will be shown in the discussion below that the major bioconversion product was in fact N-acetyl-1-adamantanamin-4α-ol (**2**),[6] and therefore the other product of the borohydride reduction was the corresponding 4β-ol (**7**). As in the case of the *t*-hydroxy amide (**3**) the C-4-hydroxy amide was readily hydrolyzed to C-4 hydroxy amine (**5**) in aqueous base.

We next turn to the discussion of the products obtained from the bioconversion of N-benzoyl-N-methyl-1-adamantanamine (**10**) (Chart II) with *S. sulfurescens*. The products in this case, unlike those described above, were more lipophilic and were extractable from the fermentation beer with methylene chloride. The residue from the extraction upon chromatography produced two hydroxylated products. The structures of these compounds were found to be interrelated with the structure of compound **2**. The major component of the microbiological oxidation proved to be a dihydroxy amide (**11**), and the minor component was found to be a monohydroxy amide (**12**).

The monohydroxy compound (**12**) upon reexposure to the action of *S. sulfurescens* was convertible into the same dihydroxy amide (**11**). This showed that compounds **11** and **12** had one hydroxyl function in common. The dihydroxy amide was readily oxidized by the Jones method[4] to a diketone, thus showing that both alcohol groups were secondary carbinols. The reaction of the diol with thionyl chloride produced a cyclic sulfite ester (**13**).[7] Consideration of a Dreiding model of adamantane showed that formation of the cyclic sulfite ester defined the stereochemical relationship of the two hydroxyl groups to each other. The possibility for formation of a cyclic product was limited to a situation where the OH functions protruded from the molecule in parallel proximity to each other. It did not, however, discriminate as to whether they were attached at a and a′, a′ and a″, or b and b′. Examination of the nmr spectrum of the diol in dimethylformamide-d_7 showed a symmetrical signal centered at 5.38 ppm for the two OH protons. The two tertiary protons attached to the carbons bearing the OH functions appeared as a symmetrical band centered at δ 3.93 ppm. The



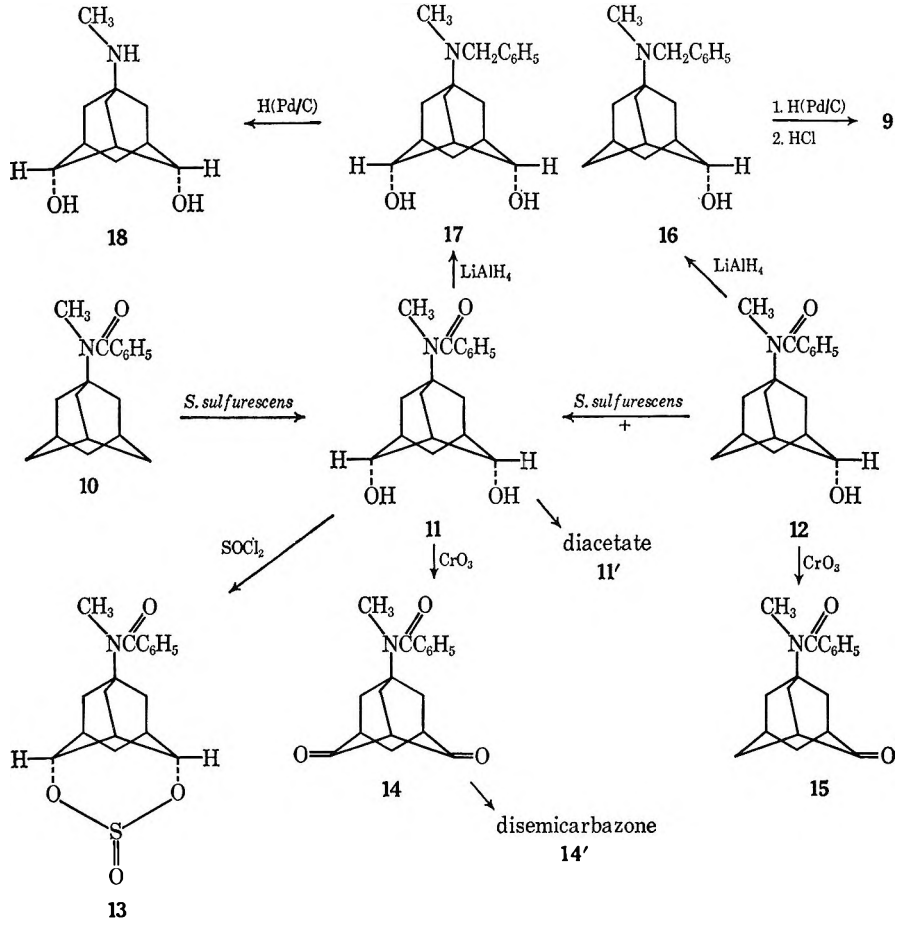
(4) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(5) Nuclear magnetic resonance spectra were determined at 60 Mcps on a Varian Model A-60 spectrometer with references to tetramethylsilane.

(6) We propose the following stereochemical notation for the C-4- (or C-6-) substituted 1-adamantanamines. The reference group is the C-1 carbon–nitrogen bond and a substituent at C-4 (or C-6) will be referred to as β or α according to whether it is *cis* or *trans* with respect to the general plane of the common six-membered ring.

(7) B. R. Brown, P. W. Trown, and J. M. Woodhous, *J. Chem. Soc.*, 2478 (1961).

CHART II



corresponding two protons of the cyclic sulfite ester produced a symmetrical signal centered at δ 4.68 ppm. These measurements showed that the two hydroxyl groups were attached to the molecule in a symmetrical pattern, thereby eliminating the a'a'' relationship.

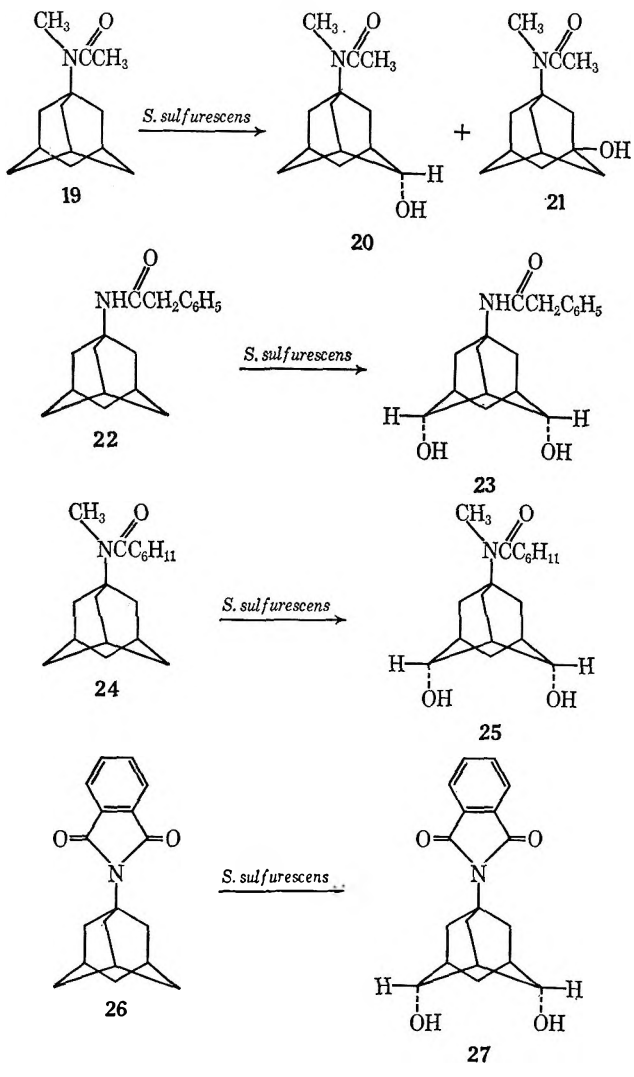
Oxidation of the monohydroxy amide (**12**) to the ketone (**15**) confirmed the presence of a secondary alcohol. Reduction of **12** with lithium aluminum hydride gave a hydroxy-N-methyl-N-benzyl amine (**16**) which upon catalytic hydrogenation produced a hydroxy-N-methyl amine, isolated as the hydrochloride salt (**9**). This salt was identical in all respects with a compound produced by the following series of reaction (shown in Chart I) on the previously described N-acetyl-1-adamantanamin-4-ol (**2**). The formic acid salt of the amine (**5**) was dehydrated to the N-formyl alcohol (**8**); the acetate of **8** upon hydride reduction gave an amine which upon treatment with hydrogen chloride produced the salt (**9**). It was thus shown that all three bioconversion products **2**, **11**, and **12** had one hydroxyl function in common. This therefore eliminated the possibility of the a and a' hydroxyl attachment sites since it was shown above that the hydroxyl group of product **2** must be at C-4 and not at C-2. This leaves only the bb' structure for the dihydroxy compounds and at the same time establishes the *trans* relationship of the hydroxyl groups to the amide nitrogen for compounds **2** and **12**.

Variation of the groups attached to the nitrogen of 1-adamantanamine produced other hydroxylated products as shown in Chart III. The structures of the two monohydroxy products obtained from the bioconversion of N-acetyl-N-methyl-1-adamantanamine (**19**) with *S. sulfurescens* were assigned on the basis of the following observations. The compound obtained as the minor product (*ca.* 7%) was shown to be a *t*-hydroxy amide (**21**) because it failed to oxidize with chromic acid. The other product obtained in *ca.* 35% yield was readily oxidized to a ketone, and the structure was determined to be **20** by chemical synthesis. The reaction of the free base of compound **9**, for which the position and orientation of the hydroxyl group is known (*vide supra*), with acetic anhydride in pyridine followed by treatment with base produced the same compound (**20**). Also comparison of the nmr spectrum ($CDCl_3$) of **20** with that of hydroxy amide **12** showed that the signals for the proton on the carbon bearing the hydroxy group appeared as identical in position and shape, centered at δ 3.96 ppm.

The remaining bioconversion products (Chart III) which were obtained from more lipophilic substrates (**22**, **24**, and **26**) were dihydroxylated compounds. We considered the nmr spectra in dimethylformamide-d_7, especially the positions and shapes of the signals for the protons in the carbons bearing the hydroxyl functions, as diagnostic when compared with similar protons of compound **11**. The dihydroxy amides (**23**, **25**, and **27**) all produced a symmetrical signal for these two protons which was centered between δ 3.80 and 4.20 ppm.

An observation of particular interest was that, in all cases where the action of *S. sulfurescens* has produced either mono or dihydroxy secondary alcohols, these groups have been introduced *trans* with references to the nitrogen substituent.[6]

CHART III



With regard to the hypothetical enzyme–substrate model described previously,[1a] the exact distance from the electron-rich site, in this case the amide carbonyl oxygen, to the position of hydroxylation on the methylene carbon cannot be measured because of the variable conformations which may be assumed by the amide function. However, the conformation of maximum distance between amide carbonyl and C-4(6) measures about 6.3 Å and that of minimum distance measures about 4.5 Å. Hydroxylation at the C-2 position was not predicted because this maximum to minimum distance varies from about 4.2 to 2.4 Å, depending on the amide conformation.

Experimental Section[8]

Fermentation Process.—The bioconversion process and description of the culture has been described previously[1a,b] with the following exceptions. When N-phenylacetyl-1-adamantanamine (**22**) and N-1-adamantanphthalimide (**27**) were added to the fermenter in N,N-dimethylformamide solution, essentially only starting material was recovered. The addition of 2.5 ml of the surfactant Ultrawet DS 30[9a] per liter of beer before adding the substrate led to almost complete dissimilation of these substrates. With the surfactant UCONLB 625[9b] was used as a defoaming agent.

The crude products were in each case extracted from the filtered beer with methylene chloride except for the isolation of the products from the fermentation of N-acetyl-1-adamantanamine (**1**) and N-(4α,6α-dihydroxy-1-adamantyl)phthalimide (**26**). These polar materials were separated from the beer by carbon adsorption.

Isolation of Products from the Bioconversion of N-Acetyl-1-adamantanamine.—The filtered beer and the mycelium wash from a 55-g bioconversion amounted to about 115 l. Granular CAL carbon[9c] (3 kg) was heated at 80–90° in deionized water, cooled to 25°, and packed into a column (10.8-cm diameter). The filtered beer was passed through the carbon. The column was stripped with 50 l. of methanol and a first dark 2-l. fraction was discarded after tlc examination showed that it contained no product. The remainder of the methanol eluate was concentrated under reduced pressure to dryness. The residue was stirred with 500 ml of methanol and filtered to remove some insoluble debris from the concentrate. The methanol filtrate was well mixed with 500 g of silica gel.[9d] This mixture was allowed to air dry and added to the top of a column (10.8-cm diameter) of 3 kg of silica gel which had been wet packed using ethyl acetate. The column was eluated as reported in Table I in fractions of 1 l. each.

TABLE I

Fractions	Amt, l.	Eluate
1–6	6	Ethyl acetate
7–12	6	2% methanol in ethyl acetate
13–18	6	5% methanol in ethyl acetate
19–24	6	8% methanol in ethyl acetate
25–30	6	12% methanol in ethyl acetate
31–35	6	15% methanol in ethyl acetate
36–41	6	18% methanol in ethyl acetate

The fraction residues were assayed on thin layer silica gel plates, developed with 10% methanol in ethyl acetate. Fractions 10–12 contained 9.16 g of unchanged substrate.

N-Acetyl-1-adamantanamin-4α-ol (2).—Fraction residues 15–26 from the above column weighed 27.32 g. Recrystallization from acetone gave 23.90 g: mp 173–175°; $\nu_{OH,NH}$ 3500, 3300, $\nu_{N-C=O}$ 1640 cm^{-1} in Nujol.

Anal. Calcd for $C_{12}H_{19}NO_2$: C, 68.86; H, 9.15; N, 6.69. Found: C, 68.87; H, 9.22; N, 6.83.

N-Acetyl-1-adamantanamin-3-ol (3).—Fraction residues 27–30 weighed 8.11 g and by tlc were found to be a mixture of **2** and **3**. Fraction residues 31–34 weighed 6.89 g and contained the C-3 alcohol. This was recrystallized from acetone: yield, 5.08 g; mp 223–225°; $\nu_{OH,NH}$ 3300, $\nu_{N-C=O}$ 1650 cm^{-1} in Nujol.

Anal. Calcd for $C_{12}H_{19}NO_2$: C, 68.86; H, 9.15; N, 6.69. Found: C, 69.00; H, 9.11; N, 6.82.

N-Acetyl-1-adamantanamin-4-one (4).—This oxidation of **2** was carried out by the method of Jones, *et al.*[4] The product was recrystallized from acetone: mp 175–177°; ν_{NH} 3330, $\nu_{C=O}$ 1730, $\nu_{N-C=O}$ 1650 cm^{-1} in Nujol.

Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.53; H, 8.27; N, 6.76. Found: C, 69.88; H, 8.51; N, 6.79.

N-Acetyl-1-adamantanamin-4α- and -4β-ol (2, 7).—Keto amide **4** (2 g) dissolved in 25.0 ml of methanol was treated with 1.0 g of sodium borohydride dissolved in 6.0 ml of 0.1 *N* sodium hydroxide solution, and the mixture was allowed to stand at room temperature for 18 hr. The mixture was chilled at 0° and carefully treated dropwise with 50% acetic acid until the pH was 6–7. The mixture was concentrated under reduced pressure, and the residue was triturated with 50 ml of tetrahydrofuran. The insoluble material was removed by filtration, and the filtrate was chromatographed over a column (1.8-cm i.d.) of 100 g of silica gel[9d] which had been prepared from a slurry of the silica gel in ethyl acetate–SSB[9e] (5:1). The column was eluted in fractions of 50 ml each with the same solvent mixture. The frac-

(8) Pertinent nmr assignment data are contained in the discussion and are not repeated in the Experimental Section. Melting points were determined on a Fisher-Johns block and are corrected. Infrared spectra were determined on a Perkin-Elmer Infracord. Tlc was on silica gel plates developed with the following solvent systems for the compounds indicated: **2** and **7**, ethyl acetate–SSB (5:1); **11**, **12**, and **25**, acetone–SSB (1:1); **20** and **21**, ethyl acetate–methanol (19:1); **27**, benzene–methanol (4:1).

(9) Trade name products: (a) an alkylaryl sulfonate detergent, Atlantic Chemical Co., Nutley, N. J.; (b) a polyalkylene glycol, Union Carbide Chemical Co., New York, N. Y., and (c) Pittsburg Activated Carbon Co., Pittsburg, Pa.; (d) no. 7734 (0.05–0.20 mm), E. Merck AG, Darmstadt, Germany; (e) SSB = Skellysolve B, a petroleum hydrocarbon fraction, bp 60–70°, Skelly Oil Co., Kansas City, Mo.; (f) a synthetic magnesium silicate product, The Floridin Co., Warren, Pa.

tions were examined by tlc.[8] Fraction residues 21–28 were combined and recrystallized from methanol–benzene to yield 0.76 g of **2**, mp 176–177°.

This was identical by melting point and infrared with the 4-hydroxy product isolated directly from the biotransformation of N-acetyl-1-adamantanamine; also the mixture melting point was not depressed.

Fraction residues 41–79 were combined and recrystallized from methanol–benzene to yield 0.72 g of product, mp 206–207°. This was the β-hydroxy isomer (**7**) (see discussion).

Anal. Calcd for $C_{21}H_{19}NO_2$: C, 68.86; H, 9.15; N, 6.69. Found: C, 68.90; H, 9.17; N, 6.53.

1-Adamantanamin-3-ol Hydrochloride (6′).—A mixture of 300 mg of hydroxy amide **3** and 20 ml of 10% aqueous sodium hydroxide solution was heated at reflux for 22 hr. The mixture was diluted with 10 ml of water and extracted with ether. The extract was dried over potassium hydroxide, and the solvent was removed to give 220 mg of crystalline free base. A sample recrystallized from ether–hexane melted at 267° in a sealed tube. The hydroxy amine (**6**, 100 mg) was dissolved in 50 ml of ether and treated with ethereal hydrogen chloride. The resulting amine salt was recovered by filtration, washed with ether, and recrystallized from methanol–methyl ethyl ketone, mp >300° dec.

Anal. Calcd for $C_{10}H_{18}NOCl$: C, 58.96; H, 8.90; N, 6.88; Cl, 17.41. Found: C, 59.07; H, 9.05; N, 7.21; Cl, 17.75.

1-Adamantanamin-4α-ol (5) and the Hydrochloride (5′).—The hydrolysis of **2** and the work-up was carried out as described above for the C-3 hydroxy amide. The free base melted at 248–250° in a sealed tube.

Anal. Calcd for $C_{10}H_{17}NO$: C, 71.81; H, 10.25; N, 8.38. Found: C, 71.67; H, 10.40; N, 8.60.

The hydrochloride salt melted at >300° dec.

Anal. Calcd for $C_{10}H_{18}NOCl$: C, 58.96; H, 8.90; N, 6.88; Cl, 17.41. Found: C, 58.79; H, 8.82; N, 6.73; Cl, 17.32.

N-Benzoyl-N-methyl-1-adamantanamine (10) was prepared from 1-adamantanamine *via* the sequence of preparation of HCOOH salt, dehydration to N-formylamide, reduction to N-methyl-1-adamantanamine, and finally reaction of this with benzoyl chloride and sodium hydroxide.

1-Adamantanamine Formic Acid Salt.—A solution of 4.0 g of adamantanamine in 50 ml of benzene was treated with 1 equiv of 98% formic acid to precipitate the formate salt. The mixture was diluted with ether, and the product was recovered, washed with ether, and dried: yield, 3.51 g; subl pt >200°.

Anal. Calcd for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10. Found: C, 66.95; H, 9.79; N, 7.28.

N-Formyl-1-adamantanamine.—1-Adamantanamine formic acid salt (80 g) was mixed gently with 200 ml of acetic anhydride for several minutes. Heat was evolved and the solid went into solution. The mixture stood for 40 min, and then was stirred for 2 hr with 800 ml of water. The solids were recovered by filtration, washed with water, and dried: yield, 54.33 g; mp 130–136°. The filtrate was neutralized with 50% sodium hydroxide solution and allowed to stand to give a second crop, 15.75 g. The analytical sample, recrystallized from acetone–water, melted at 139–140°.

Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.90; H, 9.84; N, 7.98.

N-Methyl-1-adamantanamine Hydrochloride.—N-Formyl-1-adamantanamine (70 g) dissolved in 700 ml of dry tetrahydrofuran was added with stirring to a mixture of 40 g of lithium aluminum hydride in 2000 ml of dry ether. The mixture was then heated at reflux for 4 hr and then chilled in an ice–acetone bath; 150 ml of water was cautiously added to the stirred mixture. The solids were removed by filtration and washed well with ether. The combined filtrate and wash were dried ($MgSO_4$) and treated with ether containing 1 equiv of hydrogen chloride. The solid HCl salt was recovered by filtration, washed with ether, and dried: yield, 66.0 g; mp 248–250°. The analytical sample recrystallized from methanol–methyl ethyl ketone melted at 250°.

Anal. Calcd for $C_{11}H_{20}NCl$: C, 65.49; H, 9.99; N, 6.94; Cl, 17.58. Found: C, 65.32; H, 10.25; N, 6.86; Cl, 17.55.

N-Benzoyl-N-methyl-1-adamantanamine (10).—A mixture of 25.0 g of N-methyl-1-adamantanamine hydrochloride, 250 ml of 10% sodium hydroxide solution, and 25.0 ml of benzoyl chloride chilled at 0° was stirred vigorously for 2 hr. The product was recovered by filtration, washed with water, and dried: yield, 28.12 g; mp 117–119°. A sample recrystallized from aqueous acetone melted at 117–119°.

Anal. Calcd for $C_{18}H_{23}NO$: C, 80.25; H, 8.61; N, 5.20. Found: C, 80.03; H, 8.69; N, 5.30.

Isolation of Products from the Bioconversion of N-Benzoyl-N-methyl-1-adamantanamine.—The methylene chloride extract residue from an 18-g fermentation was placed on a column of Florisil[9f] (700 g) with 850 ml of methylene chloride followed by linear gradient elution in fractions of 350 ml each with 8 l. of solvent, SSB containing increasing proportions of acetone from 10 to 70%. This was followed with 4 l. of SSB + 70% acetone and finally 4 l. of acetone. After examination of the fraction residues by ir and tlc,[8] product fractions were pooled as reported in Table II.

TABLE II

Pool	Fractions	Wt, g
I	7–13	4.08
II	18–41	13.36

N-Benzoyl-N-methyl-1-adamantanamin-4α-ol (12).—Pool I was recrystallized from aqueous acetone: yield, 2.84 g, mp 179–181°; ν_{OH} 3400, $\nu_{N-C=O}$ 1610 cm^{-1} in Nujol.

Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.75; H, 8.12; N, 4.91. Found: C, 75.77; H, 8.35; N, 4.90.

N-Benzoyl-N-methyl-1-adamantanamine-4α,6α-diol (11).—Pool II was recrystallized from aqueous methanol: yield, 10.39 g; mp 223–226°; ν_{OH} 3430, 3200, $\nu_{N-C=O}$ 5190, 1570 cm^{-1} in Nujol.

Anal. Calcd for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.87; H, 8.02; N, 4.81.

Bioconversion of N-Benzoyl-N-methyl-1-adamantanamin-4α-ol (12) to N-Benzoyl-N-methyl-1-adamantanamine-4α,6α-diol (11).—The methylene chloride extract residue from a 2.0-g fermentation was chromatographed over 150 g of silica gel.[9d] The column was eluted in 50-ml fractions with ethyl acetate which had been saturated with water. Fractions 4–6 contained unchanged substrate; fractions 7–8 were a mixture; fractions 9–14 contained product. These later fractions were pooled and recrystallized from methanol–water: yield, 0.76 g; mp 223–226°. The infrared spectrum was identical with that of the diol described in the previous experiment. The mixture melting point of this product and the dihydroxyamide described above was not depressed.

N-Benzoyl-N-methyl-1-adamantanamine-4α,6α-diol Diacetate (11′).—Dihydroxy amide **11** (0.5 g), pyridine (5.0 ml), and acetic anhydride (2.0 ml) were mixed and warmed to dissolve the reactants and allowed to stand at room temperature for 17 hr. The mixture was poured onto ice and stirred for several minutes. The product was recovered by filtration, washed with water, and recrystallized from aqueous acetone, mp 141–142°.

Anal. Calcd for $C_{22}H_{27}NO_5$: C, 68.55; H, 7.06; N, 3.63. Found: C, 68.88; H, 7.35; N, 3.75.

N-Benzoyl-N-methyl-1-adamantanamine-4,6-dione (14).—Dihydroxy amide **11** (2 g) dissolved in acetone by heating was treated dropwise with a slight excess of chromic acid solution by the Jones method.[4] The resulting product was recrystallized from aqueous methanol: yield, 1.70 g. For spectral and elemental analysis it was necessary to dry a sample at its melt temperature, 157–160°, to remove water of crystallization: $\nu_{C=O}$ 1740, 1700, $\nu_{N-C=O}$ 1620 cm^{-1} in Nujol.

Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.70; H, 6.44; N, 4.71. Found: C, 72.79; H, 6.82; N, 5.07.

The Disemicarbazone (14′) had mp 280° dec.

Anal. Calcd for $C_{20}H_{25}N_7O_3$: C, 58.38; H, 6.12; N, 23.83. Found: C, 58.15; H, 6.07; N, 23.42.

N-Benzoyl-N-methyl-1-adamantanamine-4α,6α-diol Cyclic Sulfite Ester (13).—Diol **11** (0.5 g) was treated with 1.0 ml of thionyl chloride; immediate heat of reaction was noted and after 15 min the excess reagent was removed under reduced pressure. The residue was chromatographed over 100 g of Florisil by the linear gradient method, placing the material on the column with methylene chloride and eluting in fractions of 110 ml each, with 4 l. of solvent, SSB containing increasing proportions of acetone from 0 to 40%. Fractions 13–16 contained 0.35 g of product which was recrystallized from ether–hexane: white needles; mp 172–173°; ν_{OH} no peak, $\nu_{N-C=O}$ 1705 cm^{-1} in Nujol.

Anal. Calcd for $C_{18}H_{21}NO_4S$: C, 62.22; H, 6.09; N, 4.03; S, 9.23. Found: C, 62.28; H, 5.64; N, 3.73; S, 9.21.

N-Benzoyl-N-methyl-1-adamantanamine-4α,6α-diol Hydrochloride (17′).—Dihydroxy-N-methylbenzamide **11** (4 g) was reduced with a mixture of 4.0 g of lithium aluminum hydride in 100 ml of ether. Because of low solubility, the amide was placed into a Soxhlet and leached into the reaction mixture by the refluxing solvent. The mixture was worked up in the usual manner, and the solid residue of free base was taken up in ether. Addition of ethereal hydrogen chloride precipitated the hydrochloride salt which was recrystallized from methanol–methyl ethyl ketone: yield 3.0 g; mp 267–269°.

Anal. Calcd for $C_{18}H_{26}NO_2Cl$: C, 66.75; H, 8.09; N, 4.33; Cl, 10.95. Found: C, 66.71; H, 8.34; N, 4.36; Cl, 11.17.

N-Benzoyl-N-methyl-1-adamantanamin-4-one (15).—Hydroxybenzamide **12** (70 mg) dissolved in 10 ml of acetone was oxidized with chromic acid by the method of Jones, *et al.*[4] The product was recrystallized from aqueous acetone: mp 126–127°; $\nu_{C=O}$ 1720, $\nu_{N-C=O}$ 1620 cm^{-1} in Nujol.

Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47; N, 4.94. Found: C, 76.13; H, 7.54; N, 5.07.

N-Benzyl-N-methyl-1-adamantanamin-4α-ol (16).—Hydroxyamide **12** (4 g) in 150 ml of dry tetrahydrofuran was added with stirring to a mixture of 3.0 g of lithium aluminum hydride in 100 ml of anhydrous ether. The mixture was heated at reflux for 150 min; a cold bath was applied, and 20 ml of water was added with caution while stirring was continued for 30 min. The mixture was filtered and the insoluble material was washed well with ether. The filtrate and wash was dried over magnesium sulfate and the solvent removed to give 3.36 g of product. A sample was recrystallized from ether–hexane for analysis, mp 119–120°.

Anal. Calcd for $C_{18}H_{25}NO$: C, 79.66; H, 9.29; N, 5.16. Found: C, 79.44; H, 9.10; N, 5.07.

N-Methyl-1-adamantanamin-4α-ol and the Hydrochloride (9).—Benzyl amine **16** (3 g) was dissolved in 60 ml of ethanol. 10% palladium-on-carbon catalyst (0.5 g) was added, and the mixture was shaken wih hydrogen (42 psi) for 150 min. The mixture was freed of catalyst and concentrated to dryness under reduced pressure to a solid residue. A sample of 1.0 g was recrystallized from ether, mp 141–142°.

Anal. Calcd for $C_{11}H_{19}NO$: C, 72.88; H, 10.57; N, 7.73. Found: C, 72.82; H, 10.38; N, 7.49.

The remainder of the residue was dissolved in ether and treated with ethereal hydrogen chloride, and the resulting amine salt was recovered by filtration and washed with ether, yield 1.26 g. For analysis a sample was recrystallized from methanol–acetone, mp 220–221°. This compound was identical by infrared and melting point with the hydroxy amine hydrochloride prepared from 4-hydroxy-1-adamantanamine *via* the N-formylamine and hydride reduction; their mixture melting point showed no depression.

Anal. Calcd for $C_{11}H_{20}NOCl$: C, 60.67; H, 9.26; N, 6.43; Cl, 16.29. Found: C, 60.54; H, 9.50; N, 6.42; Cl, 16.42.

1-Adamantanamin-4α-ol Formic Acid Salt.—A solution of 3.5 g of hydroxy amine (**5**) in 1 l. of ether was treated with a slight excess of 98% formic acid. The resulting precipitate of formic acid salt was recovered by filtration and washed with ether: yield 3.60 g; mp 238–239°.

N-Formyl-1-adamantanamin-4α-ol (8).—Formic acid salt (1 g) was heated at 270° for 2 min and cooled. The residue was taken up in a small volume of ethyl acetate and chromatographed over a column prepared from a slurry of 100 g of silica gel[9d] and ethyl acetate saturated with water. The column was eluted with the same solvent in fractions of 50 ml each. Product fractions (14–19) were determined by infrared inspection of the residues (0.58 g). A sample for analysis was recrystallized from methanol–benzene, mp 141–142°.

Anal. Calcd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.52; H, 8.79; N, 7.42.

N-Methyl-1-adamantanamin-4α-ol Hydrochloride (9).—A mixture of 0.5 g of hydroxyformamide (**8**), 2.0 ml of pyridine, and 1.0 ml of acetic anhydride was allowed to stand at 25° for 16 hr. The mixture was diluted with water and extracted with methylene chloride. The extract was washed with dilute sulfuric acid, water, and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was taken up in 25 ml of anhydrous tetrahydrofuran and added with stirring to a mixture of 0.5 g of lithium aluminum hydride in 25 ml of anhydrous ether. The mixture was heated at reflux for 2 hr and chilled at 0° during the addition of 5.0 ml of water. After stirring 30 min, the mixture was filtered, the solids were washed well with ether, and the combined filtrate and wash were dried ($MgSO_4$). The solution was filtered and treated with a slight excess of ethereal hydrogen chloride. The amine salt was recovered by filtration and recrystallized from methanol–acetone, mp 219–220°. This product was identical by infrared and melting point with the HCl salt prepared from N-benzoyl-N-methyl-1-adamantanamin-4α-ol *via* the benzyl amine. The mixture melting point showed no depression.

N-Acetyl-N-methyl-1-adamantanamine (19).—A solution of 6.5 g of N-methyl-1-adamantanamine hydrochloride (see above) in 100 ml of water was treated dropwise with a slight excess of 50% aqueous sodium hydroxide solution. The precipitated free base was recovered by filtration, washed with water, and dried: yield, 5.49 g.

The free base was dissolved in 25 ml of pyridine; 5 ml of acetic anhydride was added; and the mixture was allowed to stand at 25° for 56 hr. After diluting with 100 ml of water and chilling the product was recovered, washed well with water, and dried: yield, 3.65 g; mp 123–124°.

Isolation of Products from the Bioconversion of N-Acetyl-N-methyl-1-adamantanamine.—The methylene chloride extract residue from a 2.0-g fermentation was dissolved in methylene chloride and chromatographed over 100 g of Florisil. Elution was by the gradient method taking 100-ml fractions each using 4 l. of solvent, SSB containing increasing proportions of acetone from 0 to 30%. As indicated by tlc,[8] fraction residues were pooled as reported in Table III. Pool A and pool C were separate entities and pool B was a mixture of the two.

TABLE III

Pool	Fractions	Wt, g
A	25–32	0.982
B	33–35	0.210
C	36–39	0.212

N-Acetyl-N-methyl-1-adamantanamin-4α-ol (20).—Pool A was recrystallized from acetone–hexane: yield, 0.717 g; mp 151–154°; ν_{OH} 3360, $\nu_{N-C=O}$ 1610 cm^{-1} in Nujol.

Anal. Calcd for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27. Found: C, 70.09; H, 9.57; N, 6.36.

This compound was readily oxidized to ketone by the Jones method:[4] mp 119–120°; $\nu_{C=O}$ 1740, $\nu_{N-C=O}$ 1640 cm^{-1} in Nujol.

N-Acetyl-N-methyl-1-adamantanamin-3-ol (21).—Pool C was recrystallized from acetone–hexane to yield 0.140 g of **21**: mp 155–156°; ν_{OH} 3310, $\nu_{N-C=O}$ 1610 cm^{-1} in Nujol.

Anal. Calcd for $C_{13}H_{21}NO_2$: C, 69.02; H, 9.48; N, 6.27. Found: C, 69.05; H, 9.26; N, 6.24.

This compound did not oxidize to ketone with chromic acid; unchanged starting material was recovered.

N-Phenylacetyl-1-adamantanamine (22).—A mixture of 20.0 g of 1-adamantanamine hydrochloride, 40 ml of 50% aqueous sodium hydroxide solution, 160 g of ice, and 20 ml of phenylacetylchloride was stirred vigorously for 1 hr and allowed to stand. The product was recovered by filtration and washed with water and air dried: yield, 20.23 g; mp 176–179°. An analytical sample recrystallized from acetone melted at 181–183°.

Anal. Calcd for $C_{18}H_{23}NO$: C, 80.25; H, 8.61; N, 5.20. Found: C, 79.89; H, 8.88; N, 5.04.

N-Phenylacetyl-1-adamantanamine-4α,6α-diol (23).—The methylene chloride extract residue from a 2-g fermentation of **22** was triturated with 50 ml of methylene chloride and filtered to obtain 1.05 g of solid product which was combined with that obtained from the chromatograph described below.

The filtrate was placed on a column of 100 g of Florisil. Elution was by the gradient method with 6 l. of solvent, SSB containing increasing proportions of acetone from 0 to 60%. Fractions of 55 ml each were collected. Fraction residues 78–83 (0.36 g) were identical with the material obtained by direct isolation. This combined product (1.41 g) was recrystallized from acetone after treatment with activated carbon (Darco G 60) in the same solvent: mp 201–202°; $\nu_{OH,NH}$ 3300, $\nu_{N-C=O}$ 1640, 1550 cm^{-1} in Nujol.

Anal. Calcd for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.74; H, 7.94; N, 4.62.

N-Cyclohexylcarbonyl-N-methyl-1-adamantanamine (24).—A mixture of 20.0 g of N-methyl-1-adamantanamine hydrochloride and 200 ml of 10% aqueous sodium hydroxide solution was chilled at 5° and treated with 20 ml of cyclohexanecarbonyl chloride during 120 min with vigorous stirring. The mixture

was extracted with methylene chloride; the extract was washed with water, dilute hydrochloric acid, 5% sodium bicarbonate solution, and dried over sodium sulfate. Evaporation of the solvent gave 20.20 g of solid product which was recrystallized from aqueous methanol, mp 91–93°.

Anal. Calcd for $C_{18}H_{29}NO$: C, 78.40; H, 10.61; N, 5.09. Found: C, 78.29; H, 10.90; N, 5.04.

N-Cyclohexylcarbonyl-N-methyl-1-adamantanamine-4α,6α-diol (25).—The methylene chloride extract residue from a 2.0-g fermentation of **24** was chromatographed over 100 g of Florisil. The column was eluted by the gradient method with 4 l. of solvent, SSB containing increasing amounts of acetone from 0 to 40%. Fractions of 110 ml each were collected, and the residues were examined by tlc.[8] Fractions 25–29 were pooled and recrystallized from acetone to yield 0.174 g of **25**: mp 190–191°; ν_{OH} 3400, $\nu_{N-C=O}$ 1620 cm^{-1} in Nujol.

Anal. Calcd for $C_{18}H_{29}NO_3$: C, 70.32; H, 9.51; N, 4.56. Found: C, 70.31; H, 9.51; N, 5.35.

Fractions 33–37 gave another material which also analyzed for a diol. This structure has not been determined.

N-(1-Adamantyl)phthalimide (26).—A mixture of 7.5 g of 1-adamantanamine, 10.0 g of phthalic anhydride, and 100 ml of pyridine was heated at 90° for 15 min; 100 ml of acetic anhydride was added; and the mixture was again heated at 90° for 1 hr. After cooling and stirring with 500 ml of water for 1 hr the product was recovered by filtration, washed with water, and crystallized from methanol: yield, 2.13 g; mp 140–143°.

Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.75; H, 7.02; N, 5.01.

N-(4α,6α-Dihydroxy-1-adamantyl)phthalimide (27).—The filtered beer (10 l.) from the conversion of 2.0 g of **26** was poured over a column of 300 g of CAL carbon.[9c] The column was eluted first with 10 l. of methanol, followed with 5 l. of ethyl acetate, and finally 5 l. of chloroform. Thin layer chromatography[8] showed that the chloroform eluate contained the product. The residue therefrom was chromatographed over 100 g of Florisil. Elution was by the linear gradient method with 4 l. of solvent SSB containing increasing amounts of acetone from 0 to 40%; cuts were *ca.* 110 ml each. The product eluted in fractions 23–28 was recrystallized from acetone–hexane: mp 218–220°.

Anal. Calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 68.81; H, 6.39; N, 4.21.

Registry No.—**2**, 16790-57-1; **3**, 778-10-9; **4**, 16790-59-3; **5**, 16790-60-6; **5′**, 16790-61-7; **6′**, 16790-62-8; **7**, 16790-63-9; 1-adamantanamine formic acid salt, 16790-64-0; N-formyl-1-adamantanamine, 3405-48-9; N-methyl-1-adamantanamine hydrochloride, 3717-39-3; **8**, 16790-67-3; free base of **9**, 16790-68-4; **10**, 16790-69-5; **11**, 16790-70-8; **11′**, 16790-71-9; **12**, 16790-72-0; **13**, 16790-73-1; **14**, 16790-74-2; **14′**, 16790-75-3; **15**, 16790-76-4; **16**, 16790-77-5; **17′**, 16790-78-6; **19**, 3717-37-1; **20**, 16790-80-0; **21**, 16790-81-1; **22**, 16790-82-2; **23**, 16790-83-3; **24**, 16790-84-4; **25**, 16790-85-5; **26**, 16808-41-6; **27**, 16790-86-6.

Acknowledgment.—We thank J. R. Heald, I. N. Pratt, S. L. Towne, H. M. Woltersom, J. M. Noteboom, and M. J. Sutton for technical assistance; N. H. Knight and associates for microanalyses; and G. Slomp and associates for some of the nmr spectra.

The Microbiological Hydroxylation of 1-Benzoyl-*trans*-decahydroquinoline. Determination of Structure, Stereochemistry, and Absolute Configuration of the Products

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Received February 7, 1968

Microbiological hydroxylation of (±)-1-benzoyl-*trans*-decahydroquinoline [(±)-**2**] with *Sporotrichum sulfurescens* has been shown to give (4a*S*,5*S*,8a*R*)-1-benzoyl-*trans*-decahydroquinolin-5-ol (**3**), (±)-1-benzoyl-*trans*-decahydroquinolin-6-ol (**4**), and (4a*S*,7*S*,8a*S*)-1-benzoyl-*trans*-decahydroquinolin-7-ol (**5**) in a total yield of 80–90%. Under the same conditions hydroxylation of (+)-**2** gave optically pure (+)-**5** and (4a*S*,6*S*,8a*S*)-1-benzoyl-*trans*-decahydroquinolin-6-ol [(+)-**4**] in a ratio of 35:65. Hydroxylation of (−)-**2** gave optically pure (−)-**3** and (4a*R*,6*R*,8a*R*)-1-benzoyl-*trans*-decahydroquinolin-6-ol [(−)-**4**] in a ratio of 87:13. Various chemical modifications of these products were carried out in order to determine their structures and stereochemistry and included the conversions of **3**, (+)-**5**, and (+)-**4** into (4a*S*,8a*R*)-*trans*-decahydroquinolin-5-one (**24**), (4a*S*,8a*S*)-*trans*-decahydroquinolin-7-one (**26**), and (4a*S*,8a*S*)-*trans*-decahydroquinolin-6-one (**25**), respectively. Application of the octant rule to the optical rotatory dispersion curves of the latter compounds allowed assignment of absolute configurations to the hydroxylation products. The absolute configurations of the parent molecules, (−)-*trans*-decahydroquinoline [(−)-**1**] and (+)-*trans*-decahydroquinoline [(+)-**1**], can be assigned as (4a*R*,8a*S*)-*trans*-decahydroquinoline and (4a*S*,8a*R*)-*trans*-decahydroquinoline, respectively.

The increasing number of substrates which are hydroxylated by the microorganism *Sporotrichum sulfurescens* provides an opportunity to explore further the relationships of the substrate molecules to the enzymic hydroxylation site. A recent proposal[1] has suggested that an electron-rich center of the substrate molecule provides an attachment site for the hydroxylating enzyme and thus facilitates oxygenation at some point in a saturated portion of the molecule. The approximate distance of this point from the attachment site was suggested to be 5.5 Å. Among the electron-rich centers which have been found useful are the alcohol[1] and the amide[2–4] functional groups. It seemed possible that additional information concerning the stereochemical relationship of the substrate molecule to the site of oxygenation could be obtained from examination of the oxygenated products. Some information concerning the stereochemistry of hydroxylation of the steroid nucleus has been gathered.[5] It is known,

(1) G. S. Fonken, M. E. Herr, H. C. Murray, and L. M. Reineke, *J. Amer. Chem. Soc.*, **89**, 672 (1967).

(2) G. S. Fonken, M. E. Herr, H. C. Murray, and L. M. Reineke, *J. Org. Chem.*, **33**, 3182 (1968).

(3) R. A. Johnson, M. E. Herr, H. C. Murray, and G. S. Fonken, *ibid.*, **33**, 3187 (1968); R. A. Johnson, M. E. Herr, H. C. Murray, L. M. Reineke, and G. S. Fonken, *ibid.*, **33**, 3195 (1968)

(4) M. E. Herr, R. A. Johnson, H. C. Murray, L. M. Reineke, and G. S. Fonken, *ibid.*, **33**, 3201 (1968).

(5) C. Tamm, *Angew. Chem. Intern. Ed. Engl.*, **1**, 178 (1962).

for example, that both 11α hydroxylation of steroids by *Rhizopus nigricans*[6] and 11β hydroxylation by the adrenal glands[7] proceed by substitution of the hydrogen by oxygen without changing the configuration of the remaining 11-hydrogen atom.

In studies of the oxygenation of various amides, we have found that hydroxylation of (±)-1-benzoyl-*trans*-decahydroquinoline [(±)-**2**] with *S. sulfurescens* gave a mixture of monohydroxy products, some of which were optically active, in excess of 80% yield. Formation of optically active products in yields greater than 50% suggested that the hydroxylating enzyme of the organism has a specificity for oxidative attack at different methylene groups of the enantiomers of the substrate. Thus, both enantiomers are hydroxylated, but necessarily at different positions in order to produce optically active products. This bioconversion reaction has therefore been studied in depth with the hope of obtaining stereochemical information about the hydroxylation process. The characterization, the determination of structure and stereochemistry, and the determination of the absolute configuration of the products are included in the following discussion.

Characterization of Products.[8]—The products from bioconversion of (±)-1-benzoyl-*trans*-decahydroquinoline [(±)-**2**] with *S. sulfurescens* were extracted from the filtered beer with methylene chloride. Initial attempts at separation of the products by column chromatography were only partially successful. Two products, **3** (mp 121–123°, $[\alpha]_D$ −94°) and **4** (mp 149–151°, $[\alpha]_D$ +3°), were obtained from the chromatography fractions. The optical rotation of **3** indicated that it had been obtained with some degree of optical purity; however, no conclusion about the optical purity of **4** could be drawn from its rotation. In addition to these two compounds, a third (**5**, mp 185–187°, $[\alpha]_D$ +132°) was shown to be present in the later column fractions by paper chromatography. It appeared that both the problems of characterization of the bioconversion products and of the determination of their optical purity could be attacked more easily if the racemic substrate [(±)-**2**] could be resolved into the (+) and (−) enantiomers.

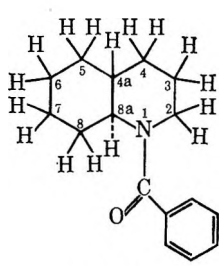
Resolution of racemic *trans*-decahydroquinoline [(±)-**1**] with *d*-tartaric acid[9] gave (−)-**1**, which was converted into (+)-**2** (+139°). Oxygenation of (+)-**2** with *S. sulfurescens* gave a mixture of two products, which were partially separated by column chromatography over silica gel. The two optically pure products, (+)-**5** (mp 185–186°, $[\alpha]_D$ +137°) and (+)-**4** (mp 138–139°, $[\alpha]_D$ +115°), had the same R_f values on paper chromatograms as did the optically impure compounds **5** and **4**, respectively.

Resolution of (±)-**1** with *d*-(α)-bromocamphor-π-sulfonic acid[10] gave (+)-**1** from which the benzamide (−)-**2** ($[\alpha]_D$ −145°) was prepared. Hydroxylation of (−)-**2** with *S. sulfurescens* gave two products, which were separated by chromatography on a silica gel column. These optically pure products, (−)-**3** (mp 125–127°, $[\alpha]_D$ −109°) and (−)-**4** (mp 136–138°, $[\alpha]_D$ −112°), had the same R_f values on paper chromatograms as did the optically impure compounds **3** and **4**, respectively.

The interrelationships between the products, suggested by paper chromatography, were confirmed by infrared and nmr spectra and are outlined in Scheme I. The pairs of compounds **3** and (−)-**3**, **5** and (+)-**5**, (+)-**4** and (−)-**4** each have identical infrared spectra. It was necessary to compare compounds (+)-**4** and **4** by the means of a solution spectra since, in the solid phase, their infrared spectra differed. Nmr spectra of (+)-**4** and **4** also are identical.

The ratios of products in this bioconversion are of interest if enzyme specificity for the enantiomeric forms of the substrate is to be considered. Estimates of product ratios can best be made from the yields obtained when the resolved forms of the substrate were oxygenated. The ratio of (+)-**5** to (+)-**4** is 35:65 as estimated from paper and thin layer chromatograms of the product mixtures. The ratio of (−)-**3** to (−)-**4** is 87:13 as determined from the yields of the two products after separation on a silica gel column. These ratios between products also should exist when racemic substrate is used. From this the ratio of (+)-**4** to (−)-**4** can be estimated as 83:17, *part* of which is represented by the racemate **4**.

Structure and Stereochemistry.—The substrate molecule, (±)-1-benzoyl-*trans*-decahydroquinoline (**2**), contains 16 geometrically different hydrogen atoms. When the enantiomers of **2** are considered, there are 32 stereoisomeric possibilities to choose from in assigning structures to the four products obtained from bioconversion of **2**. These four products are known to consist



(±)-**2**

of an enantiomeric pair of alcohols, (+)-**4** and (−)-**4** (which also form **4**), and two optically active products, **3** and **5**. The problem of structural determination is therefore essentially that of determining three unknowns. The 32 possible structures were quickly reduced to 16 by oxidation of each alcohol to a ketone. Formation of a ketone, in itself, eliminates placing the hydroxy groups at carbon atoms 4a, 8a, and 2 of the decahydroquinoline nucleus since the first two posi-

(6) M. Hayano, M. Gut, R. I. Dorfman, O. K. Sebek, and D. H. Peterson, *J. Amer. Chem. Soc.*, **80**, 2336 (1958).

(7) E. J. Corey, G. A. Gregoriou, and D. H. Peterson, *ibid.*, **80**, 2338 (1958).

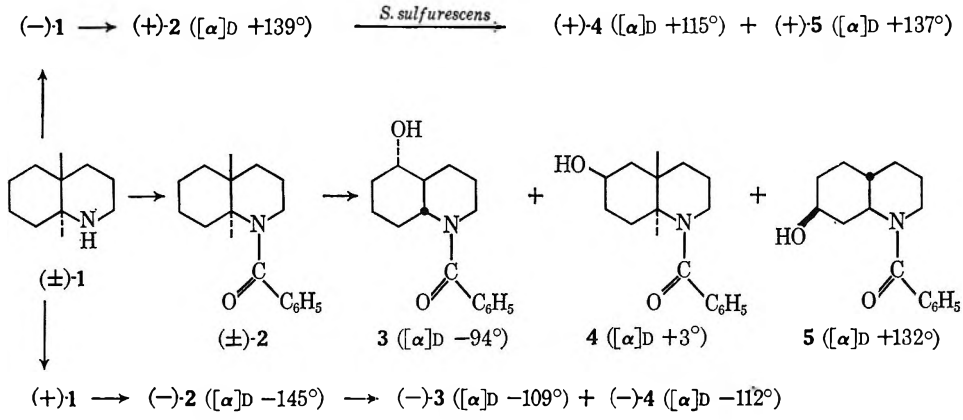
(8) Several of the compounds encountered in this work have been obtained in varying degrees of optical purity. We have adopted the following system for numbering these compounds in this paper. For compounds **1** through **5**, placement of (±)- before the number indicates that the compound is a racemate. When (+)- or (−)- is placed before the number, the optically pure enantiomer is indicated. When no sign is placed before the number, an optically impure (but still optically active) compound is indicated. Compounds **6–26** involve chemical transformations and in most cases the optical nature of the compound is apparent from the discussion. Signs, in accord with the above system, are placed before these numbers only when they add to the clarity of the discussion.

In the structural formula, the use of solid or dotted lines to depict the ring junction hydrogen atoms (4a and 8a) indicates that the compound is a racemate. Use of heavy dots to depict ring junction stereochemistry indicates that the compound is optically active and in all cases is indicative of the correct absolute configuration of the molecule.

(9) A. Popovici, C. F. Geschickter, E. L. May, and E. Mosettig, *J. Org. Chem.*, **21**, 1283 (1956).

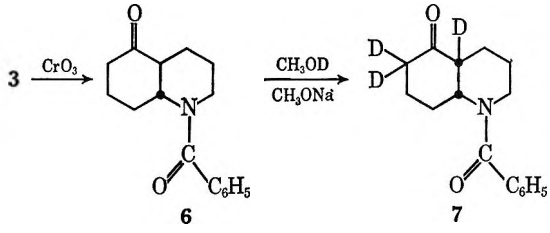
(10) L. Mascarelli and F. Nigrisoli, *Gazz. Chim. Ital.*, **45**, 106 (1915).

SCHEME I



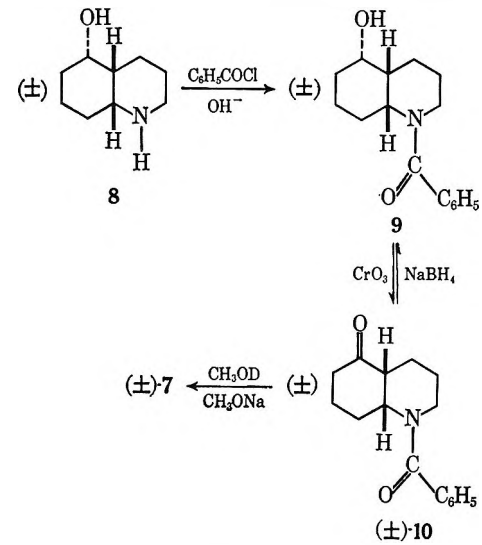
tions are tertiary and the latter would be an imide. In addition, nmr spectra of the ketones clearly eliminated carbon atoms 3 and 8 as positions of oxygenation, since the very characteristic signal expected for protons (at C-2 and C-8a) adjacent to both nitrogen and carbonyl were not observed.

The remaining possible positions of oxygenation were further differentiated by deuterium-exchange experiments with the ketones. The ketone (**6**), obtained upon oxidation of **3** with Jones reagent,[11] undergoes ex-



change of three hydrogen atoms by deuterium atoms in methyl alcohol-*d* with sodium methoxide catalyst. The incorporation of deuterium was demonstrated by an increase in the molecular ion peak from 257 to 260 in the mass spectra of the two compounds. It will be shown below that, in addition to isotopic exchange, the deuterated product (**7**) has an inverted configuration at the 4a position. To undergo exchange of only three hydrogens by deuterium, the carbonyl group must be at either C-4 or C-5 in **6**, since C-8 has already been eliminated as a possible site for oxygen. Under the same conditions, the other two ketones both underwent exchange of four hydrogens by deuterium. Consequently one ketone must be a C-6 ketone and the other a C-7 ketone, since the only other position having four α hydrogens (C-3) has been eliminated by the nmr spectra. These two ketones will be discussed more fully later.

The position of the carbonyl in ketone **6**, now known to be adjacent to C-4a, could be established by the synthesis of either the C-4 or C-5 ketone.[12] A simple route to the 5 ketone seemed feasible using (±)-5α-hydroxy-*cis*-decahydroquinoline (**8**), a compound readily available by the catalytic reduction of 5-hydroxyquinoline,[13] as a starting point. The presence of a *cis*-ring junction in **8** was not serious since the ring system of the 5 ketone could be equilibrated to the more stable ring juncture. Reaction of **8** with benzoyl chloride in the presence of an excess of sodium hydroxide gave the hydroxy amide **9** directly. Oxidation of **9** with Jones reagent[11] gave racemic keto amide (±)-**10**. The *cis*-ring junction was



shown to remain in (±)-**10** by reduction of the ketone with sodium borohydride, which gave hydroxy amide **9** starting material as the only product isolated (70%). Deuterium exchange with (±)-**10** was carried out, and the product had a mass spectrum identical with that of **7**. The position of the carbonyl in **6** must be at C-5 and likewise, the hydroxyl group of compound **3** must be at C-5.

Several additional points of interest concerning the ketone **6** may be noted. Reaction of **6** with sodium methoxide in methanol resulted in isomerization to the *cis* ketone **10**, confirming that the *cis*-ring system is the more stable for this molecule. A small amount of **10** also was separated from **6** when the products of the Jones oxidation of **3** were chromatographed on Florisil. Reduction of ketone **6** with sodium borohydride gave two alcohols, one of which was identical with **3**. The second alcohol (**11**) is assumed to be the C-5 epimer of alcohol **3**. It had been hoped that this reduction would be stereospecific and would indicate the configuration of the hydroxyl group in **3**.

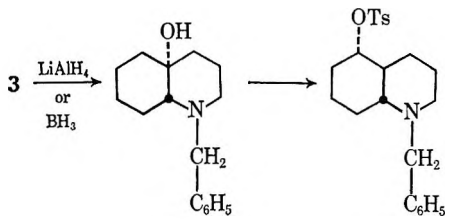
A second method for distinguishing between an axial and an equatorial hydroxyl group is that of measuring the half-band width of the nmr signal of the proton of

(11) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(12) When this synthesis was carried out, the deuterium-exchange experiments had not been completed and we felt that on the basis of previous experience[1] oxygenation at C-4 and C-5 had probably occurred and that the synthesis of either would identify one compound.

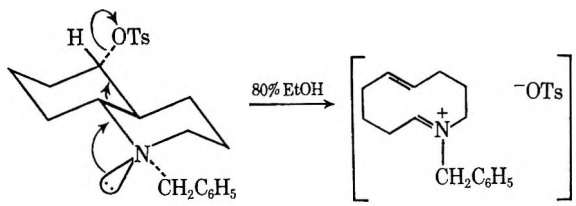
(13) C. A. Grob and H. R. Kiefer, *Helv. Chim. Acta*, **48**, 799 (1965).

the alcohol carbon.[14] This method takes advantage of the greater coupling constants between axial protons and assigns the axial configuration to protons having a half-band width of 20 cps or greater and an equatorial configuration to those having a half-band width of about 8 cps.[14] The signal of the C-5 proton in the nmr spectra of **3** and several of its derivatives is very broad, suggesting an axial configuration and therefore an equatorial configuration for the hydroxyl group. This stereochemical assignment was confirmed by carrying out a fragmentation reaction analogous to those described by Grob and coworkers.[15] To accomplish this, alcohol–amide **3** was reduced with either lithium aluminum hydride or diborane to the benzylamine (**12**). We have found that diborane is an excellent agent for the reduction of benzamides to benzyl amines, a reaction which often results in additional hydrogenolysis of the benzyl group when done with lithium aluminum hydride.



12 **13**

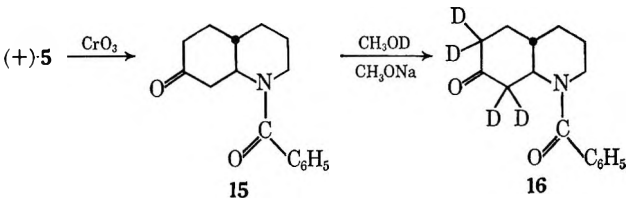
The preparation of the tosylate (**13**) of **12** gave a compound, which, if the tosyl group is equatorial, differs from a compound described by Grob and coworkers[15] only in having a N-benzyl instead of a N-methyl group. Fragmentation of this molecule would then be expected when warmed in 80% ethanol.[15] The fragmentation product (**14**) may be expected to hydrolyze to



13 **14**

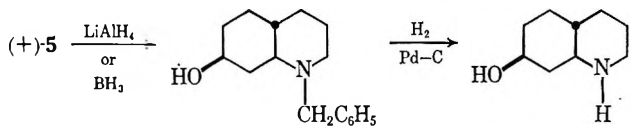
an amino aldehyde under the conditions of the reaction.[15] When **13** was heated to 75–78° in 80% ethanol, the partially insoluble compound slowly went into solution. The oil isolated from the reaction had a multiplet (integrating for 1.7 hydrogens) at 5.28 (δ) ppm in the nmr spectrum characteristic of olefinic protons, which would result in large amounts only from the fragmentation reaction. This firmly establishes that the C-5 hydroxyl group in the bioconversion product **3** has an equatorial configuration.

As outlined previously, the other hydroxylic bioconversion products also were converted to ketones and were submitted to deuterium-exchange reactions. Thus, oxidation of alcohol (+)-**5** with Jones reagent[11] gave ketone **15** of molecular weight 257 by mass spectrometry. Deuterium exchange with ketone **15** gave ketone **16** of molecular weight 261 by mass spectrometry, showing an exchange of four hydrogens by deuterium. A polymorphic crystalline form of ketone **15** was obtained from an early experiment in which the ketone was treated with a dioxane–ether solution of hydrogen chloride.



15 **16**

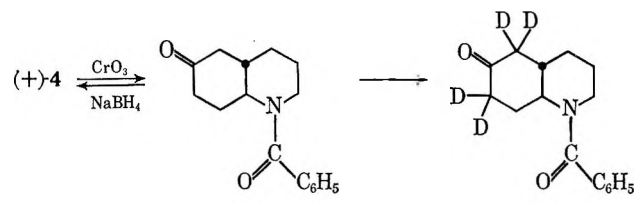
Reduction of bioconversion alcohol (+)-**5** with lithium aluminum hydride gave a mixture of benzyl amine **17** and amine **18**. When diborane was used



17 **18**

as the reducing agent, the benzyl amine **17** was the only product isolated. Compound **17** had a wide melting point range which could not be improved by varying the crystallization procedure. Elemental analysis showed an additional mole of water present in the product, presumably as a hydrate. Hydrogenolysis of the hydrate of **17** over palladium on carbon gave the amine **18**. This reaction sequence enabled us to compare compound **18** with the 7α-hydroxy-*trans*-decahydroquinoline [(±)-**18**] prepared and described by Grob and Wilkens.[16] It was necessary to compare the two samples by solution spectra since the biconversion product (**18**) is optically active while the synthetic sample of Grob and Wilkens[16] is not. The two compounds have identical infrared spectra in chloroform solution. This identity establishes the structure of **18** as being the 7-hydroxy-*trans*-decahydroquinoline having an equatorial hydroxyl configuration.

By elimination, the remaining bioconversion alcohols (**4**, obtained in both enantiomeric forms and as a racemate) must have the hydroxyl group at the 6 position. Oxidation of (+)-**4** with Jones reagent[11] gave ketone **19**, which incorporated four deuterium atoms dur-



19 **20**

ing exchange with methyl alcohol-*d*. The deuterated ketone (**20**) had a molecular ion peak at 261 mass units in the mass spectrum.

To determine the configuration of the C-6 hydroxyl group in (+)-**4**, we have relied on the stereoselective reduction of sterically unhindered ketones to equatorial alcohols by sodium borohydride.[17] Reduction of ketone **19** with sodium borohydride in ethanol gave a single alcohol in 74% yield, which was identical

(14) R. U. Lemieux, R. K. Kullnig, H. J. Bernstein, and W. G. Schneider, *J. Amer. Chem. Soc.*, **80**, 6098 (1958).

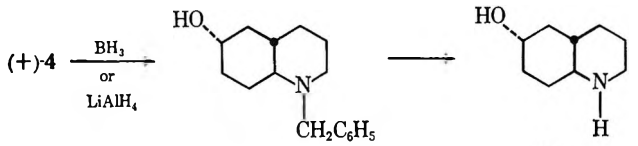
(15) C. A. Grob, H. R. Kiefer, H. J. Lutz, and H. J. Wilkens, *Helv. Chim. Acta*, **50**, 416 (1967).

(16) C. A. Grob and H. J. Wilkens, *ibid.*, **48**, 808 (1965). We thank Professor Grob for a sample of 7α-hydroxy-*trans*-decahydroquinoline.

(17) D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953).

with bioconversion product (+)-**4**. We consider this proof that the hydroxyl group of (+)-**4** has the equatorial configuration.

For the purpose of determining the optical rotatory dispersion curve of the simple unsubstituted 6-ketodecahydroquinoline molecule, several modifications of alcohol–amide (+)-**4** were necessary. First, (+)-**4** was reduced to the benzyl amine (**21**) with diborane.

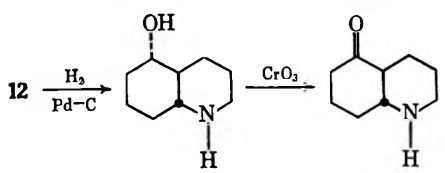


21 **22**

As before a crystalline hydrate of the benzyl amine (**21**) was obtained, as shown by elemental analyses and the infrared spectrum (see Experimental Section). Hydrogenolysis of the benzyl group of **21** was rapid over 5% palladium on carbon, giving the optically active amino alcohol **22**. Reduction of (+)-**4** with lithium aluminum hydride gave a mixture of benzyl amine **21** and amine **22**. A similar reduction of the racemic **4** gave (±)-**22**.

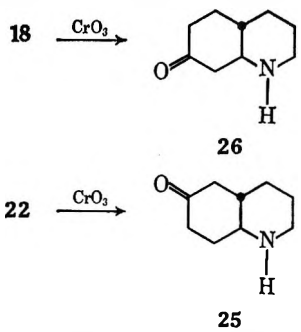
Absolute Configuration.—The application of the octant rule[18] to the optical rotatory dispersion (ORD) curves of many substances has been used extensively[19] in the determination of the absolute configuration of optically active molecules. In the present study optically active oxygenated derivatives in the *trans*-decahydroquinoline series have been obtained, which require only a few additional modifications in order to give keto-*trans*-decahydroquinoline molecules. Such molecules are closely analogous to the *trans*-decalones and similarly should give ORD curves which would be useful in the determination of their absolute configurations. This would in turn determine the absolute configuration of all the optically active compounds encountered in this study. Such information is of value when considering the relationships of the substrate molecules to the enzyme hydroxylation sites.

In considering the preparation of the keto-*trans*-decahydroquinolines, it would, in principle, be sufficient to determine the ORD curve and thereby the absolute configuration of a single ketone since all of the compounds have been related stereochemically. We chose to prepare each of the three ketones potentially available from the three different hydroxy compounds obtained in the bioconversion because little has been reported on the ORD curves of ketonic compounds containing amines. The 5 ketone (**24**) was prepared by repeated Jones oxidation of the amino alcohol **23**, which



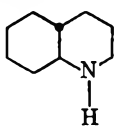
23 **24**

in turn had been prepared by the hydrogenolysis of benzyl amino alcohol **12**. We believe that the *trans*-ring juncture in **24** is the more stable even though it gives the keto amide (−)-**10** of the *cis*-decahydroquinoline series when treated with benzoyl chloride in pyridine. In the closely related 4-ketodecahydroquinoline series, the *trans*-ring juncture is the more stable.[20] Correlation of our ORD results also are consistent only if **24** is assigned the *trans*-ring junction. Similar oxidations of the amino alcohols **18** and **22** gave the 7 ketone (**26**) and the 6-ketone (**25**), respectively.



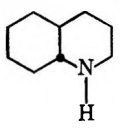
The ORD curves of the three ketones were determined in methanol solution and are illustrated in Figure 1. The curves obtained for ketones **24** and **25** appear normal and the amplitudes of +4720 and +4640°, respectively, are similar to those observed for the *trans*-decalones. *trans*-1-Decalone has an ORD amplitude of ±4000°[21] while *trans*-2-decalone has an amplitude of ±5400°.[22] However, ketone **26**, which was expected to have an ORD curve similar to that of ketone **25** shows a very weak, positive Cotton effect of +28° amplitude. The reason for this unusual curve is not apparent at the present time. The ultraviolet spectrum of ketone **26** is normal for an isolated carbonyl group, in that it has an absorption maximum at 281 mμ (ε 18).

Application of the octant rule[18] to the ORD curves of the three ketones leads to the following assignments of absolute configuration: **24** becomes (4a*S*,8a*R*)-*trans*-decahydroquinolin-5-one,[23] **25** becomes (4a*S*,8a*S*)-*trans*-decahydroquinolin-6-one, and **26** becomes (4a*S*,8a*S*)-*trans*-decahydroquinolin-7-one. These configurations are shown by the drawings used above. By employing the structural and stereochemical relationships used throughout the preceding discussion, the two epimers of *trans*-decahydroquinoline may be assigned the absolute configurations as shown. Similarly, ab-



(−)-**1**

(−)-*trans*-decahydroquinoline ([α]D −4.6°)[9] or (4a*R*,8a*S*)-*trans*-decahydroquinoline



(+)-**1**

(+)-*trans*-decahydroquinoline ([α]D +4.8°)[10] or (4a*S*,8a*R*)-*trans*-decahydroquinoline

(18) W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne, and C. Djerassi, *J. Amer. Chem. Soc.*, **83**, 4013 (1961).

(19) P. Crabbe, "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," Holden-Day, San Francisco, Calif., 1965.

(20) E. Mistryukov, *Izv. Akad. Nauk SSR, Otd. Khim. Nauk*, 929 (1963)

(21) Depending on which enantiomer is used, the amplitude will be + or −4000°.

(22) W. Klyne, *Experientia*, **20**, 349 (1964).

(23) Although use of the *R* and *S* nomenclature is sufficient to indicate the nature of the ring juncture in these compounds, inclusion of the terms *cis* and *trans* in the compound name eliminates the task of determining this feature for every name by use of the rules. For this reason we suggest that *cis* and *trans* be retained in the naming of these compounds.

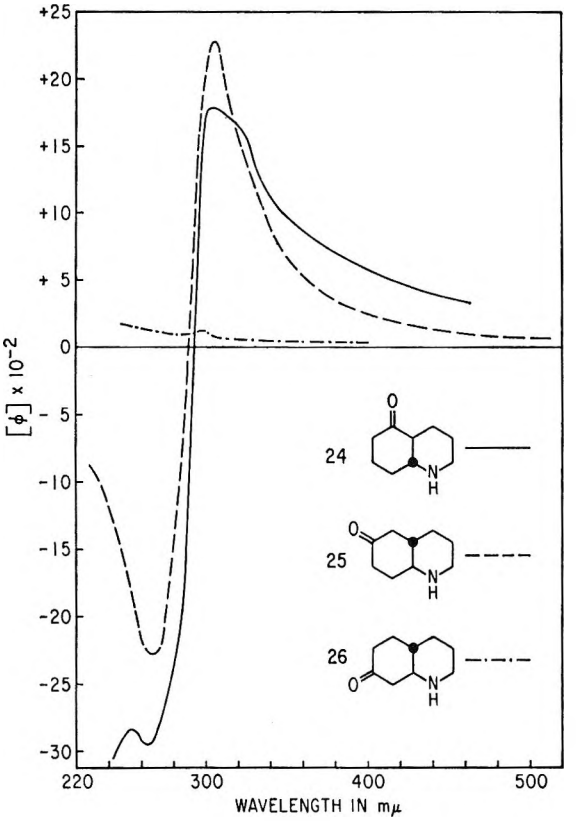


Figure 1.

solute configurations may be assigned to all other related optically active molecules in this study, and these assignments are given by the nomenclature used throughout the Experimental Section.

Experimental Section[24]

Biotransformation Process.—The culture used in these experiments was *Sporotrichum sulfurescens* V. Beyma (ATCC 7159). The biotransformation procedure has been described previously.[3]

Isolation of the Products from Bioconversion of (±)-1-Benzoyl-*trans*-decahydroquinoline [(±)-2] with *S. sulfurescens*. A. (4a*S*,5*S*,8a*R*)-1-Benzoyl-*trans*-decahydroquinolin-5-ol (3) and (±)-1-Benzoyl-*trans*-decahydroquinolin-6-ol (4).—The oily extracts from the 125-l. bioconversion of (±)-2 (25 g, 0.103 mol) were chromatographed on a column of Florisil (2.5 kg) packed with Skellysolve B. The following fractions (2.0-l. vol) were collected by elution with 25% (v/v) acetone in Skellysolve B. Fractions 19 and 20 were eluted with acetone (Table I). On the basis of infrared spectra, fractions 13 and 14 were combined in acetone, decolorized with activated charcoal, and crystallized as colorless crystals (3.925 g, first and second crops), mp 122–124°. A third crop gave 1.703 g (total 5.628 g, 0.0219 mol, 21%), mp 121–123°. Two recrystallizations from acetone–Skellysolve B gave colorless crystals of **3**: mp 121–123°; $[\alpha]_D$ −94° (c 0.648, chloroform); ν_{OH} 3350, $\nu_{C=O}$ 1610, $\nu_{C=C}$ 1600, 1575, 1525, 1500, ν_{C-O} 1210, 1125, 1065, 1010, $\nu_{C_6H_5}$ 785, 730, 700 cm^{-1} in Nujol.

Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 74.11; H, 8.27; N, 5.67.

This alcohol was shown not to be a polymorph of alcohol 4, mp 149–151°, by comparison of infrared spectra prepared from addition of a chloroform solution to KBr with subsequent pellet preparation.

(24) Melting points were determined on a calibrated Fisher-Johns hot stage and are corrected. Magnesium sulfate was used as the drying agent unless indicated otherwise. Infrared spectra were determined with either a Perkin-Elmer Infracord or Model 421 spectrophotometer. The nmr spectra were determined at 60 Mc with a Varian Model A-60 spectrometer, using tetramethylsilane as an internal standard. Mass spectra were determined on an Atlas CH4 instrument. The optical rotatory dispersion curves were obtained on a Cary Model 60 spectrophotometer.

TABLE I

Fraction.	Wt, g
12	1.02
13	4.52
14	3.33
15	1.93
16	2.69
17	3.53
18	2.25
19	1.54
20	2.10
Total	22.91

Fraction 17 (mp 131–134°) was recrystallized from acetone–Skellysolve B, giving colorless crystals (2.553 g), mp 128–135°. A portion of recrystallized fraction 17 was again recrystallized from acetone–Skellysolve B. Initially colorless crystals formed, but after standing for 5 days at room temperature the crystalline mass was composed of shiny, colorless transparent flat needles (mp 175–180°) covering a mass of opaque, chunky crystals (mp 143–148°). The two forms have different infrared spectra in Nujol. It was then discovered that the shiny crystals were more soluble in acetone. Fractions 16, 18, and 19 were recrystallized from acetone–Skellysolve B, giving a mixture of crystals (3.102 g). From this mixture a sample (0.364 g) of the product less soluble in acetone (100 ml) was obtained by decanting the acetone solution. Recrystallization of this sample from acetone gave colorless crystals, mp 148–150°. A final recrystallization from acetone gave crystals of **4** (0.212 g): mp 149–151°; $[\alpha]_D$ +3° (c 0.801, chloroform); ν_{OH} 3360, $\nu_{C-O-C-C}$ 1595, 1570, 1525, 1490, ν_{C-O} 1055, 1045, $\nu_{C_6H_5}$ 790, 735, 700 cm^{-1} in Nujol.

Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 74.22; H, 8.47; N, 5.82, 5.73.

B. Chromatography of a Large-Scale Bioconversion of Racemic 1-Benzoyl-*trans*-decahydroquinoline.—The extracts from three 250-l. bioconversions of (±)-2 (total 150.0 g, 0.618 mol) was chromatographed on a Florisil column (6 kg) packed with Skellysolve B. A fraction (3 l.) of Skellysolve B was taken followed by four fractions of 10% acetone–Skellysolve B, 15 fractions of 20% aeetone–Skellysolve B, five fractions of 25% acetone–Skellysolve B, and five fractions of 50% acetone–Skellysolve B. The products were found in fractions 14–29. Fractions 14–20 were pooled on the basis of their infrared spectra. The crude fraction weights are given in Table II. Fractions 14–20 were dissolved in acetone and decolorized with activated charcoal. Crystallization from acetone–Skellysolve B gave three crops of **3** as product: first crop, 22.097 g, mp 120–123°; second crop, 22.419 g, mp 123–125°; third crop, 5.230 g, mp 115–130°; total, 49.746 g (0.192 mol, 31%).

TABLE II

Fractions	Wt, g
14–20	58.01
21	8.57
22	11.35
23	11.14
24	9.70
25	19.15
26	21.06
27	8.54
28	4.47
29	1.64
Total	153.63 (0.593 mol, 96%)

Fractions 21–23 were combined in methylene chloride–benzene and rechromatographed on a silica gel column (2500 g) packed with benzene. No material eluted with 1% (ten 2-l. fractions) and 1.5% (nine fractions) methanol in benzene. With 2% methanol in benzene, the products were eluted with no sharp separation. On the basis of similar infrared spectra, fractions 25–27 (crude wt, 5.71 g) were combined and crystallized from acetone. The first crop (2.584 g) was colorless crystals, mp 179–185°. The second crop (1.571 g) was a mixture of products, mp 133–170°. Two recrystallizations of the first crop from acetone gave colorless, rectangular crystals of **5**: mp 185–187°; $[\alpha]_D$ +132°

(c 0.494, chloroform); infrared spectrum in Nujol is identical with that of (4aS,7S,8aS)-1-benzoyl-*trans*-decahydroquinolin-7-ol [(+)-5] from bioconversion of (+)-2.

Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 73.99; H, 8.19; N, 5.46.

From combined fractions 31–42 (crude wt, 12.089 g) of the silica gel column, crystals (first crop, 3.900 g, mp 146–149°; second crop, 3.192 g, mp 138–140°) were obtained from acetone–Skellysolve B. The infrared spectra in Nujol of the two crops were identical with that of 4. The remaining fractions (28–30 8.762 g) were a mixture of 4 and 5. Further purification of the remaining fractions from the initial chromatography has not been carried out.

(4aR,8aS)-1-Benzoyl-*trans*-decahydroquinoline [(+)-2].—(4aR, 8aS)-*trans*-Decahydroquinoline (obtained from 8.0 g of the *d*-tartrate)[9] was benzoylated by a Schotten–Baumann reaction in which the reactants were shaken with ice in a separatory funnel. The product was crystallized from Skellysolve B, giving crystals, mp 66–68°. A final crystallization from Skellysolve B gave colorless crystals of (+)-2: mp 68–69°; $[\alpha]_D$ +139° (c 0.764, chloroform).

Anal. Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 79.05; H, 8.49; N, 5.74.

Bioconversion of (4aR,8aS)-1-Benzoyl-*trans*-decahydroquinoline [(+)-2]. (4aS,6S,8aS)-1-Benzoyl-*trans*-decahydroquinolin-6-ol [(+)-4] and (4aS,7S,8aS)-1-Benzoyl-*trans*-decahydroquinolin-7-ol [(+)-5].—The dry methylene chloride extracts from two 125-l. bioconversions of (+)-2 (25.0 g each, 0.103 mol) were each chromatographed on a Florisil column (2 kg, 10.5 × 50 cm, 2-l. fractions) packed with Skellysolve B. Elution with 20–25% acetone in Skellysolve B gave 21.82 (0.0832 mol, 81%) and 25.09 g (0.0968 mol, 94%) of mostly crystalline material from the two columns. Chromatography (paper, vapor phase, thin layer) showed the product to consist of two major products distributed through all the column fractions. The two components were found to be separable, in part, by chromatography on silica gel with 1–3% methanol in benzene. Thus, for example, chromatography of 3.24 g of material chosen from the earlier fractions above (shown to be richer in less polar component) on a silica gel column (300 g, 3.8-cm diameter, 335-ml fractions) packed from a slurry in benzene gave no material in 25 fractions when eluted with 1% methanol in benzene. Elution with 2% methanol in benzene gave three fractions of less polar material (1.57 g), two fractions of a mixture (0.78 g) of the two products, and six fractions of more polar product (0.53 g). The separation of products was determined by tlc (silica gel, 20% methanol in benzene). The first three fractions of less polar product were combined and crystallized from acetone, giving a first crop (0.410 g) of crystals, mp 150° (softening), 183–188°. Two recrystallizations from acetone gave (+)-5 as colorless crystals: mp 185–186° with some sublimation; $[\alpha]_D$ +137° (c 0.678, chloroform); ν_{OH} 3360, $\nu_{C=O}$ 1605, $\nu_{C=C}$ 1595, 1570, 1555, 1495, $\nu_{C-O/other}$ 1290, 1115, 1065, $\nu_{C_6H_5}$ 775, 745, 700 cm^{-1} in Nujol.

Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 73.90; H, 8.21; N, 5.22.

Chromatography of 3.25 g of material from the latter fractions of the Florisil columns on silica gel (200 g, 3.8-cm diameter, 250-ml fractions) in benzene gave four fractions of a mixture of products and six fractions of pure more polar product. The latter fractions were combined in acetone, decolorized with activated charcoal, and crystallized from acetone–Skellysolve B, giving a first crop (0.811 g) of colorless crystals, mp 137–139°. Two recrystallizations from acetone–Skellysolve B gave (+)-4 as colorless feathers: mp 138–139°; $[\alpha]_D$ +115° (c 1.072, chloroform); ν_{OH} 3400, $\nu_{C=O}$ 1600, $\nu_{C=C}$ 1590, 1570, 1555, 1490, $\nu_{C-O/other}$ 1185, 1055, $\nu_{C_6H_5}$ 765, 745, 700 cm^{-1} in Nujol.

Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 73.99; H, 8.23; N, 5.41.

(4aS,8aR)-1-Benzoyl-*trans*-decahydroquinoline [(−)-2].—A sample of (4aS,8aR)-*trans*-decahydroquinoline (4.0 g, 0.0288 mol), prepared by basification of the *d*-[α]-bromocamphor-π-sulfonate,[10] was benzoylated under Schotten–Bauman conditions. The crude solid reaction product (7.117 g) was collected by filtration and washed with water. Crystallization from Skellysolve B gave 5.771 g (0.0238 mol, 82%) of crystals, mp 66–68°, in two crops. Recrystallization from Skellysolve B gave colorless, chunky crystals of (−)-2: mp 67–69°; $[\alpha]_D$ −145° (c 1.048, chloroform).

Anal. Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 79.01; H, 8.88; N, 5.70.

Bioconversion of (4aS,8aR)-1-Benzoyl-*trans*-decahydroquinoline [(−)-2]. (4aS,5S,8aR)-1-Benzoyl-*trans*-decahydroquinolin-5-ol [(−)-3] and (4aR,6R,8aR)-1-Benzoyl-*trans*-decahydroquinolin-6-ol [(−)-4].—The dry methylene chloride extract from the 10-l. bioconversion of (−)-2 (2.0 g, 0.00823 mol) was chromatographed on a Florisil column (3.8 × 34 cm). Elution with 20% acetone in Skellysolve B gave crude crystalline solid (1.50 g, 0.00578 mol, 70%). This material was rechromatographed on a silica gel column (120 g) packed with benzene. No material was eluted with 20 fractions (100 ml each) of 1% methanol in benzene. Elution with 2% methanol in benzene gave several fractions of crystalline solid. Recrystallization of fraction 30 from acetone–Skellysolve B gave colorless crystals (0.273 g), mp 123–125°. Two recrystallizations from acetone–Skellysolve B gave (−)-3 as colorless needles: mp 125–127°; $[\alpha]_D$ −109° (c 0.750, chloroform); infrared spectrum in Nujol is identical with that of the compound 3, mp 121–123°, obtained from bioconversion of the racemic substrate.

Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 73.53; H, 8.31; N, 5.20.

The extract from a second 10-l. bioconversion of (−)-2 (2.0 g, 0.00823 mol) was chromatographed directly on a silica gel column (250 g) packed with benzene. Elution with 20 fractions (335 ml) of 1% methanol in benzene was followed by elution with 2% methanol in benzene. Thin layer chromatography showed a separation of components between fractions 26 and 29. Fractions 19–26 were combined in acetone, decolorized with activated charcoal, and crystallized from acetone–Skellysolve B, giving colorless crystals (1.260 g, 0.00487 mol, 59%): mp 124–127°; infrared spectrum identical with that of (−)-3 described above. Fractions 28–31 were combined in acetone, decolorized, and crystallized from acetone–Skellysolve B, giving colorless crystals (0.201 g, 0.000776 mol, 9%), mp 135–138°. Two recrystallizations from acetone–Skellysolve B gave (−)-4 as colorless crystals: mp 136–138°; $[\alpha]_D$ −112° (c 0.997, chloroform); infrared spectrum in Nujol is identical with that of (+)-4.

Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 73.90; H, 8.03; N, 5.33.

Analytical Chromatography Data. A. Paper Chromatography.—The best resolution of the bioconversion products was achieved with paper chromatography. Systems B-3[25] and FBF[2] were used with Whatman No. 2 filter paper (6 × 34 in.). The R_f values for the compounds are given in Table III. On the K-1[25] system, the 5- and 7-hydroxy compounds move with the same R_f (mobility of 1.5 with respect to the 6-hydroxy compound).

TABLE III

R_f VALUES ON PAPER CHROMATOGRAPHY

Compound	R_f in system[a] FBF	B-3
4 (6-hydroxyl)	0.29	0.076
5 (7-hydroxyl)	0.33	
3 (5-hydroxyl)	0.38	0.11
2 (substrate)	0.87	...

[a] Reference 25.

B. Thin Layer Chromatography.—The bioconversion products were partially separated on Anatech prepared silica gel GF plates which were developed with 20% (v/v) methanol in benzene. Products 4 and 3 had R_f values of 0.38 and 0.43, respectively, while the substrate had a R_f value of 0.86.

C. Vapor Phase Chromatography.—The products were not separated by vapor phase chromatography.

(4aS,8aR)-1-Benzoyl-*trans*-decahydroquinolin-5-one (6).—A solution of 3 (1.049 g, 0.00404 mol) in acetone was cooled on an ice bath and oxidized by addition of excess Jones reagent. After 15 min at room temperature, the excess oxidant was consumed by the addition of isopropyl alcohol. The mixture evaporated to dryness at room temperature. The residual solids were washed twice with methylene chloride. The methylene chloride solution was dried and allowed to evaporate, leaving an oily residue (0.986 g). The oil was dissolved in acetone. Skellysolve B was added to the solution, which then was concentrated on the steam bath until it became cloudy. Cooling in the freezer caused an oily phase to separate. Crystals slowly formed in this phase and were collected after 2 days (0.261 g), mp 81–82°. Recrystal-

(25) L. M. Reineke, *Anal. Chem.*, **28**, 1853 (1956).

lization from acetone–Skellysolve B gave **6** as colorless crystals: mp 81–83°; $\nu_{C=O}$ 1700, 1635, $\nu_{C=C}$ 1595, 1580, 1490, $\nu_{C_6H_5}$ 750, 720, 700 cm^{-1} in Nujol.

Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.72; H, 7.87; N, 5.22.

This ketone was not polymorphic with ketone **19** as shown by infrared spectra prepared in potassium bromide pellets from chloroform solution.

Additional alcohol (**3**) (3.208 g) was oxidized in a manner the same as described above. The oily product (3.069 g) of this oxidation, and the oily residue (0.675 g) remaining from separation of the crystalline ketone above were combined and chromatographed on a Florisil column (300 g) packed with Skellysolve B. The combinations of fractions given in Table IV were made on the basis of infrared spectra. Recrystallization of fractions 13–19 from acetone–Skellysolve B gave colorless crystals of **6** (0.889 g): mp 79–80°; $[\alpha]_D$ −76° (*c* 0.700, chloroform).

TABLE IV

Fractions	Eluent	Wt, g
13–19	10% acetone–Skellysolve B	1.232
20–27	10% acetone–Skellysolve B	0.219
28–30	10% acetone–Skellysolve B	0.385
31 32	25% acetone–Skellysolve B	0.604
33–36	25% acetone–Skellysolve B	1.079
	Total	3.519

Recrystallization of fractions 28–30 from acetone–Skellysolve B gave part colorless crystals together with a gummy material, which solidified (0.272 g). The crystals had mp 92–94°. The infrared spectrum of this material in Nujol is identical with the spectrum of ketone **10**, mp 97–98°. Recrystallization from acetone–Skellysolve B gave crystals, mp 104–107°.

(4a*R*,8a*R*)-1-Benzoyl-*cis*-decahydroquinolin-5-one-$d_{4a}d_8d_8$ (7).—Sodium (0.005 g) was added to a solution of **6** (0.036 g) in methyl alcohol-*d* (4 ml). The solution was kept at room temperature for 22 hr and then concentrated to half-volume on the steam bath. Aqueous acetic acid-*d* (0.5 ml, prepared from 20 drops of acetic anhydride and 25 drops of deuterium oxide) and then deuterium oxide (2 ml) were added to the solution, which was concentrated under reduced pressure. Water was added to the oily aqueous mixture, which was extracted with methylene chloride. The organic phase was dried and then concentrated to an oil, which crystallized, giving 0.017 g of crystals: mp 92–96°; *m/e* 260 (M^+).

(±)-5α-Hydroxy-*cis*-decahydroquinoline (8).—The procedure of Grob and Kiefer[13] was followed. 5-Hydroxyquinoline (Aldrich Chemical Co., 3.851 g, 0.0266 mol) was hydrogenated over prereduced platinum (0.75 g of platinum oxide) in glacial acetic acid (200 ml), giving crystals of **8** (2.604 g in two crops, 0.0168 mol, 63%), mp 150–153° (lit.[13] mp 149–150°).

(±)-1-Benzoyl-*cis*-decahydroquinolin-5α-ol (9). A. From Benzoylation of (±)-5α-hydroxy-*cis*-decahydroquinoline (8).—A mixture of **8** (1.370 g, 0.00883 mol), ice, 50% aqueous sodium hydroxide solution (5 ml), and benzoyl chloride (3.2 ml, 3.84 g, 0.0273 mol) was shaken vigorously in a separatory funnel for 15 min. The mixture was transferred to a beaker and warmed on a steam bath for 10 min and then left at room temperature overnight. The mixture was extracted with three 50-ml portions of ether. The ether was dried and partially evaporated. Crystallization began and a first crop (1.494 g) of crystals was collected, mp 136–138°. The filtrate was concentrated to a gum (0.400 g, total 1.894 g, 0.00732 mol, 83%). Two recrystallizations from acetone–Skellysolve B gave **9** as colorless crystals: mp 137–139°; ν_{OH} 3390, $\nu_{C=O}$ 1600, $\nu_{C=C}$ 1590, 1570, 1490, $\nu_{C_6H_5}$ 735, 725, 700 cm^{-1} in Nujol.

Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 73.94; H, 8.22; N, 5.65.

B. From Reduction of (±)-1-Benzoyl-*cis*-decahydroquinolin-5-one [(±)-10] with Sodium Borohydride.—A solution of (±)-**10** (0.140 g, 0.545 mmol) in absolute ethanol (3 ml) was added dropwise to a mixture of sodium borohydride (0.109 g, 2.88 mmol) in absolute methanol (5 ml). The mixture was kept at room temperature for 3 hr after which tlc (silica gel, 20% methanol in benzene) showed complete disappearance of ketone. Aqueous 1 *M* sulfuric acid (~3 ml) was added until release of hydrogen gas stopped. The mixture was made alkaline with 1 *M* sodium hydroxide solution. Water (10 ml) was added, and the solution was extracted with methylene chloride (five 10-ml portions). An oil, which crystallized, was obtained and recrystallized from acetone–Skellysolve B, giving 0.100 g (0.386 mmol, 70%) of crystals, mp 135–137°. The infrared spectrum in Nujol is identical with that of the alcohol **9** obtained from benzoylation of **8** above.

(±)-1-Benzoyl-*cis*-decahydroquinolin-5-one [(±)-10].—A solution of **9** (1.043 g, 0.00404 mol) in acetone (100 ml) was oxidized with excess Jones reagent. The excess oxidant was destroyed with isopropyl alcohol, the organic solvent was removed under reduced pressure, water was added, and the resulting mixture was extracted with methylene chloride. Concentration of the dry methylene chloride solution gave an oil. Crystallization occurred in acetone–Skellysolve B, giving colorless crystals (0.825 g, 0.0321 mol, 79%), mp 138–140°. Two recrystallizations from acetone–Skellysolve B gave (±)-**10** as colorless crystals: mp 138–140°; $\nu_{C=O}$ 1705, 1625, $\nu_{C=C}$ 1600, 1575, 1490, $\nu_{C_6H_5}$ 725, 705 cm^{-1} in Nujol; *m/e* 257 (M^+), 229, 214, 188, 187, 105 ($OC{\equiv}O^+$), 97, 77 (C_6H_5)$^+$.

Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.46; H, 7.38; N, 5.61.

(±)-1-Benzoyl-*cis*-decahydroquinolin-5-one-$d_{4a}d_6d_6$ [(±)-7].—Sodium (0.004 g) was added to a solution of (±)-**10** (0.030 g, 0.117 mmol) in methyl alcohol-*d* (4 ml). The solution was kept at room temperature for 20 hr and the product isolated as described for **7**. Crystallization of the product occurred from methylene chloride–Skellysolve B when the solution was kept in the refrigerator, giving 0.006 g (0.0231 mmol, 20%) of crystals: mp 139–141°; *m/e* 260 (M^+). A mixture melting point with ketone (±)-**10** was undepressed, 139–141°.

(4a*R*,8a*R*)-1-Benzoyl-*cis*-decahydroquinolin-5-one (10). A. By Isomerization of 6 with Sodium Methoxide.—A solution of **6** (1.13 g) and sodium (0.080 g) in methanol was kept at room temperature for 24 hr. Glacial acetic acid (1 ml) was added to the solution, which then was concentrated under reduced pressure. Water was added to the solution, which then was concentrated under reduced pressure. Water was added to the residue, and the mixture was extracted with three 25-ml portions of methylene chloride. The dried extract was concentrated under reduced pressure. Crystallization of the residue from acetone–Skellysolve B gave only 0.054 g of sticky crystals. The filtrate from these crystals was allowed to evaporate slowly. Crystals formed in the residual oil. They were washed with ethyl acetate and collected by filtration, giving 0.308 g of product. Recrystallization from acetone–Skellysolve B gave 0.175 g of crystals, mp 94–97°. A second recrystallization from acetone–Skellysolve B gave some rectangular crystals: mp 108–109°; $[\alpha]_D$ −77° (*c* 0.778, chloroform); $\nu_{C=O}$ 1715, 1635, 1625, $\nu_{C=C}$ 1575, 1495, $\nu_{C_6H_5}$ 800, 745, 730, 705 cm^{-1} in Nujol.

Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.49; H, 7.48; N, 5.38.

The filtrate gave chunky crystals, mp 97–98°, when cooled: $\nu_{C=O}$ 1710, 1620, $\nu_{C=C}$ 1580, 1495, $\nu_{C_6H_5}$ 792, 740, 730, 705 cm^{-1} in Nujol.

Anal. Found: C, 74.66; H, 7.38; N, 5.43.

The two crystalline materials were shown to be polymorphic crystalline forms by identical infrared spectra in KBr pellets prepared from solutions of each.

B. From (4a*S*,8a*R*)-*trans*-Decahydroquinolin-5-one (24).—A solution of benzoyl chloride (0.203 g, 0.00144 mol) in pyridine (2 ml) was added to a solution of **24** (0.210 g, 0.00137 mol) in pyridine (2 ml). The solution darkened. The solution was heated on a steam bath for 5 min and then was left at room temperature several hours. The solution was stored in a freezer overnight. A thin layer chromatogram indicated that reaction was largely complete. Crystals, assumed to be pyridine hydrochloride, were removed from the solution. The solution was concentrated under reduced pressure until the pyridine odor was very faint. Water was added to the brownish yellow oily–crystalline residue, and the resulting mixture was extracted with three 20-ml portions of methylene chloride. The extract was dried and concentrated under reduced pressure, giving a viscous oil. The oil failed to crystallize from acetone–Skellysolve B. An infrared spectrum of the oil in chloroform solution was nearly identical with that of (±)-1-benzoyl-*cis*-decahydroquinolin-5-one [(±)-**10**] but was quite different from that of (4a*S*,8a*R*)-1-benzoyl-*trans*-decahydroquinolin-5-one (**6**).

C. From Oxidation of (4a*S*,5*S*,8a*R*)-1-Benzoyl-*trans*-decahydroquinolin-5-ol (3) with Jones Reagent.—See above under preparation of **6**.

Reduction of (4a*S*,8a*R*)-1-Benzoyl-*trans*-decahydroquinolin-5-one (6) with Sodium Borohydride. (4a*S*,5*S*,8a*R*)-1-Benzoyl-*trans*-decahydroquinolin-5-ol (3) and (4a*S*,5*R*,8a*R*)-1-Benzoyl-*trans*-decahydroquinolin-5-ol (11).—A solution of 6 (0.316 g, 1.23 mmol) in absolute ethanol (5 ml) was added to a mixture of sodium borohydride (0.255 g, 6.75 mmol) and absolute ethanol (10 ml). After 3 hr at room temperature, the product was isolated and crystallized from acetone–Skellysolve B. The crystals were a mixture of needles and chunky solid, which were separated manually by difference in density. The needles (0.097 g, 0.374 mmol, 30%) had mp 113–117° and, after recrystallization from acetone–Skellysolve B, mp 125–127°. The infrared spectrum in Nujol is identical with that of **3**, isolated from the bioconversion of (±)-**2**. The chunky crystals (0.128 g, 0.494 mmol, 40%) had mp 108–114°. Two recrystallizations from acetone–Skellysolve B gave **11** as colorless crystals: mp 110–113°; $[\alpha]_D$ −123° (c 1.058, chloroform), ν_{OH} 3460, $\nu_{C=O}$ 1635, $\nu_{C=C}$ 1605, 1490, $\nu_{C_6H_5}$ 785, 700 cm^{-1} in Nujol.

Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 74.02; H, 7.81; N, 5.62.

(4a*S*,5*S*,8a*R*)-1-Benzyl-*trans*-decahydroquinolin-5-ol (12). A. From Lithium Aluminum Hydride Reduction of 3.—A solution of **3** (14.67 g, 0.566 mol) in tetrahydrofuran (200 ml) was added to a mixture of lithium aluminum hydride (5.0 g, 0.131 mol) and tetrahydrofuran (200 ml). The mixture was heated at the reflux temperature of tetrahydrofuran for 5 hr. Following the addition of water to decompose the excess hydride, the reaction was worked up, giving an oil. The oil was transferred to a simple distillation apparatus. A liquid (2.013 g, 0.0187 mol, 33%) distilled, bp 68–70° (0.6 mm), and then crystals formed in the neck of the distillation head. The liquid was found to be largely benzyl alcohol by comparison of its infrared spectrum with a known spectrum. The undistilled material remained as oily crystals. A portion (3.78 g) of the oily crystals was chromatographed on aluminum oxide (Woelm neutral, activity I, 300 g, 335-ml fractions) packed with benzene. Elution with 20% chloroform in benzene gave **12** as a faintly pink viscous gum: $[\alpha]_D$ −74° (c 0.505, chloroform); ν_{OH} 3350, $\nu_{Na-lkyl}$ 2780, 2740, $\nu_{C=C}$ 1600, 1580, 1490, $\nu_{C_6H_5}$ 740, 700 cm^{-1} on a smear.

Anal. Calcd for $C_{16}H_{23}NO$: C, 78.32; H, 9.45; N, 5.71. Found: C, 76.38; H, 9.41; N, 5.88.

The perchlorate salt of **12** was prepared in ethanol and was crystallized three times from ethanol–ether. Colorless crystals of the product had mp 194–196°; $[\alpha]_D$ −7°; ν_{OH} 3540, ν_{NH} 3090, $\nu_{C=C}$ 1585, 1495, $\nu_{C_6H_5}$ 740, 695 cm^{-1} in Nujol.

Anal. Calcd for $C_{16}H_{24}NO_5Cl$: C, 55.57; H, 6.99; N, 4.05. Found: C, 55.40; H, 7.08; N, 3.88.

A sample of crystals, obtained by washing the above oily crystals with acetone, was shown to be (4a*S*,5*S*,8a*R*)-*trans*-decahydroquinolin-5-ol (**23**) by its infrared spectrum, which was identical with the spectrum of the compound (**23**) prepared by hydrogenolysis of **12**.

B. From Reduction with Diborane.[26]—A solution of diborane in tetrahydrofuran (*ca.* 1 *M*, 120 ml) was added cautiously to a solution of **3** (12.103 g, 0.0467 mol) in tetrahydrofuran (150 ml). The clear solution which resulted was stirred at reflux temperature for 18 hr. Methanol (20 ml) was added, the first few drops slowly. The solution was stirred 1 hr at room temperature and then was concentrated under reduced pressure, giving an oil. Ether (75 ml) and dilute hydrochloric acid (2 *M*, 25 ml) were added to the oil. The mixture was swirled occasionally while kept at room temperature for an hour. The mixture was shaken vigorously and then the layers were separated. The ether phase was washed with water and the aqueous layers were combined. Aqueous sodium hydroxide solution (25%) was added until the solution was alkaline and an oil separated. The mixture was extracted with three 60-ml portions of ether. The ether solution was dried and concentrated under reduced pressure, giving an oil. Additional product was obtained from the acid-extracted ether layer above after it had been left standing for several days. The ether layer was extracted with dilute hydrochloric acid. The aqueous acid phase was made alkaline with sodium hydroxide solution. An oil separated and was extracted with ether. The ether was dried and concentrated under reduced pressure, giving an oil. In this way, a total of 10.43 g (0.0425 mol, 91%) of colorless oily product (**12**) was obtained.

(26) *Cf.* Z. B. Papanastassiou and R. J. Bruni, *J. Org. Chem.*, **29**, 2870 (1964); H. C. Brown and P. Heim, *J. Amer. Chem. Soc.*, **86**, 3566 (1964).

(4a*S*,5*S*,8a*R*)-1-Benzyl-*trans*-decahydroquinolin-5-ol Tosylate (13).—A solution of **12** (0.943 g, 3.85 mmol) in pyridine (8 ml) was cooled on an ice bath. *p*-Toluenesulfonyl chloride (0.734 g, 3.86 mmol) was added and the resulting deep red solution was left at room temperature for 70 hr. Water (0.1 ml) was added to the solution, which was concentrated under reduced pressure to an oil. Aqueous 1 *M* sodium hydroxide was added to the oil, and the resulting mixture was extracted with two 30-ml portions of chloride. Drying and concentrating of the solution left an oil, which crystallized. Recrystallization from methylene chloride–Skellysolve B gave, in two crops, 0.808 g (2.02 mmol, 52%) of reddish tinged crystals, mp 141–143°. Three more recrystallizations, the first preceded by decolorization with activated charcoal, from methylene chloride–Skellysolve B gave faintly pink crystalline flakes: mp 148–149°; $[\alpha]_D$ −45° (c 0.874, chloroform); $\nu_{N-alkyl}$ 2790, $\nu_{C=C}$ 1600, 1490, ν_{SO_2O-} 1360, 1350, 1190, 1180, $\nu_{C_6H_5}$ 745, 700 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 7.80 and 7.31 (-$C_6H_4SO_3$-*p*, doublets, J = 8.0 cps, 4 H), 7.26 (C_6H_5, singlet, 5 H), 4.00 and 3.14 (>$NCH_2C_6H_5$, doublets, J = 13.5 cps, 2 H), 2.40 ppm (O-CH_3, singlet).

Anal. Calcd for $C_{23}H_{29}NO_3S$: C, 69.15; H, 7.32; N, 3.51; S, 8.01. Found: C, 69.07; H, 7.26; N, 3.66; S, 8.24.

Fragmentation of (4a*S*,5*S*,8a*R*)-1-Benzyl-*trans*-decahydroquinolin-5-ol Tosylate (13) in 80% Ethanol in Water.—The tosylate **13** (0.060 g) did not dissolve completely in 80% ethanol in deuterium oxide (1.0 ml) at 75°. The mixture was held at this temperature for 0.5 hr, during which time the undissolved crystals slowly went into solution. No crystals formed, even with seeding with starting compound, following cooling to room temperature. After remaining at room temperature overnight, the solution was concentrated to dryness under reduced pressure. A colorless oil remained, which was dissolved in deuteriochloroform and the nmr spectrum measured: $\delta_{TMS}^{CDCl_3}$ 7.45 (-$C_6H_4SO_3$-*p*, quartet, 4 H), 7.33 (-C_6H_5, 5 H), 5.28 (*trans*-HC=CH-, ~1.7 H), 4.08 ($\gtrless\overset{+}{N}$-CH_2-C_6H_5, 2 H), 2.75 ($\gtrless\overset{+}{N}$-CH_2-C, 2 H), 2.37 (-O-CH_3, singlet), 1.87 ppm (broad band with peak at this point).

(4a*S*,8a*S*)-1-Benzoyl-*trans*-decahydroquinolin-7-one (15).—A solution of (+)-**5** (0.160 g, 0.618 mmol) in cold acetone was oxidized with an excess of Jones reagent. The reaction was worked up as described for **6**. Crystallization of the oily product from acetone–Skellysolve B gave a first crop of slightly oily, pale yellow crystals (0.095 g) and a second crop of nearly colorless crystals (0.036 g, total 0.131 g, 0.510 mmol, 82%). A sample of the best crystals was chosen for analyses and had mp 69–72°; $\nu_{C=O}$ 1705, 1615, $\nu_{C=C}$ 1575, 1495 cm^{-1} in Nujol.

Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.55; H, 7.61; N, 5.47.

(4a*S*,8a*S*)-1-Benzoyl-*trans*-decahydroquinolin-7-one-$d_6d_6d_8d_8$ (16).—A solution of **15** (0.038 g) and sodium (0.009 g) in methyl alcohol-*d* (5 ml) was left at room temperature for 21 hr. The product was isolated in the manner described for isolation of **7**. The product was obtained as a colorless, viscous oil, *m/e* 261 (M^+).

(4a*S*,7*S*,8a*S*)-1-Benzyl-*trans*-decahydroquinolin-7-ol (17).—A solution of (+)-**5** (2.128 g, 0.00822 mol) in tetrahydrofuran was reduced with a solution of diborane (*ca.* 1 *M*, 25 ml) in tetrahydrofuran in the manner described above for reduction of **3** with diborane. An oil was obtained from the ether extract of the basic solution. Crystallization from acetone–Skellysolve B gave colorless crystals (0.165 g), mp 65–80°. The filtrate was concentrated and taken up in acetone. Addition of water caused crystallization of colorless needles (0.518 g), mp 60–75°. Recrystallization from methanol–water gave colorless needles, mp 65–80°. When first dissolved in chloroform and the clear solution decanted, crystals were obtained from acetone–water having mp 65–80° (Fisher-Johns); mp 107–109° (capillary); ν_{OH} 3360, 3200, $\nu_{C=C}$ 1605, 1590, 1500, ν_{C-O} 1060 s, $\nu_{C_6H_5}$ 750, 700 cm^{-1} in Nujol.

Anal. Calcd for $C_{16}H_{23}NO \cdot H_2O$: C, 72.96; H, 9.57; N, 5.32. Found: C, 73.73; H, 9.51; N, 5.18.

A further recrystallization from acetone–water gave colorless crystals: mp 77–80° (capillary); $[\alpha]_D$ +109° (c 0.687, chloroform); infrared spectrum in Nujol is identical with that above.

Anal. Found: C, 72.79; H, 9.73; N, 5.17.

Additional product was obtained from the dry residue remaining after the orginal acid-extracted ether solution was allowed to evaporate to dryness. Aqueous 1 *M* sodium hydroxide was added to the residue, and the resulting mixture extracted with

ether. The oily product from the dried and concentrated ether solution as crystallized from acetone–water, giving colorless needles (0.686 g, total 1.369 g, 0.00520 mol, 63%).

When reduction of (+)-**5** (2.30 g) was carried out with lithium aluminum hydride in refluxing tetrahydrofuran, oily crystals were obtained. The crystals were washed with acetone and collected by filtration (0.237 g) and had mp 181–183°. The infrared spectrum of the crystals in Nujol is identical with that of **18** taken in Nujol. Additional crystals were obtained from hydrogenolysis of the filtrate over 5% palladium on carbon.

(4a*S*,7*S*,8a*S*)-*trans*-**Decahydroquinolin-7-ol (18).**—A solution of **17** (hydrate) (1.036 g, 0.00394 mol) in methanol was shaken with hydrogen over 5% palladium-on-carbon catalyst. Hydrogen consumption was rapid. The catalyst was removed by filtration. The filtrate was concentrated under reduced pressure, giving a crystalline residue. The residue was washed with acetone and collected by filtration, giving 0.487 g (0.00314 mol, 80%) of crystalline product, mp 179–182°. Two recrystallizations from acetone gave **18** as colorless crystals: mp 182–183°: $\nu_{OH,NH}$ 3310, 3200 cm^{-1} in Nujol; $\nu_{NH,OH}$ 3600, 3170, ν_{C-O} 1047 s, 1031 m, 1010 w cm^{-1} in chloroform and identical with that of authentic (±)-7α-hydroxy-*trans*-decahydroquinoline[16] in chloroform.

Anal. Calcd for $C_9H_{17}NO$: C, 69.63; H, 11.04; N, 9.02. Found: C, 69.37; H, 11.10; N, 9.06.

(4a*S*,8a*S*)-**1-Benzoyl-*trans*-decahydroquinolin-6-one (19).**—A slight excess of Jones reagent was used to oxidize (+)-**4** (1.911 g, 7.38 mmol) in an acetone solution (30 ml). After the usual work-up, oily crystals were obtained. Crystallization from acetone Skellysolve B gave 1.59 g (6.21 mmol, 84%) of ketone as rectangular crystals, mp 129–131°. Two recrystallizations from acetone–Skellysolve B gave **19** as feathery crystals: mp 129–131°; $[\alpha]_D$ +181° (c 0.587, chloroform); $\nu_{C=O}$ 1705, 1610, $\nu_{C=C}$ 1595, 1575, 1515, 1490, $\nu_{C_6H_5}$ 790, 725, 700 cm^{-1} in Nujol.

Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.49; H, 7.46; N, 5.51.

A Polymorphic Form of 19.—Dioxane (5 ml) and an ethereal solution of hydrogen chloride (1 ml) were added to **19** (0.227 g) to determine if the compound might isomerize. The crystals went into solution and then other crystals formed. These were collected after 6 hr (0.147 g): mp 120–123°; $\nu_{C=O}$ 1705, 1605, $\nu_{C=C}$ 1590, 1570, 1530, 1490, $\nu_{C_6H_5}$ 795, 722, 703 cm^{-1} in Nujol. Recrystallization from acetone–Skellysolve B gave crystals having an infrared spectrum identical with that of the original ketone.

Reduction (4a*S*,8a*S*)-1-Benzoyl-*trans*-decahydroquinolin-6-one (19) with Sodium Borohydride. (4a*S*,6*S*,8a*S*)-1-Benzoyl-*trans*-decahydroquinolin-6-ol [(+)-4].—A solution of **19** (0.518 g, 2.01 mmol) in absolute ethanol (5 ml) was added to a mixture of sodium borohydride (0.4 g) and absolute ethanol (15 ml). The mixture was kept at room temperature for 22 hr. The mixture was first treated with 1 *M* sulfuric acid (3 ml), then was made alkaline with 1 *M* sodium hydroxide solution. Water (10 ml) was added and the solution was extracted with five 15-ml portions of methylene chloride. The organic extract was dried, then concentrated to oily crystals. Recrystallization from acetone–Skellysolve B gave a first crop (0.243 g) of hexagonal needles, mp 134–137°. Second and third crops (0.117 and 0.028 g, total 0.388 g, 1.50 mmol, 74%) of crystals, mp 122–130°, were obtained. All crops had infrared spectra in Nujol identical with that of (+)-**4**, obtained in the bioconversion of (+)-**2**.

(4a*S*,8a*S*)-**1-Benzyl-*trans*-decahydroquinolin-6-one-$d_5d_5d_7d_7$ (20).**—Sodium (0.004 g) was added to a solution of **19** (0.031 g, 0.121 mmol) in methyl alcohol-*d* (4 ml). The product was isolated exactly as described for the preparation of **7**. Crystals (0.022 g, 0.0843 mmol, 70%), mp 117–120°, were obtained, *m/e* 161 (M^+).

(4a*S*,6*S*,8a*S*)-**1-Benzyl-*trans*-decahydroquinolin-6-ol (21).**—A solution of diborane (*ca.* 1 *M*, 60 ml) in tetrahydrofuran was added cautiously to a stirred solution of (+)-**4** (6.043 g, 0.0233 mol) in tetrahydrofuran (75 ml). The reaction was run at reflux temperature for 18 hr in a flask fitted with a condenser and calcium chloride drying tube. The reaction was worked up in the same manner as was used for the diborane reduction of **3**. Crystals (2.216 g), mp 57–70°, were deposited slowly from the ether extract of the basic products. The ether was decanted from the crystals and was dried. Concentration under reduced pressure gave an oil, which crystallized from acetone–water as shiny, colorless plates (2.275 g), mp 55–65°. Several recrystallizations from acetone–water did not improve the melting point when taken on a Fisher-Johns block. In a sealed, evacuated capillary, the compound had mp 68–71°; $[\alpha]_D$ +100° (c 0.695, chloroform); ν_{OH} 3340, 3160, $\nu_{C=C}$ 1605, 1585, 1500, ν_{C-O} 1165, 1150s, 1125, 1115s, $\nu_{C_6H_5}$ 750, 700 cm^{-1} in Nujol.

Anal. Calcd for $C_{16}H_{23}NO \cdot H_2O$: C, 72.96; H, 9.57; N, 5.32. Found: C, 74.00; H, 9.42; N, 5.21.

(4a*S*,6*S*,8a*S*)-*trans*-**Decahydroquinolin-6-ol (22). A. From Lithium Aluminum Hydride Reduction of (+)-4.**—A solution of (+)-**4** (2.213 g, 8.53 mmol) in tetrahydrofuran (75 ml) was added slowly to a stirred mixture of lithium aluminum hydride (2.1 g) tetrahydrofuran (400 ml). The resulting mixture was heated at reflux temperature for 5 hr and was kept at room temperature for 16 hr. Following typical work-up, oily crystals were obtained from the organic phase. The crystals (0.527 g, mp 216–217°) were washed with acetone and collected by filtration. Recrystallization from methanol–acetone gave colorless crystals: mp 217–218° (sublime); $[\alpha]_D$ −10° (*c* 0.707, 95% ethanol); the infrared spectrum in Nujol is identical with that of (+)-**22**.

Anal. Calcd for $C_9H_{17}NO$: C, 69.63; H, 11.04; N, 9.02. Found: C, 69.29; H, 10.97; N, 9.13.

The oily residue obtained from the filtrate was assumed to be a mixture of the product (**22**) and the corresponding benzylamine (**21**). Accordingly, a solution of the residue in methanol was shaken with hydrogen over a 5% palladium-on-carbon catalyst. Additional crystalline product (**22**) (0.377 g, total 0.904 g, 5.83 mmol, 68%), mp 216–217°, was obtained from the hydrogenolysis.

B. From Hydrogenolysis of 21.—Hydrogenolysis of a solution of benzylamine (**21**) hydrate (3.00 g, 0.0114 mol) over 5% palladium on carbon (1.5 g) was rapid and complete after 10 min. Removal of the catalyst by filtration and concentration of the filtrate gave colorless crystals. Recrystallization from methanol–acetone gave two crops (total 1.446 g, 0.00932 mol, 81%) of colorless crystals, mp 213–215°. The infrared spectrum in Nujol is identical with that of the above product.

(±)-*trans*-**Decahydroquinolin-6-ol [(±)-22].**—A solution of **4** (0.546 g, 0.00211 mol) in tetrahydrofuran (100 ml) was added to a mixture of lithium aluminum hydride (0.60 g) and tetrahydrofuran (100 ml). The mixture was heated at the reflux temperature for 2.5 hr and was stirred at room temperature 16 hr. Ethyl acetate and water were added to consume the excess hydride. The solids were removed by filtration through Celite and washed with tetrahydrofuran. The organic layer was dried and concentrated under reduced pressure, giving oily crystals. Crystallization from acetone gave crystals (0.1 g), mp 180–186°. The filtrate was concentrated to an oil, which had an infrared spectrum indicating that the benzyl group was still present. The oil was dissolved in methanol and shaken with hydrogen over palladium on carbon (0.2 g) in a Parr apparatus. After removal of the catalyst and concentration of the solution, additional crystals (0.075 g, total 0.175 g, 0.00113 mol, 53%) were obtained, which had an infrared spectrum identical with the spectrum of the first crystals obtained. Three recrystallizations from acetone, the last preceded by decolorization with charcoal, gave (+)-**22** as colorless crystals: mp 189–190°; $\nu_{NH,OH}$ 3260, 3100, 2800 cm^{-1} in Nujol.

Anal. Calcd for $C_9H_{17}NO$: C, 69.63; H, 11.04; N, 9.02. Found: C, 69.46; H, 11.21; N, 9.43.

(4a*S*,5*S*,8a*R*)-*trans*-**Decahydroquinolin-5-ol (23).**—A solution of **12** (2.179 g, 0.00888 mol) in methanol was shaken with hydrogen over 5% palladium on carbon (0.62 g) for 30 min on a Parr apparatus. The catalyst was removed by filtration and washed with methanol. The filtrate was concentrated under reduced pressure, giving an oil which crystallized. Recrystallization from methylene chloride–Skellysolve B gave 0.824 g (0.00532 mol, 60%) of crystals, mp 141–144° (sublimes). Two recrystallizations from methylene chloride, the second preceded by decolorization with activated charcoal gave crystals, mp 148°. The crystalline material was sublimed and recrystallized from methylene chloride–Skellysolve B, giving **23** as colorless crystals: mp 147–148°; $[\alpha]_D$ +51° (c 0.964, chloroform); $\nu_{OH,NH}$ 3250, 3100, $\nu_{N\text{-alkyl, bonded OH,NH}}$ 2790, 2750, 2700 cm^{-1} in Nujol.

Anal. Calcd for $C_9H_{17}NO$: C, 69.63; H, 11.04; N, 9.02. Found: C, 69.38; H, 11.09; N, 9.14.

(4a*S*,8a*R*)-*trans*-**Decahydroquinolin-5-one (24).**—Jones reagent (2.5 ml) was added rapidly with stirring to a solution of **23** (0.984 g, 0.00633 mol) in warm (40°) acetone (100 ml). The resulting mixture was left at room temperature for 1 hr and then was treated with isopropyl alcohol (0.6 ml). Aqueous 1 *M* sodium hydroxide solution (50 ml) was added, and the mixture

was concentrated under reduced pressure until the acetone was removed. A little additional water was added to the remaining mixture, which was then extracted with four 35-ml portions of methylene chloride. The extract was dried and concentrated under reduced pressure. The oily product (0.721 g) crystallized. An infrared spectrum showed that some alcohol remained. The product was dissolved in acetone (50 ml) and oxidized at 40° with Jones reagent (1 ml). The isolation procedure used following the first oxidation was repeated, giving a crystalline product (0.660 g). The product in acetone solution was decolorized with activated charcoal. The acetone was replaced by Skellysolve B, and an initial deposit of crystals (**23**) in this solvent was removed by filtration. Crystallization of **24** from the filtrate at room temperature gave a first crop of 0.204 g of crystals, mp 75–77°. A second crop of colorless needles (0.085 g, total 0.289 g, 0.00189 mol, 30%), mp 76–78°, was collected: RD (*c* 0.535, CH_3OH) $[\phi]_{400}$ +572°, $[\phi]_{320}$ +1087°, $[\phi]_{314}$ +1573°, $[\phi]_{306}$ +1745°, $[\phi]_{294}$ 0°, $[\phi]_{266}$ −2975°, $[\phi]_{257}$ −2850, $[\phi]_{239}$ −3160°; ν_{NH} 3230, $\nu_{C=O}$ 1705 cm^{-1} in Nujol.

Anal. Calcd for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.14. Found: C, 70.27; H, 9.84; N, 9.11.

(4a*S*,8a*S*)-*trans*-**Decahydroquinolin-6-one (25).**—A solution of **22** (0.862 g, 0.00555 mol) in hot acetone (200 ml) was oxidized with Jones reagent (2.5 ml). The reaction was worked up following the procedure described above for **24**. A solid crystalline product was obtained, which was separated into starting material (0.124 g, identified by an infrared spectrum) and product by the insolubility of the starting material in ether. The product (0.214 g) crystallized from Skellysolve B, giving colorless needles: mp 82–83°; RD (*c* 0.584, CH_3OH), $[\phi]_{589}$ +63°, $[\phi]_{400}$ +281°, $[\phi]_{350}$ +592°, $[\phi]_{320}$ +1610°, $[\phi]_{316}$ +1972°, $[\phi]_{307}$ +2323°, $[\phi]_{290}$ 0°, $[\phi]_{268}$ −2320°, $[\phi]_{231}$ −894°; ν_{NH} 3230, 3220, $\nu_{C=O}$ 1710 cm^{-1} in Nujol.

Anal. Calcd for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.14. Found: C, 69.76, 69.86; H, 9.69, 9.77; N, 8.93.

(4a*S*,8a*S*)-*trans*-**Decahydroquinolin-7-one (26).**—A cold solution of **18** (0.487 g, 0.00314 mol) in 7 *M* sulfuric acid (2 ml) was oxidized with the dropwise addition of a solution of chromium trioxide (0.222 g) in 7 *M* sulfuric acid (3 ml) (method of Grob and Wilkens[16]). After 15 min at room temperature, the solution was made basic by the slow addition of aqueous 20% sodium hydroxide while keeping the solution cold. A precipitate formed. A saturated potassium carbonate solution (1 ml) was added. The resulting mixture was stirred with chloroform (15 ml) for 1 hr and then was extracted with four 20-ml portions of additional chloroform. The chloroform solution was dried and concentrated under reduced pressure. A crystalline product was obtained, which was shown to contain some starting alcohol by an infrared spectrum. The solid was then oxidized as described for the preparation of **24** with Jones reagent. Following the same work-up procedure, a crystalline product was obtained. Crystallization from Skellysolve B gave two crops (0.288 g, 0.00188 mol, 60%) of colorless crystals, mp 120–122°. Two recrystallizations from Skellysolve B gave colorless needles: mp 121–123°; RD (*c* 0.644, CH_3OH), $[\phi]_{370}$ +24.6°; $[\phi]_{320}$ +59.6, $[\phi]_{310}$ +95°, $[\phi]_{301}$ +114, $[\phi]_{290}$ +102°, $[\phi]_{282}$ +86°, $[\phi]_{267}$ + 102°, $[\phi]_{250}$ +176°; ν_{NH} 3220, 3210; $\nu_{C=O}$ 1710 cm^{-1} in Nujol; *m/e* 153 (M^+).

Anal. Calcd for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.14. Found: C, 70.38; H, 9.73; N, 9.88.

Registry No.—(+)-**2**, 16878-36-7; (−)-**2**, 5681-50-5; (−)-**3**, 16878-16-3; (±)-**4**, 16878-38-9; (+)-**4**, 16878-35-6; (−)-**4**, 16878-34-5; (+)-**5**, 16878-39-0; **6**, 16878-17-4; (±)-**9**, 16878-18-5; **10**, 16878-19-6; (±)-**10**, 16959-97-0; **11**, 16915-92-7; **12**, 16878-20-9; perchlorate salt of **12**, 16878-21-0; **13**, 16878-22-1; **15**, 16878-23-2; **17**, 16878-24-3; **18**, 16878-25-4; **19**, 16878-26-5; **21**, 16878-27-6; **22**, 16878-28-7; (±)-**22**, 16878-29-8; **23**, 16878-30-1; **24**, 16878-31-2; **25**, 16878-32-3; **26**, 16878-33-4.

Acknowledgments.—We thank J. R. Heald, J. M. Noteboom, I. N. Pratt, M. J. Sutton, H. M. Woltersom, and S. L. Towne for technical assistance and Dr. W. A. Struck and associates for physical and analytical data.

Stereochemistry of Microbiological Hydroxylation

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Several observations concerning the stereochemistry of a number of rigid molecules, that have been hydroxylated by *Sporotrichum sulfurescens*, in relationship to possible enzyme–substrate interactions are discussed. Rigid molecules containing the 1-benzoylpiperidine ring are hydroxylated at positions outside of the piperidine ring, supporting the idea that a 5.5-Å distance between the electron-rich center and point of hydroxylation is preferred in substrates containing the amide functional group. The hydroxyl group introduced into the substrate molecule by the microorganism has been found to be oriented *trans* with respect to the amide functional group. A spatial orientation for the methylene group which is hydroxylated has been defined on the basis of a coordinate system. Mapping of the enzyme contours may then be carried out indirectly by observing the volume of space occupied by rigid molecules when they are placed into this arbitrary orientation. Preliminary results based on optically active products obtained from hydroxylation of 1-benzoyl-*trans*-decahydroquinoline indicate a preference for placing the bulk of the molecules in the upper right (UR) rear octant of the coordinate system. The dihydroxylation of certain 1-adamantanamine derivatives is observed to result from increased lipophilic character in the amide group. Finally it is suggested that the oxidation state (alcohol or ketone) of the oxygenation products depends upon the conformational mobility of the molecule in question.

A recent report from these laboratories proposed a hypothetical enzyme–substrate model to account for the preferential hydroxylation at certain sites observed during the oxygenation of macrocyclic alcohols by the microorganism, *Sporotrichum sulfurescens*.[1] This model suggests that an electron-rich center of the cyclic substrate molecule becomes attached to the hydroxylating enzyme and that hydroxylation then occurs at a carbon atom approximately 5.5 Å distant from the attachment site.[1] In the case of the macrocyclic alcohols, the hydroxyl oxygen serves as the electron-rich center. Substrates containing other electron-rich groups are also oxygenated by *S. sulfurescens* and the amide functional group has been particularly useful in this respect.[2] Among the types of amide-containing molecules, all of a cyclic nature, which we have studied are amides of azacycloalkanes,[3] azabicycloalkanes,[4]

(1) G. S. Fonken, M. E. Herr, H. C. Murray, and L. M. Reineke, *J. Amer. Chem. Soc.*, **89**, 672 (1967).

(2) G. S. Fonken, M. E. Herr, H. C. Murray, and L. M. Reineke, *J. Org. Chem.*, **33**, 3182 (1968).

(3) R. A. Johnson, M. E. Herr, H. C. Murray, and G. S. Fonken, *ibid.*, **33**, 3187 (1968).

(4) R. A. Johnson, M. E. Herr, H. C. Murray, L. M. Reineke, and G. S. Fonken, *ibid.*, **33**, 3195 (1968).

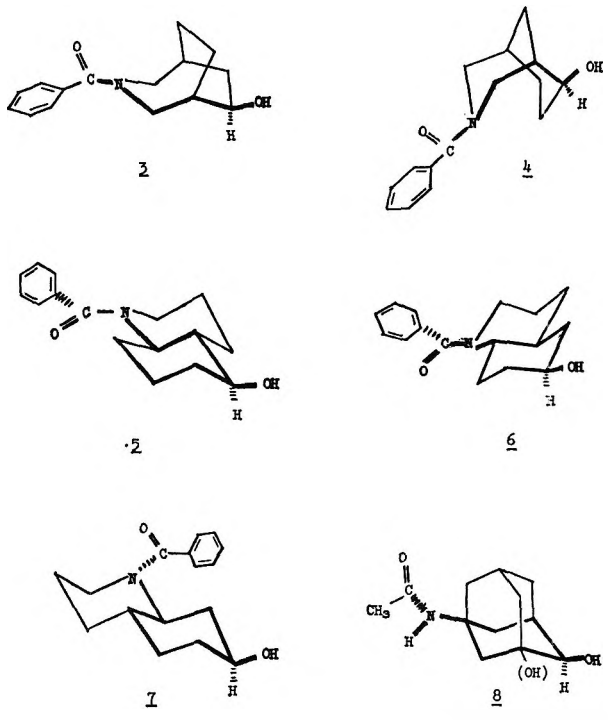
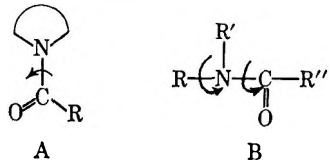


Figure 1.—Stereochemistry of products from the hydroxylation of rigid molecules with *S. sulfuescens*. Heavy lines illustrate the *trans* relationship of the hydroxyl group to the amide group.

adamantanamines,[5] and *trans*-decahydroquinoline.[6] With an increasing number of examples available, it first was of interest to determine if the above enzyme–substrate model would accurately predict the products obtained from these latter substrates.[3-6] Secondly, we hoped that the patterns of hydroxylations in these molecules would be suggestive of other conformational and steric factors which may have an effect on the hydroxylation reaction.[7] Any information of this type which may be gained would be useful in predicting the course of hydroxylations of other molecules.

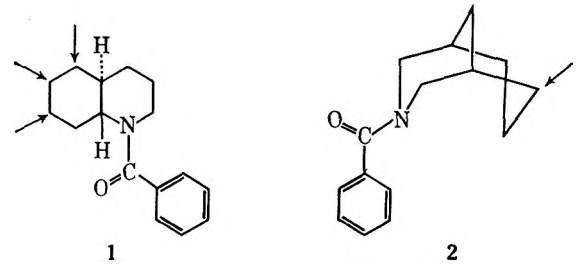
The requirements of an approximate 5.5-Å spacing between the electron-rich center and the site of hydroxylation appear to be largely met in these amides, assuming the amide carbonyl oxygen as the point of enzyme attachment. However, the amide group has several possible conformations, making predictions of hydroxylation sites according to the above model more difficult. If the amide nitrogen is part of a ring system (A), as in piperidine, two preferred conformations exist for the amide together with other less favorable conformations depending on rotation about the C–N amide bond.[8] If the amide nitrogen is primary, or not in a cyclic system (B), as in N-acetyl-1-adamantan-



A B

amine,[5] additional rotational freedom will exist around the C–N alkyl bond. These factors result in some latitude for orientation of the electron-rich amide oxygen.

Of interest with respect to the spacings between amide carbonyl and hydroxylation sites are the results obtained when relatively rigid molecules containing the piperidine ring are hydroxylated. 1-Benzoylpiperidine is hydroxylated at the 4 position.[3] The maximum distance between carbonyl oxygen and the methylene carbon at the 4 position is about 5.3 Å when the C–N amide bond is rotated so that the carbonyl is perpendicular to the plane of the piperidine ring. When the amide is in a planar conformation, this distance is reduced to about 5.0 Å. The molecules 1-benzoyl-*trans*-decahydroquinoline (**1**) and 3-benzoyl-3-azabicyclo-[3.3.1]nonane (**2**) both contain the 1-benzoylpiperidine ring system, but in each case hydroxylation occurs outside of the piperidine ring. In the former (**1**), hydroxylation occurs at three sites in the ring fused to the



1 **2**

(arrows indicate hydroxylation sites)

piperidine while in the latter (**2**), hydroxylation occurs at one site outside of the piperidine ring. It is possible, by selecting a suitable amide conformation, to obtain spacings of 5.3 Å *or greater* between these sites and the amide carbonyl. These examples suggest that, while the 5.5-Å distance between electron-rich center and point of hydroxylation is not essential, it is nevertheless preferred in substrates containing the amide functional group.

We now wish to examine the pattern of hydroxylations found[3-6] in these molecules with the idea of determining conformational and steric factors which may be effecting the hydroxylation reaction. The stereochemistry of the alcohols produced in the microbial hydroxylation of several rigid and partially rigid molecules has been determined.[4-6] These results are illustrated in Figure 1 and may be summarized as follows. The hydroxyl group in 3-benzoyl-3-azabicyclo[3.2.2]-nonan-6-ol (**3**) is *endo* with respect to the six-membered ring[4] and in 3-benzoyl-3-azabicyclo[3.3.1]nonan-6-ol (**4**) is axial with respect to the *cyclohexane* ring.[4] Hydroxylation of 1-benzoyl-*trans*-decahydroquinoline (**1**) occurs at the 5, 6, or 7 positions, giving compound **5**, **6**, and **7** in which the hydroxyl group is equatorial in each case.[6] The major product from hydroxylation of N-acetyl-1-adamantanamine (**9**) is the 4-hydroxy compound (**8**) in which the hydroxyl group is equatorial with respect to the six-membered ring common to both the nitrogen and the alcohol.[5] A minor product from hydroxylation of **9** has the hydroxyl group at the tertiary 3 position. A stereochemical feature found in all of these products and which we believe to be important is the *trans* orientation of the hydroxyl group and the amide group with respect to each other. Thus in the

(5) M. E. Herr, R. A. Johnson, H. C. Murray, L. M. Reineke, and G. S. Fonken, *J. Org. Chem.*, **33**, 3201 (1968).

(6) R. A. Johnson, H. C. Murray, L. M. Reineke, and G. S. Fonken, *ibid.*, **33**, 3207 (1968).

(7) An assumption underlying these considerations is that the same enzyme is responsible for the hydroxylations of these varied substrates.

(8) *Cf.* H. S. Gutowsky and C. H. Holm, *J. Chem. Phys.*, **25**, 1228 (1956).

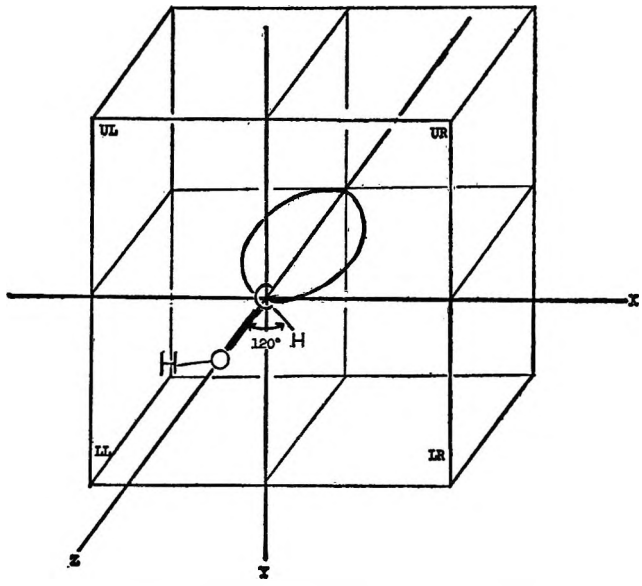


Figure 2.—Octant system for defining orientation of substrate–product molecules in space. Rear four octants are shown by boxes.

adamantanamine (**8**) and *trans*-decahydroquinoline (**5**, **6**, and **7**) examples, the hydroxyl group and the amide nitrogen are found to be 1,3- or 1,4-diequatorial substituents on a cyclohexane ring. In the two bicyclic compound (**3** and **4**), the C–O alcohol bond is oriented in a direction opposite that of the N–C amide bond. These stereochemical relationships are outlined by the heavy lines in the formulas of Figure 1. In addition to the above examples, the orientation of both hydroxyl groups in the bioconversion product N-benzoyl-N-methyl-1-adamantanamine-4α,6α-diol (**10**) has been shown to be *trans* with respect to the amide group.[5] This observation adds support to the generalization that hydroxylation occurs to give hydroxyl groups oriented *trans* to the enzyme attachment site.

Our discussions of the enzyme–substrate model to this point have centered around the electron-rich group of the substrate molecule, *i.e.*, the hydroxyl or the amide oxygen atom. We now would like to turn attention to a second important site within the enzyme, whose existence is certain. This is the site at which the oxygenation reaction occurs.[9] Although the molecular structure at this site is unknown, we will assume that the molecular geometry is quite precise at this point.[10] As the substrate molecule approaches this oxygenation site, it will undoubtedly come into contact with adjacent surfaces of the enzyme molecule. We wish to determine the contours of these surfaces indirectly by examining the stereochemical features of various rigid molecules, which have been hydroxylated successfully.

As a consequence of the precise geometry of the oxygenation site, the methylene group which is oxygenated will have a preferred orientation at this site. This in turn will determine the orientation of substrate

(9) The total enzymic site of hydroxylation of course will include both the oxygenation site and any electrophilic substrate attachment sites. However, these individual parts appear to be at opposing ends of the total site, allowing separate consideration of their character.

(10) The number of entities which must interact at this site, *i.e.*, oxygen in association with an activating moiety (such as a cytochrome), redox cofactors, enzyme bulk, and substrate molecule, suggest that a precise geometry will be required.

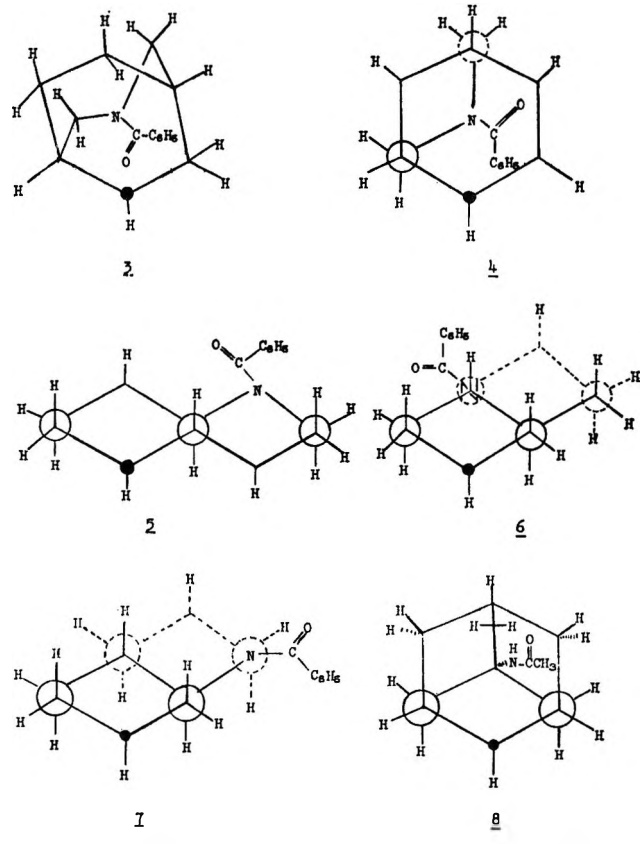


Figure 3.—Projection formulas of product molecules. Heavy dot (●) indicates C–O bond projecting toward the viewer.

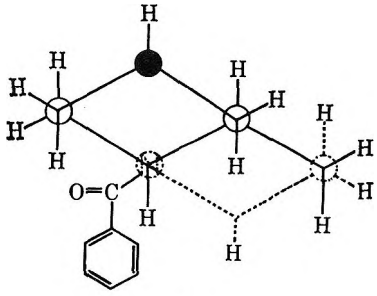
molecules having a rigid structure. The methylene group itself has tetrahedral geometry and it should be possible to transpose this from the orientation found at the oxygenation site into an arbitrarily defined spatial orientation. Such an operation will make it possible to place a variety of rigid molecules into the defined orientation so that the composite space occupied by the molecules can be mapped out. To define an arbitrary spatial orientation for the methylene group, we have chosen to place the methylene carbon at the origin of a *XYZ* coordinate system (see Figure 2). A second point then is fixed in this system by extending the C–O bond of the hydroxylated substrate molecule along the *Z* axis toward the viewer. As a third fixed point, required to prevent rotation around the C–O bond, the remaining C–H bond[11] of the hydroxymethylene group is placed in the *Y*–*Z* plane as shown in Figure 2. These three points provide the desired spatial orientation for the substrate–product molecules. As the viewer looks down the *Z* axis at molecules placed in this orientation, the atomic arrangements will be seen much as they appear in conventional Newman projection formulas. The rigid molecules discussed above are shown in such projections in Figure 3.

The mapping of the space occupied by the substrate molecules, which reflects the contours of enzyme surfaces adjacent to the oxygenation site, now may be attempted using the above orientation system. As a result of the manner in which the above model is defined, the bulk of the molecules will be found almost exclusively in the rear four octants of the coordinate

(11) In the few cases where a tertiary carbon is hydroxylated an alternative means of fixing the orientation is recognized to be necessary. This is considered briefly later in the discussion.

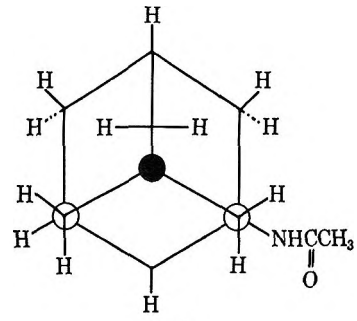
system. These octants are labeled upper left (UL), upper right (UR), lower right (LR), and lower left (LL) as seen in Figure 2. Beginning with the major product (**8**) obtained from hydroxylation of N-acetyl-1-adamantanamine,[5] we find the atoms of this symmetrical molecule evenly distributed between the UL and UR octants when seen in projection (see Figure 3). It should be remembered that the amide group in **8** may be rotated about the C–N bond. Next we examine the projection formulas of the bicyclic products **3** and **4**. Hydroxylation has introduced asymmetry into both of these molecules. Lack of significant optical rotation in **3** and **4**[4] indicates that a mixture of enantiomeric forms has been obtained in each case. Stereoselectivity of the hydroxylating enzyme for the potentially enantiomeric carbons in the bicyclic precursors to **3** and **4** is therefore absent. Projection formulas of single enantiomers of **3** and **4** (Figure 3) are also seen to be rather evenly distributed between the UL and UR octants, much as is observed for the adamantane derivative **8**. Since, qualitatively, all three of these products (**3**, **4**, and **8**) are formed rapidly and in good yield, the positions occupied by their skeletal atoms do not seriously interfere with the hydroxylation reaction. Consequently, the potential asymmetry of the substrates, which lead to **3** and **4**, is insufficient to result in a preferred steric course for the hydroxylation reaction.

It now becomes of interest to examine the projection formulas of the products obtained from hydroxylation of 1-benzoyl-*trans*-decahydroquinoline, since the optical activity of these compounds suggests that the asymmetry of the molecules is affecting the course of the reaction. The absolute configurations of these products are known and enable us to compare projection formulas in the orientation model.[6] The major products from this bioconversion were (4a*S*,5*S*,8a*R*)-1-benzoyl-*trans*-decahydroquinolin-5-ol (**5**) and (4a*S*,6*S*,8a*S*)-1-benzoyl-*trans*-decahydroquinolin-6-ol (**6**) while (4a*S*,7*S*,8a*S*)-1-benzoyl-*trans*-decahydroquinolin-7-ol (**7**) and (4a*R*,6*R*,8a*R*)-1-benzoyl-*trans*-decahydroquinolin-6-ol (**11**) were found as minor products. Placement of **5**, **6**, and **7** in the orientation model results in the projection formulas shown in Figure 3. The *S* configuration of these alcohols is reflected by the fact that greater portions of the molecules are found in the UR octant as opposed to the UL octant. The minor product (**11**) of *R* configuration at the alcohol carbon could be represented by the opposite of projection formula **6** and would have a greater portion in the UL octant. These limited examples suggest that more space is available to the substrate molecule in the UR octant with respect to the potential C–O bond.



11

Since the above orientation model has been defined in terms of the methylene group it is necessary to consider separately the case of hydroxylation of a tertiary carbon. An example of this is found in the formation of the bioconversion product N-acetyl-1-adamantanamin-3-ol (**12**).[5] This hydroxymethine carbon lacks the second C–H needed to use the above orientation model. Until more examples are available we suggest that **12** be described by a projection formula which places the axial protons of the α carbons downward in planes parallel to the *XY* plane. A similar orientation of minor product **11** provides an alternative to that indicated previously and places more of the molecule in the LR octant than in the UL octant. This type of orientation is considered to be much less favorable in most situations.



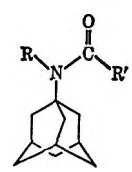
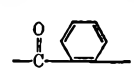
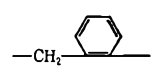
12

The general spatial orientation model which has been presented here attempts to determine important stereochemical features of the enzyme–substrate interactions during microbiological hydroxylation reactions. By examining the enzyme–substrate complex from the oxygenation site, it is hoped that this model will be complimentary to the previously outlined enzyme attachment site model[1] in predicting the course of microbial hydroxylation reactions. As the stereochemistry of other rigid molecules is determined, the validity of the present model can be tested further.

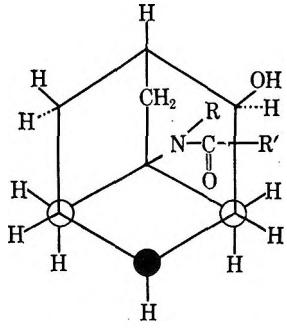
The formation of dihydroxyadamantane derivatives by the microbial hydroxylation reaction has been noted[5] and is of interest since dihydroxylation is less frequently observed. Table I shows the major product obtained from bioconversion of a series of N-substituted 1-adamantanamines with *S. sulfurescens*.[5] From the table it can be seen that the formation of dihydroxylated products is predominant where R and/or R′ are larger

TABLE I

MAJOR PRODUCTS FROM OXYGENATION OF N-SUBSTITUTED-1-ADAMANTANAMINES WITH *S. sulfurescens*

Compd	R	R′	Major product: Mono OH	Major product: Di OH
	H	CH_3	*	
	CH_3	CH_3	*	
	CH_3	C_6H_5		*
	H	$CH_2C_6H_5$		*
	CH_3	C_6H_{11}		*
				*
				*

groups, *i.e.*, phenyl rather than methyl, for example. The increased size of the groups R and R′ will impart greater lipophilic character to the molecule and it may be that this is sufficient to allow a second attachment of the molecule to the enzyme following the first hydroxylation. In terms of the above orientation model, the product of dihydroxylation[5] will have the following projection formula. Rotation of the adamantane nucleus 120° around the C–N bond will present a second "face" of the nucleus to the enzyme surface identical with the first. A second hydroxylation of this orientation results in the di-α-OH products which are observed.



The above argument implies that dihydroxylation occurs as two discreet steps. This is supported by following the course of the fermentation by thin layer chromatography. When this is done, a single spot corresponding to the monohydroxy product is seen first. With increasing time a second spot, corresponding to the dihydroxy product, appears and becomes stronger at the expense of the monohydroxy product. It is also possible to isolate the monohydroxy product and then add it to a fresh *S. sulfurescens* culture, which converts it into the dihydroxy product.[5]

The oxygenation of some substrates gives only hydroxylated products while in other cases both hydroxy and ketonic products are obtained. In the latter cases, the hydroxyl groups and the ketone groups are found at the same position, suggesting that the hydroxy compound is probably an intermediate in the formation of the ketone. We have observed that molecules having a higher degree of conformational mobility tend to give more ketonic products when oxygenated with *S. sulfurescens*, while highly rigid molecules give exclusively hydroxylated products. As examples, the macrocyclic alcohols (C_{12}–C_{14}) are oxygenated to mixtures of dialcohols, keto alcohols, and diketones.[1] Similarly, oxygenation of 1-benzoylhexamethylenimine, 1-benzoylheptamethylenimine, and 1-benzoyloctamethylenimine gave mixtures of alcohols and ketones in each case.[3] All of these molecules have several conformations differing in energy to a relatively small degree. On the other hand, molecules such as N-acetyl-1-adamantanamine, 3-benzoyl-3-azabicyclo[3.3.1]nonane, 2-benzoyl-2-azabicyclo[2.2.2]octane, and 1-benzoyl-*trans*-decahydroquinoline have either a rigid structure or a highly preferred conformation. All of these compounds give only hydroxy products.[4–6] Intermediate in conformational mobility are the six- and seven-membered-ring compounds. Cyclohexane derivatives may flip from one chair conformation to a second but they prefer the one in which substituents are equatorial. Cyclohexyl compounds generally give only hydroxylated products.[1,2] Cycloheptyl derivatives have a slightly greater conformational freedom and are found to give both hydroxy and ketonic products. The compound 3-benzoyl-3-azabicyclo[3.2.2]nonane contains both six- and seven-membered rings and has some conformational freedom as judged from Dreiding models. This compound also gives both a hydroxy and a ketonic product.[4] It seems plausible that the greater conformational mobility of some molecules permits them to be adapted to the alcohol dehydrogenating enzymes of the microorganism with the result that they are more readily converted from alcohols into ketones.

Steric Requirements for Free-Radical Substitutions. I. Phenyl Migration during Bromination[1]

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Steric hindrance can affect the course of free-radical brominations with N-bromosuccinimide (NBS) and with bromine. 1,1,1,2-Tetraphenylethane with NBS or Br_2 affords tetraphenylethylene resulting from a phenyl migration. 1,2,2-Triphenylpropane undergoes normal bromination with either reagent to give 1-bromo-1,2,2-triphenylpropane. 4,4,4-Triphenyl-1-butene, **11**, with NBS gives exclusively 1-bromo-4,4,4-triphenyl-2-butene, **12**, the product arising from allylic rearrangement. Both **11** and **12** give negative tests for unsaturation when treated with bromine in carbon tetrachloride.

The Wohl–Ziegler reaction[4] utilizing N-bromosuccinimide (NBS) is a valuable synthetic method for introducing a bromine atom at an allylic or benzylic position.[5] A free-radical chain sequence initiated by bromine atoms as suggested in 1953 by Goldfinger and coworkers[6] has been substantiated by others.[7] The

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(3) Taken in part from theses submitted in partial completion for the M. A. degree: (a) Brooklyn College, 1956; (b) City College, 1966.

(4) (a) A. Wohl, *Ber.*, **52**, 51 (1919); (b) K. Ziegler, A. Spaeta, E. Schaaf, W. Schumann, and E. Winkelmann, *Ann.*, **551**, 80 (1942).

(5) C. Djerassi, *Chem. Rev.*, **43**, 271 (1948).

(6) J. Adam, P. A. Gosselain, and P. Goldfinger, *Nature*, **171**, 704 (1953); *Bull. Soc. Chim. Belges*, **65**, 533 (1956).

(7) (a) B. P. McGrath and J. M. Tedder, *Proc. Chem. Soc.*, 1511 (1961); (b) C. Walling, A. L. Rieger, and D. Tanner, *J. Amer. Chem. Soc.*, **85**, 3129 (1963); (c) G. A. Russell and K. M. Desmond, *ibid.*, **85**, 3139 (1963); (d) R. E. Pearson and J. C. Martin, *ibid.*, **85**, 3142 (1963).

chain-propagating steps (eq 1 and 2) require small amounts of bromine formed *in situ* from HBr and NBS, designated in eq 3 as S-Br.

$$RH + Br\cdot \longrightarrow R\cdot + HBr \quad (1)$$

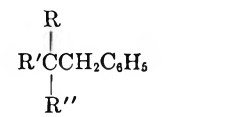
$$R\cdot + Br_2 \longrightarrow RBr + Br\cdot \quad (2)$$

$$\underset{(NBS)}{S\text{-}Br} + HBr \longrightarrow \underset{(succinimide)}{S\text{-}H} + Br_2 \quad (3)$$

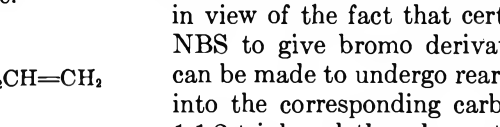
Little attention has been given to the steric requirements for this type of reaction. There is some evidence that steric factors may control the course of the reaction. For example, although there is ample evidence[5] for suggesting that an active methylene group is more reactive than an active methyl group, it has been observed that 2,4,4-trimethyl-1-pentene reacts with NBS to give 2-bromomethyl-4,4-dimethyl-1-pentene.[4b] This product arises from bromination at a methyl group rather than at the sterically hindered neopentyl methylene group.

Although the presence of a bromine atom at an active site deters the insertion of a geminal bromine atom,[5] tetrabromination of [2.2]paracyclophane with NBS gives geminal rather than vicinal tetrabromide,[8] an occurrence attributed to steric strain associated with this unique ring system.

This work was undertaken to study the steric requirements of the NBS reaction. The substrates chosen possess only one active site which is also adjacent to a quaternary carbon atom. The substrates are of two broad types: (a) compounds **1**, **4**, and **7**, in which the active site is benzylic, and (b) 4,4,4-triphenyl-1-butene, compound **11**, in which the active site is allylic.



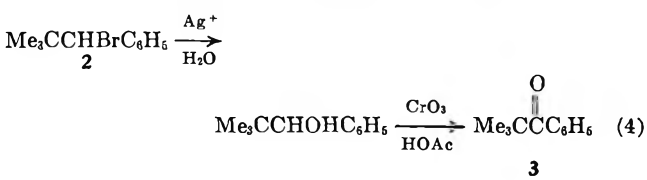
1, R = R′ = R″ = CH_3
4, R = R′ = R″ = C_6H_5
7, R = R′ = C_6H_5; R″ = CH_3



11

Results and Discussion

Neopentylbenzene,[9] **1**, was allowed to react in carbon tetrachloride with NBS in ordinary light and without initiating catalysts; the reaction time for 0.1 mol was 2.5 hr. Vacuum distillation of the crude brominated product gave a main fraction (57%) having a boiling point, density, and refractive index expected for 1-bromo-2,2-dimethyl-1-phenylpropane (**2**). Further proof of structure of **2** was achieved by the sequence steps[10] in eq 4. *t*-Butyl phenyl ketone (**3**) was characterized by preparing its 2,4-dinitrophenylhydrazone.



$$\underset{\mathbf{2}}{Me_3CCHBrC_6H_5} \xrightarrow[H_2O]{Ag^+} \underset{}{Me_3CCHOHC_6H_5} \xrightarrow[HOAc]{CrO_3} \underset{\mathbf{3}}{Me_3CCC_6H_5} \quad (4)$$

The fact that **1** is brominated in the normal manner indicates that the mere presence of a quaternary carbon atom bonded to the benzylic carbon atom does not prevent normal reaction.

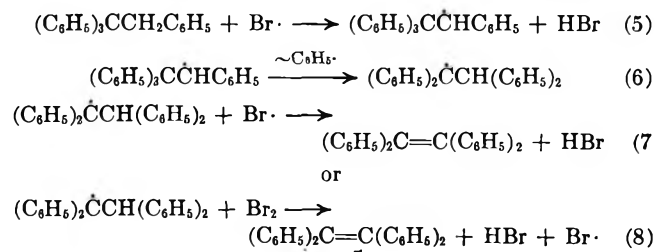
Steric hindrance could be augmented by replacing the methyl groups of **1** with bulkier phenyl groups. For this reason, 1,1,1,2-tetraphenylethane (**4**) was prepared from benzylmagnesium chloride and triphenylchloromethane.[11] As the reaction of **4** with NBS in refluxing carbon tetrachloride proceeded, an orange-brown vapor, identified as bromine, was observed. The appearance of bromine presages an elimination of hydrogen bromide as a result of the reaction shown in eq 3. The crude residue from the bromination reaction was separated by fractional crystallization into two solids, 51% starting material and 43% compound **5**, mp 220–221°. That **5** was tetraphenylethylene was confirmed by a mixture melting point determination with an authentic sample, by ultraviolet absorption [λ_{max} 310 mμ (log ϵ 4.20)], and by oxidative degradation to benzophenone, characterized as its 2,4-dinitrophenylhydrazone.

Formation of **5** requires a *migration of a phenyl group*. Aryl migration in free-radical intermediates is well known.[12] However, heretofore, they have not been observed during free-radical halogenations in solution.[13]

That free radicals were intermediates was shown by the absence of any reaction when **4** and NBS were refluxed in carbon tetrachloride in the dark under nitrogen. With a trace of benzoyl peroxide under nitrogen in the dark, the reaction was complete in 1 hr, giving a 48% yield of **5**.

It might be suggested that 2-bromo-1,1,1,2-tetraphenylethane (**6**), formed initially by a typical free-radical bromination, can rearrange *via* a carbonium ion intermediate engendered by succinimide acting as an electrophilic catalyst. This possibility is very remote in view of the fact that certain compounds react with NBS to give bromo derivatives which after isolation can be made to undergo rearrangement when converted into the corresponding carbonium ion. For example, 1,1,2-triphenylethanol reacts normally with NBS to give 1,1,2-triphenyl-2-bromoethanol; no phenyl benzhydryl ketone is obtained. The ketone, from a typical carbonium ion rearrangement, was isolated from the action of silver nitrate on the bromohydrin.[14]

Compound **5** is also obtained as the sole product when **4** is allowed to react with bromine in carbon tetrachloride at room temperature in ordinary light. It is suggested that **5** arises from **4** directly as the result of a free-radical phenyl migration as shown. No decision



$$(C_6H_5)_3CCH_2C_6H_5 + Br\cdot \longrightarrow (C_6H_5)_3\dot{C}CHC_6H_5 + HBr \quad (5)$$

$$(C_6H_5)_3\dot{C}CHC_6H_5 \xrightarrow{\sim C_6H_5\cdot} (C_6H_5)_2\dot{C}CH(C_6H_5)_2 \quad (6)$$

$$(C_6H_5)_2\dot{C}CH(C_6H_5)_2 + Br\cdot \longrightarrow \underset{\mathbf{5}}{(C_6H_5)_2C{=}C(C_6H_5)_2} + HBr \quad (7)$$

or

$$(C_6H_5)_2\dot{C}CH(C_6H_5)_2 + Br_2 \longrightarrow \underset{\mathbf{5}}{(C_6H_5)_2C{=}C(C_6H_5)_2} + HBr + Br\cdot \quad (8)$$

can be made as to whether the alkene arises by a chain-terminating step (eq 7) or a chain-propagating step (eq 8).

(8) K. C. Dewhirst and D. J. Cram, *J. Amer. Chem. Soc.*, **80**, 3115 (1958).
(9) (a) A. Bygdèn, *Ber.*, **45**, 3479 (1912); (b) V. N. Ipatieff and L. Schmerling, *J. Amer. Chem. Soc.*, **60**, 1476 (1938).
(10) P. Skell and C. R. Hauser, *ibid.*, **64**, 2633 (1942).
(11) M. Gomberg, *Ber.*, **39**, 1463 (1906).
(12) C. Walling in "Molecular Rearrangements," Interscience Publishers, Inc., New York, N. Y., 1963, p 407–455.
(13) In the gas phase chlorination of *t*-butylbenzene at 190–245° at low concentration of halogen, a small amount of 1-chloro-2-methyl-3-phenylpropane was detected: J. D. Backhurst, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 2742 (1959).
(14) J. F. Lane and D. R. Walters, *J. Amer. Chem. Soc.*, **73**, 4234 (1951).

Ordinarily, such free-radical migrations do not occur during halogenation reactions because of the low activation energy for eq 2. This step usually proceeds more rapidly than the migration which requires a higher energy of activation. However, in the halogenation of **4**, the bulky trityl group adjacent to the free-radical carbon atom retards eq 2, so that the migration (eq 6) becomes competitive. The free radical engendered in eq 5 has a relatively low-energy barrier for phenyl migration since it is a secondary free radical stabilized by one phenyl group, and the rearranged free radical in eq 6 is tertiary and stabilized by two phenyl groups. This combination of steric hindrance toward bromine insertion and formation of a much more stable radical resulting from phenyl migration enables the rearranged product to form.

It seemed pertinent to see if phenyl migration could stil occur with substrate **7**, having one of the phenyls of the trityl group replaced by a methyl group. 1,2,2-Triphenylpropane[15] (**7**) was allowed to react with NBS in carbon tetrachloride solution to yield a product (90–95%) which was analyzed as a compound in which one hydrogen of the starting material was replaced by a bromine. The crude reaction product was shown by thin layer chromatography to contain only the brominated product and starting material. Investigation of the ultraviolet spectrum of the crude reaction product gave no evidence for the presence of material containing a styrene or a 1,1-diphenylethylene-like conjugation in quantities greater than approximately 0.5%. The nmr spectrum of the purified bromination product shows a singlet at δ 1.81 integrating for three hydrogens, a singlet at 5.72 integrating for one hydrogen, and a complex multiplet of peaks from δ 6.9 to 7.4 integrating for 15 hydrogens. The interpretation of this spectrum indicates that the bromination product is either $(C_6H_5)_2CCH_3CHBrC_6H_5$ (**8**) or $(C_6H_5)_2CHC(CH_3)BrC_6H_5$ (**9**), the latter compound resulting from a rearrangement. To distinguish between these compounds, the product was reduced with lithium aluminum hydride. From the reduction was isolated a product in 52.5% yield, the remainder being unreacted starting material. The reduced product was identical with **6** by mixture melting point, thin layer R_f values, and identity of ultraviolet, infrared and nmr spectra. Furthermore, prolonged treatment of the brominated product with N,N-diethylaniline gave no reaction. These results lead to the conclusion that the brominated product is the unrearranged compound, 1-bromo-1,2,2-triphenylpropane (**8**), rather than the rearranged one, **9**. The incomplete reduction of **8** with lithium aluminum hydride is explainable by the fact that **8** is a neopentyl-type halide and hence would react sluggishly in SN2-type displacements.

$$(C_6H_5)_2CCH_3CH_2C_6H_5 \;(\mathbf{7}) \xrightarrow{\text{NBS}} \begin{cases} (C_6H_5)_2CCH_3CHBrC_6H_5 \;(\mathbf{8}) \\ \times \longrightarrow (C_6H_5)_2CHC(CH_3)BrC_6H_5 \;(\mathbf{9}) \end{cases} \quad (9)$$

The free-radical intermediate arising by hydrogen abstraction from **7** is not so sterically hindered toward bromine insertion as is the free-radical intermediate arising from **4** because a methyl group has less space requirement than a phenyl group. The energy of activation for migration of a phenyl group of the radical intermediate from **7** is greater than that for the radical intermediate from **4** because, although the rearranged radical is tertiary in both cases, the former is stabilized by only one rather than by two phenyl groups. The combination of these two factors precludes rearrangement during the bromination of **7**.

The isolation of **8** from the reaction of **7** with NBS can be used as further circumstantial evidence that **5** is formed from **4** by a free-radical rearrangement rather than by a carbonium ion rearrangement of **6**. If under the conditions of the NBS reaction **6** had been formed and had been converted into a carbonium ion, there is no reason why a carbonium ion could not likewise be formed from **8**. The 1,1,2-triphenylethyl carbonium ion undergoes phenyl migration,[16,17] and a 1,2,2-triphenylpropyl carbonium ion would be expected to behave similarly.

We hope to arrive at a definitive answer as to the free-radical character of the rearrangement observed during the bromination of **4** by studying migratory aptitudes of properly phenyl-substituted derivatives of **4**.

To examine the effect on the course of free-radical brominations of compounds having a trityl group bonded to an allylic position, 4,4,4-triphenyl-1-butene (**11**) was prepared. The coupling of triphenylmethylmagnesium bromide with allyl bromide[18] did not afford good yields. The reaction of tritylsodium with allyl bromide gave erratic yields (91–50%). The most consistently good yields (75%) were obtained by the method of Nesmeyanov and Perevalov,[19] involving the addition of a mixture of triphenylchloromethane and allyl bromide to activated magnesium and some allylmagnesium bromide. The reaction of **11** with NBS under ordinary conditions was complete after 4 hr. After one recrystallization of the crude product, there was obtained in 85.1% yield, a white needlelike solid (**12**) having a molecular formula of $C_{22}H_{19}Br$, as determined by elemental analysis. Ozonolysis of **12** afforded triphenylacetic acid, identified by melting point and as its amide, and bromoacetaldehyde, characterized as its 2,4-dinitrophenylhydrazone derivative. Formaldehyde was absent as shown by the very sensitive chromotropic acid test.[20] Hence, the structure of 1-bromo-4,4,4-tri-

$$\underset{\mathbf{11}}{(C_6H_5)_3CCH_2CH{=}CH_2} \xrightarrow{\text{NBS}} \underset{\mathbf{12}}{(C_6H_5)_3CCH{=}CHCH_2Br} \quad (10)$$

phenyl-2-butene was assigned to **12**. Confirmation of the structure and assignment of the *trans* geometry was made possible by infrared and nmr spectroscopy. The nmr spectrum of $(C_6H_5)_3CCH_A{=}CH_BCH_{C_2}Br$ has (a) a singlet at δ 7.15 integrating for 15 protons (three phenyl rings), (b) a doublet centered at 6.79 (J = 18 cps) integrating for one proton (H_A *trans* to H_B), (c) a quintet in the ratio of 1:2:2:2:1 centered at 5.48 (J_{AB} = 18 cps and J_{BC} = 9 cps) integrating for 1 proton (H_B), and (d) a doublet at 3.95 (J_{BC} = 9 cps) integrating for two pro-

(15) C. B. Wooster and J. F. Ryan, *J. Amer. Chem. Soc.*, **56**, 1133 (1934).

(16) C. J. Collins, W. A. Bonner, and C. T. Lester,, *ibid.*, **81**, 466 (1959).

(17) C. J. Collins and B. M. Benjamin, *ibid.*, **85**, 2519 (1963).

(18) W. E. Bachman and R. F. Cockerill, *ibid.*, **55**, 2932 (1933).

(19) A. N. Nesmeyanov and E. G. Perevalov, *Izv. Akad. Nauk SSSR, Otd. Khim Nauk*, 1002 (1954).

(20) F. Feigl, "Manual of Spot Tests," Reinhold Publishing Co., New York, N. Y., 1943.

tons. The infrared spectrum shows a band at 975 cm^{-1}, typical of a *trans*-dialkyl-substituted alkene.

Allylic rearrangement during bromination with NBS of terminal alkenes is to be expected. The predominant product usually results from the allylic shift but *some of the unrearranged product also is isolated.* For example, the reaction of 1-octene gives a 20% yield of the normal bromination product, 3-bromo-1-octene, and an 80% yield of the allylic rearranged product, 1-bromo-2-octene.[21] In only one case, the isolation of 3-bromo-1-phenylpropene from the reaction of allylbenzene with NBS, is complete allylic rearrangement observed.[22] In this case, total allylic rearrangement is attributable to conjugation of the newly positioned double bond and the benzene ring.

The absence of any impurity with a terminal vinyl group in once-recrystallized **12**, as evidenced by the negative test for formaldehyde in the products from ozonolysis, prompted the conclusion that the reaction of **11** with NBS might be another *instance of complete allylic rearrangement.* Hence, the infrared spectrum of the crude product from the reaction of **11** with NBS was compared with that of pure **11**, pure **12**, and mixtures of **11** and **12**. The characteristic peak at 915 cm^{-1} for a terminal vinyl group was absent in once-recrystallized **12**, but was present in **11**. It was present in crude **12**, but had an exceedingly low intensity. By comparing relative intensities of the bands at 975 (*trans*-dialkyl-substituted alkene) and at 915 cm^{-1} (terminal vinyl group), the amount of terminal unsaturation in crude **12** was determined to be less than 5%, and this slight absorption may have been due to unreacted **11**. Analysis of crude **12** by thin layer chromatography showed the presence of only **12** and **11**. Hence, it is concluded that little or no "normal" (unrearranged) bromination occurred, a fact attributable to severe steric hindrance of "normal" bromination, but not of "allylic" (rearranged) bromination.

In characterizing **12**, it was observed that bromine in carbon tetrachloride gives a negative test for unsaturation. A 2% solution of potassium permanganate was decolorized, but only after long standing and warming. Starting material (**11**) behaves in a similar manner toward these reagents. Since there is no direct conjugation between the phenyl groups and the double bond, these results were unexpected. However, the same phenomenon was observed with similarly constituted compounds. Both 2,2-diphenyl-3-pentenenitrile (**13**) and 2,2-diphenyl-3-methylbutenenitrile (**14**) are reported to give negative tests for unsaturation.[23]

$N{\equiv}CC(C_6H_5)_2CH{=}CHCH_3$ (**13**) $\qquad$ $N{\equiv}CC(C_6H_5)_2C(CH_3){=}CH_2$ (**14**)

These results are considered to be in accord with the hindered position of the double bond. There is, however, a possibility that some sort of long-range electronic interaction between the π bond of the double bond and the π bonds of any one of the three phenyl groups in **11** and **12**, or the nitrile and the two phenyl groups in **13** and **14**, may affect the reactivity of the double bond. The reason for this unexpected loss of "unsaturation" is now under study.

(21) L. C. Bateman, *Nature*, **164**, 242 (1949).

(22) E. A. Braude and E. S. Waight, *J. Chem. Soc.*, 1116 (1952).

(23) E. M. Schultz, C. M. Robb, and J. M. Sprague, *J. Amer. Chem. Soc.*, 69, 2454 (1947).

Experimental Section

Melting points were taken in capillaries and are uncorrected. Microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y., and Crobaugh Laboratories, Charleston, W. V. Ultraviolet absorption measurements were taken using both the Beckman Model DU spectrophotometer and the Cary Model 15 recording spectrophotometer. A 5×10^{-5} *M* solution in ethanol was used in most cases. Infrared measurements were taken using both the Baird double-beam Infrared spectrophotometer and the Perkin-Elmer Model 137 Infracord spectrometer. Carbon tetrachloride was used as the solvent in all cases. Nuclear magnetic resonance spectra were obtained with a Varian A-60 spectrometer, and taken in carbon tetrachloride, unless specified otherwise, with an internal standard of tetramethylsilane. Densities were taken with a Davidson Densitometer, and indices of refraction were taken with an Abbe refractometer. Thin layer plates were 400 μ thick, and were prepared from Merck silica gel HF_{254}. Materials to be analyzed were spotted in ether solvent, and the chromatograms were developed in 97% petroleum ether (bp 30–60°)–3% diethyl ether.

All solvents were dried and distilled before use. Reagent grade NBS was used and recrystallized from anhydrous benzene if the color was yellow.

Neopentylbenzene (**1**) was prepared by the method of Bygdèn[9] from benzylmagnesium chloride and *t*-butyl chloride. The crude material (76% yield) was distilled at atmospheric pressure to give a colorless, sweet-smelling oil (31%) in the boiling range 185–193°. This oil was then fractionally distilled giving **1**: bp 185–186.5°; $n^{20}D$ 1.4888 (lit.[9b] bp 185–188°, $n^{20}D$ 1.4884).

Reaction of 1 with NBS. Preparation of α-Bromoneopentylbenzene.—A mixture of 14.8 g (0.1 mol) of **1** and 17.8 g (0.1 mol) of NBS in 200 ml of carbon tetrachloride was refluxed for 2.5 hr after which time the reaction was complete. The content of the flask was cooled and the succinimide (9.8 g, 99%, mp 124–126°) was removed by filtration. The filtrate was concentrated and the residue was vacuum distilled. The main fraction (57%) was collected: bp 78–80° (2 mm); $d^{21.7}_4$ 1.244; $n^{20}D$ 1.538 [for α-bromoneopentylbenzene (**2**), lit.[24] bp 89° (3–4 mm), d^{25}_4 1.237, and $n^{20}D$ 1.540].

Conversion of 2 into Phenyl *t*-Butyl Ketone (**3**).—The bromo compound **2** was converted into the corresponding alcohol with aqueous silver nitrate.[10] The crude alcohol (0.164 g, 0.001 mol) in 0.5 ml of glacial acetic acid was oxidized with chromic acid according to the method of Cheronis.[25] An oil was obtained which, when dissolved in methanol and warmed with 2,4-dinitrophenylhydrazine reagent, gave upon cooling 0.12 g (34%) of a yellow-orange solid, mp 165–170°. The solid was recrystallized from methanol to give pure material, mp 191–193° (ref 10 reports mp 190–191° for the DNPH of phenyl *t*-butyl ketone).

Reaction of 1,1,1,2-Tetraphenylethane (**4**) **with NBS. A.**—A mixture of 3.82 g (0.0114 mol) of **4**, mp 142–143° (lit.[11] mp 144°), and 1.98 g (0.0111 mol) of NBS in 45 ml of carbon tetrachloride was refluxed in ordinary light. After 1 hr the carbon tetrachloride developed a light orange color which deepened. After 2 hr, orange-brown vapors, identified as bromine, were present in the condenser. The reaction was complete after 4.5 hr. The succinimide (1.0 g, 91%) was removed by filtration and the bromine was removed from the filtrate by a current of warm dry air. The filtrate was concentrated in stages to give two main solid fractions which, on recrystallization from 1:1 benzene–methanol, gave 1.95 g (51%) of starting material **4**, mp 137–140° (no depression in melting point on admixture with authentic sample), and 1.62 g (43%) of another compound, mp 220–221°, uv max 310 mμ (log ε 4.20). This compound was characterized as tetraphenylethylene (**5**) (lit.[26] mp 221°). Compound **5** was oxidized with potassium permanganate affording an oil which gave an orange 2,4-dinitrophenylhydrazone derivative melting at 233–235° (lit.[27] mp 237° for the DNPH of benzophenone). Admixture of this with an authentic 2,4-DNPH derivative of benzophenone gave no depression.

(24) S. Winstein and B. K. Morse, *ibid.*, **74**, 1133 (1952).

(25) N. D. Cheronis, "Micro and Semimicro Methods," Interscience Publishers, Inc., New York, N. Y., 1954, p 268.

(26) I. M. Heilbron, "Dictionary of Organic Compounds," Oxford Press, London, 1953.

(27) 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.

B.—When **4** was refluxed with NBS in carbon tetrachloride under nitrogen in the dark, no reaction was observed after 8 hr. When a few milligrams of benzoyl peroxide was added and refluxing was continued, excluding light and air, the reaction was complete after 1 hr, and **5** was isolated as the product in 48.2% yield.

Reaction of 4 with Bromine.—A solution of 1.7 g (0.0050 mol) of **4** and 1.6 g (0.010 g-atom) of bromine in carbon tetrachloride (50 ml) was warmed by a sun lamp for 12 hr. A quantitative yield of **5** was obtained.

Preparation of 1,2,2-Triphenylpropane (7).[16]—1,1,2-Triphenylethylene (5.00 g, 19.5 mmol) was added to 5 ml of liquid ammonia under a nitrogen atmosphere in an insulated flask fitted with a magnetic stirring bar, a Dry Ice condenser, and an ammonia inlet tube. Approximately 200 ml of ammonia was then added to the flask. Sodium (1.21 g, 53 mg-atoms) was added in small portions over a period of 2 hr, and the resulting black solution was stirred for an additional 0.5 hr. A solution of dimethyl sulfate (5.5 ml, 2.34 g, 58 mmol) in 15 ml of sodium-dried ether was added dropwise with stirring to the ammonia solution. The ammonia was permitted to evaporate at room temperature and the remaining white precipitate was triturated with water and filtered to yield 4.8 g of a white precipitate, mp 60–110°. An additional 0.2 g of white product was recovered by ether extraction from the water used in the trituration. After two recrystallizations of the crude reaction product (5.0 g) from absolute ethanol, 2.0 g (38% yield) of white crystals, mp 115–116.1° (lit.[28] mp 116–117°), was obtained. This purified material gave a single spot when subjected to analysis by thin layer chromatography.

Reaction of 7 with NBS. Preparation of 1-Bromo-1,2,2-triphenylpropane (8).—A mixture of **7** (1.00 g, 3.68 mmol) in 30 ml of carbon tetrachloride and NBS (0.65 g, 3.68 mmol) was refluxed under an atmosphere of nitrogen in a flask fitted with an Allihn condenser and a calcium chloride drying tube while being illuminated by a 100-W incandescent lamp. The course of the reaction was followed by thin layer chromatography, and was tested periodically for unreacted NBS with potassium iodide–starch paper. After 2 hr of refluxing, the mixture contained a small amount of starting material and no NBS. The colorless solution was cooled and succinimide (0.375 g, 102% yield) was removed by filtration. The solvent was evaporated to yield a thick yellow oil (1.434 g, 111% yield). By comparing the relative intensities of the peaks in the nmr spectrum of the crude oil at δ 1.51, assigned to the methyl group of **7**, and at 1.81, assigned to the methyl group of the product **8**, the ratio of product to starting material was found to be 94:6.

The oil (6.250 g from a larger scale reaction) was dissolved in 25 ml of *n*-hexane and the solution was kept at room temperature for 11 days. A first crop of colorless crystals (2.78 g), mp 93.5–96.5°, was obtained. On further standing, the solution deposited three additional fractions of 1.30 g (mp 94–96.8°), 0.92 g and 0.31 g (mp 95–96°). The four fractions totaled 5.31 g (87% over-all yield). Each crop was found to be contaminated by a trace of starting material as shown by thin layer chromatography. The first crop was recrystallized from 13 ml of *n*-hexane to give 2.08 g of colorless crystals of **8**: mp 94.7–96°; ir (KBr), 3050, 1597, 1577, 1493, 1443 and 1070 (C_6H_5), 760 and 705 (monsubstituted C_6H_5), 1380 (CH_3), and 2995–2850 cm^{-1} (CH_3 and C–H); nmr (CCl_4), δ 1.81 (s, 3, CH_3), 5.72 (s, 1, CHBr), and 6.97–7.4 ppm (m, 15, C_6H_5).

Anal. Calcd for $C_{21}H_{19}Br$: C, 71.80; H, 5.45; Br, 22.75. Found: C, 71.75; H, 5.62; Br, 22.92.

Lithium Aluminum Hydride Reduction of 8.—Lithium aluminum hydride (0.19 g, 5.0 mmol) was slurried in 20 ml of anhydrous tetrahydrofuran in a three-necked, 100-ml round-bottom flask, fitted with an air stirrer, condenser, drying tube, and dropping funnel. The apparatus had been flushed with dry nitrogen to remove traces of moisture prior to addition of reagents. The flask was heated in an oil bath until the gray suspension began to boil and then a solution of **8** (1.75 g, 5.0 mmol) in 10 ml of anhydrous tetrahydrofuran was added dropwise to the stirred reaction mixture. Gas was evolved following each addition of **8**. After the addition had been completed, the mixture was stirred and refluxed for 1 hr. The oil bath was removed and 10 ml of ethanol was added slowly, followed by 2 ml of water and 5 ml of 5 *N* sodium hydroxide. The solution, which turned white, was concentrated to a volume of approximately 50 ml, and an equal volume of water was added. The mixture was extracted with 500 ml of ether, and the ethereal extract was dried ($MgSO_4$) and concentrated to yield 1.29 g of off-white solid, which was dissolved in 30 ml of *n*-hexane, filtered from a trace of insoluble material, and concentrated to 20 ml. When cooled, the pale yellow solution deposited 17 mg of colorless needles (mp 160–163°) giving a negative Beilstein test and shown to be pure by thin layer chromatography. The hexane filtrate was concentrated to 15 ml and cooled to deposit large clusters of needles on standing. The solid was removed by filtration, washed with 4 ml of cold *n*-hexane, and dried to yield 471 mg, mp 115.3–116.2°. This second crop of crystals was identified as 1,2,2-triphenylpropane (**7**) by melting point, by mixture melting point, and by infrared and nmr spectra. On further concentration of the hexane solution, an additional 244 mg of **7** (mp 112–115°) was obtained. The total yield of **7** was 715 mg (52.5%). Much of the remaining solid was starting material **8**.

Reaction of 4,4,4-Triphenyl-1-butene[19] (11) with NBS. Preparation of 1-Bromo-4,4,4-triphenyl-2-butene (12).—A mixture of 10.0 g (0.0352 mol) of **11**, mp 68–70°, and 6.12 g (0.0352 mol) of NBS was added to 100 ml of carbon tetrachloride in a 250-ml, round-bottom flask. The reflux condenser was protected by a calcium chloride drying tube, and the mixture was refluxed for 4 hr. The reaction mixture was cooled and filtered leaving 3.45 g (98%) of succinimide (mp 124–126°). By removing the solvent from the filtered mother liquor there was obtained 12.0 g (94.1%) of crude solid which when recrystallized from acetonitrile gave white needles (85.1%) of **12**: mp 145–147°; ir (CCl_4), 975 cm^{-1} (*trans* RCH=CHR); nmr (CCl_4), δ 7.15 (s, 15, C_6H_5), 6.79 (d, 1, J_{AB} = 18 cps, *trans* CH=CH), 5.48 [quintet (ratio 1:2:2:2:1), 1, J_{AB} = 18 cps and J_{BC} = 9 cps, CH=CHCH$_2$], and 3.95 ppm (d, 2, J_{BC} = 9 cps, CH_2Br).

Anal. Calcd for $C_{22}H_{19}Br$: C, 72.72; H, 5.27; Br, 22.01. Found: C, 72.70; H, 5.56; Br, 21.85.

Compound **12** gave an immediate precipitate with alcoholic silver nitrate, gave a negative test for unsaturation with bromine in carbon tetrachloride, and decolorized a 2% potassium permanganate solution in acetone only after long standing or heating.

Ozonolysis of 12.—In a Welsbach ozonizer, ozone was bubbled for approximately 30 min through a solution of 0.45 g (0.00124 mol) of **12** in ethyl acetate in a flask immersed in a Dry Ice–acetone bath. The solution was hydrogenated at atmospheric pressure using palladium on charcoal as a catalyst. The chromotropic acid test[20] for formaldehyde on the solution after reduction was negative.

When mixed with water and concentrated under vacuum with a current of air bubbling through it, the ethyl acetate solution yielded a white solid, 0.094 g (30%, mp 190–200°), which when recrystallized from methanol gave white crystals, mp 257–262°, identified as triphenylacetic acid (lit.[29] mp 264–265°). The triphenylacetic acid was further characterized as the amide in the usual manner.[27] When recrystallized from toluene, white crystals were obtained, mp 238–240° (lit.[26] mp 238).

To the aqueous mother liquor of the filtration of triphenylacetic acid was added 2,4-dinitrophenylhydrazine reagent, and an immediate orange precipitate was obtained, mp 147–150°, corresponding to the DNPH derivative of bromoacetaldehyde (lit.[26] mp 150°). A mixture of the DNPH derivative of bromoacetaldehyde with that of acetaldehyde (lit.[26] mp 147°) gave a depressed melting point at 125–127°.

Registry No.—NBS, 128-08-5; bromine, 7726-95-6; **1**, 1007-26-7; **4**, 2294-94-2; **7**, 16876-18-9; **8**, 16876-19-0; **11**, 16876-20-3; **12**, 16876-21-4.

Acknowledgments.—We wish to thank Mr. Stephen Goodman for his technical assistance and the National Science Foundation Undergraduate Research Participation Program for its financial assistance.

(28) E. Grovenstein, Jr., and L. Williams, Jr., *J. Amer. Chem. Soc.*, **83**, 2537 (1961).

(29) N. A. Lange, "Handbook of Chemistry," Handbook Publishers, Inc., Sandusky, Ohio, 1952.

An Abnormal Allylic Substitution Followed by a Novel Allylic Rearrangement[1]

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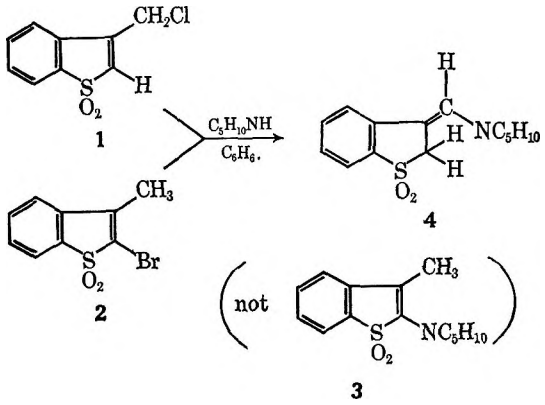
The products obtained from 2-halo-3-alkyl- and 3-α-chloroalkylbenzo[*b*]thiophene 1,1-dioxides with piperidine in benzene have been assigned structures using chemical methods combined with uv and nmr spectroscopy. Under these conditions 2-halo-3-alkylbenzo[*b*]thiophene 1,1-dioxides were found to undergo a tautomerism followed by a rapid abnormal allylic substitution. The 3-α-chloroethyl- and 3-(α-chloro-α-methylethyl)benzo[*b*]thiophene 1,1-dioxides were found to undergo an abnormal allylic substitution followed by an unusual ring opening and ring closing; the over-all result was molecular rearrangement.

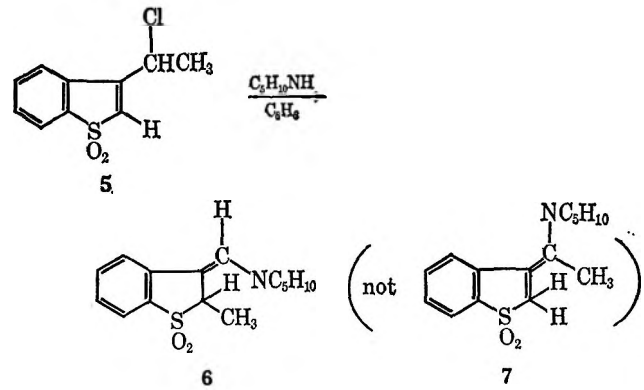
It was reported in a previous paper that 3-chloromethylbenzo[*b*]thiophene 1,1-dioxide (**1**) reacts with piperidine or morpholine in benzene, with sodium thiophenoxide in alcohol–benzene, and with thiourea in alcohol to give products in which the nitrogen atom or sulfur atom was attached to a vinylic carbon atom (from the uv spectra).[2] The reaction of 2-bromo-3-methylbenzo[*b*]thiophene 1,1-dioxide (**2**) with piperidine gave a product identical with that from **1**, but thiourea failed to react with **2**.[2] It appeared from these results that piperidine was effecting a displacement of the bromine atom in **2**, as is known to occur with 3-bromobenzo[*b*]thiophene 1,1-dioxide (which also fails to react with thiourea),[3] and was effecting an abnormal allylic substitution (SN2′) reaction on **1** to give the same product. The product from the piperidine experiment was believed, therefore, to be 2-piperidino-3-methylbenzo[*b*]thiophene 1,1-dioxide (**3**), and the other products obtained from **1** were assigned comparable structures. With the advent of nmr spectroscopy it immediately became apparent that this structure assignment was incorrrect. In place of the expected methyl singlet, the nmr spectrum of the product showed the presence of a vinylic proton and two other protons with a chemical shift and spin–spin splitting pattern consistent with allylic protons, as in structure **4**.



The nmr spectra of the products obtained from **1** and other nucleophiles (morpholine, sodium thiophenoxide, thiourea, sodium 2,4,6-trimethylthiophenoxide, sodium phenylmethanethiolate) showed that their structures were analogous to that of **4**.

Formation of **4** from **2** can be visualized as occurring by a 1,3-proton shift to form an allylic system followed by an SN2′ reaction.[4] Formation of **4** from **1** can be visualized as an SN2 displacement followed by a 1,3-proton shift, but this is an oversimplification, as will soon become apparent from a consideration of the behavior of the next higher homolog of **1**, 3-(α-chloroethyl)benzothiophenne 1,1-dioxide (**5**).

Reaction of **5** with piperidine in benzene occurs readily but, in sharp contrast to the behavior of **1**, **5** fails to react with thiourea in alcohol.[5] The nmr spectrum of the product showed, in addition to four phenyl protons and ten piperidine protons, a methyl doublet at δ 1.49 (J = 7.4 cps), a one-proton quartet at 4.11 (J = 7.4 cps), and a one-proton singlet at 6.67. This spectrum is consistent with structure **6**, but not with **7** (the product expected from SN2 displacement followed by a 1,3-proton shift).



The product has a high intensity maximum at 324 mμ, which is comparable with that of **4** (λ_{max} 325 mμ), and a strong band at 6.07 μ, which is characteristic of the enamine structure (**4** has a band at 6.11 μ).

The isomer of **6** with the enamine grouping in the 2 position is ruled out since its uv maximum should occur at a shorter wavelength.

Acid hydrolysis of the product gave a carbonyl compound, which was isolated as its 2,4-dinitrophenylhydrazone. The nmr spectrum of this product had eight protons in the δ 7.5–8.5 region (presumably seven phenyl protons and one aldehydic proton) which is consistent with structure **6a** (derived from **6**), but not with **8** (derived from the six-membered-ring isomer of **6**).

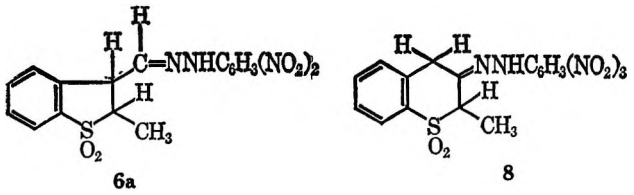
(1) Abstracted from the Ph.D. Dissertations of R. W. Hemwall, 1965, and D. A. Schexnayder, 1968. A preliminary account of part of this work has appeared: F. G. Bordwell, R. W. Hemwall, and D. A. Schexnayder, *J. Amer. Chem. Soc.*, **89**, 7144 (1967).

(2) F. G. Bordwell, F. Ross, and J. Weinstock, *ibid.*, **82**, 2878 (1960).

(3) F. G. Bordwell, B. B. Lampert, and W. H. McKellin, *ibid.*, **71**, 1702 (1949).

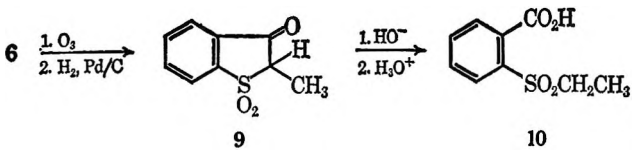
(4) The mechanism of this reaction is discussed in detail in the next paper of the present series: F. G. Bordwell, R. W. Hemwall, and D. A. Schexnayder, *J. Org. Chem.*, **33**, 3233 (1968).

(5) P. E. Sokol, Ph.D. Dissertation, Northwestern University, 1959.



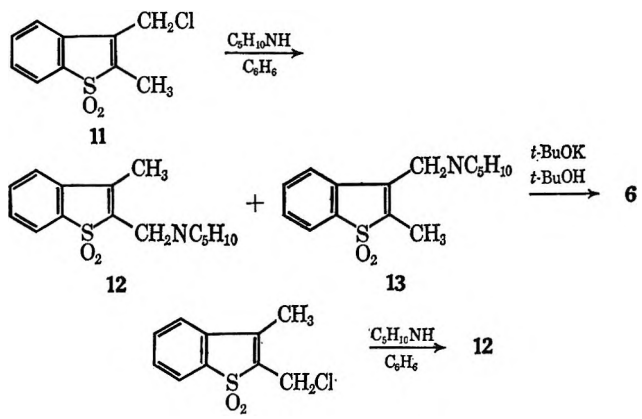
6a 8

Ozonolysis of **6** gave the (known) ketone **9**,[6] which was cleaved by base to *o*-ethylsulfonylbenzoic (**10**).[7]



9 10

Synthesis of **6** was accomplished starting with 2-methyl-3-chloromethylbenzo[*b*]thiophene 1,1-dioxide (**11**). Treatment of **11** with piperidine in benzene afforded a mixture of 2-methyl-3-piperidinomethyl- and 3-methyl-2-piperidinomethylbenzothiophene 1,1-dioxides (**12** and **13**, respectively). The structures of these products, one or both of which presumably arise by addition of piperidine to a 1,3-diene, were assigned on the basis of their nmr spectra (see Table I).

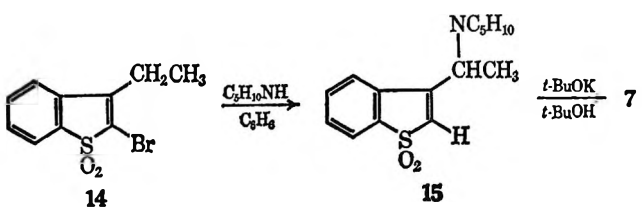


11 12 13

Treatment of **13** with potassium *t*-butoxide in *t*-butyl alcohol gave **6** (1,3-proton shift). The failure of the conversion **13** → **6** to occur with piperidine in benzene rules out the possibility of **13** being an intermediate in the conversion of **5** into **6**.

Treatment of 2-chloromethyl-3-methylbenzo[*b*]thiophene 1,1-dioxide with piperidine in benzene gave **12** as the only isolated product.

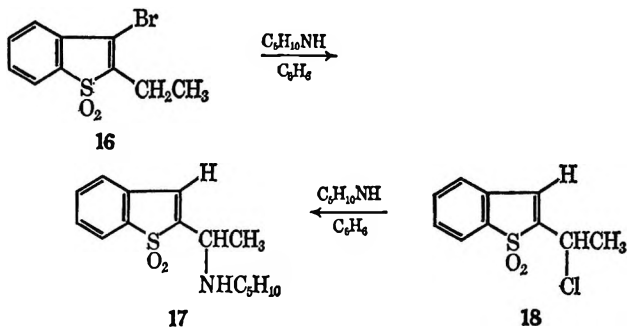
By analogy with the conversion of **2** into **4** one would expect the next higher homolog of **2**, 2-bromo-3-ethylbenzo[*b*]thiophene 1,1-dioxide (**14**) to react with piperidine to give **7**. Instead, this reaction gave 3-(α-piperidinoethyl)benzo[*b*]thiophene 1,1-dioxide (**15**) (the product expected from an SN2 reaction of **5** with piperidine). Treatment of **15** with potassium *t*-butoxide did give a compound believed to be **7**.



14 15

The failure of piperidine to effect the conversion of **15** into **6** rules out **15** as an intermediate in the conversion of **5** into **6**.

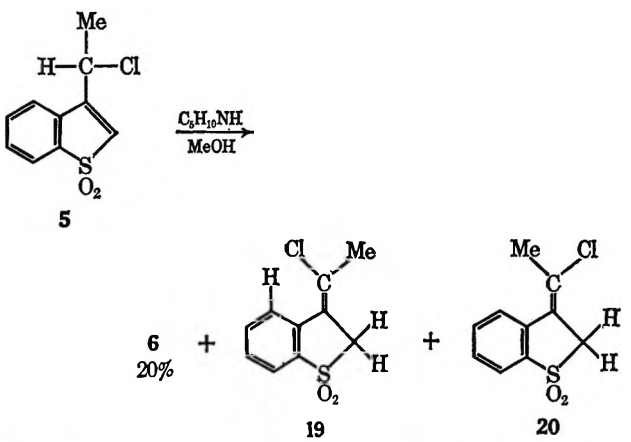
A reaction similar to the conversion **14** → **15** was observed on treatment of the isomer of **14**, 3-bromo-2-ethylbenzo[*b*]thiophene 1,1-dioxide (**16**), with piperidine in benzene.



16 17 18

The same product (**17**) was obtained from **18** under comparable conditions. This contrasts with the behavior of the 3-α-chloroethyl isomer (**5**), which gives a rearrangement product (see above).

The reaction of **5** with piperidine in methanol (0.5-hr reflux) gave only *ca.* 20% **6**. The remainder of the material was a mixture of the *cis* and *trans* tautomers of **5**, **19**, and **20**.



5 6 19 20

The chlorine atom is believed to be *cis* to the C-4 (*peri*) hydrogen atom in **19** on the basis of the nmr spectrum (Table II). Molecular models indicate that there is appreciable steric interference between the C-4 hydrogen atom and a *cis* group other than hydrogen in structures like **6**, **19**, and **20**. For this reason **6** and its analogs are assigned structures with the hydrogen atom *cis* to the C-4 hydrogen atom.

Pathways for the Reactions 2 → 4, 14 → 15, and 16 → 17.—For the reaction of 3-methyl-2-halobenzo[*b*]-thiophene 1,1-dioxides (**2**) with piperidine in benzene or methanol the sequence of steps appears to be (1) tautomerism to an allylic halide (**2a**), (2) an SN2′ re-

(6) E. W. McClelland and J. L. DaSilva, *J. Chem. Soc.*, 2972 (1931).

(7) For a comparable cleavage of 3-oxo-2,3-dihydrobenzo[b]thiophene 1,1-dioxide to *o*-methylsulfonylbenzoic acid, see F. Arndt and C. Martius, *Ann.*, **499**, 228 (1932).

TABLE I

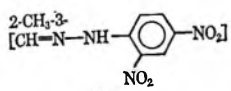
NMR PARAMETERS FOR SUBSTITUTED BENZO[*b*]THIOPHENE 1,1-DIOXIDES[a]

Substituent	Registry no.	Chemical shifts: =C(H)	(-CH₂-) (-CH-)	-CH₃	Other
None	325-44-5	6.86 (d, 7.0) 7.36 (d, 7.0)	...	...	
2-Br	5350-05-0	7.33 (s)	...	...	
3-Br	16957-97-4	7.00 (s)	...	...	
2-CH_3	6224-55-1	6.85 (q, 1.7)	...	2.17 (d, 1.7)	
3-CH_3	6406-91-3	6.58 (q, 1.5)	...	2.25 (d, 1.5)	
3-C_2H_5	16958-00-2	6.48 (t, 1.5)	2.63 (q, 7.5, 1.5)[b]	1.28 (t, 7.5)	
2,3-di-CH_3	16958-01-3	...	...	2.12 (s)	
2-Br-3-CH_3		...	...	2.25 (s)	
2-Br-3-C_2H_5		...	2.72 (q, 7.5)	1.23 (t, 7.5)	
2-C_2H_5-3-Br		...	2.73 (q, 8.0)	1.38 (t, 8.0)	
3-CH_2Cl		6.67 (t, 1.5)	4.47 (d, 1.5)	...	
2-CH_3-3-CH_2Cl		...	4.48 (s)	2.20 (s)	
2-CH_2Cl-3-CH_3	16958-02-4	...	4.55 (s)	2.28 (s)	
2-CH_3-3-$CH_2NC_5H_{10}$		...	3.43 (s)	2.20 (s)	Piperidine protons (σ, 2.45; β, γ, 1.50)
2-$CH_2NC_5H_{10}$-3-CH_3		...	3.49 (s)	2.28 (s)	Piperidine protons (σ, 2.48; β, γ, 1.50)
3-$CHOHCH_3$	16958-03-5	6.73 (d, 1.4)	4.98	1.52 (d, 7.0)	OH, 3.46 (d, 4.7)
3-$CHClCH_3$		6.72 (d, 1.3)	5.02 (q, 7.0, 1.3)[b]	1.82 (d, 7.0)	
2-$CHClCH_3$		7.25 (d, 1.5)	5.10 (q, 6.9, 1.5)[b]	1.98 (d, 6.9)	
3-$CH(NC_5H_{10})CH_3$		6.55 (s)	3.70 (q, 6.3)	1.28 (d, 6.3)	Piperidine protons (σ, 2.48; β, γ, 1.46)
2-$CH(NC_5H_{10})CH_3$		7.03	3.87 (q, 6.8, 1.1)[b]	1.42 (d, 6.8)	Piperidine protons (σ, 2.55; β, γ, 1.51)
3-CH_3O(*p*-anisoyl)	16958-04-6	6.75 (t, 2.0)	5.35 (d, 2.0)	...	OCH_3, 3.85 (s)
3-CH_2O(mesitoyl)	16958-05-7	6.77 (t, 1.7)	5.38 (d, 1.7)	...	*o*,*p*-CH_3, 2.29 (s)
3-$CH_2OCH_2CH_3$	16958-06-8	6.65 (t, 1.5)	4.48 (d, 1.5)	...	CH_2, 3.60 (q, 7.0) CH_3, 1.23 (t, 7.0)
3-$CH_2NC_5H_{10}$[c]	16958-07-9	6.84 (t, 1.5)	3.55 (d, 1.5)	...	Piperidine protons (α, 2.5; β, γ, 1.5)

[a] Chemical shifts are in δ values measured in parts per million (ppm) relative to TMS. The multiplicity and coupling constant (cps) are given in parentheses following the chemical shift (s = singlet, d = doublet, t = triplet, q = quartet). [b] Quartet of doublets. [c] Tentative assignment.

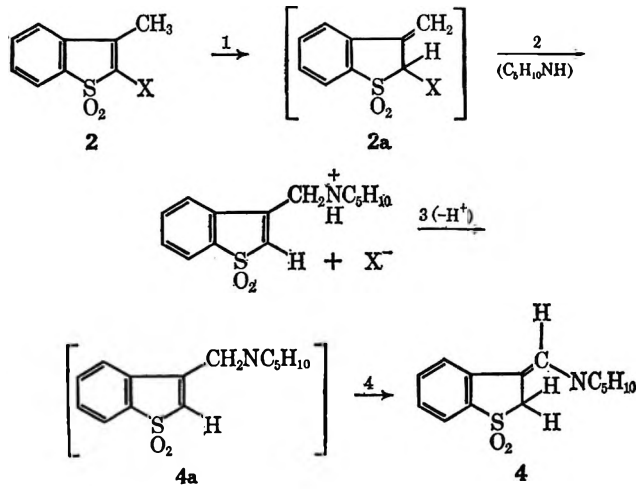
TABLE II

NMR PARAMETERS FOR SUBSTITUTED 2,3-DIHYDROBENZO[*b*]THIOPHENE 1,1-DIOXIDES[a]

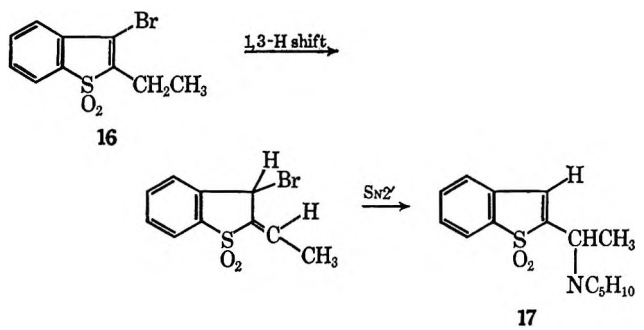
Substituent	Registry no.	Chemical shifts: =C(H)	(-CH₂-) (-CH-)	-CH₃	Other
None	14315-13-0	...	3.38 (s)	...	
3-(=CHCl)	16958-09-1	6.84 (t, 2.2)	4.12 (d, 2.2)	...	
2-CH_3-3-oxo		...	3.98 (q, 7.5)	1.66 (d, 7.5)	
3-[=CHS(mesityl)]	16958-10-4	6.72 (t, 2.3)	4.09 (d, 2.3)	...	*o*-CH_3, 2.46 (s) *p*-CH_3, 2.32 (s)
3-[=CH(N-morpholinyl)]	16958-11-5	6.87 (t, 1.7)	4.27 (d, 1.7)	...	O-CH_2, 3.8 N-CH_2, 3.3
3-[=$CHSC(NH_2)_2^+$]Cl^-	16958-12-6	*ca.* 7.9[b]	4.58 (d, 1.9)	...	C-4 proton, 8.4[c]
3-[=$CH(NC_5H_{10})$]	16934-29-5	6.82 (t, 1.6)	4.24 (d, 1.6)	...	Piperidine protons (α, 3.31; β, γ, 1.63)
3-[=$CHSCH_2C_6H_5$]	16958-14-8	6.99 (t, 2.2)	4.03 (d, 2.2)	...	CH_2, 4.11 (s)
3-[=CHO(mesitoyl)]	16958-15-9	8.39 (t, 2.3)	4.20 (d, 2.3)	...	*o*-CH_3, 2.37 (s) *p*-CH_3, 2.32 (s)
2-CH_3-3-[=$CH(NC_5H_{10})$]		6.67 (s)	4.11 (q, 7.4)	1.49 (d, 7.4)	Piperidine protons (α, 3.3; β, γ, 1.6)
3-(CH=N—NH—C_6H_5)	16958-16-0	*ca.* 7.8[b]	C-2, 3.98 (d, 6.7) C-3, 4.67 (q, 6.7)	...	N-H, 10.27 (s)
2-CH_3-3-[CH=N—NH— ]	16958-17-1	*ca.* 7.8[b]	4.2	1.55 (d, 6.5)	N-H, 11.79 (s)
3-(=C<$^{CH_3}_{NC_5H_{10}}$)[c]	16958-49-9	...	4.03 (s)	1.96 (s)	Piperidine protons (α, 2.9; β, γ, 1.6)
3-(=C<$^{Cl}_{CH_3}$)[c]		...	4.17 (q, 1.0)	2.37 (t, 1.0)	C-4 proton, 8.67[c]
3-(=C<$^{CH_3}_{Cl}$)[c]		...	4.31 (q, 1.8)	2.62 (t, 1.8)	
2-Cl-3-oxo	16958-50-2	...	5.94 (s)	...	
3-(=CH_2)[c]	16958-51-3	5.52 6.03	4.21 (t, 1.9)	...	

[a] Chemical shifts are in δ values measured in parts per million (ppm) relative to TMS. The multiplicity and coupling constant (cps) are given in parentheses following the chemical shift (s = singlet, d = doublet, t = triplet, q = quartet). [b] Obscured by the phenyl protons. [c] Tentative assignment; the isomer in which the signal for the C-4 proton appears at δ 8.67.

action initiated by piperidine, (3) loss of a proton to give **4a**, and (4) tautomerism to form an enamine (**4**).[4]



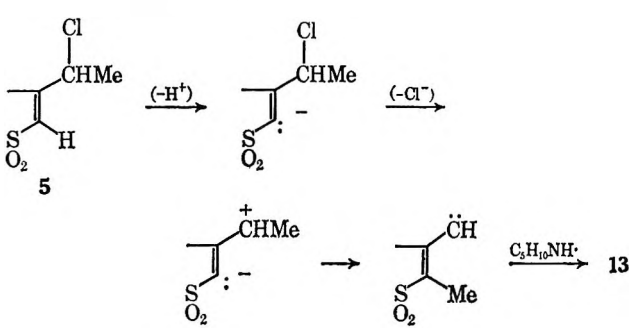
Comparable reaction paths are visualized for the conversion of **14** into **15** and of **16** into **17**, except that the final 1,3-proton shift fails to occur from **15** or **17** under the reaction conditions.



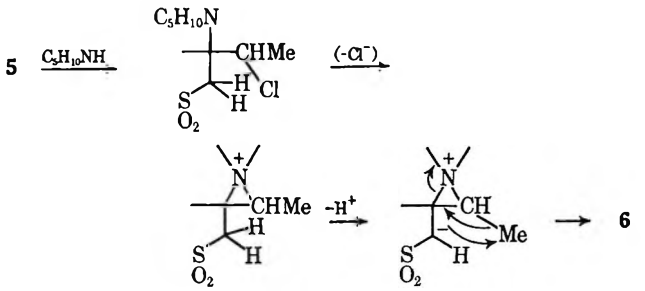
The formation of **17** from **18** shows that the latter takes the SN2 pathway in preference to the SN2′ pathway (in contrast to its isomer **5**, which has the α-chloroethyl group in the 3 position). This may be rationalized by noting that the SN2′ pathway for **18**, but not for **5**, requires the C=C bond to go out of conjugation with the benzene ring.

Mechanisms for the Reaction 5 → 6.—Of the various mechanisms that can be envisioned for the transformation of **5** to **6**, one has already been ruled out. The failure of **15** to form **6** under the reaction conditions shows that the sequence is not an SN2 reaction to form **15** followed by shift of a methyl group and the C=C bond.

A mechanism involving carbene formation and methyl migration can be imagined, but this leads to **13** and, although **13** can be converted into **6** by the action of *t*-butoxide ion, it does not form **6** under the reaction conditions (see above).

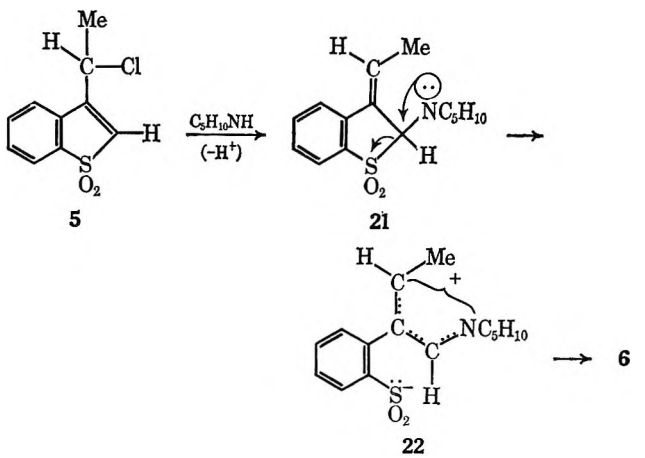


Another possibility is that piperidine adds to the double bond of **5** and that this adduct reacts in a series of steps to give **6**. The only evidence against this

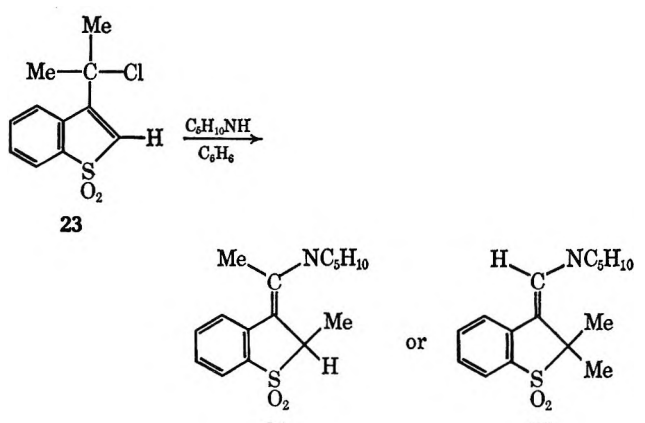


sequence is that 3-methylbenzo[*b*]thiophene 1,1-dioxide fails to add piperidine;[8a] addition occurs very readily with the parent heterocycle in 95% ethanol but not in benzene.[8b]

A final possibility is that **5** undergoes an SN2′ reaction and that the product (**21**) thus obtained rearranges by a ring opening to form a dipolar ion (**22**) which closes the ring in a different position.

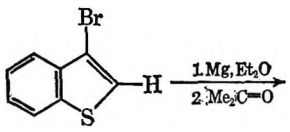


It is possible to distinguish between the mechanisms involving methyl migration and that involving ring opening and ring closing by putting a label at C-2 or on the side chain. This was accomplished by synthesis of **23**, which has an additional methyl group on the side chain. Methyl migration during reaction with piperidine would give **24** (or the *cis* isomer), whereas the interchange mechanism would give **25**.

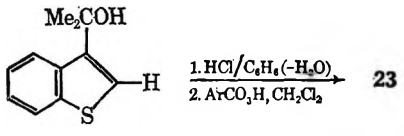


(8) (a) F. Ross, Ph.D. Dissertation, Northwestern University, June 1952. (b) W. H. McKellin, Ph.D. Dissertation, Northwestern University, June 1950.

The desired chloride (**23**) was prepared from 3-bromobenzo[*b*]thiophene (**26**) in a conventional manner.

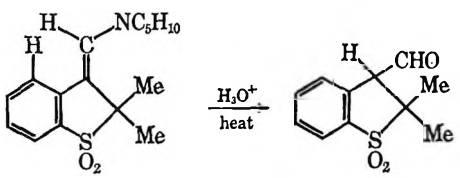


26



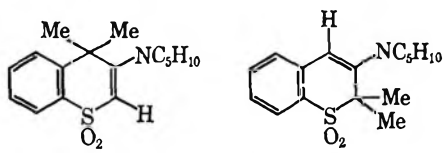
27

Treatment of **23** with piperidine in refluxing benzene, ethanol, or acetone gave a high yield of an enamine [λ_{max} 332 mμ (ϵ_{max} 11,100)]. Its nmr spectrum revealed four aromatic protons, ten piperidino protons, and a dimethyl singlet (δ 1.52, 6 H). This is the spectrum expected for **25**. Structure **24** should have two distinct methyl groups, one of which should appear as a doublet. Acid hydrolysis of the enamine gave a carbonyl compound whose ir spectrum revealed an aldehydic hydrogen (λ_{max} 3.50, 3.60 μ) and whose nmr spectrum differed from that of the enamine only in that the signals for the vinyl and piperidino protons were replaced by those of an aldehydic and a methinyl hydrogen [doublet at δ 9.72 (1 H) coupled (J = 3.7 cps) with a doublet at 3.87 (1 H, J = 3.7 cps)]. This is consistent with the transformation of **25** to **28**.



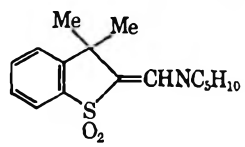
25 **28**

The isomeric enamine structures **29** and **30**, which might be considered to be consistent with the nmr spectrum, are ruled out since they would give ketones on hydrolysis. Structure **31** is eliminated by the uv data.



29

30



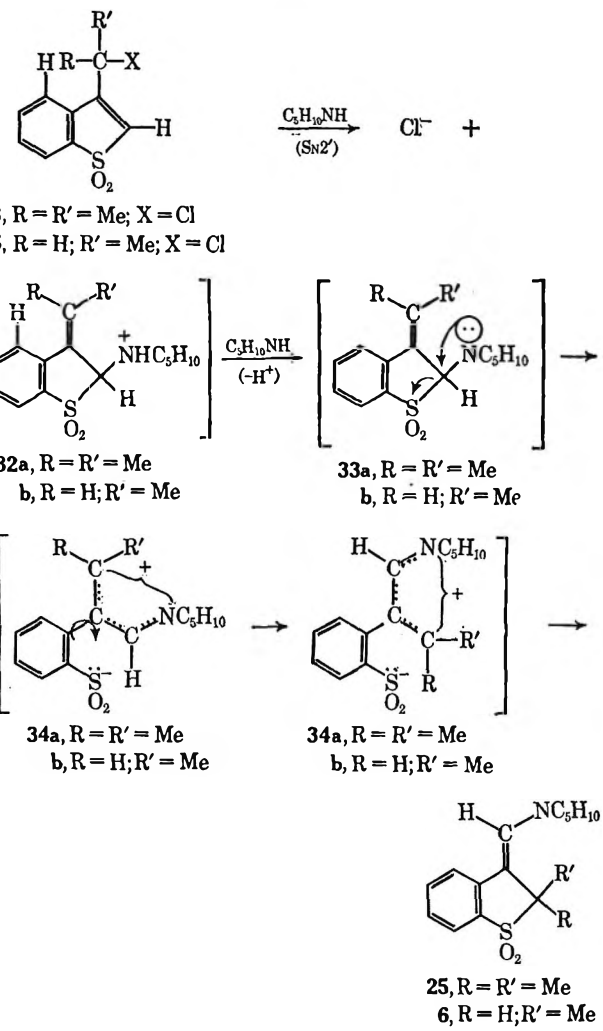
31

The assignment of structure **25** to the enamine is supported further by the similarity of its properties and behavior to that of **6**, the structure of which has been firmly established (see above).

Stereoisomers (*cis*, *trans*) are possible for **25**. Examination of molecular models shows, however, that there will be steric interference between the *peri* hydrogen (shown) at C-4 and the 1-piperidyl grouping in the isomer in which these groups are *cis*. Therefore, these groups are placed *trans* in the assigned structure **25**.

The most likely route for formation of **25** from tertiary chloride **23** by reaction with piperidine in benzene appears to be (1) abnormal substitution (SN2′) to form **32a**, (2) loss of a proton to give **33a**, and (3) rearrangement of **33a** by way of dipolar intermediate **34a** to **25**. The route for the formation of **6** from the secondary chloride **5** under comparable conditions would be **5** → **32b** → **33b** → **34b** → **6** (see Scheme I).

SCHEME I



23, R = R′ = Me; X = Cl
5, R = H; R′ = Me; X = Cl

32a, R = R′ = Me
b, R = H; R′ = Me

33a, R = R′ = Me
b, R = H; R′ = Me

34a, R = R′ = Me
b, R = H; R′ = Me

34a, R = R′ = Me
b, R = H; R′ = Me

25, R = R′ = Me
6, R = H; R′ = Me

Experimental Section[9]

Nmr Spectra of Substituted Benzo[*b*]thiophene 1,1-Dioxides.—Examination of the nmr spectra of a variety of compounds in this series (Tables I and II) has revealed the following correlations useful for structural assignments. (1) The C-3 proton in the 2-substituted compounds absorb at least 0.3 ppm downfield from the analogous C-2 proton in the 3-substituted isomers. (2) Protons at the α position of C-3 alkyl group usually absorb downfield (*ca.* 1 ppm) from comparable protons of a C-2 alkyl group. (3) Coupling of 0.5–2 cps between the α- and γ-carbon atoms of the allylic system was observed in most instances.

Ozonolysis of 2-Methyl-3-(1-piperidyl)methylene-2,3-dihydrobenzo[*b*]thiophene 1,1-Dioxide (4).—Ozone was bubbled through a solution of 1.0 g (0.0036 mol) of **4** in 30 ml of ethyl acetate at −78° until no further reaction occurred. The ozonide was then decomposed by hydrogenation at room temperature, using a 5% palladium-on-charcoal catalyst. Filtration and distillation of the solvent at reduced pressure gave a yellow oil. Trituration of the oil with 95% ethanol gave 0.24 g (41%) of 2-methyl-3-oxo-2,3-dihydrobenzothiophene 1,1-dioxide (**9**), as white crystals, mp 108–110°. Recrystallization from ethanol raised the melting

(9) Microanalyses were by Micro-Tech Laboratories, Inc., Skokie, Ill.

point to 109.5–110° (lit.[6] mp 110–111°). An additional 0.15 g (21%) of product melting at 107–110° was obtained by concentration of the mother liquor.

An authentic sample of **9** was prepared by refluxing a solution of 0.2 g (80 mmol) of 2-methyl-3-acetoxybenzo[*b*]thiophene 1,1-dioxide[10] in 10 ml of methanol and 1 ml of concentrated hydrochloric acid for 1 hr. Partial evaporation of the solvent and cooling in an ice bath gave 0.09 g (57%) of **9**: mp 109.5–110°, mmp 110–110.5°. The infrared spectra of the two samples were superimposable.

Basic Hydrolysis of 4.—A mixture of 10 ml of a 20% aqueous sodium hydroxide solution and 0.1 g of **4** was heated on a steam bath for 30 min, during which time the solid slowly dissolved. The solution was then acidified with concentrated hydrochloric acid, and evaporated to give an oily, solid residue, which was extracted with benzene. Filtration, and evaporation of the filtrate, gave a water-soluble oil, which would not crystallize from hexane, ether–hexane, ether, methanol, or methanol–water. The nmr spectrum of the oil showed four phenyl protons, a broad, one-proton singlet at δ 10.48 (carboxyl proton), a two-proton quartet at 3.67 (methylene protons) (J = 7.5 cps), and a three-proton triplet at 1.32 (methyl protons) (J = 7.5 cps). This spectrum is consistent with that expected for *o*-ethylsulfonylbenzoic acid (**10**).

Reaction of 3-Chloromethylbenzo[*b*]thiophene 1,1-Dioxide (1) with Thiophenoxide Ion.—A solution of 0.4 g (0.01 mol) of sodium hydroxide and 1.1 g (0.01 mol) of thiophenol in 20 ml of absolute ethanol was heated for 10 min on a steam bath. The solution was then treated with 0.51 g (0.002 mol) of **1**, refluxed for 4 hr, and poured into 300 ml of cold water. Recrystallization from methanol of the resulting amorphous, brown solid gave 0.35 g (56%) of yellow crystals melting at 162–164.5°. Further recrystallization methanol, with charcoal decolorization, gave white crystals, mp 164.5–166° (lit.[2] mp 165–167°).

Reaction of 2-Bromo-3-methylbenzo[*b*]thiophene 1,1-Dioxide (2) with Thiophenoxide in Alcohol.—A solution of 0.06 g (0.0015 mol) of sodium hydroxide and 0.165 g (0.0015 mol) of thiophenol in 10 ml of absolute ethanol was treated with 0.26 g (0.001 mol) of **2** and refluxed for 0.5 hr. Processing as above gave 0.07 g (25%) of white crystals, mp 164.5–165.5°. The product was identical, by infrared spectra and mixture melting point with the product of **1** with thiophenoxide ion.

Reaction of 2 with Piperidine in Methanol.—2-Bromo-3-methylbenzothiophene 1,1-dioxide (100 mg, 0.386 mmol) was dissolved in 4 ml of hot absolute methanol, and piperidine (197 mg, 2.32 mmol) was added with 1 ml of methanol. The yellow solution was heated at reflux for 16 hr. Cooling and filtering afforded long yellow needles (73.7 mg, 72.7%), mp 177.7–182.7°; the mixture melting point with authentic 3-(1-piperidyl)methylene-2,3-dihydrobenzothiophene 1,1-dioxide[2] was undepressed.

2-Chloro-3-methylbenzo[*b*]thiophene 1,1-Dioxide.—A suspension of 21 g (0.05 mol) of 2-mercuriacetoxy-3-methylbenzothiophene in 200 ml of chloroform was treated with a solution of 3.6 g (0.05 mol) of chlorine in 70 ml of chloroform, added dropwise with ice-bath cooling. After stirring at room temperature overnight, the mixture was filtered and the solvent was removed *in vacuo*. The resulting brown oil was dissolved in 35 ml of glacial acetic acid and 30 ml of acetic anhydride and treated with 30 ml of 30% hydrogen peroxide. After cooling to room temperature, the solution was poured over 300 g of crushed ice. Chromatography of the resulting yellow solid (3 g; mp 115–150°) on a 60 × 3 cm silica gel column (eluted with 20% ether–hexane) gave 1.3 g (12%) of product, mp 152–154°. Recrystallization from methanol followed by vacuum sublimation gave the analytical sample, mp 152–154.5°.

Anal. Calcd for $C_9H_7ClO_2S$: C, 50.37; H, 3.23. Found: C, 50.73; H, 3.22.

Preparation of 3-(α-Hydroxyethyl)benzo[*b*]thiophene 1,1-Dioxide.—A solution of 3.6 g (0.02 mol) of 3-(α-hydroxyethyl)-benzothiophene[5] in 10 ml of chloroform was treated with a solution of 8.9 g (0.044 mol) of 85% *m*-chloroperoxybenzoic acid in 90 ml of chloroform, added dropwise with stirring. The reaction temperature was kept below 40° by controlling the rate of addition. Stirring was continued for 15 hr. The excess per acid was then destroyed with aqueous sodium sulfite, and the mixture was filtered. The filtrate was washed with 5% aqueous sodium bicarbonate and water and dried over magnesium sulfate. The solvent was distilled at reduced pressure, leaving a yellow oil which crystallized upon trituration with cold 95% ethanol. Two recrystallizations from 95% ethanol gave 2.16 g. (51%) of 3-(α-hydroxyethyl)benzothiophene 1,1-dioxide as white crystals, mp 109–110°.

Anal. Calcd for $C_{10}H_{10}O_3S$: C, 57.12; H, 4.79. Found: C, 56.91; H, 4.70.

Preparation of 3-(α-Chloroethyl)benzo[*b*]thiophene 1,1-Dioxide (5).[5]—A solution of 20.95 g (0.118 mol) of 3-(α-hydroxyethyl)benzothiophene[5] in 50 ml of chloroform was cooled in an ice bath while 16.5 g (0.14 mol) of thionyl chloride was added in small portions with stirring. The solution was then refluxed for 2 hr. The solvent and excess thionyl chloride were distilled under reduced pressure, leaving a brown oil. The oil was dissolved in 30 ml of ether, and a solution of 53 g (0.26 mol) of 85% *m*-chloroperoxybenzoic acid in 150 ml of ether was added dropwise, with stirring, over an 8-hr period. Stirring was continued for an additional 12 hr. Processing as before gave 19.02 g (70%) of yellow solid, mp 97–104°. An additional recrystallization from 95% ethanol raised the melting point to 107.5–108.5° (lit.[5] mp 108–109°).

Reaction of 5 with Piperidine in Dry Benzene.—A solution of 0.91 g (0.004 mol) of **5** and 1.7 g (0.02 mol) of piperidine in 15 ml of dry benzene was refluxed for 2 hr. Cooling and filtration gave 0.44 g (91%) of piperidine hydrochloride. The filtrate was evaporated to a gummy, brown oil under an air jet. Trituration with cold methanol gave 0.78 g (70%) of 2-methyl-3-(1-piperidyl)methylene-2,3-dihydrobenzothiophene 1,1-dioxide (**6**) as yellow crystals: mp 142–143°, mp 144–145° after two recrystallizations from 95% ethanol; λ_{max} 323 mμ (ϵ 22,900), 6.07 and 6.27μ).

Reaction of 5 with Piperidine in Absolute Methanol.—A solution of 0.92 g (0.004 mol) of **5** and 1.7 g (0.02 mol) of piperidine in 15 ml of absolute methanol was refluxed. After 0.5 hr, the dark-brown solution was evaporated yielding an oily solid, and the residue was treated with 20 ml of dry benzene. Piperidine hydrochloride (0.20 g; 41%) was collected and the filtrate was evaporated. The residue was crystallized from 95% ethanol, giving 0.27 g of a yellow solid, mp 120–145°. Recrystallization from ethanol did not improve the melting point. The nmr spectrum of the product showed the mixture to be composed of three compounds, one of which was **6**, in *ca.* 20% yield based on the isolated product mixture. The other two compounds appeared to be the *cis* and *trans* isomers of 3-(α-chloroethylidene)-2,3-dihydrobenzo[*b*]thiophene 1,1-dioxide (**19** and **20**) in *ca.* a 2:1 ratio, comprising about 80% of the isolated product.

2-Bromo-3-ethylbenzothiophene 1,1-Dioxide.[5]—To a suspension of 1.94 g (0.010 mol) of 3-ethylbenzothiophene 1,1-dioxide[11] in 20 ml of carbon tetrachloride was added 1.76 g (0.011 mol) of bromine and the reaction mixture was shaken about 10 min and allowed to stand at room temperature for 2 hr. The oil obtained on evaporation was dissolved in 20 ml of acetone and treated with a solution consisting of 2 g of sodium acetate, 5 ml of methanol, 20 ml of water, and 10 ml of acetone. Heating and evaporating on a steam bath followed by addition of cold water gave 2.3 g (85%) of a colorless solid melting at 133–138°. Two recrystallizations from ethanol–water mixtures gave an analytical sample, mp 147.5–148.5°.

Anal. Calcd for $C_{10}H_9BrO_2S$: C, 43.97; H, 3.32. Found: C 43.74; H, 3.39.

Reaction of 2-Bromo-3-ethylbenzo[*b*]thiophene 1,1-Dioxide (14) with Piperidine.—A solution of 0.54 g (0.002 mol) of 2-bromo-3-ethylbenzothiophene 1,1-dioxide and 0.85 g (0.01 mol) of piperidine in 10 ml of dry benzene was refluxed for 22 hr. Cooling and filtration gave 0.32 g (96%) of piperidine hydrobromide. Trituration of the oil obtained on evaporation with cold, aqueous methanol gave 0.32 g (58%) of 3-[α-(1-piperidyl)ethyl]benzothiophene 1,1-dioxide (**15**), as pale yellow crystals, mp 93–95°. Two recrystallizations from hexane raised the melting point to 94–95° [λ_{max} 221 mμ (ϵ 28,700), no strong absorption in the 6.0–6.4-μ region of the infrared spectrum].

Anal. Calcd for $C_{15}H_{19}NO_2S$: C, 64.95; H, 6.90. Found: C, 65.14; H, 7.02.

Preparation of 2-Ethyl-3-bromobenzo[*b*]thiophene 1,1-Dioxide (16).—A sample of 8 g of 2-ethylbenzo[*b*]thiophene, prepared by the method of Shirley and Cameron,[12] was dissolved in 20 ml of chloroform and treated with a solution of 8.0 g (0.05 mol) of

(10) J. D. Spainhour, Ph.D. Dissertation, Northwestern University, 1957.

(11) J. C. Petropoulus, M. A. McCall, and D. S. Tarbell, *J. Amer. Chem. Soc.*, **75**, 1133 (1953).

(12) D. A. Shirley and M. D. Cameron, *ibid.*, **74**, 664 (1952).

bromine in 40 ml of chloroform, added dropwise with stirring. After stirring for 10 hr, the solvent was distilled under reduced pressure, leaving a brown, oily solid, which was dissolved in 60 ml of 1:1 acetic acid–acetic anhydride and treated with 30 ml of 30% hydrogen peroxide. The solution was stirred for 4 hr, then poured over 300 g of crushed ice. Crystallization of the resulting yellow solid gave 1.7 g (12.5%) of **16**, mp 100–102°. Recrystallization from ethanol raised the melting point to 103–104°.

Anal. Calcd for $C_{10}H_9BrO_2S$: C, 43.97; H, 3.32. Found: C, 43.86; H, 3.51.

Reaction of 16 with Piperidine.—A solution of 0.54 g (0.002 mol) of **16** and 0.85 g (0.01 mol) of piperidine in 15 ml of dry benzene was refluxed for 8 hr (81% of piperidine hydrobromide). The filtrate was evaporated under an air jet, leaving a pale yellow, solid residue. Recrystallization from methanol gave 0.31 g (55%) of 2-[α-(1-piperidylethyl]benzo[*b*]thiophene 1,1-dioxide (**17**), as lustrous, white crystals, mp 162–165°. Two recrystallizations from ethanol raised the melting point to 167–168°.

Anal. Calcd for $C_{15}H_{19}NO_2S$: C, 64.95; H, 6.90. Found: C, 64.72; H, 7.11.

Preparation of 2-(α-Chloroethyl)benzo[*b*]thiophene 1,1-Dioxide (18).—A solution of 6.7 g (0.05 mol) of benzothiophene in 70 ml of anhydrous ether, under nitrogen, was treated at 0° with 35.5 ml (0.055 mol) of 1.55 *N* butyllithium in hexane. The mixture was stirred for 15 min, then treated with a solution of 2.4 g (0.055 mol) of acetaldehyde in 40 ml of anhydrous ether, added dropwise. After 10 min of additional stirring, water was added, the layers were separated, and the water layer was extracted with ether. The combined organic extracts were washed with water and dried over magnesium sulfate. Removal of the solvent gave a yellow oil which solidified on standing. The solid was recrystallized from ether–hexane, giving 4.33 g (49%) of 2-(α-hydroxyethyl)benzothiophene, melting at 56–60°. An additional recrystallization from ether–hexane raised the melting point to 60–61°. The nmr spectrum was consistent with the assigned structure. A solution of 3.01 g (0.017 mol) of 2-(α-hydroxyethyl)benzo[*b*]thiophene in 30 ml of chloroform was treated with 2.4 g (0.02 mol) of thionyl chloride. The solution was refluxed for 1.5 hr, and solvent and excess thionyl chloride were then distilled under reduced pressure, leaving a brown oil. The oil was dissolved in 10 ml of chloroform and oxidized with a solution of 7.5 g (0.037 mol) of 85% *m*-chloroperoxybenzoic acid in 78 ml of chloroform as described above. Trituration of the resulting oil with cold ethanol gave 1.53 g (39%) of **18** as pale yellow crystals, mp 53–54°. Two recrystallizations from ethanol raised the melting point to 54–55°.

Anal. Calcd for $C_{10}H_9ClO_2S$: C, 52.51; H, 3.97. Found: C, 52.60; H, 4.09.

Reaction of 18 with Piperidine.—A solution of 0.46 g (0.002 mol) of **18** and 0.85 g (0.02 mol) of piperidine in 10 ml of dry benzene was refluxed for 30 min (99% piperidine hydrobromide). Crystallization of the product from 95% ethanol gave 0.16 g (29%) of **17**, mp 162–164°. The melting point of recrystallized material was not depressed upon mixture with a sample of **17** obtained from **16** (see above).

2-Chloromethyl-3-methylbenzo[*b*]thiophene 1,1-Dioxide.—A solution of 3.07 g (0.017 mol) of 2-hydroxymethyl-3-methylbenzothiophene[13] in 30 ml of chloroform was treated with 2.4 g (0.02 mole) of thionyl chloride. Processing and oxidation in the manner described above for **18** gave 2.63 g (67%) of material, mp 128–131°. Two additional recrytallizations from 95% ethanol gave the analytical sample, mp 132–133°.

Anal. Calcd for $C_{10}H_9ClO_2S$: C, 52.51; H, 3.97. Found: C, 52.72; H, 4.19.

Reaction of 2-Chloromethyl-3-methylbenzo[*b*]thiophene 1,1-Dioxide with Piperidine.—A solution of 0.46 g (0.002 mol) of the chloride and 0.85 g (0.01 mol) of piperidine in 10 ml of dry benzene was refluxed for 1 hr (99% of piperidine hydrochloride). Recrystallization of the residue from ether–hexane gave 0.44 g (79%) of 2-(1-piperidyl)methyl-3-methylbenzothiophene 1,1-dioxide (**12**) as white crystals, mp 98.5–99.5°. Recrystallization from ether–hexane raised the melting point to 99–100°.

Anal. Calcd for $C_{15}H_{19}NO_2S$: C, 64.95; H, 6.90. Found: C, 64.86; H, 6.83.

2-Methyl-3-chloromethylbenzo[*b*]thiophene 1,1-Dioxide (11).[10]—Chloromethylation of 30 g of 2-methylbenzo[*b*]thiophene[12] gave a 45% yield of 3-chloromethyl-2-methylbenzo[*b*]thiophene, mp 69.5° (hexane).

Anal. Calcd for $C_{10}H_9ClS$: C, 61.06; H, 4.61. Found: C, 60.80; H, 4.38.

Oxidation with 40% peracetic acid gave a 68% yield of **11**, mp 138–139° (ethanol).

Anal. Calcd for $C_{10}H_9ClO_2S$: C, 52.52; H, 3.97. Found: C, 52.35; H, 3.96.

Reaction of 11 with Piperidine.—A solution of 1.4 g (0.006 mol) of **11** dioxide and 2.5 g (0.03 mol) of piperidine in 15 ml of dry benzene was refluxed for 30 min (85% of piperidine hydrochloride). Trituration of the oil obtained on evaporation with cold methanol gave 0.12 g (7%) of 2-methyl-3-(1-piperidyl)-methylbenzothiophene 1,1-dioxide (**13**), mp 141–142° (lit.[10] mp 145–146°). Concentration of the reaction solution gave 0.35 g (20%) of a product, mp 92–98°; the mixture melting point with **12** undepressed.

Base-Catalyzed Isomerization of 13 to 6.—A solution of 2.5 mmol of potassium *t*-butoxide in 10 ml of *t*-butyl alcohol was treated with 0.055 g of **13**. After 30 min at room temperature, the alcohol was partially distilled under reduced pressure and then evaporated under an air jet, leaving an oily residue. The residue was dissolved in 5 ml of 95% ethanol; cooling gave 0.12 g (22%) of **6**, mp 145–146°; the mixture melting point was undepressed and the ir spectra were identical.

Isomerization of 3-[α-(1-piperidyl)ethyl]benzothiophene 1,1-Dioxide (15).—A solution of 2.5 mmol of potassium *t*-butoxide in 10 ml *t*-butyl alcohol containing 0.10 g of **15** was heated on a steam bath for 22 hr. The solvent was partially evaporated, and the solution was diluted with 10 ml of water and cooled in an ice bath. The nmr spectrum of the solid (0.04 g), mp 118–120°, showed, in addition to ten piperidine protons and four phenyl protons, a broad three-proton singlet at δ 1.96 (methyl protons) and a broad two-proton singlet at 4.03 (methylene protons). The product is tentatively identified as 3-[α-(1-piperidyl)ethylidene]-2,3-dihydrobenzothiophene 1,1-dioxide (**7**).

3-(α-Hydroxy-α-methylethyl)benzo[*b*]thiophene 1,1-Dioxide.—Reaction of the Grignard reagent prepared from 20 g (94.3 mmol) of 3-bromobenzo[*b*]thiophene with 17.3 ml (0.2 mol) of dry acetone gave 10.6 g (61%) of tertiary alcohol, mp 74–78°. Recrystallization from hexane gave material with mp 83.5–84.3°. A 3-g (15.7 mmol) sample of this alcohol was oxidized with 5.7 g (35.7 mmol) of 85% *m*-chloroperoxybenzoic acid in 60 ml of methylene chloride at room temperature for 13 hr. The filtrate obtained from this mixture was washed successively with 30-ml portions of 10% aqueous sodium sulfite, 10% sodium hydroxide (twice), and water. After drying, concentration gave 3.1 g (88.6%) of sulfone alcohol, mp 124.5–126.5°. An analytical sample crystallized from methanol melted at 133.5–135°: nmr ($CDCl_3$), δ 7.5–8.2 (4 H multiplet), 6.72 (1 H singlet), 3.1 (1 H singlet, temperature dependent), 1.64 (6 H singlet).

Anal. Calcd for $C_{11}H_{12}O_3S$: C, 58.92; H, 5.37. Found: C, 59.20; H, 5.36.

3-(α-Chloro-α-methylethyl)benzo[*b*]thiophene 1,1-Dioxide (23).—A solution of 6.0 g (31.4 mmol) of 3-(α-hydroxy-α-methylethyl)-benzo[*b*]thiophene in 80 ml of dry benzene was saturated with hydrogen chloride. The benzene–water azeotrope was distilled over a period of 20 min while the introduction of hydrogen chloride was continued. The solution was cooled to room temperature and saturated with hydrogen chloride, and the solvent was removed under reduced pressure. The yellow oil was dissolved in 20 ml of anhydrous CH_2Cl_2 and added to a solution of 12.5 g (63 mmol) of 85% *m*-chloroperoxybenzoic acid in 140 ml of dry CH_2Cl_2 at 10° with stirring. After 30 min the temperature was allowed to rise to 20°. After 30 min the solution was filtered and the filtrate was washed with 40-ml portions of 10% NaOH, 10% Na_2SO_3, saturated $NaHCO_3$, and water. After drying over $CaCl_2$, filtering, and removing the solvent, there remained a pale yellow oil; the oil solidified upon trituration with methanol. Crystallization (MeOH) gave 3.4 g (50%) of colorless solid, mp 136–140°. Successive recrystallizations (benzene–hexane; ethyl acetate; benzene–hexane) gave **23**: mp 141–142°; nmr ($CDCl_3$), δ 7.43–8.09 (4 H multiplet), 6.64 (1 H singlet), 1.95 (6 H singlet); uv, λ_{max}^{MeOH} 299 mμ (ε 2.36 × 10³), 237.5 (2.26 × 10⁴); ir ($CHCl_3$), 7.63 (s), 8.42 (s), 8.55 μ (s).

Anal. Calcd for $C_{11}H_{11}ClO_2S$: C, 54.43; H, 4.57. Found: C, 54.63; H, 4.62.

3-(1-Piperidylmethylene)-2,2-dimethyl-2,3-dihydrobenzo[*b*]-thiophene 1,1-Dioxide (25).—A solution of 483.4 mg (2.0

(13) R. Gaertner, *J. Am. Chemer. Soc.*, **74**, 2185 (1952).

mmol) of **23** and 1.022 g (12 mmol) of piperidine in 10 ml of benzene was refluxed for 4 hr. Filtration gave 238.3 mg (98%) of piperidinium chloride. Evaporation of the filtrate gave 594 mg of crystals, mp 148–152°. After crystallization (MeOH), the yield of **25** was 81%, mp 150–155° (nmr analysis of the residue from the mother liquor indicated a total yield of 97%). An analytical sample prepared by additional crystallizations (EtOH, benzene–hexane) melted at 154–155°: nmr ($CDCl_3$), δ 7.2–7.9 (4 H multiplet), 6.18 (1 H singlet), 2.94 (4 H multiplet), 1.67 (6 H multiplet), 1.52 (6 H singlet, partially superimposed with δ 1.67 signal); uv, λ_{max}^{MeOH} 332 mμ (ε 11,900); ir ($CHCl_3$), 3.31 (m), 3.38 (m), 3.48 (w), 3.52 (w), 6.05 (s), 6.23 (m), 6.81 (s), 7.22 (m), 7.77 (vs), 8.11 (m), 8.22 (m), 8.56 (m), 8.99 μ (vs).

Anal. Calcd for $C_{16}H_{21}NO_2S$: C, 65.94; H, 7.26. Found: C, 66.31, 66.27; H, 7.51, 7.32.

A similar reaction was carried out using 100 mg (0.412 mmol) of **23** and 851 mg (10 mmol) of piperidine in 10 ml of benzene at 33.8° for 3 hr (*ca.* one half-life). After processing as before there was obtained 97 mg of an amphorous solid. The nmr ($CDCl_3$) peaks could all be accounted for as being due to starting chloride **23** and enamine **25**; from the ratio of the vinyl proton singlet of **23** (δ 6.65) to that of **25** (δ 6.13) and from the ratio of the methyl singlet of **23** (δ 1.95) to the multiplet for the α-piperidino protons of **25** (δ 2.92) the relative amounts of **23**:**25** was 1:1.

A reaction mixture from **23** and piperidine (1:6 molar ratio) in absolute ethanol (7.5 hr reflux) ws concentrated with the aid of an air jet. The residue was extracted with benzene and the solid obtained from the filtrate was crystallized from methanol to give 70% of **25**, mp 146–153° (mmp 149.5–154°). Nmr analysis of the mother liquors indicated a total yield of 84%. A comparable result was obtained after an 11.5-hr reflux in acetone.

Hydrolysis of 25.—When 50 mg (0.2 mmol) of **25** was added to 3 ml of 6 *N* hydrochloric acid on the steam bath, solution occurred immediately, and an oil separated within 10 min. After 15 min the solution was cooled and extracted with *ca.* 0.2 ml of $CDCl_3$ and the extract was dried over $CaCl_2$: nmr ($CDCl_3$), δ 9.72 (1 H doublet, J = 3.7 cps), 7.3–8.4 (4 H multiplet), 3.87 (1 H doublet, J = 3.7 cps), 1.55 (3 H singlet), 1.53 (3 H singlet). The integration for the aldehydic and methinyl protons was low (relative to the aromatic protons) and an additional peak (0.7 H) was present at δ 1.58 (methyl singlet for the enol). Evaporation of the solvent left 25.7 mg (60%) of clear oil: ir (neat), 2.98 [m (broad, enol H)], 3.51 (w), 3.64 (w), 4.4 (w), 5.8 (s), 5.97 (m), 6.26 (m), 6.81 (s), 7.19 (m), 7.30 (m), 7.74 (s), 8.5 (m), 8.7 μ (s).

In a separate run 70 mg (0.24 mmol) of **5** was hydrolyzed as above; the solution was then treated with 52 mg (0.26 mmol) of 2,4-dinitrophenylhydrazine in 4.5 ml of ethanol containing 0.7 ml of sulfuric acid. The derivative was obtained as fine yellow needles, mp 218–221°, after two recrystallizations from ethanol–nitromethane: nmr ($CDCl_3$), δ 11.30 (1 H singlet), 8.21 (1 H doublet, J = 2.6 cps), 7.32–8.65 (8 H multiplet) 4.18 (1 H doublet, J = 8.4 cps), 1.57 (3 H singlet), 1.52 (3 H singlet).

Anal. Calcd for $C_{17}H_{16}N_4O_6S$: C, 50.49; H, 3.99; N, 13.85. Found: C, 49.90; H, 4.16; N, 13.35.

Registry No.—**1**, 16957-75-8; **2**, 16934-26-2; **4**, 16957-77-0; **5**, 16934-30-8; **9**, 16957-79-2; **11**, 16957-80-5; **12**, 16957-81-6; **13**, 16957-82-7; **14**, 16957-83-8; **15**, 16957-84-9; **16**, 16957-85-0; **17**, 16957-86-1; **18**, 16957-87-2; **19**, 16958-18-2; **20**, 16957-88-3; 2-chloro-3-methylbenzo[*b*]thiophene 1,1-dioxide, 16934-27-3; 3-chloromethyl-2-methylbenzo[*b*]thiophene, 16957-90-7; **23**, 16934-31-9; **25**, 16957-92-9; **28** (2,4-dinitrophenylhydrazone), 16957-93-0; 3-(α-hydroxy-α-methylethyl)benzo[*b*]thiophene 1,1-dioxide, 16957-94-1.

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An Abnormal Allylic Displacement in the Reaction of 2-Halo-3-methylbenzo[*b*]thiophene 1,1-Dioxides with Piperidine

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A kinetic study has shown that the reaction of 2-halo-3-methylbenzo[*b*]thiophene 1,1-dioxides (**1**) with piperidine in methanol to give 3-(1-piperidylmethylene)-2,3-dihydrobenzo[*b*]thiophene 1,1-dioxide (**5**) occurs in the following steps: (1) rapid tautomeric equilibration to form the allylic halide **2**, (2) SN2′ displacement, (3) loss of a proton to give **4**, and (4) tautomerism to **5** (rate controlling). In the presence of added methoxide ion step 2 becomes rate controlling. The Br:Cl rate ratio for SN2′ displacement is estimated to be *ca.* 1.4:1.0.

In a previous paper it was shown that 3-methyl-2-bromobenzo[*b*]thiophene 1,1-dioxide (**1**) undergoes reaction with piperidine in benzene to give 3-(1-piperidylmethylene)-2,3-dihydrobenzo[*b*]thiophene 1,1-dioxide (**5**).[1] The reaction course suggested was (1) base-catalyzed tautomerism to 3-methylene-2,3-dihydrobenzo[*b*]thiophene 1,1-dioxide (**2**), (2) abnormal allylic (SN2′) displacement to give **3**, (3) loss of a proton, and (4) base-catalyzed tautomerism to give **5**.

In order to obtain additional information concerning the mechanism of this reaction the rates of halide ion release from the reaction of piperidine with **1** (X = Cl, Br, and I) in methanol were followed conductometrically (Table I). In addition, the rates of formation of the product (**5**) from these halides were determined spectrophotometrically (Table II).

It will be observed that both the conductometric and spectrophotometric rates are first order in piperidine (second order over-all), but that the latter are two to five times slower than the former. No product formation was detected from **1** in the ultraviolet (uv) until three or four conductometric half-lives had elapsed. After this "induction" period, a steady rate of product formation (**5**) took place. These observations suggest the formation of an intermediate (**4**), which reacts slowly to form **5**. This interpretation was supported by examination of the changes in the nmr spectrum of **1** in deuteriochloroform containing piperidine. Absorption at δ 3.52 (doublet, J = 1.5 cps) and 6.77 (triplet, J = 1.5 cps) with peak areas of approximately 2:1, respectively, began to develop within 2 min after the reactants were mixed. The signal at δ 3.52 is in the region expected for the $-CH_2-N$ group of **4** and the signal at 6.77 is in the region expected for the vinyl proton of **4**. Absorptions due to approximately four pi-

(1) F. G. Bordwell, R. W. Hemwall, and D. A. Schexnayder, *J. Org. Chem.*, **33**, 3226 (1968).

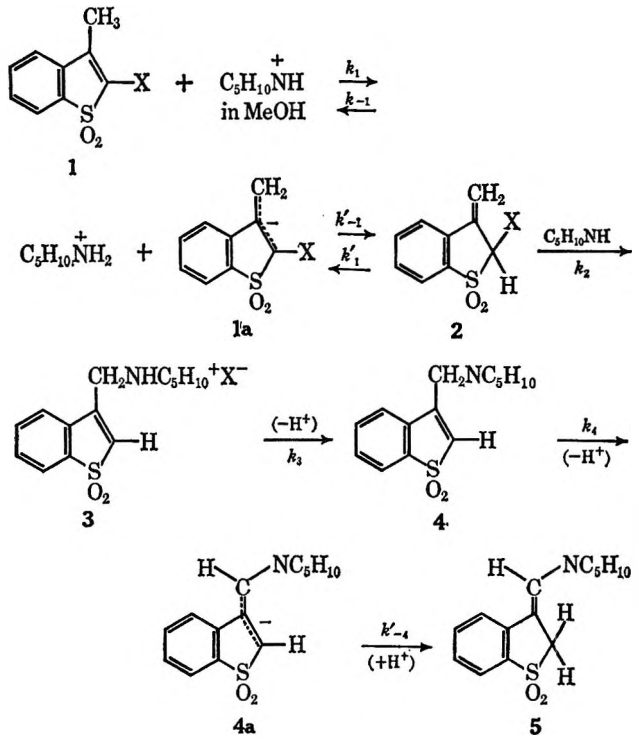


TABLE I

KINETIC DATA FOR THE REACTION OF 2-HALO-3-METHYLBENZO[*b*]THIOPHENE 1,1-DIOXIDES (1) WITH EXCESS PIPERIDINE IN ABSOLUTE METHANOL

Halide	Temp, °C	k_2, M^{-1} sec^{-1} [a]	E_a, kcal/mol	$\Delta S\ddagger$, eu
Cl	25.0	$1.04 \pm 0.02 \times 10^{-4}$		
	45.0	$5.46 \pm 0.04 \times 10^{-4}$	16	−24
	45.0	(5.48×10^{-4})[b]		
Br	25.0	$3.08 \pm 0.04 \times 10^{-4}$		
	45.0	$1.54 \pm 0.02 \times 10^{-3}$	15	−23
		(1.58×10^{-3})[b]		
I	25.0	$(1.40 \pm 0.15 \times 10^{-4})$[c]		
	25.0	(1.52×10^{-4})[d]	17	−19
	45.0	(8.46×10^{-4})[e]		
	45.0	$(8.60 \pm 0.06 \times 10^{-4})$[b]		

[a] From a plot of log $(R_t/R_t - R_\infty)$ *vs. t*. [b] Plotted by the Guggenheim method. [c] Runs made with 0.103 and 0.206 *M* piperidine. [d] Halide concentration doubled. [e] Single run.

TABLE II

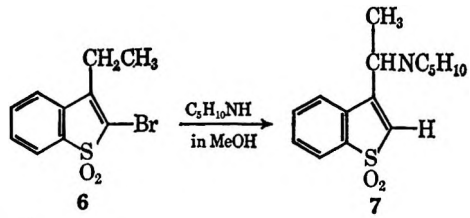
RATES OF FORMATION OF 3-(1-PIPERIDYLMETHYLENE)-2,3-DIHYDROBENZO[*b*]THIOPHENE 1,1-DIOXIDE (5) FROM 2-HALO-3-METHYLBENZO[*b*]THIOPHENE 1,1-DIOXIDES (1) AND PIPERIDINE IN METHANOL AT 45°

Halide	Piperidine concn, *M*	k_2, M^{-1} sec^{-1}[a]
Cl	0.315	$2.02 \pm 0.01 \times 10^{-4}$
Br	0.315	3.25×10^{-4}
	0.105	3.08×10^{-4}
I	0.315	2.29×10^{-4}

[a] Determined spectrophotometrically.

peridine protons at δ 2.5 and six piperidine protons at 1.5 developed at the same rate. The signal due to the 3-methyl of **1** diminished rapidly, but no absorptions attributable to **2** could be detected.

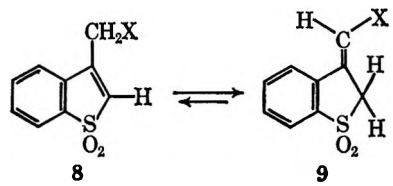
Formation of **4** as an intermediate is supported further by the behavior of 2-bromo-3-ethylbenzo[*b*]thiophene 1,1-dioxide (**6**), the next higher homolog of **1**. Here the SN2′ product (**7**) is the end result.[1] Evidently the presence of the methyl group in **7** greatly retards the rate of proton removal which controls the final tautomerism step. A similar result was obtained with 3-bromo-2-ethylbenzo[*b*]thiophene 1,1-dioxide.[1-3]



The low order of the halogen leaving group effect ($k_{Br}:k_{Cl} \cong 3:1$; $k_I:k_{Cl} \cong 1.4:1$) in the conductometric rates can be accounted for in one or more of the following ways: (a) equilibrium between **1** and **2** is established, but the concentration of **2** changes with changing halogen [*i.e.*, **2** (X = Cl) > **2** (X = Br) > **2** (X = I)] so as to offset the usual leaving group effect (I > Br > Cl);[4] (b) proton removal in the first step (**1** → **1a**) is rate controlling (*i.e.*, $k'_{-1} \gg k_{-1}$ and $k_2 \gg k'_1$ and k'_{-1}; in other words, equilibrium between **1** and **2** is not established); or (c) there is only a small leaving group effect in the SN2′ reaction of **1** with piperidine in methanol.

The first explanation can be ruled out because the positions of the tautomeric equilibria in a similar system, HCC=CX ⇄ C=CCHX, have been found to change in the *reverse manner* (vinylic chloride > vinylic bromide > vinylic iodide).[3] This requires that in the equilibrium **1** ⇄ **2** the change of X from Cl to Br favor **2**, which should give an apparent *increase* in the Br:Cl rate ratio.

The second explanation also appears to be inadmissable, because proton transfers from piperidinium ion to a carbanion like **1a** would be expected to be very rapid. Therefore, k_{-1} and k'_{-1} would be expected to be rapid relative to k_2. Nevertheless, the over-all rate does appear to be of a magnitude comparable with the rate of proton removal. Thus, the rate of proton removal for **8**, an isomer of **1**, by piperidine in methanol is *ca.* 6.5×10^{-2} M sec^{-1} at 25°.[3] That for **1** might be expected to be several powers of ten slower, which places it at the same order of magnitude as the observed conductometric rate (Table I).



In order to obtain additional evidence with regard to the rate-determining step the reaction of **1** with piperidine was studied in the presence of methoxide ion. The rate of proton abstraction by methoxide ion from **8** is

(2) Additional evidence for the intermediacy of **4** is provided by the observation that the spectrophotometric rate for **1** is the same as that for the reaction of 3-halomethylbenzo[*b*]thiophene 1,1-dioxides (**8**) with piperidine in methanol, where **5** is also the product. The intermediate **4** was also isolated in this reaction; its nmr spectrum agreed with that described herein.[3]

(3) D. A. Schexnayder, Ph.D. Dissertation, Northwestern University, June 1968.

(4) Average values for $k_{Br}:k_{Cl} \cong 50:1$ and $k_I:k_{Br} \cong 4:1$: A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill Book Co., New York, N. Y., 1962, p 29.

about 250 times that by piperidine.[3] If proton abstraction from **1** is rate determining, addition of methoxide ion should lead to a marked increase in rate. Titrimetric rate constants for the reaction of **1** with piperidine in benzene with and without added methoxide ion are summarized in Table III.

TABLE III

TITRIMETRIC RATES FOR THE REACTION OF 2-HALO-3-METHYLBENZO[*b*]THIOPHENE 1,1-DIOXIDE (1) WITH PIPERIDINE IN METHANOL AT 50°

Halide (X)[a]	$[C_5H_{10}NH]$, M	$[MeO^-]$, M	k, M^{-1} sec^{-1} [b]
Cl	0.1092	...	$8.7 \pm 0.5 \times 10^{-4}$
Cl	0.04775	0.075	$1.4 \pm 0.1 \times 10^{-3}$
Br	...	0.10	9.4×10^{-4}
Br	0.01910	0.037	1.00×10^{-2}
	0.03820	0.075	1.08×10^{-2}
	0.3350	0.090	1.13×10^{-2}
		Av	$1.07 \pm 0.05 \times 10^{-2}$
Br	0.06767	0.13	$(1.07 \pm 0.06 \times 10^{-2})$[c]

[a] The halide concentration was about 10^{-3} M in each instance. [b] Calculated from the pseudo-first-order constant by dividing by the piperidine concentration. [c] Spectrophotometric rate.

Examination of Table III shows that inclusion of 0.075 M sodium methoxide caused a 61% increase in the titrimetric rate constant for chloride **1**. (The titrimetric rate constant is in reasonably good agreement with the conductometric rate constant, which is 8.1×10^{-4} M^{-1} sec^{-1} at 50°.) The titrimetric rate constant for bromide **1** is seen to be independent of methoxide concentration.

The fact that only a 61% increase in rate for chloride **1**, rather than a several-hundred-fold increase, occurs on addition of methoxide ion shows that equilibration of **1** and **2** must be nearly complete even in the presence of the much weaker base piperidine. Therefore, in the absence of methoxide ion, the conductometric (and titrimetric) rate constants are essentially equal to Kk_2, where K is the equilibrium constant for **1** $\rightleftarrows$ **2**. On the other hand, the spectrophotometric rate constant is determined primarily by k_4, the rate constant for the removal of a proton from **4** by piperidine to give carbanion **4a**. According to this analysis inclusion of methoxide ion should greatly accelerate the conversion of **4** into **4a**, and this step should no longer be rate determining. Indeed, it was found that in the presence of 0.13 M sodium methoxide the spectrophotometric rate constant for the reaction of bromide **1** with piperidine in methanol at 50° was 1.07×10^{-2} M^{-1} sec^{-1} (Table III) compared with 3.2×10^{-4} M^{-1} sec^{-1} at 45° in the absence of methoxide ion (Table II). Furthermore, in the presence of methoxide ion the titrimetric and spectrophotometric rates for bromide **1** were equal (Table III). These results clearly establish the pathway

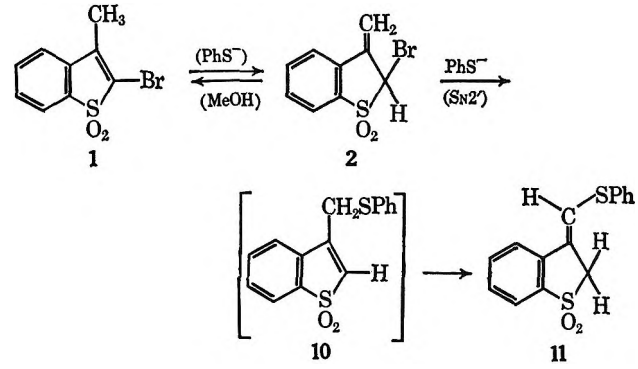
$$1 \underset{}{\overset{}{\rightleftarrows}} 2 \xrightarrow{k_2} 3 \longrightarrow 4 \xrightarrow{k_4} 5$$

for the reaction of **1** with piperidine in methanol, with k_2 being rate determining for halide loss and k_4 being rate determining for product formation.

A further point of interest is that inclusion of methoxide ion did not lead to the formation of a methyl ether. Instead, **5** remained as the product, even when the molar concentration of methoxide ion to piperidine was 2:1. This shows that piperidine must be at least one hundred times more effective as a nucleophile in attacking **2** in an SN2′-type reaction than is methoxide ion.

The relative rates of release of halide ion from **1**, as judged by the conductometric rate constants (Table I), are Cl:Br:I = 1.0:2.9:1.6. These leaving group effects are a composite, however, of the equilibrium constants for **1** $\rightleftarrows$ **2** and the k_2 values for the various halides **2** (X = Cl, Br, or I). The equilibrium constants for a somewhat analogous system, **8** $\rightleftarrows$ **9**, have been measured. Here the relative per cents of allylic halides (**8**) present at equilibrium are Cl:Br:I = 5.4:11:34.[3] Assuming comparable values for the **1** $\rightleftarrows$ **2** equilibria and correcting the k_{obsd} values gives relative k_2 values for Cl:Br:I of 1.0:1.4:0.25. Clearly, the leaving group effects for the conversion of **2** into **3** by abnormal allylic displacements are much smaller than for comparable SN2 displacements.[4-6]

Reaction of **1** with sodium thiophenoxide in methanol results in the formation of a product (**11**) having a structure analogous to that of **5**.[7,8] This product is no doubt formed in a comparable manner.



Discussion

The failure of appearance of vinylic hydrogens characteristic of **2** in the nmr spectrum during the reaction of **1** with piperidine is not surprising since the equilibrium should strongly favor **1**. The α,β-unsaturated isomer is favored for 3-methyldihydrothiophene 1,1-dioxide (92:8),[9] and the same is true for 3-methylbenzo[*b*]thiophene 1,1-dioxide. For the latter the equilibrium appears to be *ca.* 3:1.[3] By analogy with the equilibrium **8** $\rightleftarrows$ **9**, the presence of the halogen should favor **1** over **2** by an additional factor (about 95:5 for the chloride and about 90:10 for the bromide). The equilibrium **1** $\rightleftarrows$ **2** should, then, favor **1** by a factor of over 50:1 for the chloride and over 25:1 for the bromide. This places the value of k_2, the SN2′ displacement rate of **2** with piperidine in methanol, at *ca.* 7×10^{-2} M^{-1} sec^{-1} for the chloride at 50° and *ca.* 2.7×10^{-1} M^{-1} sec^{-1} for the bromide ($k_{obsd} \times K$ in Table II). Comparison of

(5) F. G. Bordwell, P. E. Sokol, and J. D. Spainhour [*J. Amer. Chem. Soc.*, **82**, 2881 (1960)] reported a normal Br:Cl leaving group effect in an SN2′ reaction, but this conclusion was invalidated by later results.[1]

(6) N. H. Cromwell, unpublished results privately communicated, has found a small Br:Cl ratio for an SN2′ reaction of a similar type in which the activating group is carbonyl rather than sulfonyl.

(7) The product was originally believed to be 3-methyl-2-phenylthiobenzo[*b*]thiophene 1,1-dioxide,[8] but later work showed that this structure assignment was incorrect.[1]

(8) F. G. Bordwell, F. Ross, and J. Weinstock, *J. Amer. Chem. Soc.*, **82**, 2878 (1960).

(9) D. E. O'Conner and W. I. Lyness, *ibid.*, **86**, 3840 (1964).

these values with those for analogous SN2′ reactions will be made in the next paper in this series and the mechanism will be discussed therein.

Experimental Section

Reaction of 2-Bromo-3-methylbenzo[*b*]thiophene 1,1-Dioxide (1, X = Br) with Piperidine in Absolute Methanol in the Presence of Sodium Methoxide.—To a solution of 259.1 mg (1.00 mmol) of **1** (X = Br) in 10 ml of absolute methanol there was added 341 mg (4.00 mmol) of piperidine and 432 mg (8.00 mmol) of sodium methoxide. The mixture was refluxed 1 hr. Cooling to room temperature and filtering gave 160.6 mg (64.1%) of yellow needles, mp 178.8–181.8°; a mixture melting point with authentic **5**[3] was undepressed.

Kinetic Procedures.—Piperidine solutions were prepared from freshly distilled reagent grade piperidine (bp 106°) and standardized by titrating with potassium biphthalate, using a pH meter to determine the end point.

A. Conductometric Determination.—An appropriate weight of halide was placed in one arm of a Y-shaped conductance cell, and dissolved in a known volume of absolute methanol, delivered by volumetric pipet. An appropriate volume of standard piperidine solution was then delivered into the other arm by volumetric pipette. After allowing 20 min for temperature equilibration in a bath controlled to ±0.05° with a thermoregulator, the contents of the two arms were thoroughly mixed and drained into the arm containing the platinized platinum electrodes. The resistance of the solution was then recorded as a function of time.

A plot of log $(R_t/R_t - R_\infty)$ *vs.* time gave straight lines. The slope of the line times 2.303 gave the pseudo-first-order rate constant. The second-order rate constants were then obtained by dividing the pseudo-first-order rate constants by the piperidine concentration. The infinity point was chosen to be between ten and twelve half-lives. For the Guggenheim procedure, the time interval was chosen to be about two to three half-lives. A plot of log $(1/R_{\Delta t} - 1/R_t)$ *vs.* time gave straight lines. Second-order rate constants were then derived from the slope of the line, as described above.

B. Spectrophotometric Determination.—Solutions of twice the desired concentration of halide and piperidine were placed in separate arms of a Y-shaped cell. After allowing 20 min for temperature equilibration in a water bath at 45.0°, the contents of the arms were thoroughly mixed. At appropriate times, 1.00-ml aliquots were withdrawn and diluted to 25.00 ml with absolute methanol. The absorbances of these solutions at 324 mμ were then determined in a Beckman DU spectrophotometer.

Alternatively, 3-ml samples of standard piperidine solutions were equilibrated in the spectrophotometer cuvettes contained in a thermostated cell holder. A 20–50-μl sample of halide solution was then added and the change of absorbance was followed with time.

A plot of log $(D_\infty/D_\infty - D_t)$ *vs.* time gave straight lines. The infinity point was chosen to be between ten and twelve half-lives. The second-order rate constants were then calculated from the slope of the line as described above.

C. Titrimetric Determinations.—Standard solutions of piperidine (100 ml) in 250-ml volumetric flasks with Teflon screw caps were equilibrated 1 hr in a bath controlled to ± 0.02° with a thermoregulator. Halide solutions were prepared by weighing appropriate amounts and dissolving these samples in 25 ml of the desired solvent. Portions (4–10 ml) of the halide solutions were added to the standard piperidine solutions and mixed thoroughly. Aliquots were withdrawn, quenched with 10 ml of 0.25 *M* HNO_3, and titrated with 1.5×10^{-3} *M* silver nitrate solution, using an autotitrator. The volume of titrant was then recorded as a function of time.

A plot of $\log(V_\infty - V_t)$ *vs.* time gave straight lines. The slope of the lines times 2.303 gave the pseudo-first-order rate constant. The second-order rate contants were then obtained by dividing the first-order rate constants by the piperidine concentration. The infinity point was chosen to be at ten or more half-lives.

Registry No.—**1** (X = Br), 16934-26-2; **1** (X = Cl), 16934-27-3; **1** (X = I), 16934-28-4; piperidine, 110-89-4; **5**, 16934-29-5.

Acknowledgment.—This investigation was supported by the Public Health Service Research Grant No. CA-07351 from the National Cancer Institute.

Rates of SN2′ and SNi′ Rearrangements in 3-(α-Haloalkyl)benzo[*b*]thiophene 1,1-Dioxides[1]

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Rate constants have been determined for the reactions of 3-(α-chloroethyl)- and 3-(α-chloro-α-methylethyl)-benzo[*b*]thiophene 1,1-dioxides (**1a** and **1b**, respectively) with piperidine in benzene. For **1a** the rate of (enamine) product formation (spectrophotometric rate) is slower than the rate of chloride release (titrimetric rate) indicating that the SNi′ type of rearrangement is rate determining. This kinetic analysis predicts formation of an intermediate, and evidence is presented to show that such is formed. For **1b** the rate of (enamine) product formation is equal to the rate of halide release indicating that in this instance the SN2′ step, rather than the SNi′ step, is rate determining.

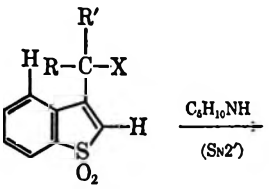
In a previous paper the reaction of secondary and tertiary chlorides **1a** and **1b** with piperidine in benzene was shown to give the enamines **5a** and **5b**, respectively. The suggested pathway involved intermediates **2**, **3**, and **4**.[2] The present paper provides additional experimental evidence for this route and considers the mechanisms of two of the steps in some detail.

The kinetics of the reaction of **1a** and **1b** with excess piperidine in benzene were examined under pseudo-first-order conditions by following the rates of release of chloride ion (titrimetric rates) and the rates of formation of enamines **5a** and **5b** (spectrophotometric rates). The results are summarized in Tables I and II.

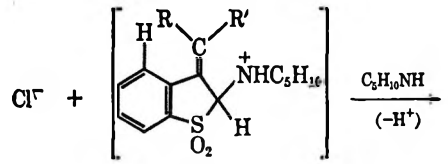
Examination of Tables I and II reveals that for tertiary chloride **1b** the titrimetric and spectrophotometric rates are equal within experimental error. In terms of the suggested reaction scheme this requires that the abnormal allylic displacement (**1b** → **2b**) be rate determining and that the rearrangement steps (**3b** → **4b** → **5b**) be rapid. (Proton removal from **2b** to give **3b** is expected to be fast.) Variation of the piperidine con-

(1) A preliminary account of part of this work has appeared: F. G. Bordwell, R. W. Hemwall, and D. A. Schexnayder, *J. Amer. Chem. Soc.*, **89**, 7144 (1967).

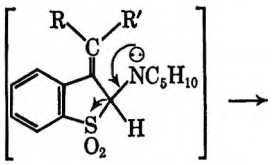
(2) F. G. Bordwell, R. W. Hemwall, and D. A. Schexnayder, *J. Org. Chem.*, **33**, 3233 (1968).



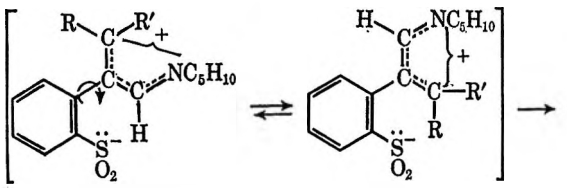
1a, R = H; R′ = Me
b, R = R′ = Me



2a, R = H; R′ = Me
b, R = R′ = Me

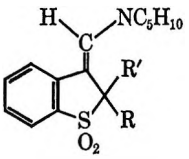


3a, R = H; R′ = Me
b, R = R′ = Me



4a, R = H; R′ = Me
b, R = R′ = Me

4a, R = H; R′ = Me
b, R = R′ = Me



5a, R = H; R′ = Me
b, R = R′ = Me

TABLE I

TITRIMETRIC RATES FOR THE REACTIONS OF 1a AND 1b WITH EXCESS PIPERIDINE IN BENZENE

Chloride[a]	Temp, °C	[Piperidine], M	k_2, M^{-1} sec^{-1} [b]	E_a, kcal/mol	ΔS^*, eu
1a	25.90	0.3017	$5.9 \pm 0.2 \times 10^{-4}$	10	−42
1a	33.80	0.3084	$9.5 \pm 0.5 \times 10^{-4}$		
1a	50.0	0.1195	$2.2 \pm 0.1 \times 10^{-3}$		
1a	50.0	0.2962	$2.0 \pm 0.1 \times 10^{-3}$		
1b	33.82	0.3084	$6.4 \pm 0.2 \times 10^{-5}$	11	−43
1b	50.0	0.2962	$1.7 \pm 0.2 \times 10^{-4}$		
1b	50.0	0.08839	$1.5 \pm 0.2 \times 10^{-4}$		

[a] The halide concentration was of the order of 10^{-3} M. [b] Calculated by dividing the pseudo-first-order rate constants by the piperidine concentration; the values are averages of at least three runs.

centration (Tables I and II) showed that the reaction was first order in piperidine.

For secondary chloride **1a** the titrimetric and spectrophotometric rates are not equal; moreover, they are not even of the same kinetic order. Whereas the titrimetric rate shows a first-order dependence on the piperidine concentration, the spectrophotometric rate does not. Instead, the rate actually decreases somewhat with increasing piperidine concentration. We interpret these results to mean that in the reaction sequence **1a** → **2a** → **3a** → **4a** → **5a** the (first order) cleavage of the intermediate **3a** to form dipolar ion **4a** is rate controlling.

The closeness of the activation energy and activation entropy values for the reactions in which halide ion is lost from the secondary chloride **1a** and the tertiary chloride **1b** supports the view that these reactions are proceeding by comparable (SN2′) mechanisms. The 13-fold faster rate for **1a** is the result of a 1 kcal/mol smaller activation energy; the activation entropies are identical within experimental error.

The activation energies and entropies derived from the spectrophotometric constants for the reaction of **1a** are both greatly increased over those derived from the titrimetric rate constants (E_a is increased by 10 kcal/mol and ΔS^* is increased by 24 eu). This is consistent with the suggested difference in rate-determining steps for halide ion loss compared with product formation.

The kinetic data indicate that in the reaction of tertiary chloride **1b** the α-(1-piperidyl) sulfone **3b** was being formed only in steady-state concentrations, but that in the reaction of secondary chloride **1a** the corresponding α-(1-piperidyl) sulfone (**3a**) was being formed as an intermediate. This was confirmed in preparative experiments. When the reaction of **1b** with piperidine was quenched near the (calculated) first half-life the product was shown by nmr analysis to consist of about 50% enamine **5b** and 50% starting chloride **1b**. On the other hand, a similar experiment with **1a** carried out for about four titrimetric half-lives gave a product containing little or no starting chloride (**1a**) or enamine (**5a**). The product of this reaction is believed to be compound **3a** on the basis of its nmr spectrum which consisted of a four-proton multiplet at δ 7.0–7.8 (aromatic protons), a one-proton doublet of doublets at 6.09 (J = 1.3 cps) assigned to the α-methinyl proton (coupled with the allyl proton), a one-proton quartet at 3.85 (J = 1.3 cps, J' = 6.7 cps) assigned to the vinyl proton (coupled with C_α and Me), a three-proton doublet at 1.42 (J = 6.7 cps) assigned to the methyl group, and a complex multiplet centered at 2.81 for the β and γ piperidino protons (the α piperidino protons were partially superimposed with the methyl doublet). This material was rearranged to enamine **5a** by refluxing in benzene for 15 hr. The absorption at δ 6.09 disappeared and a peak at 6.65 appeared (characteristic of **5a**). The rate of enamine production in methanol based on preliminary measurements of the rate of appearance of the 324-mμ band is of the order of 10^{-3} to 10^{-4} sec^{-1}.

Attempts to prepare the tertiary bromide corresponding to **1b** have thus far been unsuccessful, but the secondary bromide (**1a′**) corresponding to **1a** has been prepared;[3] rate data for its reaction with piperidine in methanol and in benzene are given in Table III.

A preparative study of the reaction of the secondary bromide (**1a′**) with piperidine in methanol revealed

(3) P. E. Sokol, Ph.D. Dissertation, Northwestern University, Aug 1959.

TABLE II

SPECTROPHOTOMETRIC RATES FOR THE REACTION OF 1a AND 1b WITH EXCESS PIPERIDINE IN BENZENE

Chloride	Temp, °C	[Piperidine], *M*	*k*	E_a, kcal/mol	ΔS^*, eu
1a	26.0	0.3207	2.7×10^{-6} sec^{-1}		
	26.0	0.3207	2.9×10^{-6} sec^{-1}		
	26.0	0.1069	4.2×10^{-6} sec^{-1}	20	−18
1a	50.0	0.3081	3.5×10^{-5} sec^{-1}		
	50.0	0.3081	3.6×10^{-5} sec^{-1}		
	50.0	0.1849	4.5×10^{-5} sec^{-1}		
1b	50.0	0.3076	1.4×10^{-4} M^{-1} sec^{-1}		
	50.0	0.3076	1.5×10^{-4} M^{-1} sec^{-1}		
	50.0	0.1846	1.4×10^{-4} M^{-1} sec^{-1}		

TABLE III

RATES OF REACTION OF SECONDARY BROMIDE (1a′) WITH EXCESS PIPERIDINE IN METHANOL

Temp, °C	[Piperidine], *M*	k_2, M^{-1} sec^{-1} [a]	k, sec^{-1} [b]	E_a, kcal/mol	ΔS^*, eu
25.0		$4.3 \pm 0.1 \times 10^{-4}$		15	−26
30.2		$6.5 \pm 0.1 \times 10^{-4}$			
50.0		$3.1 \pm 0.1 \times 10^{-3}$			
50.0	0.3383		3.2×10^{-4}		
50.0	0.1115		2.9×10^{-4}		
50.0		$(3.4 \pm 0.1 \times 10^{-2})$[c]			

[a] Conductometric rates measured by P. E. Sokol.[3] [b] Spectrophotometic rates. [c] Titrimetric rate in benzene.

that about equal amounts of enamine **5a** and SN2 displacement product were formed (by nmr analysis). The rate of halide release in the abnormal allylic displacement reaction with **1a′** is therefore 1.5×10^{-3} M^{-1} sec^{-1} at 50°.[4] Comparison of this value with that obtained in benzene (Table III) shows that this reaction is about 23 times *slower* in methanol than in benzene.[5]

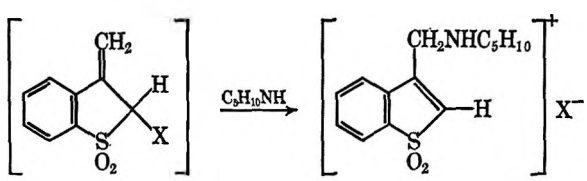
The conductometric rate constants for the reaction of **1a′** with piperidine in methanol were first order in piperidine, whereas the spectrophotometric rate constants were independent of piperidine concentration. This is comparable with the results obtained in benzene. Evidently ring opening is rate determining for secondary bromide **1a′** in methanol, just as it is for secondary chloride **1a** in benzene. The eightfold faster spectrophotometric rate for **1a′** in methanol than for **1a** in benzene indicates that rearrangement of **3a** is faster in methanol by this factor.

Comparison of the rate of halide release for **1a′** in benzene with that of **1a** reveals a Br:Cl leaving group effect of 16:1.

Discussion

SN2′ Displacement Step.—The abnormal allylic displacements for secondary chloride **1a** and **1b** with piperidine in benzene to give **2a** and **2b**, respectively, may be compared with similar (SN2′) reactions of α-methylallyl chloride with diethylamine,[6,7] or dimethylamine[8] under comparable conditions. The rate constant for **1a** with piperidine is, however, two or three powers of ten greater than those for α-methylallyl chloride with secondary amines. The acceleration in rate is due to a sharp drop in activation energy.[9,10]

In the previous paper in this series a comparable SN2′ reaction was observed with secondary halides **6** (X = Cl, Br, or I) with piperidine in methanol to give **7** (not isolated as such).[11] Here the rate constant for halide loss was estimated to be about 2.7×10^{-1} M^{-1} sec^{-1} (X = Br).



6 **7**

It is clear from these results that the sulfonyl group has a strong accelerating effect on the SN2′-type process. This is no doubt associated with its electron-withdrawing property, which reduces the electron density in the π bond and thereby increases the susceptibility of the carbon atom of the C=C bond to nucleophilic attack. The sulfonyl group may also facilitate the SN2′-type process by delocalizing the negative charge developing on the β-carbon atom of the allylic system in the transition state. The relatively small leaving-group effect observed for the reactions of the secondary bromide **1a′** and the secondary chloride **1a** with piperidine in benzene (Br:Cl = 16:1) suggests a dipolar transition state in which there is relatively little C–X bond breaking. The even smaller leaving group effect for the reaction of **6** in methanol (Br:Cl:I = 1.4:1.0:0.25)[11] suggests that in this solvent a (delocalized) dipolar intermediate

(4) For chloride **1** tautomerism to the vinyl chloride has been found to be competitive in methanol (but not in benzene) with the rate of chloride displacement [F. G. Bordwell, R. W. Hemwall, and D. A. Schexnayder, *J. Org. Chem.*, **33**, 3226 (1968)]. This is not true for bromide **1** as shown by the absence of nmr peaks characteristic of the tautomer in a reaction quenched after one half-life.

(5) The rate of reaction of tertiary chloride **1b** also is slower in methanol than in benzene. This unusual solvent effect is discussed further in the next paper in this series: F. G. Bordwell and D. A. Schexnayder, *J. Org. Chem.*, **33**, 3240 (1968).

(6) W. G. Young, J. D. Webb, and H. L. Goering, *J. Amer. Chem. Soc.*, **73**, 1076 (1951).

(7) D. C. Dittmer and A. F. Marcantonio, *ibid.*, **86**, 5621 (1964).

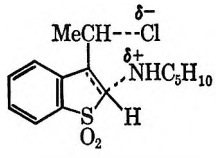
(8) W. G. Young and I. J. Wilk, *ibid.*, **79**, 4793 (1957).

(9) For diethylamine in benzene, $k = 5.8 \times 10^{-6}$ M^{-1} sec^{-1} at 60°; E_a = 15 kcal/mol; $\Delta S^* = -39$ eu.[7] For dimethylamine, $k = 1.5 \times 10^{-5}$ M^{-1} sec^{-1} at 49.6°; E_a = 18 kcal/mol; $\Delta S^* = -26$ eu.[8]

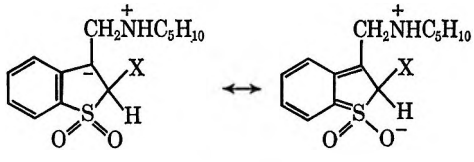
(10) The activation energies and entropies are also low for SN2 reactions in benzene solution. Thus, for the reaction of aniline with phenacyl bromide, E_a = 8.1 ($\Delta S^* = -56$) compared with E_a = 12.4 ($\Delta S^* = -33$) in methanol; see H. E. Cox, *J. Chem. Soc.*, **119**, 142 (1921).

(11) Compound **6** is formed *in situ* from the 2-halo-3-methylbenzo[*b*]thiophene 1,1-dioxide by tautomerism; **7** loses a proton and is then tautomerized to an enamine.[2]

may actually be formed. If a dipolar intermediate is formed irreversibly (*i.e.*, rate of halide loss ≫ rate of reversal of piperidine addition) the addition step would be rate determining and the leaving-group effect would be negligible.



transition state for
1a + piperidine

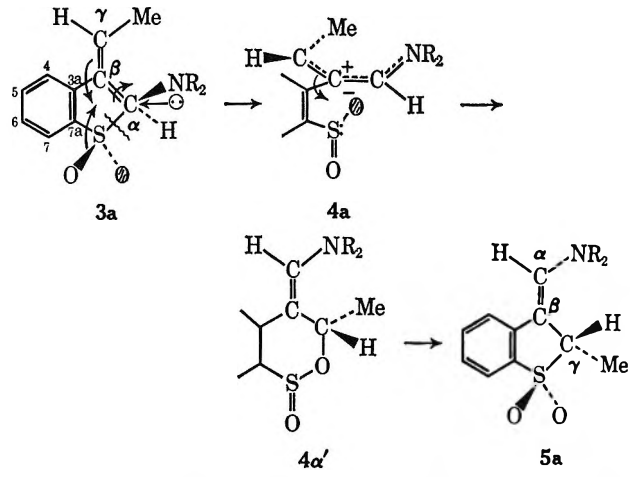


intermediate from **6** + piperidine

SNi′ Rearrangement Step.—The rearrangement of intermediates **3a** and **3b** to **5a** and **5b**, respectively, *via* dipolar ions **4a** and **4b** is related to SNi′-type rearrangements.[12] Intermediates **3a** and **3b** are α-amino sulfones. Few members of this functional class appear to have been prepared to date, which suggests that they may be labile.[13] In any event the lability of α-hydroxy sulfones[14] provides ample precedent for the strong driving force attributed herein to the 1-piperidyl group in the solvolysis of **3a** and **3b**.[15,16]

The enaminium cation part of **4a** can be formed by C–S bond rupture accompanied by a slight clockwise twist around C_α–C_β and rehybridization of C_α. If at the same time a slightly clockwise rotation occurs around C_{7a}–S and a comparable counterclockwise rotation occurs around C_{3a}–C_β, an intermediate will be formed in which an oxygen atom (shaded) of the sulfinite ion is held above the plane of the enaminium moiety (**4a**).[17,18] (This geometry is precisely that suggested for the ion pair in the SNi′ rearrangement of allylic chlorides.[12])

One would expect this to lead to the sulfinate ester **4a′**, but sulfinates are known to isomerize to sulfones,[19]



3a **4a** **4a′** **5a**

and this type of isomerism (by C–O bond cleavage and further rotation) should be particularly facile for the allylic transformation **4a′** → **5a**. According to this picture the rearrangement of **4a** to **5a** is somewhat analogous to the SNi′ rearrangement of an allyl carboxylate ester in which scrambling in the (labeled) carboxylate ion of the ion pair occurs by internal return.[20] In the present system both the cation and anion parts of the "ion pair" are ambident. Since the species is a dipolar ion rather than an ion pair, ionization and internal return can occur until the most stable species is obtained.

The limited amount of data available indicate that, as expected, the rearrangement **3a** → **5a** is faster in methanol than in benzene, a solvent of poorer ionizing power.

For the tertiary chloride **1b**, the SN2′ reaction forming **2b** is 13 times slower than that for the secondary chloride **1a** (forming **2a**). This is probably due to the steric effect associated with placing a methyl group (compared with a hydrogen atom) in opposition to the *peri* hydrogen atom (shown) in the transition state. In the rearrangement of **3b** to **5b** this same steric effect provides an accelerating factor, which is no doubt aided by the stabilization of the incipient cation by the extra methyl group. The result is that for the transformation of **1b** to **5b** in benzene the rearrangement **3b** → **5b** is rapid and the SN2′ reaction (**1b** → **2b**) is rate controlling. For the transformation of **1a** to **5a** the SN2′ step is faster and the rearrangement step (**3a** → **5a**) is slower; the latter becomes rate controlling in this series.

Registry No.—**1a**, 16934-30-8; **1b**, 16934-31-9; **1a′**, 16934-32-0.

Acknowledgment.—This investigation was supported by the Public Health Service Research Grant No. CA-07351 from the National Cancer Institute.

(12) See (a) R. H. DeWolfe and W. G. Young, *Chem. Rev.*, **56**, 753 (1956); (b) A. Streitwieser, Jr., *ibid.*, 571 (1956); (c) P. B. D. de la Mare, "Molecular Rearrangements," P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, Chapter 2, for reviews of allylic rearrangements.

(13) E. Meyer, R. Nacke, and M. Gmeiner {*J. Prakt. Chem.*, [2] **63**, 167 (1901)} report the preparation of $(p\text{-MeC}_6H_4SO_2CH_2)_2NH$ and $p\text{-MeC}_6H_4SO_2CH_2NHC_6H_5$, which would be expected to be more stable than **3a** or **3b**. They are decomposed by alcoholic alkali. See H. Hellmann and G. Opitz, *Chem. Ber.*, **90**, 8 (1957), for an example of a facile hydrolysis of an α-amino sulfone.

(14) E. P. Kohler and M. Reimer, *Amer. Chem. J.*, **31**, 163 (1904).

(15) Note also that the RO grouping provides about a 10^8 accelerating rate on the solvolysis of alkyl halides ($ROCH_2X$ *vs.* RCH_2X).[16] The R_2N group should produce a considerably larger activating effect.

(16) See H. Böhme and K. Sell, *Chem. Ber.*, **81**, 123 (1948), and ref 12c, p 103.

(17) By analogy with allyl cations the enaminium ion would be expected to maintain its configuration.[18]

(18) W. G. Young, S. H. Sharman, and S. Winstein, *J. Amer. Chem. Soc.*, **82**, 1376 (1960); J. H. Brewster and H. O. Baeyer, *J. Org. Chem.*, **29**, 105 (1964).

(19) J. Kenyon and H. Phillips, *J. Chem. Soc.*, 1676 (1930); C. L. Arens, M. P. Balfe, and J. Kenyon [*ibid.*, 485 (1938)] report that a small amount of optically active sulfone of *retained* configurations is formed in such an isomerizaton.

(20) H. L. Goering, J. P. Blanchard, and E. F. Silversmith, *J. Amer. Chem. Soc.*, **76**, 5409 (1954); H. L. Goering and E. F. Silversmith, *ibid.*, **77**, 1129 (1955).

Mechanistic Classification of Abnormal Allylic Substitution (SN2′) Reactions

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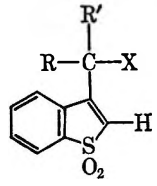
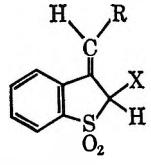
The secondary and tertiary chlorides, 3-(α-haloethyl)- and 3-(α-chloro-α-methylethyl)benzo[*b*]thiophene 1,1-dioxides (**2** and **3**), which are much more reactive than α-methylallyl chloride in SN2′ reactions with secondary amines in benzene, fail to give reactions with a number of other nucleophiles claimed to be effective for SN2′ reactions (thiourea, bromide ion, alkoxide ions, tertiary amines). The applicability of the SN2′ mechanistic label to a number of abnormal substitutions of allylic halides is reviewed in the light of these results and it is concluded that very few unambiguous assignments of this label can be made. Changing the solvent from benzene to methanol was found to *decrease* markedly the rate of the SN2′ reaction of piperidine with bromide **2** or **3**. This information, together with the small Br–Cl leaving-group effect for **2**, is used in discussing mechanisms for SN2′ reactions.

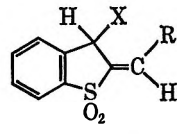
Evidence is now on hand to indicate that the seven halides **1**–**7** (one primary, one tertiary, and five secondary) react with piperidine in benzene by abnormal allylic substitution mechanisms.[1-3]



1, R = R′ = H; X = Cl
2, R = H, R′ = Me; X = Br, Cl
3, R = R′ = Me; X = Cl



4, R = H; X = Br, Cl, I
5, R = Me; X = Br



6, R = H; X = Br
7, R = Me; X = Br

Four of these halides (**4**–**7**) were produced as transient intermediates; further evidence for the mechanistic classification of these reactions is therefore difficult to obtain. A further study of the behavior of **2** and **3** has now been made, however, using additional nucleophiles and solvents. As a result of this study we have reached the conclusion that, although the SN2′ mechanistic classification has been suggested for numerous abnormal allylic substitutions, and many of these have been accepted as bonafide by workers prominent in the field,[4] relatively few completely unambiguous examples have been described.

In order to evaluate and compare potential nucleophiles for further investigation, the kinetic data for all previous studies wherein abnormal substitution products were obtained in a second-order process, presumably by an SN2′ mechanism, were collected. The rate constants, expressed in common units (M^{-1} sec^{-1}) and, where possible, at comparable temperatures (at or near 50°) are compared in Table I[5-17] with data obtained on the rates of halide release for compounds **1**–**4**.

Examination of Table I reveals that SN2′ reactions have been claimed for only a rather select group of nucleophiles. Six types are represented: (a) secondary amines, (b) tertiary amines, (c) ethyl sodiomalonate, (d) sodium ethoxide, (e) sodium thiophenoxide, and (f) lithium bromide. Thiourea may be added to this list since it has been reported to give abnormal substitution with α,α-dimethylallyl chloride with a second-order rate constant about ten times less than the SN2 rate constant for γ,γ-dimethylallyl chloride.[18] Most of these nucleophiles have been used in only one or two allylic systems. Judging from the results with α-methylallyl halide systems and ignoring solvent effects, ethyl sodiomalonate, secondary and tertiary amines, and lithium bromide all react at rates of a comparable order of magnitude; sodium thiophenoxide is several powers of ten more reactive (based on the α,α-dimethylallyl system), and sodium ethoxide is several orders of magnitude less reactive (based on the α-*t*-butylallyl system). Secondary chloride **2** in the 3-α-haloalkylbenzo[*b*]-thiophene 1,1-dioxide series is about 500 times as reactive toward piperidine as is α-methylallyl chloride toward dimethylamine, and tertiary chloride **3** is ten times as reactive. In view of the high reactivity of **2** and **3** toward secondary amines it was anticipated that these halides would react readily with the other nucleophiles on the list. Surprisingly enough, this was not the case.

Results

Excess thiourea failed to react to any appreciable extent with either **2** or **3** in alcohol even after extended reflux. With the secondary chloride (**2**) the reaction was

(1) F. G. Bordwell, R. W. Hemwall, and D. A. Schexnayder, *J. Org. Chem.*, **33**, 3226 (1968).

(2) F. G. Bordwell, R. W. Hemwall, and D. A. Schexnayder, *ibid.*, **33**, 3233 (1968).

(3) F. G. Bordwell and D. A. Schexnayder, *ibid.*, **33**, 3236 (1968). See F. G. Bordwell, R. W. Hemwall, and D. A. Schexnayder, *J. Amer. Chem. Soc.*, **89**, 7144 (1967), for a preliminary account of the present work.

(4) (a) R. H. DeWolfe and W. G. Young, *Chem. Rev.*, **56**, 769 (1956); (b) P. B. D. de la Mare, "Molecular Rearrangements, P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, Chapter 2, pp 62–68.

(5) R. D. Kepner, S. Winstein, and W. G. Young, *J. Amer. Chem. Soc.*, **71**, 115 (1949).

(6) W. G. Young, I. D. Webb, and H. L. Goering, *ibid.*, **73**, 1076 (1951).

(7) (a) D. C. Dittmer and A. F. Marcantonio, *Chem. Ind.* (London), 1237 (1960); (b) D. C. Dittmer and A. F. Marcantonio, *J. Amer. Chem. Soc.*, **86**, 5621 (1964).

(8) W. G. Young and I. J. Wilk, *ibid.*, **79**, 4793 (1957).

(9) W. G. Young, R. A. Clement, and C. H. Shih, *ibid.*, **77**, 3061 (1955).

(10) P. B. D. de la Mare, E. D. Hughes, P. C. Merriman, L. Pichet, and C. A. Vernon, *J. Chem. Soc.*, 2563 (1958).

(11) B. D. England, *ibid.*, 1615 (1955).

(12) P. B. D. de la Mare and C. A. Vernon, *ibid.*, 3555 (1953).

(13) P. B. D. de la Mare and C. A. Vernon, *ibid.*, 3331 (1952).

(14) P. B. D. de la Mare and C. A. Vernon, *ibid.*, 3325 (1952).

(15) P. B. D. de la Mare and C. A. Vernon, *ibid.*, 3628 (1952).

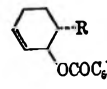
(16) (a) G. Stork and W. N. White, *J. Amer. Chem. Soc.*, **78**, 4609 (1956); (b) G. Stork and F. H. Clarke, *ibid.*, **78**, 4619 (1956).

(17) D. A. Schexnayder, Ph.D. Dissertation, Northwestern University, June 1968.

(18) Unpublished work cited in ref 4a, p 779.

TABLE I

KINETIC DATA FOR BIMOLECULAR ABNORMAL ALLYLIC (SN2′) SUBSTITUTIONS

Ref	Halide	Nucleophile	Solvent	Temp, °C	k_2, M^{-1} sec^{-1}	E_a, kcal/mol	ΔS^*, eu
5	CH_2=CHCH(Et)Cl	$NaCH(CO_2Et)_2$	EtOH	50	2.2×10^{-5}		
6	CH_2=CHCH(Me)Cl	Et_2NH	C_6H_6	62.7	6.4×10^{-6}		
7	CH_2=CHCH(Me)Cl	Et_2NH	C_6H_6	60	5.8×10^{-6}	15	−39
7	CH_2=CHCH(Me)Cl	Et_2ND	C_6H_6	60	5.8×10^{-6}		
7	CH_2=CHCH(Me)Cl	PhNHMe	C_7H_{16}	80	(3.9×10^{-3})[a]		
8	CH_2=CHCH(Me)Cl	Me_2NH	C_6H_6	49.6	1.5×10^{-5}	18	−26
9	CH_2=CHCH(Me)Cl	Me_3N	Me_2C=O	49.7	1.1×10^{-5}	14.5	−38
10	CH_2=CHCH(*t*-Bu)Cl	NaOEt	EtOH	50	1.0×10^{-7}	26	−12
11	CH_2=CHCH(Me)Br	LiBr*	Me_2C=O	50	1.7×10^{-4}	19	−19
11	MeCH=$CHCH_2$Br	LiBr*	Me_2C=O	50	5.8×10^{-6}	~19	−21
12	CH_2=$CHC(Me)_2Cl$[b]	NaSPh	EtOH	50	1.9×10^{-2}		
13	CH_2=$CHCHCl_2$	NaSPh	EtOH	50	6.8×10^{-4}		
14	CH_2=$CHCHCl_2$	NaOEt	EtOH	100	2.4×10^{-4}		
15	CH_2=$C(Me)CCl_3$	NaOEt	EtOH	64.8	1.3×10^{-5}		
15	CH_2=$C(Me)CCl_3$	NaSPh	EtOH	50	1.4×10^{-3}		
16a		$C_5H_{10}NH$	$Me_2C_6H_4$	129.5	1.7×10^{-7} (R = Me)		
16a		$C_5H_{10}NH$	$Me_2C_6H_4$	129.5	3.9×10^{-7} (R = *i*-Pr)		
16a		$C_5H_{10}NH$	$Me_2C_6H_4$	129.5	9.7×10^{-7} (R = *t*-Bu)		
16a		$NaCH(CO_2Et)_2$	BuOH	104.7	2.2×10^{-5} (R = *i*-Pr)		
16a		$NaCH(CO_2Et)_2$	BuOH	104.7	3.6×10^{-5} (R = *t*-Bu)		
16b	α-Chlorococide	$C_5H_{10}NH$	C_6H_6	50	4.7×10^{-5}	14	−37
17	**1**, R = R′ = H	$C_5H_{10}NH$	C_6H_6	50	1.3×10^{-2}		
1	**2**, R = H; R′ = Me	$C_5H_{10}NH$	C_6H_6	50	2.1×10^{-3} (X = Cl)	10	−42
3	**2**, R = H, R′ = Me	$C_5H_{10}NH$	C_6H_6	50	3.4×10^{-2} (X = Br)	8	−43
3	**2**, R = H, R′ = Me	$C_5H_{10}NH$	MeOH	50	1.5×10^{-3} (X = Br)	15	−26
1	**3**, R = R′ = Me	$C_5H_{10}NH$	C_6H_6	50	1.6×10^{-4}	11	−43
1	**3**, R = R′ = Me	$C_5H_{10}NH$	MeOH	50	1.8×10^{-5}	17	−32
1	**3**, R = R′ = Me	$C_5H_{10}NH$	Me_2C=O	50	2.2×10^{-4}		
1	**3**, R = R′ = Me	$C_5H_{10}NH$	DMF	50	6.5×10^{-4}		
1	**3**, R = R′ = Me	Bu_2NH	C_6H_6	50	3.4×10^{-5}		
2	**4**, X = Br	$C_5H_{10}NH$	MeOH	50	$(>2 \times 10^{-1})$[c]		

[a] The rate expression also contains a second-order term in PhNHMe. [b] CH_2=CHCH(Me)Cl reacts with PhSNa by an SN2 process; the maximum SN2′ rate has been estimated to be 1.9×10^{-3} M^{-1} sec^{-1}.[12] [c] Estimated. The rates were corrected for per cent SN2′ component where pertinent.

tried for periods ranging from 2 to 48 hr in refluxing methanol, ethanol, and ethylene glycol monomethyl ether. From 70 to 90% starting material was recovered from these runs.[19] With the tertiary chloride (**3**) starting material was recovered after 3-hr reflux in ethanol or acetonitrile. The failure of thiourea to effect SN2′ reactions with halides **2** or **3** is striking in view of their reactivity toward piperidine (Table I), and the small difference between thiourea and piperidine as nucleophiles in SN2 reactions of the parent allyl halides (Table II).

Recalling that SN2 reactions are ordinarily greatly favored over SN2′ reactions, it is interesting to note that the rate of SN2 reaction of allyl chloride with piperidine in benzene (Table II) is an order of magnitude *slower* than the rate of SN2′ reaction of **2** with piperidine under comparable conditions (Table I), and that the SN2′ rate for **3** with piperidine in methanol is not much slower than the SN2 rate of allyl chloride with piperidine in methanol. In contrast, the SN2 rate for thiourea and allyl chloride in methanol must be many orders of magnitude *faster* than the SN2′ reactions of **2** or **3** with this nucleophile. It is apparent that piperidine is a highly favored nucleophile for the SN2′ reaction.

Reaction of **2** with sodium bromide in refluxing acetone for 48 hr gave a good yield of the corresponding secondary bromide (SN2 product).[19] On the other hand, tertiary chloride **3** was recovered unchanged from a comparable reaction run for 65 hr. A solution of **3** in anhydrous acetone was allowed to stand for 31 days with lithium bromide. The nmr spectrum of the recovered organic material resembled that of the starting material closely; there was no indication of the presence of an abnormal substitution or rearranged product. Microanalysis of the crude organic product for carbon and hydrogen gave close agreement with the calculated values for **3** indicating that no more than 1% bromide

TABLE II

COMPARISON OF PIPERIDINE, N-METHYLPIPERIDINE, AND THIOUREA AS NUCLEOPHILES IN SN2 REACTIONS

Halide	Nucleophile	Solvent	Temp, °C	k_2, M^{-1} sec^{-1}
$CH_3CH_2CH_2Br$[a]	$C_5H_{10}NH$	MeOH	25	1.9×10^{-5}
$CH_3CH_2CH_2Br$[a]	S=$C(NH_2)_2$	MeOH	25	1.7×10^{-5}
$CH_3CH_2CH_2Br$[a]	$C_5H_{10}NH$	MeOH	50	1.9×10^{-4}
$CH_3CH_2CH_2Br$[a]	S=$C(NH_2)_2$	MeOH	50	1.7×10^{-4}
H_2C=$CHCH_2Br$[a]	$C_5H_{10}NH$	MeOH	25	3.4×10^{-3}
H_2C=$CHCH_2Br$[a]	S=$C(NH_2)_2$	MeOH	25	2.3×10^{-3}
H_2C=$CHCH_2Br$[a]	$C_5H_{10}NH$	MeOH	50	2.4×10^{-2}
H_2C=$CHCH_2Br$[a]	S=$C(NH_2)_2$	MeOH	50	1.4×10^{-2}
H_2C=$CHCH_2Br$[a]	$C_5H_{10}NH$	C_6H_6	50	8.9×10^{-3}
H_2C=$CHCH_2Br$[b]	$C_5H_{10}NCH_3$	C_6H_6	50	6.6×10^{-4}
H_2C=$CHCH_2Cl$[b]	$C_5H_{10}NH$	C_6H_6	50	8.9×10^{-5}
H_2C=$CHCH_2Cl$[b]	$C_5H_{10}NH$	MeOH	50	5.3×10^{-3}
H_2C=$CHCH_2Cl$[b]	$C_5H_{10}NCH_3$	MeOH	50	1.1×10^{-4}

[a] Conductometric rates measured by P. E. Sokol.[19] [b] Titrimetric rates; only one or two runs were made in most instances.

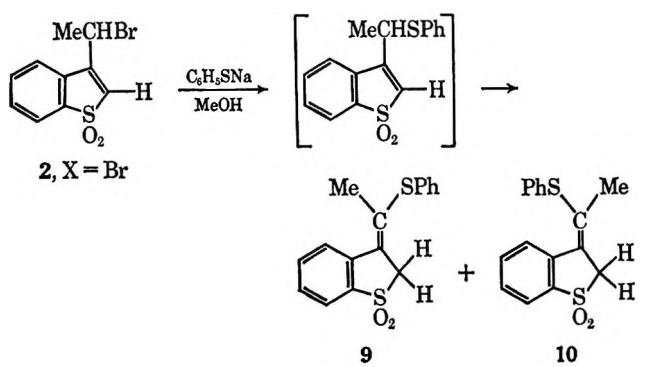
(19) P. E. Sokol, Ph.D. Dissertation, Northwestern University, Aug 1959.

could have been formed. It is evident from these results that **2** is much more prone to undergo SN2 than SN2′ displacement with bromide ion, and that **3** is essentially inert toward bromide ion.

When **3** was heated with sodium methoxide in methanol, chloride ion was slowly released. The products of this reaction have not been identified as yet, but the nmr spectrum of the crude material did not reveal absorption in the vinyl hydrogen region. The methyl enol ether corresponding in structure of the enamine formed from **3** and piperidine under these conditions[3] is evidently not present. In another investigation **4** has been found to react at least 10^2 times faster with piperidine than with methoxide ion in an SN2′ reaction.[3]

A calculation based on the rate constant in Table I shows that at 50° the reaction of **2** with piperidine in benzene is essentially complete in 40 min using 1 *M* concentrations of reagents. From a run made with **2** and 10 equiv of 2 *M* triethylamine in refluxing benzene for as long as 48 hr 60% or more of starting material was recovered. The reaction of the tertiary chloride **3** with piperidine in benzene is essentially complete in 15 hr at 50°. In preparative runs with excess piperidine in benzene high yields of enamine product were obtained in a 4-hr reflux period. Under comparable conditions with triethylamine a nearly quantitative recovery of starting material was obtained. A similar result was obtained using N-methylpiperidine in methanol (7 hr reflux). A solution of **3** and excess N-methylpiperidine in benzene was kept at 50° and aliquots were titrated periodically for chloride ion. None was detectable even after 23 days. A further 35 days at room temperature still failed to produce chloride ion. Even granting 2% completion for the reaction the *maximum* second-order rate constant would be 2×10^{-7} M^{-1} sec^{-1}, which is 10^3 slower than the rate observed with **3** and piperidine. These results indicate that piperidine is remarkably more effective than N-methylpiperidine in SN2′ reactions. On the other hand, in SN2 reactions the difference is relatively small (Table II).[20]

Secondary bromide **2** reacts with piperidine in methanol to give about equal amounts of SN2 and SN2′ products.[3] On the other hand, the product from bromide **2** and thiophenoxide ion in methanol appears to consist entirely of a mixture of products formed by SN2 displacement and subsequent tautomerism (**9** and **10**). These results once again demonstrate the unusual effectiveness of secondary amines in promoting SN2′ reactions as compared to other nucleophiles.



(20) Diethylamine reacts about twice as rapidly with the methyl iodide in methanol as do the tertiary amines, triethylamine and N,N-dimethylcyclohexylamine: R. G. Pearson, H. R. Sobel, and J. Søngstad, *J. Amer. Chem. Soc.*, **90**, 319 (1968).

Tertiary chloride **3** reacts readily with sodium thiophenoxide in ethanol, but resolution of the mixture of products obtained has not been accomplished as yet. The one successful SN2′ reaction with thiophenoxide ion thus far achieved in our systems is that with **4**.[2]

Our experience with **1**, **2**, and **3** confirms that of previous workers (Table I) in singling out secondary amines as the nucleophiles of choice for SN2′ reactions and singling out benzene as the solvent of choice. With α-methylallyl chloride all nucleophiles other than secondary amines, with the possible exception of trimethylamine in acetone (see below), prefer the SN2 to the SN2′ route. The choice of benzene as a solvent for secondary amines is important here because in changing from alcohol to benzene the SN2 reaction is *retarded* (by 16-fold for allyl chloride, see Table II), whereas the results with **2** (bromide) and **3** indicate that SN2′ reactions are *accelerated* by this solvent change (by about 9- to 22-fold, see Table I). The rate for **3** with piperidine is increased only slightly in changing from benzene to acetone, but is increased about fourfold in changing from benzene to dimethylformamide (Table I).[21,22]

The relatively low activation energies and high negative activation entropies recorded in Table I for the SN2′ reactions with amines in benzene are in line with the results obtained in SN2 reactions of amines with alkyl halides in benzene, nitrobenzene, and the like.[23,24] Brown and Eldred[23b] found that in the reaction of triethylamine in nitrobenzene the activation energies increased from 9.7 to 12.5 to 16.0 kcal/mol in the series MeI, EtI, *i*-PrI, whereas the activation entropies remained essentially constant (−34.7, −35.6, and −33.7).[23d] Cox observed that, for the reaction of aniline with phenacyl bromide, E_a increased from 8.1 in benzene to 11.1 in acetone to 12.4 in methanol while ΔS^* increased from − 56 to −39 to −33; at 37.8° the rates were 9.84×10^{-4}, 2.69×10^{-2}, and 7.48×10^{-2} M^{-1} min^{-1}, respectively.[23] The effect on the activation parameters of changing the solvent from benzene to methanol for the SN2′ reactions of **2** and **3** with piperidine is similar. With **2** (X = Br), E_a increases from 8 to 15 in going from benzene to methanol (ΔS^* increases from −43 to −26); for **3** the change in E_a is from 11 to 17 (ΔS^* increases from −43 to −32). The difference between SN2 and SN2′ reactions is that in the latter the increase in activation energy in changing from benzene to methanol overshadows the increase in activation entropy and the rate decreases, whereas the reverse is true in the SN2 reactions.

Discussion

The inertness of **2** and **3** toward thiourea, lithium bromide, and tertiary amines contrasts sharply with earlier results which suggests that these nucleophiles have about the same reactivity in SN2′ reactions as do secondary amines (Table I). It would seem that either **2** and **3** are not as good models for assessing the SN2′

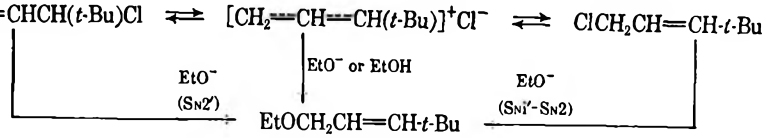
(21) The rates of SN2 reactions involving *anionic* nucleophiles are greatly accelerated by dimethylformamide (DMF) and related aprotic dipolar solvents, but the rates with neutral nucleophiles are not much affected.[22]

(22) A. J. Parker, *Quart. Rev.* (London), **16**, 163 (1962).

(23) (a) K. J. Laidler and C. N. Hinshelwood, *J. Chem. Soc.*, 853 (1938); (b) H. C. Brown and N. R. Eldred, *J. Amer. Chem. Soc.*, **71**, 455 (1949); (c) H. C. Brown and A. Cahn, *ibid.*, **77**, 1715 (1955); (d) summarized by A. W. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill Book Co., New York, N. Y., 1963, p 22.

(24) H. E. Cox, *J. Chem. Soc.*, **119**, 142 (1921).

SCHEME I



reactivity of nucleophiles as their behavior toward piperidine would indicate, or the SN2′ mechanistic label has not been applied correctly in the previous instances. As will be brought out in the following discussion, there is reason to believe that the latter may be the correct interpretation.

The variety of reaction courses available to allylic halides makes mechanistic labeling of their reactions unusually hazardous. It has been suggested that the SN2′ label can be applied with reasonable certainty only after it has been established (1) that the reaction shows a first-order dependence on nucleophile concentration and on allylic halide concentration (to rule out the SN1 mechanism) and (2) that the abnormal product does not arise either from prior (rapid) rearrangement of the allylic halide (followed by SN2 displacement) or subsequent rearrangement of an SN2 (normal) product.[4a] The most difficult condition to meet is to rule out prior rearrangement of the allylic halide, since such rearrangements (SNi′ reactions) are known to occur very readily.[25] One test that has been applied is to recover the allylic halide from an incomplete reaction (of secondary halide) and examine it for rearranged (primary) halide. If this is shown to be absent, it is presumed not to be an intermediate in the reaction. Even this test may not be wholly convincing unless it can be demonstrated that an appreciable quantity of the primary halide is to be expected at equilibrium (the usual case) and that the primary halide has not been removed selectively by reaction with the nucleophile. The latter is a distinct possibility if an equimolar quantity of nucleophile is used since primary allylic chlorides undergo SN2 displacements at rates about 100 times that of the isomeric secondary chlorides.[23d] Unfortunately, the test, in any form, has been applied to only a few of the reactions listed in Table I.[6,9,16]

In the reaction of α-*t*-butylallyl chloride with sodium ethoxide prior rearrangement to the primary chloride followed by a rate-controlling SN2 reaction appears to offer an alternative to the SN2′ mechanism suggested.[10] Still another possibility is that there is rapid formation of an ion pair which is attacked by the nucleophile selectively at the primary carbon atom.[26] Support for this view can be derived from the observations that ethanolysis of this halide gives only the abnormal product and that the concentration of ethoxide ion must be about 2 *N* in order to make the reaction predominantly second order. The mechanistic possibilities may be summarized as shown in Scheme I.

As has been pointed out,[4a] the SNi′–SN2 route remains as a reasonable alternative to the SN2′ route for the exchange reactions of α- and γ-methylallyl bromides with radioactive lithium bromide in acetone solution.[11] The inertness of **3** toward lithium bromide in acetone makes the SNi′–SN2 alternative appear more likely.

From a consideration of the probable structure of the transition state for SN2′ reactions it has been concluded that alkyl substitution at the α- and γ-carbon atom will have an accelerating effect.[4a] However, α-alkyl substitution strongly favors SN1 and SNi′ mechanisms, and γ-allyl substitution is known to favor the SN2 mechanism. Because the SN2′ mechanism requires the nucleophile to attack an electron-rich carbon atom, it is already at a disadvantage with respect to SN1, SNi′, and SN2 mechanisms; it would be surprising, then, to find the SN2′ mechanism ever winning out in simple allylic systems, if this is indeed a proper view of the transition state and a proper assessment of the effect of alkyl substitution. This was, in effect, the conclusion arrived at by the English school after failing to realize the SN2′ mechanism with sodium ethoxide and α-methylallyl chloride and in other systems.[27] Later this view was altered when systems were devised which contained structural features presumably prejudicing them in favor of the SN2′ mechanism.[10–15] According to the present analysis, however, the SNi′–SN2 route (either involving rearrangement to a primary halide or formation of the abnormal product from an ion-pair intermediate) remains as a reasonable alternative for all of these systems. For the α-*t*-butylallyl chloride[10] and α-methylallyl bromide[11] systems the SNi′–SN2 route appears more likely than the SN2′ route. The presence of two or three chlorine atoms at C_α should favor the SN2′ pathway,[13–15] but even here some reservations must be held as to the mechanistic label.

If the SN2′ process is to succeed it will be necessary for the nucleophile to overcome the energy barrier it encounters in approaching the π bond. That this barrier is sizable is evident from the difficulty experienced by even the most powerful bases, including isopropyllithium,[28] solvated electrons,[29] or dimsyl ion ($DMSO^-$)[30] in adding to unconjugated C=C bonds. Even when the C=C bond is conjugated to the strongly electron-withdrawing nitro group the rate of addition of a basic nucleophile, such as methoxide ion, to the C=C bond is only moderate.[31] In view of the reluctance of even powerful bases to add to ordinary C=C bonds, nonbasic nucleophiles such as thiourea and bromide ion would be expected to experience great difficulty in initiating SN2′ reactions. The inertness of **2** and **3** toward these reagents is understandable on this basis. Negatively charged nucleophiles, such as alkoxide ions, would

(25) W. G. Young, S. Winstein, and H. L. Goering, *J. Amer. Chem. Soc.*, **73**, 1958 (1951). See ref 4 for additional examples.

(26) The possibility of ion-pair intermediates for SN2′ reactions is given credence by the recent demonstration of an ion pair in an SN2 reaction; see R. A. Sneen and J. W. Larson, *ibid.*, **88**, 2593 (1966).

(27) A. G. Catchpole, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 8 (1948).

(28) (a) J. E. Mulvaney and Z. G. Gardlund, *J. Org. Chem.*, **30**, 917 (1965); (b) J. A. Landgrebe and J. D. Shoemaker, *J. Amer. Chem. Soc.*, **89**, 4465 (1967).

(29) R. A. Benkeser, *J. Org. Chem.*, **28**, 1094 (1963), and references cited therein.

(30) C. Walling and L. Bollyky, *ibid.*, **29**, 2698 (1964).

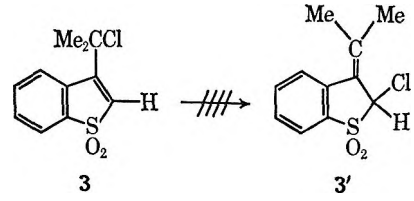
(31) The rate constant for addition of methoxide ion to *trans*-β-nitrostyrene to form the nitronate ion $C_6H_5CH(OMe)CH{=}NO_2^-$ is about 2 M^{-1} sec^{-1} at 25° (unpublished results of W. J. Boyle, Jr.).

be expected to be less effective than neutral, basic nucleophiles such as amines. There is qualitative evidence to support this view from the behavior of 2 and 3, but the best example is with 4 where piperidine has been found to be over 100 times as reactive as methoxide ion in initiating an SN2′ reaction.[2] The best established examples of SN2′ reactions appear to be those involving secondary amines in benzene solution (Table I). The reason for this appears to be that the neutral nucleophile is best for effecting an approach to the C=C bond and that the nonpolar, aprotic solvent accelerates the SN2′ process and retards the SN2 process. Hydrogen bonding between the nucleophile and leaving halide ion, as is possible with secondary (or primary, but not tertiary) amines, also appears to provide an important driving force for the reaction.[5,6]

The particular success of systems 1–7 in promoting SN2′ reactions is no doubt associated with the presence of the electron-withdrawing sulfonyl grouping, which renders the C=C bond more susceptible to attack by the nucleophile.[32] The group not only reduces the electron density in the C=C bond, but also serves to delocalize the negative charge developing at the β position in the transition state.[3]

The presence of the sulfonyl group also serves to eliminate competition from SN1- or SNi′-type processes by greatly retarding the rate of formation of allylic carbonium ions. This is made clearly evident by the reluctance of tertiary allylic chloride 3 to undergo solvolysis. It can be crystallized without change from hot methanol; a solution of 3 in methanol was kept at 50° for 21 days and then at 25° for 35 days. During this time aliquots were removed periodically and titrated. No chloride ion was detected in any of these, which means that no more than 2% could have been released. The methanolysis rate for 3 must then be less than 10^{-8} sec^{-1} at 50°; for comparison, the ethanolysis rate for α,α-dimethylallyl chloride is 2×10^{-4} sec^{-1} at 44.6°.[33] In view of its low solvolysis rate there appears to be little danger that 3 will react by the SNi′–SN2 pathway discussed above, and this is even more true for the primary and secondary chlorides 1 and 2. If an SNi′ reaction did occur, SN2 attack at the carbon atom α to the sulfone group would be extremely slow under these conditions.[34] The SNi′ product would be 4 (from 1), 5 (from 2), or 3′, an analogous *exo*-dimethylmethylene compound (from 3). These compounds would give SN2′ reactions, not SN2 reactions.[2] Thus the SNi′–SN2 route is excluded for the reaction of 1, 2, or 3 with nucleophiles.

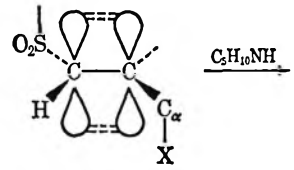
Although rearrangement of tertiary chloride 3 to the isomeric allylic chloride 3′ by a carbonium ion mechanism is highly unlikely, this could conceivably occur by a carbanion mechanism. No evidence for this isomerization was obtained in runs with 3 carried to partial completion. As discussed above, even if 3′ were to be formed it would not be expected to react by an SN2 process,[34] but, instead, it should undergo an SN2′ reaction



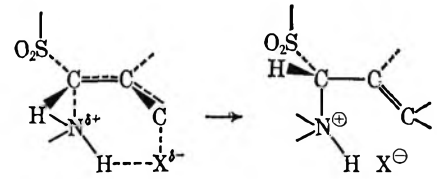
3 3′

in a manner analogous to 4 or 5. Products of this type have not been observed from reactions of 3.

It has been argued that specific hydrogen bonding between the entering and leaving groups is probably helpful, but not necessary, for the SN2′ reaction of amines.[5,6,9] In view of the remarkably greater effectiveness of secondary amines than tertiary amines or thiourea in bringing about SN2′ reactions with 2 and 3 the presence of the hydrogen atom appears to be indeed necessary. Aside from exerting a smaller steric effect than an alkyl group, hydrogen may be more effective in delocalizing the positive charge developing on the nitrogen atom, probably through hydrogen bonding.[5,6] No isotope effect is observed when an N-deuterio secondary amine reacts with α-methylallyl chloride,[7] but the isotope effect would be expected to be small and hydrogen bonding is not excluded by this evidence.



1, 2, or 3



dipolar transition state SN2′ product

Hydrogen bonding, together with a lesser steric requirement, appears to offer the best explanation for the much greater rate of reaction of 3 with piperidine than with N-methylpiperidine. Since 3 is at least as reactive as α-methylallyl chloride toward secondary amines, it is surprising to find that 3 is inert to tertiary amines, whereas α-methylallyl chloride reacts nearly as rapidly with trimethylamine in acetone as it does with dimethylamine in benzene (Table I). It is also noteworthy in this connection that α-methylallyl chloride reacts very slowly with tertiary amines in benzene,[6] and that the SN2′ reaction between 3 and piperidine is accelerated only slightly in changing from benzene to acetone (Table I). One possible explanation is that the reaction of α-methylallyl chloride with trimethylamine in acetone proceeds by an SNi′–SN2 mechanism, which is not available to 3 (see above). A mechanism involving rapid rearrangement of α-methylallyl chloride to γ-methylallyl chloride has been ruled out,[9] but rapid formation of an ion pair which reacts with trimethylamine

$$CH_2{=}CH{-}CH(Me)Cl \underset{}{\overset{\text{acetone}}{\rightleftharpoons}} Me_3NCH_2CH{=}CHMe^+Cl^- \quad (70\%)$$

$$[CH_2{=}CH{=}CHMe]^+Cl^- \xrightarrow[(s_{low})]{Me_3N} CH_2{=}CHCH(Me)NMe_3^+Cl^- \quad (30\%)$$

(32) The carbonyl group can serve a similar function; see N. H. Cromwell and R. P. Rebman, "*Tetrahedron Lett.*," No. 52, 4833 (1955); N. H. Cromwell and E. Ming Wu, *ibid.*, 1499 (1966); N. H. Cromwell and E. Doomes, *ibid.*, 4037 (1966). An anion-radical mechanism has not been rigorously excluded for such systems, but it appears unlikely that the kinetic data can be accommodated by a mechanism of this type.

(33) C. A. Vernon, *J. Chem. Soc.*, 4462 (1954).

(34) F. G. Bordwell and G. D. Cooper, *J. Amer. Chem. Soc.*, **73**, 5184 (1951); F. G. Bordwell and B. B. Jarvis, *J. Org. Chem.*, **33**, 1182 (1968).

to give normal and abnormal products remains as a possibility.[26]

One unattractive feature of this mechanism is that the ion pair must give only secondary chloride on internal return.

The reason for the reversal of solvent effects on the rates of SN2′ compared with SN2 reactions of secondary amines in changing from benzene to methanol is not immediately apparent. The increase in SN2 rate in going from benzene to methanol is explained qualitatively by the Hughes–Ingold solvation rule, the more polar solvent providing greater stabilization of the highly polar transition state.[35] A similar factor should operate in SN2′ reactions. Factors which might lead to a reversal of this effect for SN2′ reactions are (1) hydrogen bonding between the nucleophile and leaving halide ion,[5,6,9] (2) greater nucleophilicity of the secondary amine for the C=C bond in benzene than methanol due to lesser solvation of the donor electron pair, and (3) electrostatic attraction between the nucleophile and the substrate.

Intramolecular hydrogen bonding between the nucleophile and leaving halide ion would be expected to be stronger in benzene than in methanol because of the strong intermolecular hydrogen bonding in methanol.

The greatly enhanced reactivity of anionic nucleophiles in solvents which are poor at solvating anions (dipolar aprotic) suggests that the lesser solvation of secondary amines in benzene than in methanol may be important in enhancing their nucleophilicities in benzene.[22] This cannot be the controlling factor, however, unless the resulting change in nucleophilicity is manifested to a much greater extent in an attack on a C=C bond than in attack on an sp^3 carbon atom (in SN2 reactions this effect is apparently completely overshadowed by other factors—see Table II).

Electrostatic attraction between the nucleophile and the substrate might be invoked to explain the unusual reactivity of **1**–**3** and **6** and **7** in SN2′ reactions if it is assumed that this unusual reactivity can be compared with the higher reactivity of *o*-nitroaryl halides toward secondary amines, compared with their *para* isomers, in nucleophilic aromatic substitution reactions. The higher reactivity of the *ortho* isomers toward amines may be explained in terms of electrostatic attraction between the amine and the nitro group in the transition state; this attraction is probably enhanced by hydrogen bonding.[36,37] The sulfone grouping in **6** and **7** could conceivably play an electrostatic role akin to that of the nitro group in *o*-nitroaryl halides. A similar effect could be imagined in **1**–**3**, although here the sulfone group would be α rather than β to the carbon atom being attacked. That this is not the dominant factor is indicated, however, by the ability of **4** and **5** to undergo SN2′ reactions. In these systems attack of piperidine cannot be aided by the sulfone grouping since the latter is in a γ position. It is interesting to note in this respect that **4** actually appears to be more reactive in SN2′ reactions than **1**–**3**.[2]

A reversal of solvent effects is observed for *o*- when compared with *p*-nitrochlorobenzenes, whereas the rate for the *para* isomer with piperidine is retarded by 12.5-fold in changing from ethanol to benzene; that for the *ortho* isomer is accelerated by 1.3-fold.[38] Again these effects are similar to those observed for SN2 *vs.* SN2′ reactions, although the reversal is more dramatic for the latter. Bunnett and Morath have suggested that electrostatic attraction between the nitro group and piperidine, which probably involves hydrogen bonding,[37] may act as "built-in solvation" allowing the reaction to proceed more rapidly in benzene than in ethanol. This factor conceivably could be important also in accounting for the reversal of solvent effects for SN2′ *vs.* SN2 reactions, but, for reasons given above, we prefer to visualize the hydrogen bonding as occurring between piperidine and the leaving halide ion rather than between piperidine and the sulfone group.[39]

Whatever the basis for this solvation effect it often seems to provide the decisive factor in allowing SN2′ reactions to compete successfully with SN2 reactions. Thus the unusual effectiveness of secondary amines in producing SN2′ reactions in allylic halides in benzene (or other aprotic solvents) appears often to arise as a result of (a) a decrease in the rate of the competing SN2 reaction (relative to other nucleophiles and other solvents) and (b) an increase in the rate of the SN2′ reaction (relative to other nucleophiles and other solvents).

It is possible to represent the SN2′ reactions of **1**–**7** with piperidine as proceeding through either a dipolar transition state (see above) or a dipolar intermediate. In methanol the formation of a dipolar intermediate by reaction of piperidine with **4** accounts better for the absence of a leaving-group effect.[3] If a dipolar intermediate is formed from **2** and piperidine in benzene it must be formed reversibly to account for the leaving group effect, *i.e.*, $k_{Br}:k_{Cl} = 16:1$ (E_a for bromide **2** is 2 kcal/mol less than that of chloride **2**; see Table I). This small leaving group effect can also be accommodated by assuming the formation of a dipolar ion transition state in which C–X bond breaking has not progressed very far.

The argument can be made that systems containing electron-withdrawing groups are not representative of SN2′ processes because they permit the formation of dipolar ion or carbanion intermediates or transition states. Our view is that systems of this type represent an important mechanistic class of SN2′ reactions. The other major mechanistic class appears to relate to reactions involving allylic halides with primary or secondary amines in benzene or like solvents.[6–8,16] Here either dipolar transition states or ion-pair intermediates may in involved. (Relatively few unambiguous examples of SN2′ reactions initiated by anionic nucleophiles appear to have been recorded.[5,16]) There is little evidence to indicate that bond making and bond breaking in SN2′ reactions is synchronous, although the limited evidence available with respect to the stereochemistry of the reaction is most readily interpreted in this way.[16] Finally, it seems clear that additional mechanistic studies are desirable, that some of the earlier SN2′ mechanistic classifications need to be reexamined, and that the SN2′

(35) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, pp 345–349.

(36) M. F. Hawthorne [*J. Amer. Chem. Soc.*, **76**, 6358 (1954)] found no deuterium isotope effect for the displacement of the chlorine atom from *o*-nitrochlorobenzene using piperidine and N-deuteriopiperidine. Nevertheless, a strong case for hydrogen bonding has been made on the basis of the failure of *ortho* acceleration to materialize when a tertiary amine is used.[37] The *ortho* isomers are less reactive toward alkoxides than are the *para* isomers.

(37) S. D. Ross and M. Finkelstein, *ibid.*, **85**, 2603 (1963).

(38) J. F. Bunnett and R. J. Morath, *ibid.*, **77**, 5051 (1955).

(39) Note that built-in solvation is not essential to the success of the SN2′ reaction in our systems since **2** (bromide), **3**, and **4** give SN2′ reactions in methanol as well as in benzene.

mechanistic classification needs to be assigned with increased caution in the future.

Experimental Section[40]

Kinetic Data.—The preparation of halides **1**, **2**, and **3** has been described previously.[1-3] The rates reported in Tables I and II were determined titrimetrically by the method described earlier.[2]

Attempted Methanolysis of 3-(α-Chloro-α-methylethyl)benzo[*b*]thiophene 1,1-Dioxide (3).—A solution of 12.24 mg of **3** in 100 ml of absolute methanol was thermostated at 50° for 21 days and then kept at room temperature (*ca.* 25°) for 35 days. Samples were withdrawn periodically, treated with 10 ml of 0.25 *M* nitric acid, and titrated using a Sargent automatic constant-rate buret (Model C) with 1.5×10^{-3} *M* silver nitrate as the titrant. End points were determined graphically from the inflection points of the titration curves and compared with end points found for standard methanolic solutions, using the same pipet. None of the samples taken, including three taken after 56 days, gave measurable amounts of chloride ion. Check runs with known standards showed that as little as 2% chloride ion could have been detected readily. Assuming that the conditions were equivalent to about 30 days at 50° and that 2% of **3** has solvolyzed

$$k = \frac{-2.3 \log (0.98)}{2.7 \times 10^6 \text{ sec}} = 7 \times 10^{-9} \text{ sec}^{-1}$$

Thus, the solvolysis rate is less than 1×10^{-8} sec^{-1} at 50°.

Attempted Reactions of 3 with Nucleophiles. A. With Triethylamine.—A solution of 300 mg of **3**, 10 ml of benzene, and 623 mg (0.6 *M*) of triethylamine was refluxed 4 hr. No solid formed. The solution was evaporated under an air jet, leaving 309 mg of white solid, mp 143.5–145.5°; the mixture melting point with authentic **3** was undepressed. The sample was dissolved in 20 ml of boiling triethylamine. After 15 min the solution was cooled in an ice bath and filtered. There was thus obtained 216 mg (72%) of long white needles, mp 140–142°; the mixture melting point with authentic **3** was undepressed.

B. With N-Methylpiperidine in Benzene.—A solution of 6.14 mg of **3** in 50 ml of 0.30 *M* N-methylpiperidine in benzene was thermostated at 50° for 23 days and then kept at room temperature for 35 days. Titration as described above showed that less than 2% of **3** had reacted; therefore

$$k_2 < \frac{-2.3 \log (0.98)}{0.30\ M \times 2 \times 10^{-6} \text{ sec}} \text{ or } 2 \times 10^{-7}\ M^{-1} \text{ sec}^{-1} \text{ at } 50°$$

C. With Lithium Bromide in Acetone.—A solution of 121 mg of **3** and 86.9 mg of anhydrous lithium bromide (1 mmol) in 12.5 ml of anhydrous acetone was kept at room temperature (*ca.* 25°) for 31 days. The solvent was distilled at reduced pressure and the residue was extracted with deuteriochloroform: nmr, δ 7.0–8.3 (aromatic, 4 H), 6.55 (singlet, 1 H), and 1.98 (singlet, 1 H) attributed to **3** and 2.7, 2.2, and 1.3. These latter peaks, due to impurities, were reduced in intensity when the solvent was evaporated and a new spectrum was taken. The solvent was evaporated and the sample was digested in 15 ml of water at room temperature for 2 days.

Anal. Calcd for $C_{11}H_{11}O_2ClS$: C, 54.43; H, 4.57. Calcd for $C_{11}H_{11}O_2BrS$: C, 46.00; H 3.86. Found: C, 54.33; H, 4.71.

D. With Thiourea.—A solution of 243 mg of **3**, 254 mg (3.33 mmol) of thiourea, and 7 ml of absolute methanol was refluxed 3 hr. Cooling and filtering gave 72.5 mg of thiourea, mp 165–177° dec. A second fraction amounted to 192 mg (79%), mp 134–142°; the mixture melting point with authentic **3** was 135.5–144°. A similar result was obtained in acetonitrile.

Reaction of 3-(α-Bromoethyl)benzo[*b*]thiophene 1,1-Dioxides (2b) with Thiophenoxide Ion in Absolute Methanol.—A mixture of 100 mg (0.366 mmol) of 3-(α-bromoethyl)benzo[*b*]thiophene 1,1-dioxide, 1.5 ml (205 mg, 1.83 mmol) of absolute methanol, and 0.85 ml of 0.21 *M* sodium methoxide solution (1.8 mmol) was dissolved and heated at reflux for 9 hr. The solution was evaporated with a stream of nitrogen and extracted with three 10-ml portions of benzene. The mixture was filtered and the filtrate was evaporated, leaving 125 mg of a yellow oil: nmr ($CDCl_3$), δ 7.5–8.25 (aromatic), 4.58 (quartet, 1.4), 4.35 (broad singlet), 2.34 (triplet, 1.4), and 2.09 (broad singlet). Because of the absence of absorptions in the δ 5–7.5 region (vinyl region), it was possible to rule out structures corresponding to the abnormal displacement product, its S_Ni' rearrangement product, starting material, and the normal displacement product. Because of the absence of absorption in the region δ 0.5–2, it was possible to rule out 2-phenylthio-3-ethylbenzo[*b*]thiophene 1,1-dioxide as the structure. The chemical-shift data and coupling constants were consistent with a mixture of geometric isomers of 3-(phenylthio)ethylene-2,3-dihydrobenzo[*b*]thiophene 1,1-dioxide. Integration of the spectrum showed the ratio of methyl absorptions (2.34, 2.09) to methylene absorptions (4.58, 4.35) to aromatic was 3.0:2.2:14. Thus about 20% by weight was benzenethiol. The remainder (*ca.* 110 mg, 99%) was attributed to displacement products. Trituration with methanol failed to give a solid.

Anal. Calcd for $C_{16}H_{14}O_2S_2$: C, 63.55; H, 4.67. Found: C, 63.80; H, 4.63.

Registry No.—**9**, 16958-52-4; **10**, 16958-53-5.

Acknowledgment.—This investigation was supported by Public Health Service Research Grant No. CA-07351 from the National Cancer Institute.

(40) Microanalyses were by Micro-Tech Laboratories, Inc., Skokie, Ill.

Direct Observation of Reaction Intermediates in Debromodecarboxylation Reactions

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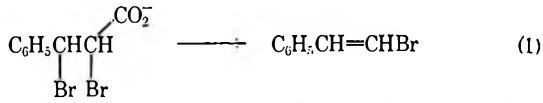
Solvolysis of citraconic acid hydrobromide leads to the formation of a well-defined intermediate which has the properties of a β-lactone. The eventual product is methacrylic acid. The solvolysis of citraconic acid dibromide is very complex, but again involves a β-lactone, and leads to a variety of products including acetone. The lactone resulting from addition of bromine to citraconic acid had a similar spectrum and similar properties as the solvolysis intermediate. A time study of the solvolysis is given which is characteristic of a series of consecutive reactions. Solvolysis of mesaconic acid dibromide exhibits no discernible intermediate. Solvolysis of itaconic acid derivatives lead to five-membered lactones.

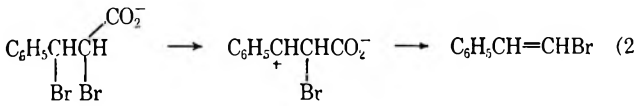
Several reaction pathways are open to β-bromocarboxylate anions. The reaction may involve a simple substitution of a solvent fragment for the leaving group. In other systems a dehydrohalogenation is observed. The most striking possibility is debromodecarboxylation, a reaction first observed in the 1870's. This reaction is of considerable utility in preparing pure *cis*- or *trans*-alkenes. Bachman and Farrell[1] have discussed the structural factors in the substrate that favor debromodecarboxylation over the other reaction pathways.

Two main pathways have been postulated for the debromodecarboxylation of 2,3-dibromo-3-phenylpropionate anions.[2-5] One pathway, a stereospecific "E2-like" process yields olefin by a concerted elimination of carbon dioxide and bromine (eq 1).

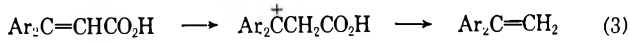


(1)

The second pathway is a stereoselective, stepwise "E1-like" process[2-5] (eq 2), which bears some similarity to the acid-catalyzed decarboxylation of substituted cinnamic acids[6] (eq 3).

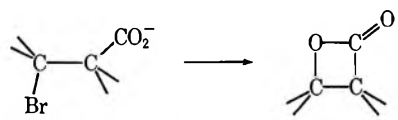


(2)

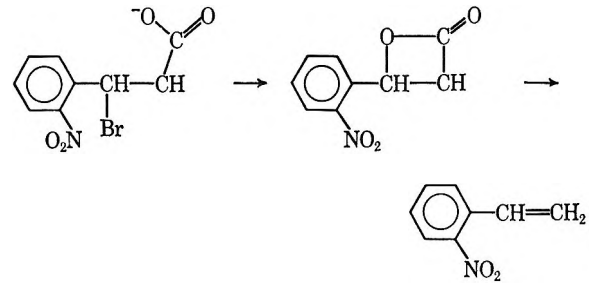


(3)

A second possibility for the reaction of β-bromocarboxylates is solvolysis with neighboring-group participation to form a β-lactone (eq 4).[7]



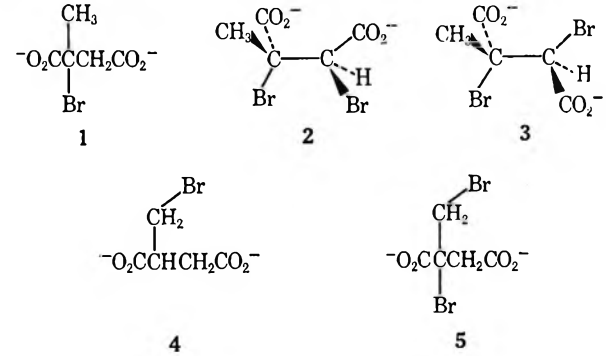
Older workers in fact considered such a ring closure to precede decarboxylation.[8] This idea was supported by the isolation of an intermediate[9-11] from the reaction of β-bromocarboxylate systems (eq 5). This intermediate or side product did not contain bromine and readily decarboxylated to yield olefins. Later Staudinger[12] showed authentic β-lactones were capable of decarboxylation. More recently Noyce and Banitt showed the decarboxylation of β-lactones was stereospecific.[13]



(5)

In other cases, epoxide products resulting from reaction of certain β-bromocarboxylate systems were interpreted in terms of a β-lactone intermediate.[3]

In considering a given system it is still not clear if mechanisms as in eq 1 and 2 apply or if ring closure occurs to give a lactone intermediate which subsequently decarboxylates.[14,15] It seems likely that a β-lactone would decompose by a zwitterionic route,[13,15] and the stereochemistry of this process is a question of great interest.[13]



1 2 3 4 5

The present study involves five substrates, citraconic acid hydrobromide (1), citraconic acid dibromide (2),

(1) (a) G. B. Bachman, *J. Amer. Chem. Soc.*, **55**, 4779 (1933); (b) J. Farrell and G. B. Bachman, *ibid.*, **57**, 1281 (1935).

(2) (a) E. Grovenstein and D. Lee, *ibid.*, **75**, 2639 (1953); (b) **77**, 3795 (1955).

(3) (a) S. Cristol and W. Norris, *ibid.*, **75**, 632 (1953); (b) **75**, 2645 (1953).

(4) E. Trumbull, T. Finn, K. Ibne-Rasa, and C. Sauers, *J. Org. Chem.*, **27**, 2339 (1962).

(5) J. F. Bunnett, *Angew. Chem. Intern. Ed. Engl.*, **1**, 225 (1962).

(6) (a) W. S. Johnson and W. Heinz, *J. Amer. Chem. Soc.*, **71**, 2913 (1949); (b) D. S. Noyce, S. Brauman, and F. Kirby, *ibid.*, **87**, 4335 (1965).

(7) (a) J. F. Lane and H. Heine, *ibid.*, **73**, 1348 (1951); (b) E. P. Kohler, and R. Kimball, *ibid.*, **56**, 729 (1934).

(8) R. Fittig and F. Binder, *Ann. Chem.*, **195**, 131 (1897).

(9) A. Einhorn, *Chem. Ber.*, **16**, 2208 (1883).

(10) A. Basler, *ibid.*, **16**, 3001 (1883).

(11) H. Erlenmeyer, *ibid.*, **13**, 303 (1880).

(12) H. Staudinger, *ibid.*, **41**, 1355 (1908).

(13) D. S. Noyce and E. H. Banitt, *J. Org. Chem.*, **31**, 4043 (1966).

(14) H. E. Zaugg, *Org. Reactions*, **8**, 305 (1954).

(15) (a) H. T. Liang and P. D. Bartlett, *J. Amer. Chem. Soc.*, **80**, 3585 (1958); (b) T. L. Gresham, *ibid.*, **76**, 486 (1954), and many related papers.

mesaconic acid dibromide (**3**), itaconic acid hydrobromide (**4**), and itaconic acid dibromide (**5**). The rates of solvolysis of these substrates in their dianion form was studied. In other experiments the course of the solvolysis was monitored by nmr in an effort to observe reaction intermediates.[16,17]

Results and Discussion

Rates of Halide Ion Formation.—The rates of halide ion formation are given in Table I for substrates **1–5** (dianions).[18] Certain activation parameters are also listed. The extreme rapidity of solvolysis of **1** and **4** prevented studies at higher temperatures than 30.1°. The rate solutions were made up to 0.10 ± 0.01 *M* in sodium acetate in an effort to ensure the substrate salts remained predominately in the dianion form. Reactions of these substrates as the monoanion and free acids were approximately 10 and 100 times slower, respectively (**3**, however, was less sensitive to its anionic state).

The relative rates were in the order **4** > **1** > **5** > **2** > **3**. The most reactive material itaconic acid hydrobromide (**4**) was *ca.* 1800 times more reactive than mesaconic dibromide, **3**. In general the monobromides **4** and **1** were substantially more reactive than the dibromides.

The activation parameters are of interest in that **2**, **3**, and **5** show positive entropies. Lane and Heine[7] found positive activation entropies in reactions considered to involve neighboring group participation by carboxylate.

TABLE I

RATES OF HALIDE FORMATION BY SUBSTRATES **1–5** IN WATER

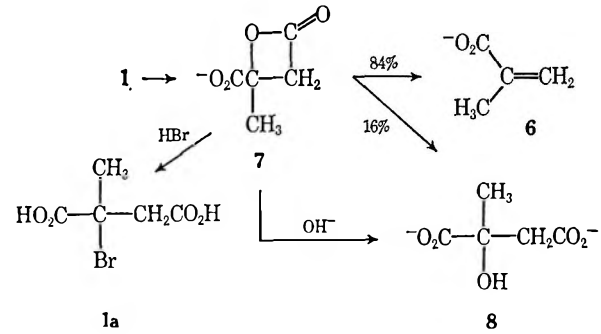
Substrate	$k_{obsd.}$,[a] sec^{-1} 30.1°	50.1°	k_{rel}	ΔH^*, kcal/mol	ΔS^*, eu
1	$1.5 \pm 0.1 \times 10^{-3}$		250		
2	$3.5 \pm 0.1 \times 10^{-4}$	$5.7 \pm 0.2 \times 10^{-3}$	59	26 ± 1	12 ± 3
3		$9.7 \pm 0.3 \times 10^{-5}$	1	28 ± 1	11 ± 3
4	$1.1 \pm 0.3 \times 10^{-2}$		1800		
5	$3.9 \pm 0.1 \times 10^{-4}$	$5.6 \pm 0.1 \times 10^{-3}$	64	26 ± 1	10 ± 4

[a] No correction was made for the number of bromines which react. For **2** the observed rate is that of loss of one bromide; for **3** and **5** the rate reflects loss of both bromides.

Reaction Products from 1.—In the reaction of citraconic acid hydrobromide (**1**), Fittig and coworkers reported the major product to be methacrylic acid (**6**), which was confirmed in this study. However observation of the course of the reaction by nmr in deuterium oxide showed that an intermediate **7** builds up to high concentration during the period of bromide ion formation. Upon heating, the resonance absorption of the intermediate disappeared, carbon dioxide was emitted in large quantities and the spectrum of methacrylic acid appeared. If the intermediate **7** were treated with excess base, the spectrum of citramalic acid (**8**) appeared, very similar to that of authentic material. When treated with large quantities of bromide ion, little change in the concentration of the intermediate **7** was observed. However when trifluoroacetic acid (plus bromide ion) was added, the spectrum of starting material reappeared.

The decarboxylation of intermediate **7** to form **6** took place smoothly when bromide had been removed with silver. These reactions are summarized in Scheme I, and the pertinent nmr data are given in the Experimental Section. These reactions are consistent with a β-lactone intermediate. The point of interest here is that the decarboxylation step involves the intermediate **7** itself.[19] It does not seem likely that **7** reverts to **1** which subsequently debromocarboxylates by a concerted mechanism.

SCHEME I



Reaction Products from 2.—The solvolysis of citraconic dibromide (**2**) is a complex reaction of which only the major sequences can be identified. Fittig and coworkers[20] reported propionaldehyde and bromomethacrylic acid (**9**) as the major products. The nmr results of this study in deuterium oxide confirm **9** as well as its isomer **10** which is formed in part from **9** as the reaction progresses. In our hands acetone (**11**) was apparent, but no propionaldehyde, *per se*, although some small rather diffuse resonance absorptions appeared late in the reaction, possibly owing to decomposition products of propionaldehyde. Similar absorptions were noted when authentic propionaldehyde was allowed to stand in the reaction mixture. Mass balance determinations showed that *ca.* 93% of the original starting material could be accounted for by well-defined products discussed below neglecting possible deuteration of the acetone. It was not possible to isolate propionaldehyde from the runs at 30.1°. However in an attempt to duplicate Fittig's reaction conditions, at *ca.* 80° and using nitrogen to sweep out volatile products, propionaldehyde was indeed obtained in small yield.

In the solvolysis of **2** the kinetic runs showed that the two substrate bromines are lost at markedly different rates. During the period of the first equivalent of bromide ion formation, the starting material resonance absorption decreases monotonically and is replaced in large part by an intermediate, **12** (methyl δ 1.82, methine δ 5.65), plus some of the unsaturated acid **9**. Figure 1 shows a time study of the concentrations of starting material, the intermediate, and the various products. Figure 2 shows a partial nmr spectrum of a typical run in which the major absorptions are identified as shown in Scheme II. The time study of Figure 1 is fairly typical of an A → B → C, D . . . set of consecutive

(16) R. S. Bly, R. K. Bly, A. Bedenbaugh, and O. Vail, *J. Amer. Chem. Soc.*, **89**, 880 (1967).

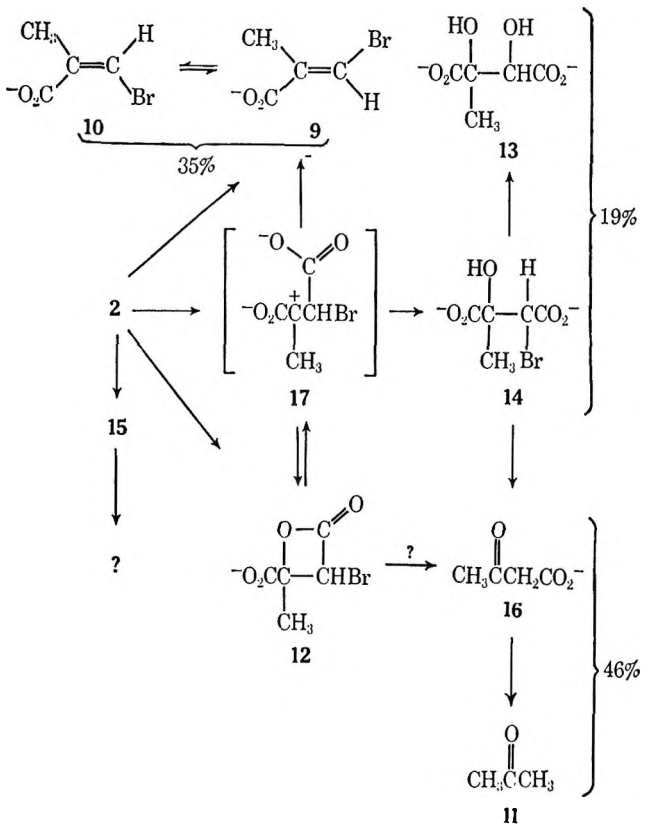
(17) In related systems the presence of an intermediate has been inferred from kinetic evidence, H. Johannson, *Chem. Ber.*, **48**, 1262 (1915), and stereochemical evidence, B. Holmberg, *Svensk Kem. Tidskr.*, **30**, 215 (1918), or by isolation.[7b]

(18) For earlier kinetic studies on **5** see B. Holmberg, *ibid.*, **30**, 190 (1918).

(19) A concerted decarboxylation of a β-lactone is considered unlikely by some workers since this would not be thermally allowed: R. Hoffman and R. B. Woodward, *J. Amer. Chem. Soc.*, **84**, 2046 (1965). A zwitterionic mechanism (ref 15) would be more probable.

(20) R. Fittig and P. Krausemark, *Ann. Chem.*, **206**, 7 (1880); R. Fittig and B. Landolt, *ibid.*, **188**, 77 (1877).

SCHEME II



reactions. A second intermediate **15** is also apparent in low concentration compared to **12**. Due to its low level, it was not possible to determine the eventual fate of **15**.

A group of two products or intermediates **13** and **14** is apparent in rather low yield (19%) at δ 1.3–1.5. The former is also the eventual product of solvolysis of the free acid of **2** and is assigned the diol structure as shown in Scheme II. The latter could be produced by NBS bromination of citraconic acid in aqueous solution or by the base-catalyzed cleavage of **12** and is assigned the bromohydrin structure. The bromohydrin **14** (methyl δ 1.32, eventually reacts to form **13** (methyl δ 1.36), and acetoacetic acid **16** in somewhat variable ratios depending upon pH. The acetoacetic acid **16** in turn slowly produces acetone. The decomposition is faster if the reaction mixture is acidified.

It is clear, however, that the precursor of some of the unsaturated acid **9** and most of the acetoacetic acid **16** is the intermediate **12**. Thus when starting material is nearly gone, **12** reaches a maximum of *ca.* 40% of total material present (at this point **9** is 16% and **16** is 25% of the total). As **12** disappears, **9** plus **10** increase to 35% and **11** plus **16** increase to *ca.* 46% of the total.

In a separate run using excess potassium carbonate (pH *ca.* 8.5), the intermediates **12** and **15** were not apparent. It seems likely that the lactone is rapidly cleaved by base or else it does not form. Under these conditions, the concentration of the diol product **13** is larger (22%) and that of **9** is less (21%) than in runs of neutral pH (**16** was the same (47%)). Thus in these basic solutions the capture of the carbonium ion by solvent, **17** → **14**, is more probable than the decarboxylation reaction **17** → **9**. However the fact that **9** still occurs in substantial yield is suggestive that **9** may be

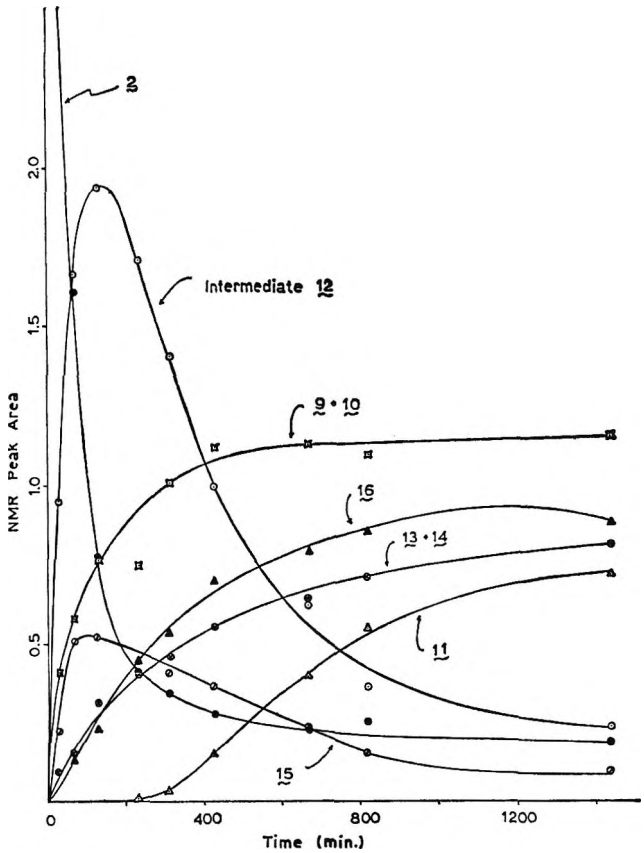


Figure 1.—Time study of the reaction of **2** in D_2O, *ca.* 25°. The nmr peak intensities were determined relative to $(CH_3)_4NBr$.

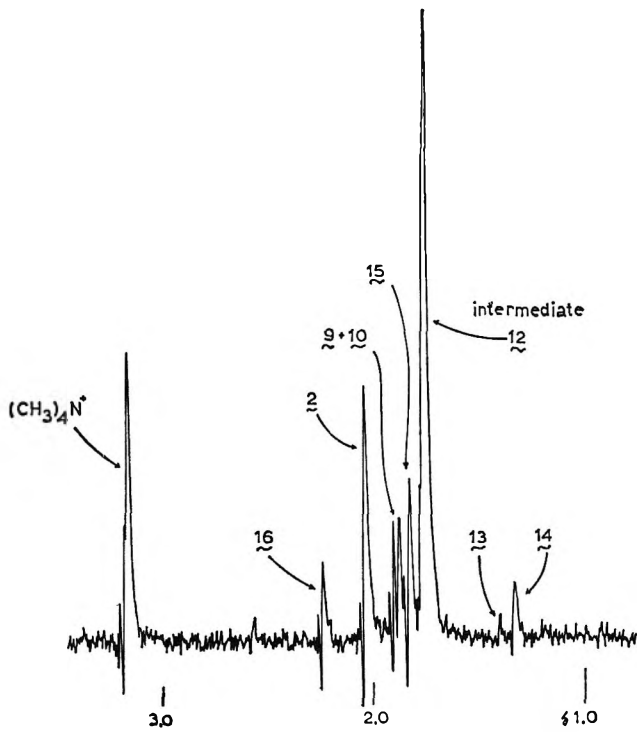


Figure 2.—Partial nmr spectrum of the solvolysis of **2**. Time is 130 min after dissolution.

formed in part from other pathways. The direct debromodecarboxylation **2** → **9** is one possibility.[3]

It was possible to produce **12** by another pathway. Addition of bromine[21] to a cold, neutral aqueous solu-

(21) D. S. Tarbell and P. D. Bartlett, *J. Amer. Chem. Soc.*, **59**, 402 (1937).

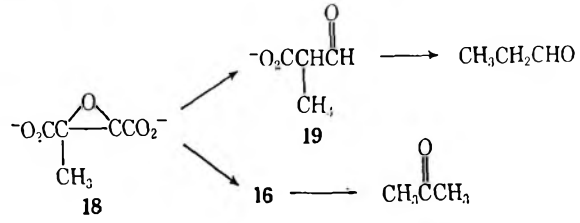
tion of citraconic acid produced a material with a nmr spectrum very similar to **12**. The subsequent reactions of this material were similar to **12**, yielding **9** (40%), **13** plus **14** (6%), and **16** (54%).

In an attempt to isolate intermediate **12**, the solution was acidified to pH 2 with HBr. An oil separated which was mainly **2**. Some **12** remained however, whose infrared spectrum showed an absorption at 1860 cm^{-1}, consistent with its formulation as a β-lactone.[13]

Reaction Products from 3.—The kinetic runs on mesaconic dibromide (**3**) showed that both equivalents of halogen appeared at essentially the same rate. Accordingly the reaction at 30.1° as monitored by nmr showed no intermediate corresponding to **12** in any sizable concentrations. Unfortunately in these runs several small, rather diffuse resonance absorptions appeared at *ca.* δ 0.8–1.3, and accurate product ratios could not be determined. Mass balance determinations were poor (*ca.* 70%) if these diffuse peaks were neglected. In the low temperature runs **9** and **10** amounted to *ca.* 30%; **16** and **11**, *ca.* 25%; and **13** and **14**, *ca.* 10% of the total.

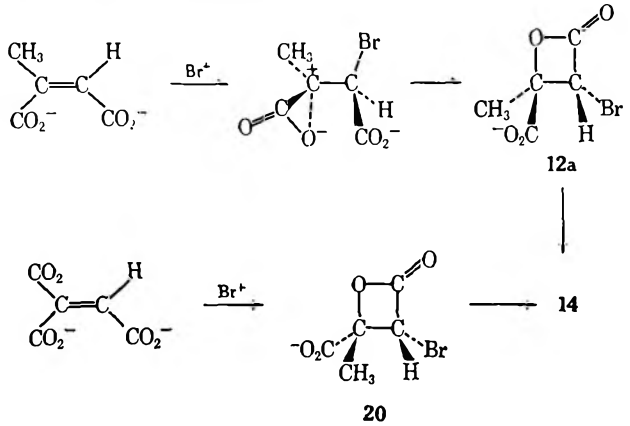
In runs of 75°, the unsaturated acids **9** and **10** amounted to *ca.* 70% of the total. Thus the increase in temperature produced a considerable change in the character of the products.

In the reaction of **3** Fittig and coworkers again reported propionaldehyde, which was verified in cases in which nitrogen was used to sweep out this product. One possible explanation for the production of propionaldehyde as well as acetone centers around a possible epoxide intermediate, **18**. One mode of cleavage of the oxirane ring would yield **19** and eventually propionaldehyde. The other mode of cleavage would produce acetone.



18 **19**

This epoxide was apparent in the low temperature reactions in a maximum yield of 7%. The same material (δ 1.51) as **18** was produced by base-catalyzed ring closure on the bromohydrin **14**.



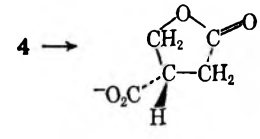
12a **20**

Although a β-lactone was not observed in the solvolysis of **3**, this material **20** (methyl δ 1.74, methine δ 5.57) could be produced by addition of bromine to mesaconic acid. The yield in this case was rather poor (26%), and a plethora of other products included **9**, **10**, **16**, **13**, and mainly **14**. The subsequent reactions of **20** again produced more of these same materials. It is interesting however that both the lactone from citraconic acid (**12**) and the lactone **20** form the same bromohydrin **14** upon hydrolysis, somewhat similar to the results of Tarbell and Bartlett.[21]

Since the lactone **12** can be made from and can be cleaved to citraconic dibromide (**2**), it is assigned the structure **12a**. A tentative structure for **20** is given.

The mode of addition of Br^+ and carboxylate to yield **12a** and **20** is rather unusual, amounting to an over-all *cis* addition. It is felt that participation by the α-carboxyate stabilizes the carbonium ion and allows internal rotation to occur. The β-carboxylate then closes the lactone ring from the same side of the molecule as the original bromine attack.

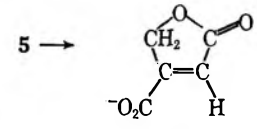
Reaction Products from 4.—The solvolysis of itaconic acid hydrobromide was a comparatively simple process. The reaction of the "monoanion" was followed instead of the dianion owing to the extreme rapidity of reaction



21

of the latter. Paraconic acid[20] (**21**) appeared to be the sole product. The nonequivalent methylenes of **4** (*ca.* δ 2.70 and 3.7) changed smoothly to the absorptions of product (*ca.* δ 2.9 and 4.6).

Reaction Products from 5.—The solvolysis of itaconic acid dibromide (**5**) also was straightforward. The only observable product was the unsaturated lactone,

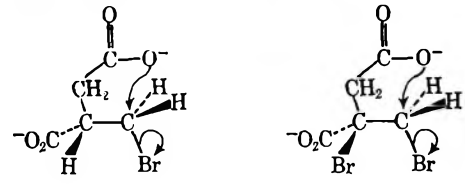


22

aconic acid (**22**) (methylene δ 5.11, vinyl δ 6.42). It was not possible to tell by nmr experiments if ring closure preceded dehydrohalogenation or if the reverse was true.

It is clear, however, that debromodecarboxylation does not compete with closure to the stable five-ring lactone.

Since both **4** and **5** have similar structures and both give five-membered lactones, it is interesting to speculate on the *ca.* 30-fold greater reactivity of the monobromide. Part of the slowness of **5** may be due to the electron-withdrawing character of the second bromine. More important are the steric interactions involved. In the transition state the leaving group is *gauche* to both a carboxylate and a bromine, a sterically unfavorable situation. The dianion of **4** has no difficulty in approaching the transition state.

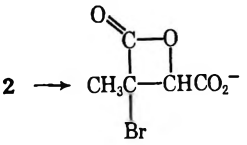


4 **5**

Other Comments.—The solvent isotope effects were measured for the five substrates; k_{H_2O}/k_{D_2O} for **1**, 1.2; **2**, 1.2; **3**, 1.3; **4**, 1.1; **5**, 1.2. These values may be compared to the values from solvolysis of *t*-butyl chloride in water (1.3–1.5) and methyl bromide (1.1–1.2).[22,23] Thus the solvent isotope effect for substrates that form well-defined lactone products is very similar to that of substrates thought to form lactone intermediates but eventually yield other products.

In conclusion the evidence seems quite strong that a β-lactone is a true intermediate in the debromodecarboxylation of **1** and **2**, but probably not of **3**.

In the reactions of **2** it is interesting to note that the lactone closes at the tertiary center to form **12** rather than at the secondary center, which would form **23** (however, **23** and **15** may be the same, but **15** is a minor product). Although a direct displacement of bromide by carboxylate is possible, the sequence most likely involves the carbonium ion **17**. The reactions of **17** appear to be highly stereoselective in that usually just one of two possible stereoisomers is formed.[13] The zwitterion **17** must be a tight internal ion pair.[13]



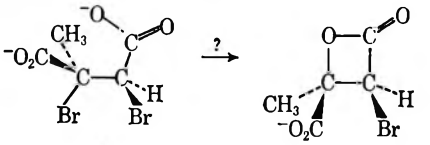
23

The *ca.* 60-fold greater reactivity of **2** over **3** deserves additional comment. In part this difference is due to the greater thermodynamic stability of **3** ground state. In the solvolysis of the free acids of **2** and **3**, which very likely go by similar mechanisms, **2** is *ca.* sevenfold more reactive. This latter ratio parallels the differences observed with many *erythro–threo* pairs of diastereomers.

In addition to the rather small difference in the solvent isotope effect, other differences between **2** and **3** are thought to reflect a fundamental difference in solvolysis mechanism. The solvent dimethyl sulfoxide (DMSO) has been shown to increase the rates of reactions that involve assistance by carboxylate.[24] Going from water to a solution of 60% DMSO–40% water involves a 15-fold rate increase for **2**, a 12-fold increase for **5** and a fivefold increase for **3**. The addition of ion-pairing cations such as calcium diminish the rate of reaction where carboxylate participation is important. Again the rates of **2** and **5** are rather strongly diminished. The relative ratios of rates of reaction in the absence and presence of 0.16 *M* calcium nitrate are 0.7 for **2** and 0.6 for **5**. On the other hand, **3** shows >0.8 rate ratio (at 70° rather than at 50° for **2** and **5**).

In toto, the *threo* substrate **2** appears rather more sensitive to the state of the carboxylate than does the *erythro* isomer **3**. It does not seem likely that **2** reacts by a direct SN2-like displacement of bromide by carboxylate. If a SN2 were in evidence **23** would very likely result rather than the tertiary product **12**. More likely the reaction is an ionization in which the separation of the bromide is materially assisted by a properly oriented β-carboxylate, although a full covalent carbon–oxygen bond is not present.

In the basic aqueous solution the solvated carboxylates are probably very large groups. The conformation needed for assistance by the β-carboxylate in **3** is destabilized by having both carboxylates *gauche* to other sizable groups.



3 **20**

Furthermore if the substrate **3** did close to the lactone **20** (for which no evidence exists in the solvolysis) the lactone **20** would be destabilized by the carboxylate–bromine interaction (compare the relative stabilities of **9** and **10**).

The substrate **3** may react by other pathways than β-carboxylate participation. A bromonium ion structure is a strong possibility.

Experimental Section

Materials were produced as follows. The starting material **2** and **3** were prepared by Vaughan and Milton's procedure,[25] the procedure of Fittig being worthless.[20] The materials **2** and **3** exhibited melting points of 151–152°, respectively. The material **1** was prepared by the procedure of Fittig and Landolt,[20] mp 143–145° (lit. mp 140°). This material had a slight impurity that was not removed under repeated recrystallization. The resonance absorptions of the impurity occurred at 1.41 and 1.28 ppm and did not change in the course of the hydrolysis.

The substrate itaconic acid dibromide (**4**) was prepared by addition of bromine to itaconic acid, mp 166–168°, and itaconic acid hydrobromide was prepared by the method of Ingold, *et al.*, mp 134–136° (lit. mp 137°).[26]

The nmr product studies were run by dissolving *ca.* 200 mg of substrate in 0.7 ml of deuterium oxide (Columbia Chemical Co.) with *ca.* 10 mg of tetramethylammonium bromide as a standard (the chemical shift was taken as 191 cps). The faster runs were run at probe temperature, *ca.* 35°. The slower runs were stored in a constant temperature bath at 30.1° between readings. Readings were taken on a Varian A-60 instrument. The tubes were usually shaken with CCl_4, the layers were separated, and the organic layer was checked for propionaldehyde (never found).

Product studies were attempted by isolation of the product acids, esterification by diazomethane or by the Fisher procedure, and analysis by vpc. In general these results were not regarded as trustworthy. Apparently some decomposition occurred in the evaporation of the water or in the esterification, particularly in the case of **1**.

The data for a typical nmr run follow. The substrate **1**, 0.150 g, was placed in a small vial and mixed with 0.161 g of lithium bromide, 0.014 g of tetramethylammonium bromide, 0.1045 g of potassium carbonate, and *ca.* 1.0 ml of deuterium oxide. The tetramethylammonium bromide was used as an internal standard, whose integral was compared to the substrate and product integrals. The pH was adjusted to *ca.* 7, and the solution scanned. The starting material absorption (methyl at 2.07 ppm and methylene at 3.19 ppm) changed smoothly to that of the intermediate (1.92 and 3.72 ppm, respectively, ratio 2:1). The change was essentially complete in 90 min. Similar to the run without LiBr only a small amount of olefin was evident at the end of this period. The solution was divided; part was heated on a steam bath for *ca.* 30 min. The spectrum of methacrylic acid (**6**) appeared, very similar to the literature spectrum.[27] The final solution showed 84% **6** and 16% **8**. The remainder of the solution was treated with trifluoroacetic acid to give a solution pH 1. The spectrum of starting material free acid reappeared (methyl, 2.02; nonequivalent methylene, *ca.* 3.34 ppm).

In another experiment, the preformed intermediate was treated

(22) P. Laughton and K. Robertson, *Can. J. Chem.*, **34**, 1214 (1956).
(23) C. G. Swain, R. Cardinaud, and A. Ketley, *J. Amer. Chem. Soc.*, **77**, 934 (1955).
(24) C. A. Kingsbury, *ibid.*, **87**, 5409 (1965).
(25) W. R. Vaughan and K. Milton, *ibid.*, **74**, 5673 (1952).
(26) C. K. Ingold, C. Shoppee, and J. Thorpe, *J. Chem. Soc.*, 1488 (1926).
(27) N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "NMR Spectra Catalog," Varian Associates, Palo Alto, Calif., 1962, No. 62.

with base. The spectrum of citramalic acid (**8**) appeared which also was evident in the previous run in small amounts (methyl, 1.48; nonequivalent methylene, 2.41, 2.77 ppm). This spectrum was very similar to that of authentic material (Aldrich).

Product Identification Runs.—Citraconic acid (0.302 g) plus potassium carbonate (320 mg) was heated briefly in deuterium oxide (1.0 ml) plus 10 mg of tetramethylammonium bromide. Bromine was added in small amounts with intermittent cooling. An aliquot was taken and checked by nmr which showed the absorptions of **12**, δ 1.74, 5.71 (53%); unreacted starting material, (21%); **9** and **10** δ *ca.* 1.92 (16%), **13** and **14**, δ 1.38 and 1.31, respectively (10%). The spectrum was rerun at intervals, eventually forming **9** and **10** (38%), **13** and **14** (12%), and **16** (28%).

In another run on large scale the intermediate **12** was carefully treated with HCl in the cold, to pH 2. An oil slowly separated (*ca.* 3.5 g from 10 g of starting material). The infrared spectrum showed a strong absorption at 1860 cm^{-1} plus the carboxylic absorption at 1720 (broad). The nmr of this material showed the material to be 25% of the lactone **12**, 30% **9**, and 45% of a material very similar to **2**. If HBr were used for acidification, the latter gave a spectrum identical with authentic **2**.

In another run, the lactone **12** was formed similarly, then treated with excess potassium carbonate. The spectrum of **12** diminished rapidly and was replaced by the bromohydrin **14** and acetocetic acid (**16**), δ 2.25 (three protons) and 3.47 (two protons). The final solution showed 30% **14**, 13% **13**, and 26% **10**. This solution was basified with potassium hydroxide to pH 13. The bromohydrin changed in large part to **16**, but a new peak appeared δ 1.58, believed to be the epoxide **18**.

The bromohydrin **14** was also produced by treatment of citraconic acid (10.0 g) with N-bromosuccinimide (14.4 g) stirred in 20 ml of H_2O overnight with 0.1 ml of sulfuric acid. The aqueous solution was mixed with 20 g of ammonium chloride and repeatedly extracted with ether. The organic layers were dried over $MgSO_4$, evaporated, and checked by nmr. The product, 5.0 g, was *ca.* 70% **9** and 30% **14**.

Mesaconic acid (320 mg) was treated with potassium carbonate in deuterium oxide until the pH was *ca.* 6.5. Bromine was added dropwise with intermittent cooling. The nmr showed the following absorptions, in addition to **20** (20%), **14** (17%), **13** (8%), unidentified peak δ 1.66 (4%), unreacted mesaconic (11%), unidentified peak δ 2.08 (4%), and **16** (12%) were produced.

Upon acidification with hydrobromic acid **20** rather slowly formed **14**, then **13**. No more than a small quantity of **3** was formed, by comparison of spectra before and after addition of authentic **3**.

In another run **20** was formed as before, then treated with potassium carbonate; **14**, **13**, and **16** were again the major products similar to the experiments with **12**.

To check that **12** and **20** produced the same bromohydrin **14**, 1.0 g of citraconic acid and 1.4 g of mesaconic acid were treated with Br_2 in a neutral, aqueous solution, forming **12** and **20**; upon treatment with K_2CO_3 only a single absorption due to **14** and a single absorption due to **13** was apparent in addition to **16**.

To test for propionaldehyde, **2** or **3** (10.0 g) was added to 50 ml of water plus an equimolar amount of potassium carbonate at *ca.* 80° (steam bath). Two traps were used, one filled with ice, the other with Dry Ice–acetone. Nitrogen was passed through the reaction mixture for *ca.* 30 min. The ice trap contents were analyzed by nmr and vpc and showed water and traces of organic material. The Dry Ice trap contents showed about 1 ml of a liquid, mainly water in the case of **2** with about 20% of an equal mixture of acetone and propionaldehyde. In the case of **3** the trapped material (*ca.* 1 ml) showed equal quantities of water and organic material of which there was 60% propionaldehyde and 40% acetone.

The rate solutions were prepared in volumetric flasks to which *ca.* 20 ml of redistilled water, 200 mg of substrate, and the requisite amount of sodium acetate had been added. This mixture was allowed to come to temperature. The rate was begun by addition of a twofold molar equiv of standard sodium hydroxide, which also had been equilibrated. The evolution of bromide was followed by adding 5-ml aliquots to cooled, pretitrated solutions of standard silver nitrate and sodium thiosulfate. The titration was rapidly completed after addition. Rate constants and activation parameters were calculated by standard procedures.[28]

Registry No.—**7**, 16520-64-2; **9**, 16503-84-7; **10**, 16503-85-8; **11**, 67-64-1; **12**, 16503-86-9; **13**, 16503-87-0; **14**, 16520-63-1; **16**, 141-81-1; **18**, 16503-89-2; **20**, 16503-86-9; **21**, 16503-91-6; **22**, 16503-83-6.

Acknowledgment.—This work was begun at Iowa State University and was supported in part by National Science Foundation Grant GP6765. Permission by ISU to use equipment purchased with this grant is gratefully acknowledged.

(28) B. Stevens, "Chemical Kinetics," Chapman and Hall, London, 1961, pp 17, 37.

Conformational Preferences in Diastereomers. IV. 1,2,3 Diastereomers

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The four diastereomers of the 1,2-dibromo-1,3-diphenylbutane system and two of the three diastereomers in the 1,2,3-tribromo-1,3-diphenylpropane system are assigned relative configurations on the basis of nmr studies in deuteriochloroform, dipole moment, and stereospecific reaction data. Iodide-catalyzed debrominations proved to be nonstereospecific. The *erythro* dibromide centers in the former system are nearly conformationally pure, whereas the *threo* centers here conformationally mixed. In the latter system the reverse is true. The results are discussed in terms of possible unfavorability of *gauche* bromine interactions. The importance of 1,3 eclipsing interactions is emphasized. The mechanistic implication of the bromination product yields from the isomeric 1,3-diphenylbutenes is discussed in terms of possible bromonium ions.

The use of nuclear magnetic resonance spectra to aid in the assignment of configurations of acyclic molecules has found increasing application in recent years.[1-8] Most frequently use is made of the Karplus relationship[9,10] which suggests that predominantly *trans* vicinal protons will exhibit large coupling constants (J) in the vicinity of 11–13 cps, whereas predominantly *gauche* protons show low J values of *ca.* 1–3 cps.

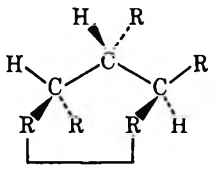
(1) J. Canceill, J. Basselier, and J. Jacques, *Bull. Soc. Chim. Fr.*, 1906 (1963).
(2) M. Barbieux and R. Martin, *Tetrahedron Lett.*, 2919 (1965).
(3) M. Stiles, R. Winkler, Y. Chang, and L. Traynor, *J. Amer. Chem. Soc.*, **86**, 3337 (1964).
(4) R. C. Fahey, *ibid.*, **88**, 4611 (1966).
(5) M. Dewar and R. Fahey, *ibid.*, **85**, 3645 (1963).
(6) G. J. Karabatsos and N. Hsi, *ibid.*, **87**, 2864 (1965).
(7) A. Bothner-By and D. Jung, *ibid.*, **86**, 4025 (1964).
(8) S. Brownstein, *Can. J. Chem.*, **39**, 1677 (1961).
(9) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); *J. Amer. Chem. Soc.*, **85**, 2870 (1963).
(10) H. Gutowsky, *J. Chem. Phys.*, **38**, 3353 (1962).

In studies of simple diastereomers,[11] the *erythro* isomer frequently has a larger coupling constant than the *threo* isomer (the definition of "*erythro*" being based on the size of the groups). The *erythro* isomer thus has a larger population of a rotomer with *trans* protons. This generalization is not to be expected when strong intramolecular hydrogen bonding is possible,[1,12,13] and possibly not when extreme steric hindrance is present,[4,11,14,15] such as in compounds with *t*-butyl substituents.

Earlier work[15-19] has emphasized the importance of 1,3 interactions between sizable groups, as well as 1,2 (*i.e.*, *gauche*) interactions as factors which determine conformational preferences in diastereomers.

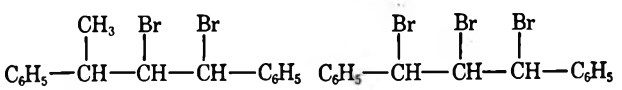
It appeared desirable to move to the more complex system of diastereomers which involve three asymmetric centers. The simpler systems suffer from the difficulty that the two rotomers with *gauche* protons are not distinguishable since both have similar, low J values.

In the system of 1,2,3 diastereomers, one *gauche* H–H rotomer is prohibited by 1,3 repulsions. Thus if the nmr spectrum exhibits a low coupling constant for a given set of protons, the rotomer can be specifically identified.



improbable *gauche* rotomer

The major system of interest in this study is 1,2-dibromo-1,3-diphenylbutane, **1**, studied earlier by Stoermer and Kootz.[20] The system 1,2,3-tribromo-1,3-diphenylpropane, **2**, will be briefly considered.



1 **2**

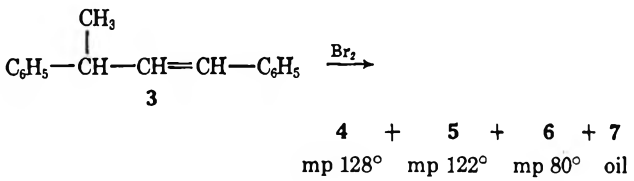
The system **1** has three asymmetric centers and a total of four possible diasteromers. The system **2** has two *meso* and a single DL diastereomer.

It is the object of this study (i) to attempt to elucidate the configuration at the three asymmetric centers of **1**, (ii) to attempt to arrive at some meaningful conclusion about the conformational preferences in these complex systems, and (iii) to elucidate the modes of attack of bromine upon the parent olefin yielding the diastereomers of formula **1**.

(11) (a) C. A. Kingsbury and W. Thornton, *J. Org. Chem.*, **31**, 1000 (1965); (b) C. A. Kingsbury and W. Oliver, unpublished results.
(12) J. B. Hyne, *Can. J. Chem.*, **38**, 125 (1966).
(13) J. Huffman and R. P. Elliott, *J. Org. Chem.*, **30**, 365 (1965).
(14) See, however, G. Whitesides, J. P. Sevenair, and R. Goetz, *J. Amer. Chem. Soc.*, **89**, 1135 (1967).
(15) C. Kingsbury and D. Best, *J. Org. Chem.*, **32**, 6 (1967).
(16) C. G. Overberger and T. Kurtz, *ibid.*, **31**, 388 (1966).
(17) Y. Fujimara and S. Fujiwara, *Bull. Chem. Soc. Jap.*, **37**, 1005 (1964).
(18) D. Doskocilova and B. Schneider, *Collect. Czech. Chem. Commun.*, **29**, 2290 (1964).
(19) T. Shimanouchi and T. Tasumi, *Spectrochim. Acta*, **17**, 755 (1961).
(20) R. Stoermer and B. Kootz, *Chem. Ber.*, **58**, 2613 (1928).

Results and Discussion

Analysis of Configuration.—Addition of bromine to either *cis*- or *trans*-1,3-diphenyl-1-butene, **3**, yielded four diastereomers. Three of these were obtained crystalline in agreement with Stoermer and Kootz,[20] and will be identified by melting point for the present. The fourth diastereomer was an oil, somewhat impure by a mixture with **4** and **5**, which defied all attempted means of purification. The resonance absorptions of the oil, **7**, fortunately were fairly well separated from its impurities, **4** and **5**, and the coupling constants and

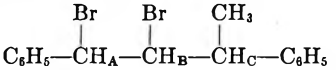


3

4 + **5** + **6** + **7**
mp 128° mp 122° mp 80° oil

chemical shifts could be accurately determined. These data for **7** as well as similar data for **4**, **5** and **6** are listed in Table I.

TABLE I
NMR COUPLING CONSTANTS, CHEMICAL SHIFTS AND DIPOLE MOMENTS FOR DIASTEREOMERS **4–7**

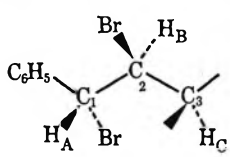


Diastereomer	Assignment[a]	Mp, °C	J_{AB}	J_{BC}	—Chemical shifts[b]— H_A	H_B	H_C	Dipole moment[c]
4	EE	128	11.6	3.0	4.64	4.78	4.00	1.30
5	ET	122	11.1	2.8	5.15	4.71	3.90	1.20
6	TE	78	4.2	8.2	4.90	4.30	3.15	2.55
7	TT	Oil	6.2	6.2	5.15	4.50	3.20	...

[a] Justification for this assignment of configuration is given in the Discussion. [b] Approximately 10–15% solutions in $CDCl_3$ using tetramethylsilane as an internal standard taken as 0 ppm. Spectra taken on a Varian A-60 instrument. [c] These data are considered good ±0.20; these data have duplicated the spectrum, by computer simulation.

It is apparent from the coupling constant data that **4** and **5** are characterized by strong conformational preferences involving predominately *trans* A and B protons and *gauche* B and C protons.

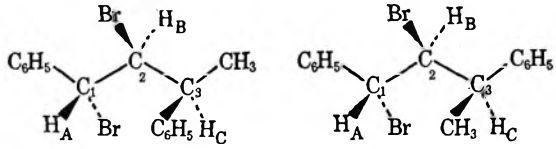
The dipole moment data are not as definitive as other data;[21] however, a tentative conclusion may be made. The major contributor to the resultant moment is the bromine (group moment 1.7 D) although the phenyl group is also a fairly strong contributor (group moment 0.8–1.2 D). The resultant moment for **6**, 2.55 D, is fairly close to other examples thought to contain *gauche* bromines.[15,22] The somewhat lower values **4** and **5** are taken as probably indicative of *trans* bromines with the major contributor to the resultant being the phenyl groups. The similarity of the dipole moments for **4** and **5** probably indicates similar orientation of the halogens. A tentative assignment of the configuration for **4** and **5** at carbons 1 and 2 may



(21) L. O. Smith and S. J. Cristol, "Organic Chemistry," Reinhold Publishing Corp., New York, N. Y., 1966, pp 679, 681.
(22) A. L. McClellan, "Tables of Experimental Dipole Moments," W. H. Freeman and Co., San Francisco, Calif., 1963, p 206.

now be made. *trans* bromines and *trans* protons A and B define the *erythro* configuration at C-1,2. Compounds **4** and **5** then differ at C-3. If **4** and **5** are *erythro* at C-1,2, then **6** and **7** are *threo*.

Consideration of the chemical shift data for H_A permits a decision concerning configuration at C-2 and C-3. In one diastereomer, models show H_A is opposite the face of a phenyl group at C-3. In the other diastereomer it is opposed to a methyl group. The former diastereomer should exhibit H_A far upfield from the latter diastereomer. The data in Table I show **4** has the upfield proton H_A. Complete configurations are assigned as shown. Configurations of **4** then are



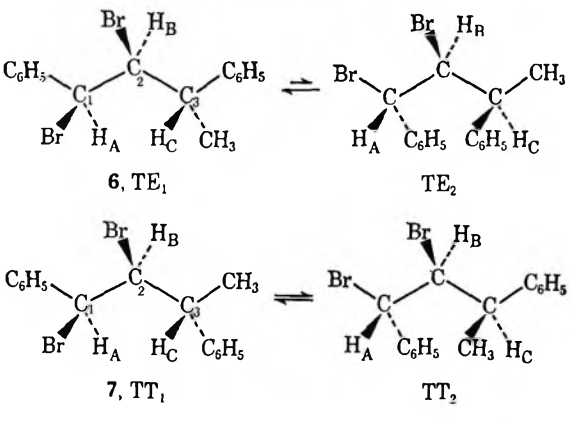
4, EE_1 **5**, ET_1

erythro at C-1,2 and *erythro* at C-2,3, hereafter called EE. Configuration of **5** is ET.

Compounds **4** and **5** provide one more example of the alternation of coupling constants in a three-center system.[15] If J_{AB} is large, J_{BC} will invariably be small and *vice versa* (compare compound **6**). This arrangement allows 1,3 interactions between sizeable groups to be minimized as discussed earlier.[23,24] If J_{AB} and J_{BC} were either both large or both small a severe 1,3 interaction between sizeable groups would result.

A decision concerning configurations at C-2 and C-3 is much less secure for **6** and **7** since these compounds are not conformationally pure and chemical shift data are the result of an average of at least two conformations. A tentative assignment is given in Scheme I for reasons brought out below.

SCHEME I



6, TE_1 TE_2

7, TT_1 TT_2

The coupling constant data show TE_1 is more important than TE_2 (J_{AB} = 4.2, J_{BC} = 8.2) whereas TT_1 and TT_2 have equal weight ($J_{AB} = J_{BC}$). Examination of Stuart–Breigleb models shows a possible reason for this difference. The models clearly show that TE_1 is more stable than TE_2 due to steric interference of the phenyls at C-1 and C-3 in the latter. Even though one phenyl is canted downward and the other upward, the *ortho* positions interfere with one another severely.

(23) E. J. Corey and R. B. Mitra, *J. Amer. Chem. Soc.*, **84**, 2938 (1962).
(24) D. J. Millen, "Progress in Stereochemistry," Vol. III, W. Klyne, Ed., Butterworth and Co. Ltd., London, England, 1962, p 158.

On this basis the most conformationally pure diastereomer, **6**, mp 80°, is assigned the TE configuration, and **7** the TT configuration. These assignments are also consistent with the usual observation that the *erythro* centers exhibit the larger J values.

Unfortunately, consideration of the chemical shift data leads one to the opposite conclusion. In TE_1 neither H_A or H_C is opposed to a phenyl, whereas in TT_1 and TT_2 the same protons are opposed to a phenyl at least part of the time. Diastereomer **7** should exhibit upfield absorptions compared to **6**, which is not the case, although the difference is small. Attempts to account for the chemical shifts of a given proton in terms of a preferred conformation of the phenyl group at the same carbon were unsuccessful.

Additional data on the bromination yields will be given later. These data are best interpreted in terms of the configurations given above.

It had been hoped that additional data concerning configuration could be obtained from debromination experiments. However, iodide-catalyzed debromination[25] in methanol proved to be stereoselective rather than stereospecific. All four diastereomers yield predominately the most stable olefin, *trans* **3**. The data are recorded in Table II. It is noteworthy

TABLE II

PER CENT *trans* OF A *cis–trans* MIXTURE OF **3** RESULTING FROM REACTION OF **4–7** IN CH_3OH WITH KI

	4	**5**	**6**	**7**
trans, %	100	100	87	67[a]

[a] Corrected for contribution of impurities **4** and **5**.

that the most *cis* isomer observed was with diastereomers **6** and **7** thought to possess the *threo* configuration at C-1,2. Nevertheless, the major reaction of **6** and **7** was unexpectedly an over-all *cis* debromination. Control experiments proved no isomerization of *cis* to *trans* olefins was important under the reaction conditions. These results were similar to the zinc-catalyzed debromination experiments of Stoermer and Kootz.

Similar experiments[26] on authentic *threo*-1,2-dibromo-1-phenyl-3-methylbutane likewise yielded predominately *trans*-1-phenyl-3-methyl-1-butene.

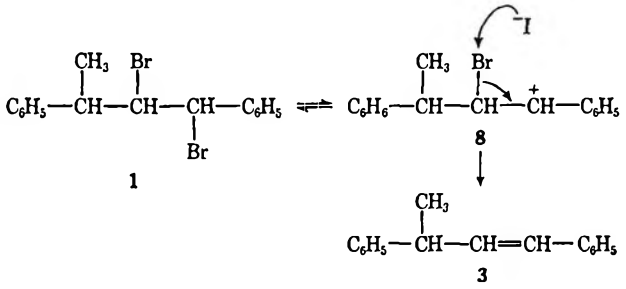
A reaction course involving a preliminary SN2 by iodide, then rapid dehalogenation by iodide,[27] does not seem likely in view of the steric hindrance of the substrate.

In our experience[26] nonstereospecific debrominations are frequently observed in diastereomers containing benzylic halogens. A carbonium ion mechanism as shown in Scheme II seems attractive. The intermediate carbonium ion is presumed to be sufficiently long lived to achieve rotational equilibrium.

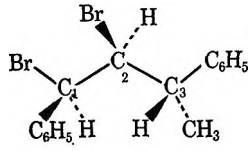
Conformational Preferences.—An interesting point brought out previously is that the C-1,2 *erythro* isomers **4** and **5** are nearly conformationally pure, whereas the *threo* isomers involve equilibria between at least two conformers. From molecular models the following

(25) S. Winstein, D. Pressman, and W. G. Young, *J. Amer. Chem. Soc.*, **61**, 1645 (1939).
(26) Experiments performed by Mr. Gary Underwood.
(27) (a) See, however, H. L. Goering and H. Espy, *J. Amer. Chem. Soc.*, **77**, 5023 (1955); (b) W. M. Schubert, H. Steadly, and B. S. Rabinovitch, *ibid.*, **77**, 5755 (1955).

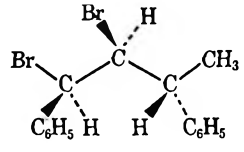
SCHEME II



forms of **4** and **5** (called EE_2 and ET_2) also seem quite stable. Severe 1,3 interactions are not significantly



4, EE_2

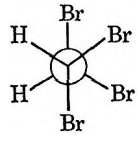


5, ET_2

different in EE_1 and EE_2 of **4** although the 1,3 phenyl interactions would seem to make ET_2 less somewhat stable than ET_1 of **5**. The question is then, what forces or interactions impose rigidity on **4** and **5** but not on **6** and **7**.

If one accepts the fact that 1,3 interactions are potent factors in determining conformations, the only possible conformations are TE_1 and TE_2 and TT_1 and TT_2 for **6** and **7** shown in Scheme I. Each of these involves *gauche* Br–Br interactions. The experimentally observed conformation for **4** is EE_1 and for **5** is ET_1, neither of which involves *gauche* bromines. The possible, but not observed, conformations EE_2 and ET_2 both involve such interactions. It is possible that such interactions are energetically unfavorable and this factor dominates the choice of conformation in **4** and **5**. Where such interactions are unavoidable in either conformer as in **6** and **7**, both conformers are populated. By a rough calculation the dipole–dipole repulsion of *gauche* bromines is on the order of 1 kcal. Polarization interactions of the two bromines may provide a slight counteracting attractive force.

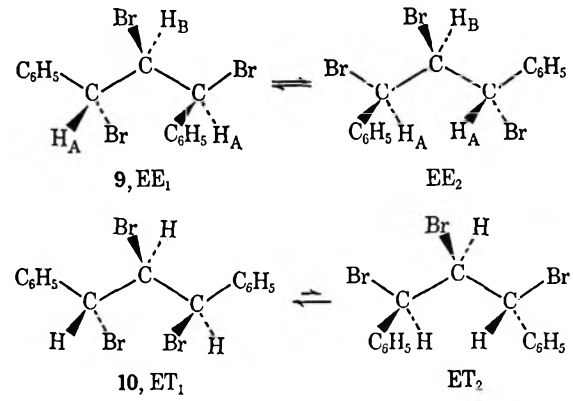
We are hesitant to ascribe a dominating influence totally to this factor, however. In other studies, vicinal halogens showed no overwhelming disposition to be *trans*.[15,26,28,29] Of particular interest is the infrared study of tetrabromoethane which showed the totally *gauche* conformation to be highly populated in solution, although *trans* bromines were evident in part



in dibromoethane (dependent upon the experimental conditions).[24]

It is perhaps instructive now to consider the second set of diastereomers **2**.[30] Only two of the three diastereomers were obtained; the first, **9**, mp 182°, is thought to be one of the *meso* structures, specifically the EE diastereomer, whereas the second, **10**, mp 138°, is assigned the DL structure (ET or TE) based on data given in the Experimental Section. The spectrum of **9** is a classic A_2B case[31] with J_{AB} *ca.* 6.3 cps ($CDCl_3$). It is not thought that A protons are equivalent in a given conformer, but that rapid interconversion of two equivalent mirror image structures exists (Scheme III).

SCHEME III



On the other hand, the DL compound, **10**, is strongly held in a single conformation thought to be ET_1 (Scheme III). The spectrum of **10** is an AMX, with J_{AM} = 1.9 cps, and J_{MX} = 10.9 cps. These data are consistent with either ET_1 or ET_2; however, the far downfield chemical shifts of A, 6.13 ppm, and X, 5.35 ppm (in $CDCl_3$), are much more consistent with ET_1 (*cf.*, the differences between **5** and **6**). Molecular models likewise show ET_1 to be the least sterically crowded. The dipole moment of **10**, 1.9 D, similarly is more consistent with the ET_1 structure.

If ET_1 is indeed the dominant rotomer, the same reasoning can be applied as with **4**–**7**. The rotomer ET_1 involves a single *gauche* Br–Br interaction whereas the presumably less stable ET_2 involves two such interactions.

A second factor should perhaps be mentioned as a possible reason for the stability of certain rotomers over others. Certain types of 1,3 interactions may be attractive rather than repulsive, particularly where atoms of dissimilar electronegativity are involved. It can be seen that the stable rotomers frequently involve 1,3 interactions between bromines and protons. Two exceptions to this generalization exist; the apparent equivalent stability of TT_1 and TT_2 of **7** being the most serious of this study. Similar ideas have been proposed in studies of bromocyclohexanes.[32]

Bromination Studies.—Bromination of either *cis* or *trans* olefin **3** produced all four diastereomers **4**–**7** in unequal yields. The data are recorded in Table III. Beginning with highly reactive *cis* isomer, the yield of the TT isomer **7** is much larger than from *trans* **3**. The reverse is true for the yields of EE **4**.

Initial attack of the brominating species very likely occurs at C-2, and the resulting benzylic ion for the present is assumed to be an open ion.[33] The initial mode of attack determines stereochemistry at C-2,3. The situation is the most clear for the *cis* isomer which

(28) N. Sheppard, *Advan. Spectrosc.*, **1**, 295 (1959).
(29) R. E. Kagarise, *J. Chem. Phys.*, **24**, 300 (1956).
(30) R. Lespieau and R. Wakeman, *Bull. Soc. Chim. Fr.*, **51**, 384 (1932).
(31) The authors thank Dr. R. W. King for elucidation of the spectrum and interpretation of its significance.
(32) E. Eliel and R. Haber, *J. Amer. Chem. Soc.*, **81**, 1249 (1958).
(33) (a) M. L. Poutsma, *ibid.*, **87**, 4293 (1965), and earlier papers; (b) R. Fahey and C. Shubert, *ibid.*, **87**, 5172 (1965).

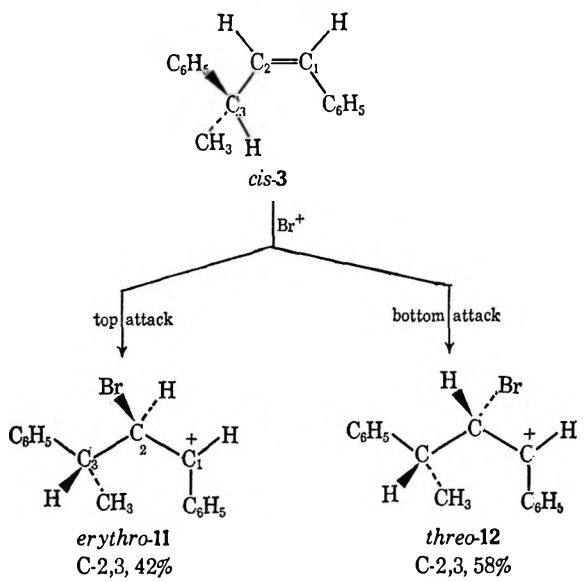
TABLE III
RELATIVE YIELDS OF DIASTEREOMERS 4–7 FROM *cis* AND *trans* 3

Alkene 3	Diastereomeric yield,[a] %: 4, EE	5, ET	6, TE	7, TT
cis[b]	17	41	25	17
trans[c]	40	39	17	5

[a] Determined by integration of expanded nmr spectrum. The yields are considered good to ±4%. [b] Brominated in CCl_4 solution at 0°C, protected from light. [c] Brominated in CS_2 solution at 0° in diffuse light.

is nearly conformationally pure, as shown by the large methine–vinyl *J* value (11 cps) indicative of *trans* protons (the methine proton is eclipsed with the double bond). The less sterically hindered *trans* isomer may accommodate other groups[34] eclipsed with the double bond. The stereochemistry of attack is illustrated in Scheme IV. As shown, top attack, where the brominating species enters over the phenyl, yields the *erythro* isomer in 42% yield (sum of 4 and 6), whereas a somewhat preferred attack over methyl yields the *threo* isomer in 58% yield. The difference in yields is not large, but it is consistent with this model. Attack on an unsaturated center next to an asymmetric center

SCHEME IV



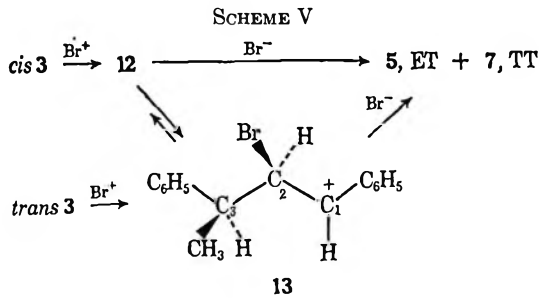
is also the basis of the very successful Cram rule,[35] from which predictions are made using a conformation of the aldehyde or ketone other than the most stable.[36]

Initial attack on *trans* 3 yields 56% *erythro* at C-2,3. Predominant attack over hydrogen on a conformation with methyl eclipsed with the double bond seems attractive. If the hydrogen were eclipsed with the double bond, the *threo* isomer would probably again predominate. Again the differences are not large.

Completion of the reaction sequence involves attack of the bromide at C-1 after varying amounts of internal rotation have occurred. This attack determines stereochemistry at C-1,2. Hindrance to approach of the bromide by substituents at C-2 and C-3 must be considered. It is of interest to know which dominates.

The intermediate ion or ions of *threo* configuration at C-2,3 will be considered first. The total yield of products of *erythro* configuration at C-1,2 (5) is larger than the *threo* (7). Furthermore, the yields are rather similar beginning with either the *cis* olefin 3 (71% 5, 29% 7) or the *trans* olefin 3 (89% 5, 11% 7). It seems likely that a common intermediate exists in the bromination of either *cis* or *trans* 3 as shown in Scheme V. Very likely the highly hindered ion 12 formed initially from *cis* 3 rotates about the C-1,2 bond to form the

SCHEME V



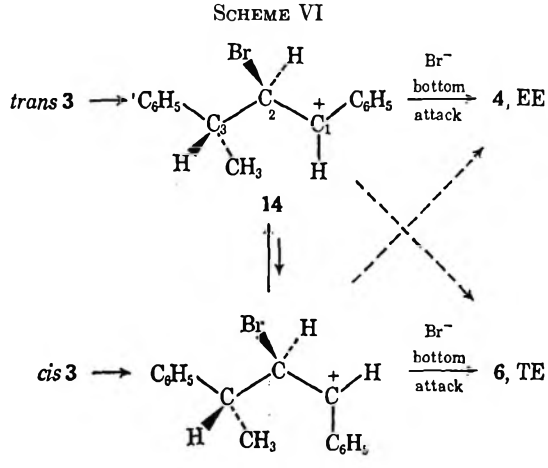
more stable structure 13 (the conformer shown appears to be the most stable from Stuart–Breigleb models). Some capture of 12 by bromide occurs so that the relative yields of 5 and 7 are not quite the same as from *trans* 3.

It is noteworthy that the predominant mode of attack by bromide on 13 is from the opposite side of the molecule from the bromine at C-2, to yield the *erythro* isomer 5. Whether or not there is bridging by the bromine at C-2 is not answerable from the data of this study, but it seems likely that bromine does bridge in part.

The intermediate ion or ions of the *erythro* configuration at C-2,3 behave rather differently depending upon their origin. Thus product of *threo* configuration at C-1,2 (6) predominates (60% 6, 40% 4) where *cis* 3 is the starting material, whereas the *erythro* product predominates from the *trans* isomer (30% 6, 70% 4).

The interpretation of the results is perhaps more straightforward beginning with *trans* 3 (Scheme VI). Initial attack of Br^+ yields the sterically unhindered

SCHEME VI



(34) A. A. Bothner-By, C. Naar-Colin, and H. Gunther, *J. Amer. Chem. Soc.*, **84**, 2742 (1962).
(35) D. J. Cram and F. A. Abd Elhafez, *ibid.*, **74**, 5828 (1952).
(36) E. Eliel, N. Allinger, S. Angyal, and G. Morrison, "Conformational Analysis," John Wiley and Sons, Inc., New York, N. Y., 1965, p 34.

ion **14**. Again the bromine at C-2 may form the bridged species in part. The predominant products again results from bromide attack remote from the bromine at C-2 to yield **4**.

Beginning with *cis* **3**, the ion **11** is formed, which shows severe steric crowding. Some internal rotation about the C-1,2 bond occurs giving **14**. The ion **14** would then yield the same product ratio as that observed from *trans* **3**. From models, this rotation seems rather difficult and involves the breaking of overlap between the p orbital at C-1 and the aromatic group.

The predominate pathway is attack of bromide directly on **11**. Again attack occurs predominantly on the side of the molecule remote from the bromine at C-2 yielding the *threo* isomer **6**.

The difference between the reaction model shown in Scheme V and that in Scheme VI is that extensive internal rotation occurs in the former case but not in the latter.[37]

The primary conclusion from the above data is that a bromine substituent at C-2 is dominant over a phenyl or methyl at C-3 in its effect on bromide attack at C-1.

Experimental Section

1,3-Diphenyl-1-butenes.—To a solution of 26.8 g (0.2 mol) of 2-phenylpropanol (Aldrich Chemical Co., Inc.) and 77.6 g (0.2 mol) of triphenylbenzylphosphonium chloride in 500 ml of commercial absolute ethanol was added dropwise, under nitrogen, 1 l. at 0.2 *M* lithium ethoxide. After the addition was complete, the reaction was stirred for an additional 24 hr at room temperature. Sufficient water was added to give a 60% ethanol solution and the entire mixture was poured into a large separatory funnel. The dark brown oil which separated was collected and washed two times with 50-ml portions of 60% ethanol and then dried over Molecular Sieve (Linde 4A). The crude mixture of *cis* and *trans* olefins was separated by distillation through an 18-in. spinning band column at reduced pressure (*ca.* 2 mm). Twenty-four 2-cc fractions were collected and analyzed by vapor phase chromatography using a 0.25 in. × 8 ft QF_1 column (5% QF_1 on 60–80 mesh HMDS treated Chromosorb W) at a column temperature of 195° using a 65 cc/mm helium flow. The retention times of *cis* and *trans* were 3 and 4.5 min, respectively. Fractions 2–10, bp 109–112° (2 mm), were *cis* **3** of 99% purity, fractions 11–14 were a mixture of *cis* and *trans* **3** and fractions 15–24 were *trans* **3** of 99% purity. The nmr spectral data for the olefins are identical with those reported by Ela and Cram.[38]

Triphenylbenzylphosphonium Chloride.—To a solution of 100 g (0.382 mol) of triphenylphosphine (Aldrich Chemical Co., Inc.) in 250 ml of xylene was added 48.59 g (0.38 mol) of benzyl chloride. The reaction mixture was stirred at reflux temperature overnight. The white salt was filtered, washed with pentane, and dried in an oven at 60°, yield 128 g (86.5%).

Bromination of *cis* 3.—A solution of 10 g (0.027 mol) of the olefin in 50 cc of carbon tetrachloride was cooled to 0°. The reaction flask was wrapped in aluminum foil and a solution of 4.4 g (0.0275 mol) of bromine in 20 ml of carbon tetrachloride was added dropwise. After the addition was complete (30 min), the reaction mixture was stirred for an additional 60 min and then poured over ice and extracted with carbon tetrachloride. The carbon tetrachloride layer was washed with dilute sodium bisulfite, water, and then dried over anhydrous magnesium sulfate. A small amount of the carbon tetrachloride solution was concentrated by rotary evaporation at room temperature. The resulting residue was dissolved in deuteriochloroform and an nmr spectrum was recorded. The portion of the spectrum from 220 to 320 cps was again recorded using a 100-cps sweep width. Integration over this expansion allowed calculation of yield of each diastereomer.

The carbon tetrachloride was removed from the major portion of the crude product by rotary evaporation and the residue crystallized upon standing. The crystals (crop A) were collected and the residual oil was allowed to stand. After several days the oil crystallized in large plates, mp 61–67°. The crystals were taken up in fresh CCl_4 and pentane was added. The first crystals to separate were filtered off and the mother liquor was cooled yielding dibromide **6**, mp 78–80° (lit.[20] mp 78–80°).

Dibromide (**5**), mp 122–123° (lit.[20] mp 122°), was obtained by dissolving crop A in a suitable volume of solvent prepared by mixing 100 ml of ethanol with 50 ml of ethyl acetate and 25 ml of water. After four recrystallizations from this solvent the pure dibromide was obtained.

Dibromide **7** was not obtained free from diastereomeric impurities; however, a mixture of dibromide **4**, **5**, and **7** was obtained by repeated fractional recrystallization. This mixture contained 34% dibromide (**7**), 28% dibromide (**4**), and 38% dibromide (**5**) *via* nmr integration. Dibromide (**4**) is most easily obtained from the product mixture derived from bromination of *trans* olefin.

Bromination of *trans* 3.—A solution of 4.4 g of bromine in 25 ml of carbon disulfide was added dropwise to a solution of 10 g (0.027 mol) of the olefin in 50 ml of carbon disulfide. The reaction mixture was stirred at 0° for 2 hr and then allowed to warm to room temperature. The carbon disulfide was removed by rotary evaporation at room temperature and the residue was dissolved in carbon tetrachloride and again stripped of solvent. The crude product was taken up in fresh carbon tetrachloride and washed with sodum bisulfite, water, and then dried over magnesium sulfate. A small portion of the carbon tetrachloride solution was concentrated and the residue was dissolved in deuteriochloroform and an nmr spectrum was recorded. The portion of the spectrum from 220 to 320 cps was again recorded using a 100-cps sweep width. Integration over this expansion allowed calculation of yield of each diastereomer.

After removal of the solvent from the bulk of the product, the residue was dissolved in a large excess of ethanol and allowed to stand at room temperature. Long needles of the pure dibromide **4**, mp 128–129° (lit.[29] 128–129°),[20] separated after several hours.

Dipole Moments.—The technique of dipole moment measurement has been discussed previously.[15] Cyclohexane was the usual solvent. The nmr spectra of the diastereomers were also determined in cyclohexane to be sure no large change in conformation resulted form change in solvent from deuteriochloroform to cyclohexane. These data are **5**, J_{AB} = 10.8 cps, J_{BC} = 2.7 cps; **6**, J_{AB} = 3.5 cps, J_{BC} = 8.5 cps; and **7**, J_{AB} = 6.4 cps, J_{BC} = 6.4 cps.

Elimination Procedure.—A solution of 1 g of potassium iodide in 50 ml of commercial absolute methanol was prepared and 5 ml of this solution was pipetted into a test tube containing 0.10 g of the dibromide. The tubes were sealed and placed in a bath at 60° for 85 hr. The tubes were cooled to room temperature, broken and the contents poured over ice. The reaction mixture was extracted with ether and the ether layer was washed with cold, dilute sodium thiosulfate, water, and then dried over anhydrous magnesium sulfate. The ether was removed by distillation and the residue was analyzed by vpc using the QF_1 column previously described. The results are given in Table II.

***cis–trans* Isomerization of 3.**—A solution of 0.05 g of iodine, 0.1 g of potassium iodide, and 0.1 g of *cis* **3** in 5 ml of commercial absolute methanol was placed in a test tube. The tube was sealed and maintained at 60° for 160 hr. No *trans* olefin could be detected in the reaction mixture by vpc analysis.

1,2,3-Tribromo-1,3-diphenylpropanes were prepared similar to the method of Lespieau and Wakeman,[30] by addition of excess bromine in carbon disulfide to 1-bromo-1,3-diphenyl-2-propene. The reaction product precipitated and was recrystallized by the triangle scheme. The high melting isomer **9**, 1.1 g, mp 180.5–182.5° (nmr absorptions centered at *ca.* 5.2), and one lower melting isomer **10**, 0.7 g, mp 137–138° (nmr absorptions of 5.36, 4.56, and 6.12 in deuteriochloroform), were easily obtained. Two other polymorphic forms of the latter, mp 128–129 and 114–115°, were apparent. These showed very similar nmr patterns to the 138° material.

The configurations of **9** and **10** were assigned by means of nmr spectra and by the following reaction. To *erythro*-1,2-dibromo-1,3-diphenylpropane, mp 110°, 5.0 g, was added 2.6 g of N-bromosuccinimide, and the mixture was heated at reflux in

(37) This can be easily seen if the reader will take the trouble to make the molecular models. The C-1 phenyl of **12** may fairly easily slip past two protons (at C-2 and C-3) to form **13**. However, such rotation is difficult in **11** although it is possible in another C-2,3 conformer of **11**.

(38) S. W. Ela and D. J. Cram, *J. Amer. Chem. Soc.*, **88**, 5777 (1966).

carbon tetrachloride for 2 days. The succinimide was filtered off and the remaining solution concentrated. In the absence of equilibration, this bromination could only give EE and ET products as well as 1,1,2-tribromo-1,3-diphenylpropane (15). The material 9 was isolated, 9.6 g, mp 181–182°, as well as 0.96 g of 10, mp 131–133°. A third fraction, mp 93–95°, 1.7 g, was a mixture of starting material and 10. The remaining oil (1.3 g) was a similar mixture with traces of 15 apparent.

Registry No.—4, 16793-35-4; 5, 16793-36-5; 6, 16793-37-6; 7, 16793-38-7; 9, 16793-39-8; 10, 16793-40-1.

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The Hydrogenation of Dialkylcyclohexenes with Rhodium Catalysts[1]

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The *cis/trans* product ratios observed in the hydrogenation of six dialkylcyclohexenes on rhodium catalysts at 25° and 1 atm are given. These are compared with the results when platinum and palladium catalysts are used. The effect of temperature on the product ratios from three of these cycloalkenes with rhodium and platinum catalysts are reported, as are the results of their disproportionation and the hydrogenations of the corresponding arenes at 100°. Rhodium and platinum are found to be closely similar, and quite different from palladium, in their promotion of hydrogen addition to carbon unsaturation. Platinum appears to be the more effective of the two for the straightforward addition of hydrogen to 1,2-diadsorbed alkanes.

There have been several reports of the stereochemical results observed when platinum and palladium catalysts are used to effect the hydrogenation of dialkylcycloalkenes which can form *cis* and *trans* products.[2] It seems clearly established that palladium catalysts furnish a product mixture at pressures near one atmosphere which approaches equilibrium composition, whereas platinum catalysts lead to an entirely different mixture. Furthermore, isomerization of the initial cycloalkene has been found to be pronounced with palladium catalysts but to be relatively minor or insignificant for most cycloalkenes with platinum.[2,3] The nonintervention of isomerization with platinum catalysts, even where this is thermodynamically favored, has been demonstrated in recent reports of the kinetics of this reaction[4] and in studies of the competitive hydrogenation of pairs of cycloalkenes.[5]

It was of interest to compare the catalytic properties of rhodium catalysts with those of palladium and platinum. We report here the stereochemical results observed when several dialkylcyclohexenes are hydrogenated over rhodium, together with the effect of temperature on the product ratios using both rhodium and platinum.

Results

The data in Table I summarize the results of the hydrogenations of several dialkylcyclohexenes at 25° near one atmosphere with rhodium, platinum, and palladium catalysts. Most of these data are averages of replicate analyses of replicate hydrogenation experiments (usually three, occasionally more) and include, for rhodium and platinum, the results from several experiments interrupted between 15 and 50% hydrogenation. The data for the hydrogenations using palladium catalysts are all from complete hydrogenations; extensive isomerization of the cycloalkenes are observed with this catalyst and the *cis/trans* product ratios for the unsymmetrical dialkylcyclohexanes vary ±4–5% depending upon the extent of hydrogenation when samples are removed for analysis.[2e] In contrast, isomerization is small at 25° when moderate amounts of rhodium catalysts are used (1–4% near 50% hydrogenation). Isomerization is unobservable with platinum at this temperature. When an excessive amount of rhodium catalyst is used, a hydrogen deficiency is created at the catalyst surface because of transport limitations[6] and isomerization increases. This effect is less pronounced with platinum. However, as long as the amount of catalyst is reasonably small (10–40 mg), the product composition from reactions at 25° is the same, within the ±1% precision of our analyses, at various stages in the hydrogenations with both catalysts. This is not true with palladium.

TABLE I

HYDROGENATION OF DIALKYLCYCLOHEXENES WITH RHODIUM, PLATINUM, AND PALLADIUM CATALYSTS[a]

	% *cis* isomer[b] with		
Cyclohexene	Rh[c]	Pt	Pd
1,4-DiMe	61	57[d]	28[e]
1-Me-4-Et	55	48[d]	24
1-Et-4-Me	55	58[d]	27
1,4-DiEt	54	49	25
1-Me-4-*i*-Pr	52	43[d]	26[e]
1-*i*-Pr-4-Me	54	58[d]	21[e]

[a] In purified glacial acetic acid, 25° (1 atm). [b] Precision of analysis ±1%. [c] 5% on charcoal. [d] Data from ref 2d. [e] Data from ref 2e.

The data in Table II summarize the effect of temperature with three of the cycloalkenes of Table I. At 50° and above, disproportionation to form arenes and cyclohexanes becomes competitive with the hy-

(1) Support of a part of this research through GP 4656 from the National Science Foundation is gratefully acknowledged.

(2) (a) S. Siegel, *J. Amer. Chem. Soc.*, **75**, 1317 (1953); (b) S. Siegel and M. Dunkel, *Advan. Catal.*, **9**, 15 (1957); (c) S. Siegel and G. V. Smith, *J. Amer. Chem. Soc.*, **82**, 6082, 6087 (1960); (d) J-F. Sauvage, R. H. Baker, and A. S. Hussey, *ibid.*, **82**, 6090 (1960); (e) J-F. Sauvage, R. H. Baker, and A. S. Hussey, *ibid.*, **83**, 3874 (1961); (f) S. Siegel and B. Dmuchovsky, *ibid.*, **86**, 2192 (1964).

(3) (a) D. J. Cram, *ibid.*, **74**, 5518 (1952); (b) G. V. Smith and R. L. Burwell, *ibid.*, **84**, 925 (1962); G. C. Bond, J. J. Phillipson, P. B. Wells, and J. M. Winterbottom, *Trans. Faraday Soc.*, **60**, 1847 (1964); (d) G. V. Smith and J. R. Swoap, *J. Org. Chem.*, **31**, 3904 (1966); (e) A. W. Weitkamp, *J. Catal.*, **6**, 431 (1966).

(4) A. S. Hussey, G. W. Keulks, G. P. Nowack, and R. H. Baker, *J. Org. Chem.*, **33**, 610 (1968).

(5) A. S. Hussey, G. W. Keulks, and R. H. Baker, *J. Catal.*, **10**, 258 (1968).

(6) H. C. Yao and P. H. Emmitt, *J. Amer. Chem. Soc.*, **81**, 4125 (1959).

TABLE II
THE EFFECT OF TEMPERATURE ON HYDROGENATIONS OF DIALKYLCYCLOHEXENES WITH PLATINUM AND RHODIUM CATALYSTS

Temp,	% *cis* isomer[a]					
	1,4-DiMe		1-Et-4-Me		1-Me-4-IsoPr	
°C	Pt	Rh	Pt	Rh	Pt	Rh
100	48	54	48	47	42	51
50	54		52			
25	57	61	58	55	43	52
18	59		59			
0	61	62	62	63	43	52
−17	63					
−30	66	66	67	68	46	51

[a] Precision of analysis ±1%.

drogenation reactions. It is most extensive with palladium, appreciably less with platinum, still less with rhodium. Isomerization of olefin also increases with increasing temperature with rhodium and it becomes easily detectable at 100° with platinum. It is still small at 100° with both of these catalysts relative to that observed with palladium at 25° however.[2e] In order to minimize the contribution of cycloalkene isomers and arenes to the cycloalkane product ratios, the experiments at 50° and 100° in Table II were interrupted at 10 to 30% hydrogenation. Accordingly the data represent the stereochemical consequences of the hydrogen addition and disproportionation reactions with little contribution from the other two pathways.

At very low hydrogen pressures, the disproportionation reaction becomes the only pathway to dialkylcycloalkanes. In order to check the stereochemistry of this process, we carried out a number of disproportionation experiments in which the hydrogen atmosphere was replaced by nitrogen or helium. These reactions were interrupted in the early stages while isomerized olefin was still small, and below 30° the ratios of dialkylcycloalkanes were within experimental error of the values given in Table I. The values at 100° are slightly different and are summarized in Table III. At high conversions at this temperature, significantly more *cis* product is obtained. We also carried out the hydrogenation of the corresponding arenes at 100° and one atmosphere (Table IV).

TABLE III
STEREOCHEMICAL CONSEQUENCES OF THE DISPROPORTIONATION OF DIALKYLCYCLOHEXENES AT 100°

Cyclohexene	% *cis* isomer	
	Rh	Pt
1,4-Dimethyl	57	47
1-Ethyl-4-methyl	49	48
1-Methyl-4-isopropyl	53	41

TABLE IV
HYDROGENATION OF 4-ALKYLTOLUENES AT 100°

4-Alkyltoluene	% *cis* isomer	
	Rh	Pt
4-Methyl	70	61
4-Ethyl	72	59
4-Isopropyl	69	55

In several blank experiments with known mixtures of *cis* and *trans* products, of products with their unsaturated precursor, and of products with their arene counterparts, we determined that (1) there was no incidental enrichment in one component as a result of differential vaporization at elevated temperatures; (2) the rate of isomerism of *cis* to *trans* product at 100° was too slow to effect the ratios observed if the reactions were allowed to go to completion; (3) there was no inadvertent change in the mixture compositions in the course of separating hydrocarbons from catalyst (filtration) and solvent (washing with water) prior to analysis by glpc.

Discussion

The results summarized in Table I and Table II furnish some empirical guidelines for the choice of catalyst and conditions for the preferential formation of one dialkylcyclohexane *via* the hydrogenation of its dialkylcyclohexene precursor. If a preponderance of the thermodynamically more stable cycloalkane is desired, the use of a palladium catalyst is indicated. The use of platinum or rhodium catalysts, on the other hand, will result in a larger proportion of a thermodynamically unstable *cis*-1,4-dialkylcyclohexane, and this proportion will often be increased by a hydrogenation procedure at low temperatures. Of these two catalysts, rhodium appears more likely to favor the formation of an unstable *cis* isomer from 1,4-dialkylcyclohexenes when the group at a distance from the double bond is larger than methyl. Platinum, on the other hand, is the catalyst of choice if desorption of isomerized olefin is to be avoided. Olefin isomerization is a minor surface reaction but it is detectable when rhodium catalysts are used; it is an exceptional olefin which isomerizes on platinum catalysts near room temperature.[2-5] Olefin isomerization is very extensive when palladium catalysts are used.

The close resemblance of rhodium and platinum catalysts (and the difference of palladium) in the hydrogenation of cyclohexenes is also reflected in the hydrogenation of arenes. Here the order of effectiveness is Rh > Pt ≫ Pd.[7] Similarly we have found the order of effectiveness in promoting the disproportionation of cyclohexenes to be Pd ≫ Pt > Rh. Clearly rhodium and platinum catalysts closely resemble one another while palladium catalysts are quite different.

In addition to the surface reactions which result in the hydrogenation of the original dialkylcyclohexane, three other surface reactions intervene to varying degrees with these three catalysts to lead to differences in the stereochemical results observed in the hydrogen addition reaction. All three of these reactions become pronounced, even with platinum and rhodium, in the higher temperature reactions summarized in Table II. At the outset, the second most important pathway is the disproportionation route through which one cyclohexene molecule furnishes the four hydrogen atoms necessary for the reduction of two others, and is itself converted into the arene. At more advanced stages of the higher temperature hydrogenation more and more of the product mixture is derived from isomers of the original cyclohexene (except for 1,4-dimethylcyclohexene, of course). Finally, when the cycloalkene is nearly gone, arene begins to hydrogenate to product also. At lower temperatures, all of these are minor processes with platinum and rhodium, and arene hydrogenation does not occur on palladium.

(7) A. Amaro and G. Parravano, *Advan. Catal.*, **9**, 716 (1957).

Although it seemed unlikely that the disproportionation reactions would generate a different dialkylcyclohexane isomer ratio than is observed from hydrogenations, we carried out a number of disproportionation experiments to check this. Below 30°, no significant difference in hydrogenation and disproportionation product ratios was observed, but at 100° higher proportions of *cis* isomers were formed when the disproportionation reactions were carried to completion. This probably results in part from hydrogen addition to the 4-methyl isomer[2d] of 1-methyl-4-isopropylcyclohexene, but the observed increase of *cis*-1,4-dimethyl- and 1-ethyl-4-methylcyclohexane[2d] can only come from the hydrogenation of some of the corresponding arenes.

We therefore carried out the hydrogenation of the three corresponding arenes at 100° and one atmosphere. The results of Table IV show that the increased *cis* product observed at high conversions can be ascribed, at least in part, to the hydrogenation of small amounts of the arenes generated by the disproportionation reactions. Without question, however, some of the additional *cis* product also stems from the 4-methyl isomer[2d] of the last cycloalkene at higher conversions. Therefore the data given in Table II at the higher temperatures were obtained from experiments which we interrupted at low conversions when olefin isomerization was still small and arene hydrogenation could be ignored. The trend exhibited by two of the three cyclohexenes in Table II is therefore real and is worthy of brief discussion.

We have recently proposed that 1,2-diadsorbed cycloalkanes with alkyl groups in a *cis* configuration can interconvert on platinum surfaces with their *trans* counterparts.[5] This proposal is consistent with the observed kinetics for the hydrogenation of cycloalkenes[4] and with the results from the competitive hydrogenations of pairs of cycloalkenes.[5] It also satisfactorily explains the pressure-variable *cis/trans* ratio both from the xylenes[8] and from their tetrahydro counterparts[2] as well as the failure to observe isomerization of the latter.[3-5] We choose to apply much the same explanation here.

We cannot demonstrate in an unequivocal way that the trend of the data in Table II does not simply reflect a temperature-variable equilibrium chemisorption of the cycloalkene in the two modes, along with different temperature coefficients for the rate constants for the over-all reactions.[9] Nevertheless, we prefer to view the decrease in *cis* product with increasing temperature as a reflection of an increase in the surface concentration of hydrocarbon in a *trans* geometry which results from a *cis,trans* interconversion *on the surface*.[5] Different temperature coefficients for the two hydrogen addition reactions may also be a contributing factor. We acknowledge that alkene does desorb to a small extent from rhodium at 25° and from platinum at higher temperatures. However, we hasten to point out that the trend continues as the temperature decreases below 25° (Table II) where no desorption is detectable with either catalyst. The absence of a similar trend in the hydrogenation of 1-methyl-4-isopropylcyclohexene simply implies that the temperature coefficients for all of the steps in the *cis* and in the *trans* pathways, including the *cis,trans* surface interconversion, are identical over-all. The temperature response of rhodium and platinum emphasizes their similarity as catalysts for the addition of hydrogen to unsaturated hydrocarbons.

(8) F. Hartog and P. Zwietering, *J. Catal.*, **2**, 79 (1963); S. Siegel, V. Ku, and W. Halpern, *ibid.*, **2**, 348 (1963); S. Siegel and V. Ku, *Proc. Intern. Congr. Catal., 3rd, Amsterdam, 1964*, **2**, 1199; F. Hartog, J. H. Tebben, and C. A. M. Wetering, *ibid.*, **2**, 1210.

(9) S. Siegel, *Advan. Catal.*, **16**, 138 (1966).

Experimental Section

Dialkylcyclohexenes.—The preparation and purification of most of the dialkylcyclohexenes used here have been described earlier.[2d]

1,4-Diethylcyclohexene was prepared as follows. A solution of 31.5 g (0.250 mol) of 4-ethylcyclohexanone[2d] in 150 ml of ether was added to a stirred solution of the Grignard reagent from 32.7 g (0.300 mol) of ethyl bromide in 200 ml of ether under nitrogen. After 1 hr, 30 ml of water was added dropwise with stirring. The ether solution was decanted and the precipitated magnesium salts were extracted with 4–100 ml portions of warm ether. The crude product weighed 45.0 g (99%) and this was distilled and redistilled to give 36.0 g (79%) of 1,4-diethylcyclohexanol: bp 98–101° (15 mm); $n^{25}D$ 1.4600. The latter was dehydrated by dropping it onto 50 g of sodium bisulfate and heated to 150° (120 mm) over 20 min. The alkene distilled as fast as it was formed at 98–100° and consisted mostly of 1,4-diethylcyclohexene (78%) and 4-ethylethylidenecyclohexane (22%), with traces of other isomers (analysis through silver nitrate–triethylene glycol on 60–80 mesh firebrick). The 31.0 g (76%) of mixed cycloalkenes was distilled through a five-plate column and then redistilled through a 100-plate column. A 5.6-g middle fraction which distilled at 174.8° (747 mm) was of "single peak" purity by glpc (silver nitrate in triethylene glycol on firebrick).

Hydrogenation and Analyses.—The cyclohexenes were hydrogenated in purified glacial acetic acid, ethyl alcohol, or mixtures of the two in a microhydrogenation apparatus as described earlier.[2d] Part hydrogenations were interrupted at 10–70% uptake of theoretical hydrogen. Analyses were by glpc procedures which had been found to be capable of separation of the several components in known mixtures.

Temperature control in these experiments was maintained in the reaction flask and only to ±3° in many of them. Initial experiments showed that the change of product ratios with temperature was small; hence it was not necessary to pay elaborate attention to temperature control.

For experiments carried out above 50°, the hydrogenation flask was fitted with a cold-finger condenser to return vaporized substrate and solvent. Experiments with prepared mixtures of known composition showed that there was no enrichment in one component as a result of vaporization at 100° or as a result of the method of isolation. Likewise the rate of isomerization of *cis* to *trans* was found to be too slow at 100° to be of significance.

Catalysts.—Several different samples of commercial 5% rhodium-on-carbon catalysts, several samples of commercial platinum oxide, and several palladium catalysts were used in these studies. Variations in product composition for any one metal were less than the precision of our analyses (±1%) except occasionally when large excesses were used.

Disproportionation Reactions.—These reactions were carried out in the hydrogenation system. The catalyst and solvent were shaken in hydrogen following which the system was evacuated and flushed three or four times with nitrogen or helium. The sample of dialkylcyclohexene was then injected through the serum cap on the side arm and the reaction carried out with continuous agitation.

There was no change in the gas volume of the system (*i.e.*, no hydrogen escaped to the gas phase) and, in experiments carried to completion, the arene/cyclohexane ratio did not vary greatly from the stoichiometric 1:2 although it was usually a little larger. The catalysts were found to be in the order Pd ≫ Pt > Rh in effectiveness for the disproportionation reaction.

Registry No.—Rhodium, 7440-16-6; platinum, 7440-06-4; 1,4-diethylcyclohexene, 3454-04-4.

Cyclohexenone-4-acetic Acid Derivatives from the Addition of Diazoacetic Ester to β,γ-Unsaturated Ketals[1]

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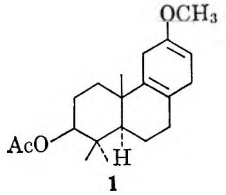
Received February 19, 1968

The addition of ethyl diazoacetate to various β,γ-unsaturated ketals varying in the degree of substitution of the double bond has been investigated. Satisfactory yields of cyclopropane derivatives were obtained in the monocyclic cases that have been examined. The reaction failed in bicyclic systems in which the double bond was present at the ring fusion. Ketal cleavage and ring opening of the cyclopropanes that were successfully prepared yielded cyclohexenone-4-acetic acid derivatives, which are of interest as synthetic intermediates.

Various terpenoids of current interest, *e.g.*, kaurene, phyllocladene, gibberellic acid, etc., contain a substituted bicyclo[3.2.1]octane system as a prominent structural feature. Several solutions to the synthetic problem presented by this arrangement have been published.[3] The present work was undertaken with a view toward incorporation of the elements of the bridged system, after construction of the polycyclic nucleus was complete, by introduction of a functionalized angular substituent followed by directionally controlled cyclization. The preparation of intermediates of type **4** was of interest in this connection.

As an approach to the synthesis of compound **4** it appeared that addition of diazoacetic ester to the unsaturated ketal **2** would afford a cyclopropane derivative **3** which on hydrolysis to the corresponding ketone



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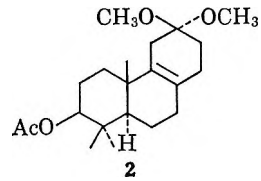

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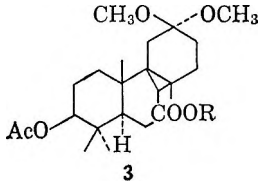

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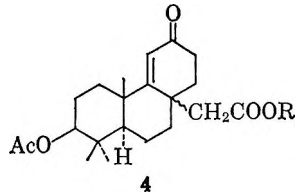


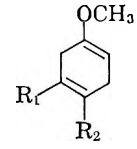
4

could undergo base-catalyzed cleavage to the desired product. This procedure represents an extension of the methods employed by Birch[4] and by Winstein[5] for angular alkylation through the use of carbenoid reagents.

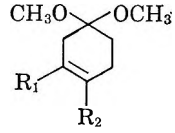
The dihydro anisole derivative (**1**), obtained as described in the Experimental Section, was accordingly treated with methanol and *p*-toluenesulfonic acid,[4] under which conditions ketal (**2**) was produced in good yield. However, the reaction of this substance with diazoacetic ester in the presence of copper–bronze powder[6] under a variety of conditions led only to recovery of starting material. We were, therefore, prompted to undertake an examination of the reaction sequence in simpler model compounds.

Dihydroanisoles **5a**, **b**, and **c** were prepared by Birch reduction of the appropriate anisoles and were smoothly converted into the ketals **6a**, **b**, and **c** by reaction with methanol and *p*-toluenesulfonic acid.[4] The products obtained in this way were then treated with diazoacetic ester and copper–bronze powder without solvent at temperatures ranging from 120 to 135°.

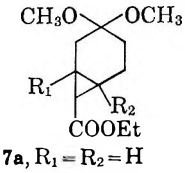
Material derived from **6a** proved to be thermally unstable and, although a pure sample of **7a** could be isolated by vapor chromatography, some elimination of methanol occurred and afforded an additional peak which appeared from nmr analysis to consist of a mixture of enol–ethers (**10**). It is of interest to note that the molecular ion of mass 228 is not observed in the mass spectrum of **7a**, but instead an ion, *m/e* 197, appears corresponding to the loss of a methoxyl group.[7]



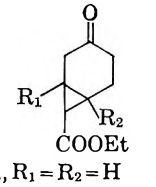
5a, $R_1 = R_2 = H$
b, $R_1 = H$; $R_2 = CH_3$
c, $R_1 = R_2 = CH_3$



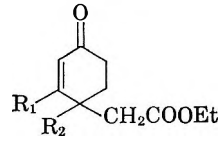
6a, $R_1 = R_2 = H$
b, $R_1 = H$; $R_2 = CH_3$
c, $R_1 = R_2 = CH_3$



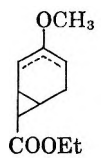
7a, $R_1 = R_2 = H$
b, $R_1 = H$; $R_2 = CH_3$
c, $R_1 = R_2 = CH_3$



8a, $R_1 = R_2 = H$
b, $R_1 = H$; $R_2 = CH_3$
c, $R_1 = R_2 = CH_3$



9a, $R_1 = R_2 = H$
b, $R_1 = H$; $R_2 = CH_3$
c, $R_1 = R_2 = CH_3$



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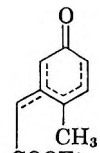


11

Cleavage of the ketal function in **7a** by exchange with acetone afforded keto ester **8a**, which was further transformed into the cyclohexenone **9a** by the action of *p*-

(1) Support of this work by the Robert A. Welch Foundation is gratefully acknowledged.

(2) Department of Chemistry, Texas A & M University, College Station, Texas 77843.

(3) See for example (a) R. B. Turner and K. H. Gänshirt, *Tetrahedron Lett.*, 231 (1961); (b) R. A. Bell, R. E. Ireland, and R. A. Partyka, *J. Org. Chem.*, **27**, 3741 (1962); (c) S. Masamune, *J. Amer. Chem. Soc.*, **86**, 288 (1964); *ibid.*, **86**, 289 (1964); (d) G. Stork, S. Malhotra, H. Thompson, and M. Uchibayashi, *ibid.*, **87**, 1148 (1965).

(4) A. J. Birch, J. M. Brown, and G. S. R. Subba Rao, *J. Chem. Soc.*, 3309 (1964).

(5) T. Hanafusa, L. Birladeanu, and S. Winstein, *J. Amer. Chem. Soc.*, **87**, 3510 (1965).

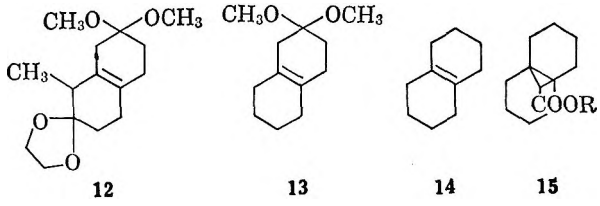
(6) S. Akiyoshi and T. Matsuda, *ibid.*, **77**, 2476 (1955).

(7) We are indebted to Professor J. L. Franklin of this department for the mass spectral data.

toluenesulfonic acid in refluxing benzene. The over-all yield in the latter two steps was 88%, and the structure of the final product (**9a**) was established by palladium-catalyzed dehydrogenation and hydrolysis to *p*-hydroxyphenylacetic acid, identical in all respects with an authentic sample.

Cleavage of ketal ester **7b** similarly afforded keto ester **8b**, which, however, furnished a mixture of products on acid-catalyzed ring opening. On the basis of the assumption that in this case acid treatment can result in competitive cleavage to yield substances of type **11**, sodium acetate in ethanol was substituted for the *p*-toluenesulfonic acid, and **9b** was thus obtained cleanly and in good yield. The acid-catalyzed procedure permitted conversion of the dimethyl derivative **7c** into **9c**, which was obtained in an over-all yield of 63% from the starting β,γ-unsaturated ketal (**6c**).

The question of the behavior of bicyclic systems in the reaction scheme was next explored. Ketals **12** and **13** were prepared by procedures described in the Experimental Section, and the reaction of these substances and of Δ^9-octalin (**14**)[8] with diazoacetic ester and copper–bronze were examined. Only in the case of **14** was any evidence of reaction obtained. In this instance 17% of a product was isolated by vapor chromatography, which possessed spectral properties (nmr)



12 **13** **14** **15**

compatible with those expected for the cyclopropane derivative **15**. The photolytic and uncatalyzed thermal reactions of diazoacetic ester with Δ^9-octalin were also attempted, but no recognizable products could be obtained. It would appear, therefore, that direct application of this method to bicyclic systems containing a double bond at the ring fusion is, for practical purposes, precluded.

Experimental Section[9]

Preparation of Dihydroanisole (1).—A 1.0-g sample of 1,1,12-trimethyl-2-hydroxy-6-methoxy-1,2,3,4,9,12-hexahydrophenanthrene[10] in 30 ml of acetic acid was shaken with 500 mg of 10% palladium-on-charcoal in an atmosphere of hydrogen until the uptake of hydrogen ceased. The catalyst was removed by filtration, and the filtrate was diluted with water and extracted with ether. The organic phase was then washed successively with water, diluted sodium hydroxide solution, water, and a saturated solution of sodium chloride. After drying over anhydrous magnesium sulfate, the solvent was removed under reduced pressure, and the product was crystallized from ether–petroleum ether (bp 30–60°) to yield 650 mg: mp 110–110.5°; $\lambda_{max}^{CS_2}$ 2.79 μ.

Anal. Calcd for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 79.00; H, 9.54.

Birch reduction of the product (1.49 g) obtained in the previous paragraph was carried out in a mixture of 100 ml of absolute ether and 300 ml of dry liquid ammonia containing 24 ml of ethanol. Lithium metal was added in small pieces to this solution at a rate which permitted maintenance of a blue color for a period of 45 min. The ammonia was then allowed to evaporate under a nitrogen atmosphere. Ice water and ether were added, and the product was isolated by ether extraction. After the usual washing and drying operations, the solvent was removed, and the product was crystallized from ether–petroleum ether to yield 1.16 g: mp 142–143°; $\lambda_{max}^{CH_2Cl_2}$ 2.81, 5.90, 6.01, 9.70 μ.

Anal. Calcd for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 78.39; H, 10.22.

Acetylation of this material with acetic anhydride and pyridine afforded the corresponding acetate (1) (77% yield): mp 152–153°; $\lambda_{max}^{CH_2Cl_2}$ 5.80, 5.90, 6.01, 9.71 μ.

Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.37; H, 9.46.

Preparation of Acetoxy Ketal 2.—To a solution of 206 mg of compound **1** in 8 ml of anhydrous ether were added 0.2 ml of methanol and a catalytic amount of *p*-toluenesulfonic acid. The solution was maintained at 0° for 2 hr and was then heated under reflux for 30 min. At the end of this time the reaction mixture was poured into cold, dilute sodium bicarbonate solution, and the ether phase was washed with water and saturated sodium chloride solution. After drying over anhydrous sodium sulfate, the solvent was removed, and the residue was crystallized from ether–petroleum ether. The yield of compound **2** was 165 mg: mp 120–121°; $\lambda_{max}^{CH_2Cl_2}$ 5.80, 8.94, 9.50, 9.70 μ.

Anal. Calcd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 71.95; H, 9.70.

Preparation of Ketal 6a.—A solution of 100 g of anisole in a mixture of 100 ml of anhydrous ether, 200 ml of absolute ethanol, and 550 ml of liquid ammonia was treated with small pieces of lithium metal added at a rate sufficient to maintain a blue color for a period of 45 min. The excess lithium was then destroyed by addition of ammonium chloride, and the ammonia was then allowed to evaporate. Addition of 1.5 l. of cold water followed by thorough extraction with ether furnished an ethereal solution which was washed, and dried over anhydrous sodium sulfate.

The ether solution (800 ml) was then treated with 125 ml of anhydrous methanol and several crystals of *p*-toluenesulfonic acid. The reaction mixture was allowed to stand at room temperature for 8 hr and was finally heated under reflux in a nitrogen atmosphere for 8 hr. At the end of this time the solution was cooled, washed with sodium bicarbonate solution, water, and saturated sodium chloride. After drying over anhydrous sodium sulfate, the solvent was removed by careful distillation through a Vigreaux column. The crude product was purified by preparative vapor chromatography yielding 93.4 g of compound **6a**. The analytical sample was obtained by resubmitting a portion of this material to vapor chromatography. The nmr spectrum of the material taken in carbon tetrachloride showed a two-hydrogen multiplet centered at 5.53 (tetramethylsilane standard), a six-hydrogen singlet at 3.11 and a broad six-hydrogen multiplet in the 1.5–2.2-ppm region.

Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.52; H, 9.87.

Preparation of Ketal 6b.—A 60.0-g sample of *p*-methylanisole was reduced with lithium by the procedure of the previous experiment. The crude dihydro derivative was then treated with methanol in the presence of *p*-toluenesulfonic acid as described above, and the product was purified by distillation through a spinning-band column to yield 40.0 g, bp 82–84° (21 mm).

Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.23; H, 10.15.

Preparation of Ketal 6c.—This substance was prepared from 3,4-dimethylanisole by the previously described procedure. A 26.0-g sample of starting anisole afforded 25.5 g of 4,4-dimethoxy-1,2-dimethylcyclohexene, bp 70–71° (7 mm).

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.67; H, 10.64.

Preparation of 4,4-Dimethoxynorcarane-7-carboxylic Acid Ethyl Ester (7a).—The unsaturated ketal (**6a**), 6.7 g, was heated to 120–130° in an oil bath, and a mixture of 13.5 g of ethyl diazoacetate and a further 6.7-g sample of ketal (**6a**) was added dropwise over a period of 7 hr in the presence of copper and bronze powders in a 1:1 ratio. Filtration and distillation of the crude reaction product afforded 9.9 g of material, bp 95–105° (0.06 mm). Vapor chromatography (column temperature, 200°) afforded the sample for analysis with nmr characteristics compatible with structure **7a**.

(8) W. P. Campbell and G. C. Harris, *J. Amer. Chem. Soc.*, **63**, 2721 (1941).

(9) Infrared and nmr spectra were taken routinely on all products.

(10) J. D. Tauber, Ph.D. Thesis, Rice University, 1967.

Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.14; H, 8.83. Found: C, 63.63; H, 8.75.

There was obtained in addition a second peak which proved to be a mixture of unsaturated isomers (10). It was subsequently established that elimination of methanol occurred during chromatography.[11]

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.34; H, 8.20.

Preparation of 4-Ketonorcarane-7-carboxylic Acid Ethyl Ester (8a).—A solution of 6.0 g of compound **7a** in 300 ml of acetone was treated with 1.0 g of *p*-toluenesulfonic acid monohydrate, and the mixture was allowed to stand at room temperature for 18 hr. At the end of this time cold, dilute sodium bicarbonate solution was added, and the product was isolated by ether extraction. After the usual washing and drying operations, the solvent was removed affording 6.02 g of crude material which was shown to contain 75% of compound **8a** by vapor chromatography. A chromatographically pure sample (λ_{max}^{film} 5.78, 5.83 μ) was analyzed.

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.97; H, 7.77.

The 2,4-dinitrophenylhydrazone, prepared as a derivative, melted at 129–132° (95% ethanol).

Anal. Calcd for $C_{16}H_{18}N_4O_6$: C, 53.04; H, 5.01; N, 15.46. Found: C, 53.01; H, 5.03; N, 15.50.

Preparation of Conjugated Keto Ester 9a.—A solution of 3.7 g of keto ester (**8a**) in 125 ml of dry benzene was heated under reflux for 8 hr in the presence of a catalytic amount of *p*-toluenesulfonic acid. The reaction mixture was then cooled, washed successively with dilute sodium bicarbonate solution, water, and saturated sodium chloride, and finally dried over anhydrous magnesium sulfate. Removal of the solvent followed by vapor chromatography of the residual oil furnished a 90% yield of **9a**, λ_{max}^{film} 5.78, 5.92 μ.

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.92; H, 7.61.

Conversion of Compound 9a into *p*-Hydroxyphenylacetic Acid.—A 300-mg sample of (**9a**) was dissolved in 1 ml of xylene and 300 mg of 10% palladium on charcoal was added. The mixture was heated in an oil bath (180°) for 5 hr, and was then cooled, diluted with ether, and filtered. Extraction with dilute sodium hydroxide and acidification furnished 55 mg of phenolic material, which was hydrolyzed by treatment with 1.5 ml of 10% potassium hydroxide solution for 50 min at reflux temperature. Routine work-up afforded 27 mg of crystalline material, which was purified by sublimation and recrystallization from ether–petroleum ether. The product melted at 153–154.5° and was identified as *p*-hydroxyphenylacetic acid by direct comparison with an authentic sample.

Preparation of 4,4-Dimethoxy-1-methylnorcarane-7-carboxylic Acid Ethyl Ester (7b).—The unsaturated ketal (**6b**), 14.8 g, was heated to 120°, and was treated by dropwise addition with 11.4 g of ethyl diazoacetate in the presence of copper bronze powder. Distillation of the resulting dark oil afforded 4.7 g of starting material (**6b**) and 10.7 g of product **7b**, bp 78–79° (0.007 mm).

Anal. Calcd for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.31; H, 8.90.

Preparation of 4,4-Dimethoxy-1,2-dimethylnorcarane-7-carboxylic Acid Ethyl Ester (7c).—Unsaturated ketal (**6c**), 11.5 g, was treated with 16.7 g of ethyl diazoacetate at 125–135° by the procedure of the previous experiment. Distillation furnished 2.3 g of starting material and 10.2 g of ester **7c**, bp 76–96° (0.02–0.05 mm). The analytical sample was prepared by vapor chromatography.

Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.62; H, 9.25.

Preparation of Compound 8b.—Ketal ester **7b**, 6.33 g, was cleaved by exchange with acetone according to the procedure described for the preparation of keto ester (**8a**). The product was purified by vapor chromatography: yield 84%; λ_{max}^{film} 5.78, 5.82 μ.

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.00; H, 8.16.

Preparation of Keto Ester 8c.—Cleavage of 1.8 g of ketal ester **7c** was carried out by the procedure described above. The product was isolated by vapor chromatography, but since some attendant decomposition occurred, the exact yield could not be determined. A pure sample absorbed in the infrared at 5.78 and 5.81 mμ.

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.86; H, 8.41.

Preparation of Compound 9b.—A solution of 1.0 g of keto ester (**8b**) in 40 ml of absolute ethanol containing a catalytic amount of sodium acetate was heated under reflux (nitrogen atmosphere) for 5 hr. The reaction mixture was then diluted with water and extracted with ether. After standard washing and drying procedures, the solvent was removed, and the residue was subjected to vapor chromatography: yield 87%; λ_{max}^{film} 5.78, 5.92 μ.

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 66.61; H, 7.92.

The dinitrophenylhydrazone prepared as a derivative melted at 116–117.5° (95% ethanol).

Anal. Calcd for $C_{17}H_{20}N_4O_6$: C, 54.25; H, 5.36; N, 14.89. Found: C, 54.07; H, 5.52; N, 15.09.

Preparation of Conjugated Keto Ester 9c.—A 1.37-g sample of crude keto ester **8c** was dissolved in 50 ml of dry ethanol and a trace of *p*-toluenesulfonic acid was added. The solution was heated under reflux in a nitrogen atmosphere for 3 hr at the end of which time the bulk of the solvent was evaporated under reduced pressure. Routine washing and drying furnished crude material which was purified by vapor chromatography: yield 63%; λ_{max}^{film} 5.78, 5.99 μ.

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.41; H, 8.66.

The 2,4-dinitrophenylhydrazone prepared as a derivative melted at 119.5–120° (95% ethanol).

Anal. Calcd for $C_{18}H_{22}N_4O_6$: C, 55.38; H, 5.68; N, 14.35. Found: C, 55.21; H, 5.91; N, 14.42.

Preparation of Ketal 12.—A solution of 44.4 g of 1-methyl-7-methoxy-2-tetralone[12] in 500 ml of dry benzene and 100 ml of ethylene glycol containing a small amount of *p*-toluenesulfonic acid was heated to reflux temperature under a water separator for a period of 6 hr. The product, isolated in the customary way, crystallized after removal of the solvent. The analytical sample was prepared by sublimation at 65° (0.004 mm), followed by recrystallization from ether–petroleum ether, and had mp 73.5–74°.

Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.89; H, 7.69.

A 1.0-g sample of this ketal in 120 ml of liquid ammonia, 60 ml of absolute ether, and 20 ml of dry ethanol was treated with small pieces of lithium added at a rate sufficient to maintain a blue color for 45 min. Evaporation of the ammonia, addition of water, and extraction with ether furnished a dihydro derivative as a crude oil which resisted all attempts at crystallization, λ_{max}^{film} 5.87, 5.96 μ. The material was hence treated directly with methanol and *p*-toluenesulfonic acid in ether as described for preparation of acetoxy ketal **2**. Distillation of the crude product afforded 1.08 g of ketal **12**, bp 98–111° (0.01 mm).

Anal. Calcd for $C_{15}H_{24}O_4$: C, 67.14; H, 9.01. Found: C, 67.03; H, 8.97.

Registry No.—**1**, 16831-46-2; free base of **1** (mp 110–110.5°), 10064-10-5; $C_{18}H_{28}O_2$ (mp 142–143°), 16831-66-6; **2**, 16831-47-3; **6a**, 16831-48-4; **6b**, 16831-49-5; **6c**, 16831-50-8; **7a**, 16831-51-9; **7b**, 16831-52-0; **7c**, 16831-53-1; **8a**, 16831-54-2; **8a** 2,4-dinitrophenylhydrazone, 16831-55-3; **8b**, 16831-56-4; **8c**, 16831-57-5; **9a**, 16831-58-6; **9b**, 16831-59-7; **9b** 2,4-dinitrophenylhydrazone, 16831-60-0; **9c**, 16831-61-1; **9c** 2,4-dinitrophenylhydrazone, 16831-62-2; **12**, 16831-63-3; diazoacetic ester, 623-74-5; $C_{14}H_{18}O_3$ (mp 73.5–74°), 16831-64-4.

(11) A. Serini and H. Koster, *Ber.*, **71**, 1766 (1938).

(12) M. E. Kuehne, *J. Amer. Chem. Soc.*, **83**, 1492 (1961).

The Base-Catalyzed Intermolecular Condensation of α,β-Unsaturated Ketones. Self-Condensation of Styryl Methyl and Styryl Ethyl Ketones to 5-Aryl-3-styryl-2-cyclohexen-1-ones

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Styryl methyl and styryl ethyl ketones, $ArCH{=}CHCOCH_2R$ (R = H, CH_3), having suitable aryl substituents (methoxy, dimethylamino) undergo self-condensation in aqueous ethanolic sodium hydroxide to 5-aryl-3-styryl-2-cyclohexen-1-ones (**6a–d**) and 5-aryl-2,4-dimethyl-3-styryl-2-cyclohexen-1-ones (**11a–g**), respectively. Similarly, 1-(2-methoxyphenyl)-2-methyl-1-buten-3-one undergoes self-condensation to 5-(2-methoxyphenyl)-3-[1-methyl-2-(2-methoxyphenyl)vinyl]-6-methyl-2-cyclohexen-1-one (**9**). This behavior contrasts with that of styryl alkyl ketones having R groups larger than methyl; they undergo self-condensation to 4-alkanoyl-2-alkyl-3,5-diarylcyclohexanones (**3**) under the same reaction conditions. Spectral data for all compounds agree with the structural assignments. Retroaldol cleavage of 2,4-dimethyl-5-(2-methoxyphenyl)-3-(2-methoxystyryl)-2-cyclohexen-1-one (**11a**) by heating in aqueous ethanolic sodium hydroxide at 150° led to 2-methoxybenzyl alcohol and epimeric 5-(2-methoxyphenyl)-2,3,4-trimethyl-2-cyclohexen-1-ones, **12a** and **b**. Equilibration data and nmr spectra suggest that cyclohexenones **11a–f** have a *trans* diequatorial C-4 methyl, C-5 aryl configuration. The scope of the reaction is discussed with respect to substituents in the reactant styryl alkyl ketone including number, position, and type of aryl substituents. A comparison is made, with respect to substituents, between the two possible cyclization paths (Michael or aldol) by which the intermediate acyclic olefinic diketone **2** forms cycloalkanones (**3**) or cycloalkenones (**6, 11**).

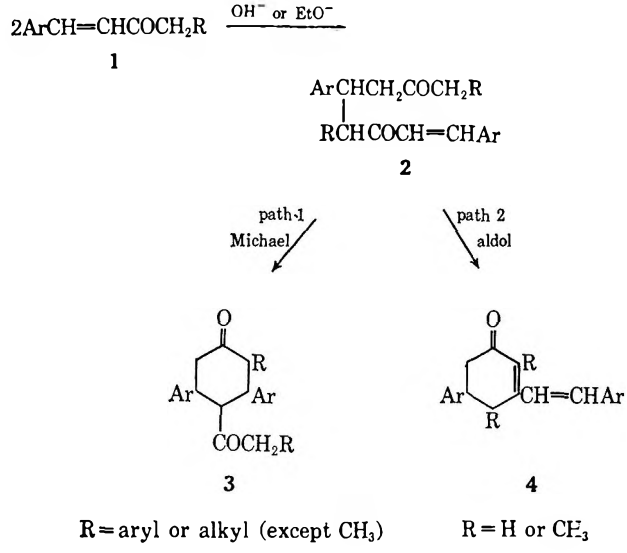
We have extended our studies of the base-catalyzed self-condensation of styryl alkyl ketones to include styryl methyl and styryl ethyl ketones (**1**, R = H, CH_3). These ketones are conveniently prepared *in situ* by

$$ArCHO + CH_3COCH_2R \xrightarrow{OH^- \text{ or } EtO^-} ArCH{=}CHCOCH_2R + H_2O$$
1

aldol condensation of aromatic aldehydes with methyl ketones. Styryl alkyl ketones having structure **1** may undergo intermolecular Michael addition to an acyclic 1,5-diketone **2** (isolated where Ar = C_6H_5, R = i-C_3H_7[1]). See Scheme I.

When substituent R is an alkyl group larger than methyl, diketone **2** (obtained *in situ*) undergoes Michael cyclization to 3,5-diaryl-4-alkanoylcyclohexanone **3** (path 1).[2] Styryl methyl and styryl ethyl ketones exhibit different behavior. They have been shown in the present work to form 5-aryl-3-styryl-2-cyclohexen-1-ones (**4**) by aldol cyclization of diketone **2** (path 2). Successful cyclizations by either path depend on the substituents in the aryl group.

SCHEME I



The condensations leading to cyclohexenone **4** are usually run by reaction of an aromatic aldehyde with an excess of methyl ketone to minimize formation of dibenzal ketones. Sodium hydroxide in ethanol is used with 2-butanone, aqueous medium with acetone. Condensations to diketone **3** employ equimolar amounts of aldehyde and ketone (ethanolic sodium hydroxide).[2] Successful condensations require use of pure reagents in a nitrogen atmosphere. The slightly soluble products (both **3** and **4**) crystallize from the reaction mixture after a few days; each is readily purified by recrystallization from ethanol or ethyl acetate. Cyclohexanones (**3**) are colorless and show weak ultraviolet absorption due to isolated aryl groups. The cyclohexenones (**4**) are distinguished by their yellow color and strong ultraviolet absorption near 370 mμ.

The base-catalyzed condensation of aromatic aldehydes with acetone (employed in molar excess) readily leads to styryl methyl ketones, and with 2-butanone to styryl ethyl ketones; yields are often high. Sodium hydroxide, in water or ethanol solvent, is most frequently employed as catalyst. Over 100 examples of these reactions are known.[3–5] There are very few reports of other products resulting from these condensations.[6] In particular, products derived by intermolecular self-condensation of a styryl methyl or styryl ethyl ketone have been mentioned in only a few publica-

(1) A. T. Nielsen, to be published.

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(3) A. T. Nielsen and W. J. Houlihan, *Org. Reactions*, **16**, 186 (1968).

(4) N. L. Drake and P. Allen, Jr., "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1944, p 77.

(5) (a) R. Fabinyi and T. Széki, *Ber.*, **39**, 1211 (1906); (b) H. Bauer and P. Vogel, *J. Prakt. Chem.*, [2] **88**, 329 (1913); (c) N. F. Albertson, *J. Amer. Chem. Soc.*, **72**, 2594 (1950); (d) J. H. Burckhalter and S. H. Johnson, *ibid.*, **73**, 4835 (1951); (e) K. W. Bentley, J. Dominguez, and J. P. Ringe, *J. Org. Chem.*, **22**, 418 (1957); (f) K. W. Bentley and S. F. Dyke, *J. Chem. Soc.*, 3151 (1961); (g) Kalle A.-G., British Patent 943,266; *Chem. Abstr.*, **60**, 14696 (1964).

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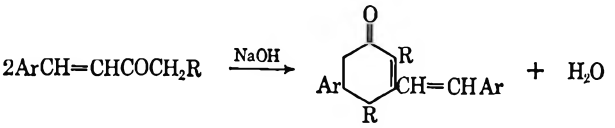
TABLE I

SYNTHESIS OF 5-ARYL-3-STYRYL-2-CYCLOHEXEN-1-ONES

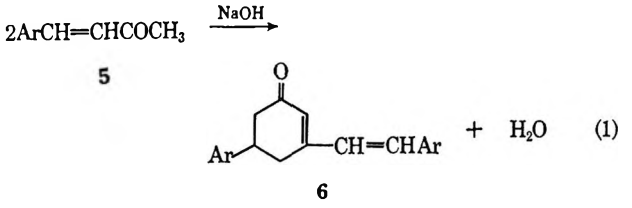


Compd	Ar	R	Yield, %	Mp, °C	Molecular formula	Anal. Calcd C, %	Calcd H, %	Calcd Mol wt	Found C, %	Found H, %	Found Mol wt
6a	2,4-$(CH_3O)_2C_6H_3$	H	9	169–170	$C_{24}H_{26}O_5$	73.07	6.64	394.45	72.91	6.54	397
6b	3,4-$(CH_3O)_2C_6H_3$	H	18[a]	168–169[b]	$C_{24}H_{26}O_5$	73.07	6.64	394.45	72.97	6.66	391
6c	3-CH_3O-4-*n*-$C_3H_7OC_6H_3$	H	Low[c]	152–153[c]	$C_{28}H_{34}O_5$	74.64	7.61	450.55	74.5[c]	7.6[c]	
6d	3,4-$(CH_2O_2)C_6H_3$	H	8	177–177.5	$C_{22}H_{18}O_5$	72.92	5.01	362.36	72.88	4.95	362
6e	2,4,5-$(CH_3O)_3C_6H_2$	H	10	191–193	$C_{26}H_{30}O_7$	68.70	6.65	454.50	68.63	6.64	460
11a	2-$CH_3OC_6H_4$	CH_3	64	186–187	$C_{24}H_{26}O_3$	79.53	6.93	378.45	79.42	6.84	370
11a′	2-$CH_3OC_6H_4$	CH_3	*d*	118–120	$C_{24}H_{26}O_3$	79.53	6.93	378.45	79.60	7.14	377
11b	2,4-$(CH_3O)_2C_6H_3$	CH_3	19	186–187	$C_{26}H_{30}O_5$	73.91	7.16	422.50	73.91	7.30	415
11c	2,5-$(CH_3O)_2C_6H_3$	CH_3	29	162–163	$C_{26}H_{30}O_5$	73.91	7.16	422.50	74.07	7.23	427
11d	3,5-$(CH_3O)_2C_6H_3$	CH_3	30	114–115	$C_{26}H_{30}O_6$	73.91	7.16	422.50	74.29	7.07	431
11e	2,4,5-$(CH_3O)_3C_6H_2$	CH_3	50	190–192	$C_{28}H_{34}O_7$	69.69	7.10	482.55	69.76	7.21	488
11f	3,4,5-$(CH_3O)_3C_6H_2$	CH_3	20	191–193	$C_{28}H_{34}O_7$	69.69	7.10	482.55	69.91	7.17	481
11g	4-$(CH_3)_2NC_6H_4$	CH_3	12	174–175	$C_{26}H_{32}N_2O$[e]	80.37	8.30	388.53	80.16	8.53	395

[a] Heilbron[7] reports a yield of 20% under similar conditions. [b] Lit.[7] mp 168°. [c] Data of Heilbron.[7] The preparation of 6c was not repeated. [d] Isolated by epimerization of 11a at 180° (aqueous ethanolic sodium bicarbonate). [e] Calcd: N, 7.21. Found: N, 7.47.

tions.[7-9] The present investigation shows the scope of the base-catalyzed self-condensation reactions of styryl alkyl ketones.

Self-Condensation of Styryl Methyl Ketones.—The base-catalyzed intermolecular condensation of styryl methyl ketones (**5**) has been examined previously by Heilbron and coworkers.[7] They found two 3-methoxy-4-alkoxybenzalacetones to give products described as 5-aryl-3-styryl-2-cyclohexen-1-ones (**6**) (eq 1). These



were obtained when 4-alkoxy was methoxy (20% yield of **6b**; *cf.* Table I) and *n*-propoxy (very low yield of **6c** not stated). We have repeated Heilbron's preparation of **6b** and confirm his results. 3-Methoxy-4-alkoxybenzalacetones with 4-alkoxy groups ethoxy, isopropoxy, and benzyloxy failed to produce isolable cyclohexenones.[7] Catalysts tried in these experiments included aqueous sodium hydroxide and piperidine.[7,10] Resinous materials were reported as products of most of the condensations.

We have extended the reaction of eq 1 to the preparation of three new cyclohexenones: **6a**, **d**, and **e** (Table I). Styryl methyl ketones derived from piperonal and 2,4,5-trimethoxybenzaldehyde were produced *in situ* from the aldehyde and excess acetone in dilute aqueous sodium hydroxide. On standing at room temperature or below, the cyclohexenones (**6d** and **e**) crystallized from the reaction mixture. In the preparation of **6a** the pure styryl methyl ketone, 1-(2,4-dimethoxyphenyl)-1-buten-3-one, was allowed to react in aqueous ethanolic sodium hydroxide–acetone. Attempts to self-condense several other styryl methyl ketones to cyclohexenones failed, using a variety of procedures; these experiments are discussed below in a summary of the scope of the reaction.

Yields of all cyclohexenones derived from acetone (**6a–e**) are low (8–18%). It is likely that the experimental procedure employed and the scale of most of the runs (*ca.* 0.05 mol) preclude isolation of cyclohexenones formed in very low yields. Yields of cyclohexenones obtained from *in situ*-generated styryl methyl ketones were usually about the same as those obtained from the pure styryl methyl ketone itself. Several modifications of procedure failed to increase the reported yields.

Proof of structure of **6a**, **b**, **d**, and **e** rests on spectral (Table II) and chemical evidence. (Preparation of Heilbron's compound **6c** was not repeated.) Ele-

TABLE II

INFRARED AND ULTRAVIOLET SPECTRA OF 5-ARYL-3-STYRYL-2-CYCLOHEXEN-1-ONES

Compd	ν^{KBr}, cm^{-1}	Principal absorptions in 95% ethanol, λ_{max}, mμ (ϵ_{max})[a]		
6a	1655	260 (12,600)	284 (8,500)	369 (27,500)
6b	1655	260 (10,600)	269 (10,300)	362 (28,800)
6d	1660	242 (10,000)	287 (10,900)	362 (23,500)
6e	1650	266 (10,000)	290 (11,000)	386 (23,000)
9	1640	250 (8,300)	295 (15,000) sh	325 (16,400)
11a	1640	247 (7,700)	278 (6,600)	354 (28,000)
11a′	1640	247 (8,100)	274 (7,200)	355 (25,300)
11b	1655	257 (8,200)	285 (5,640)	372 (19,800)
11c	1660	264 (5,700)	322 (20,200)	372 (16,500)
11d	1650	252 (6,900)	285 (7,700) sh	337 (30,800)
11e	1660	260 (9,150)	295 (10,900)	387 (24,400)
11f	1660	257 (8,300)		352 (29,000)
11g	1640	257 (21,900)		416 (27,600)

[a] Measurements made within a few minutes after preparation of solutions which decompose on standing: 11a, λ_{max} 352 mμ (16,600), 280 (6700), 247 (9850), and 11e, λ_{max} 383 mμ (ε 16,200), 294 (10,900), 257 (10,700), after 15 hr at 25°.

(7) R. Dickinson, I. M. Heilbron, and F. Irving, *J. Chem. Soc.*, 1888 (1927).

(8) C. V. Gheorghiu, *Bull. Soc. Chim. Fr.*, (4) **53**, 1442 (1933).

(9) C. V. Gheorghiu and B. Arwentiev, *ibid.*, (4) **47**, 195 (1930).

(10) In two instances Heilbron found that heating styryl methyl ketones on the steam bath with piperidine gave low yields (<5%) of unidentified, white, amorphous substances.[7] From 3,4-dimethoxy-1-buten-3-one there resulted a substance, $C_{24}H_{28}O_2$ (mp 209–210°), and from 4-ethoxy-3-methoxy-1-buten-3-one a substance, $C_{26}H_{32}O_2$ (mp 187°).

TABLE III

NMR SPECTRA OF 5-ARYL-3-STYRYL-2-CYCLOHEXEN-1-ONES[a]

Compd	Chemical shifts, τ: CH=[b] (multiplets)	CH=[c] (singlet)	CH_3O (singlets)	CH_2, CH (multiplets)	CH_3[d] (singlet)	CH_3[e] (doublet)
6a	2.30–3.65	3.92	6.20	6.80–7.55		
6b	2.58–3.50	3.87	6.08, 6.12	6.55–7.55		
6d	2.50–3.30	3.88	*f*	6.55–7.55		
6e	2.40–3.75	3.88	6.06, 6.14	6.60–7.55		
9	2.50–3.20	3.69	6.17, 6.19	6.30–7.50	7.95	9.03
11a	2.26–3.28		6.16	5.80–7.80	7.94	9.04
11a′	2.25–3.25		6.15	6.25–7.50	8.00	8.53
11b	2.30–3.70		6.14, 6.16	6.30–7.65	7.96	9.04
11c	2.58–3.50		6.18	6.30–7.50	7.95	9.02
11d	2.50–3.70		6.16	6.40–7.50	7.95	9.02
11e	2.60–3.60		6.13	6.20–7.50	7.96	*g*
11f	2.53–3.60		6.08	6.50–7.70	7.92	8.98
11g	2.45–3.60		*h*	6.50–7.50	8.00	8.57

[a] Measurements were taken in $CDCl_3$; tetramethylsilane was the internal reference. [b] Aryl and side-chain vinyl protons. [c] Vinyl hydrogen of cyclohexenone ring at C-2. [d] Vinyl methyl at C-2 except in 9. [e] Center of doublet; $J = 7$ Hz (three protons); C-4 methyl except in 9. [f] CH_2O_2 singlets at τ 3.97 (2), 3.99 (2). [g] Complex multiplet centered at τ 8.75. [h] $(CH_3)_2N$ singlets at τ 7.03 (6), 7.15 (6).

mental analyses and molecular weight data support the molecular formulas (Table I). The single oxygen atom is represented in each compound by a conjugated carbonyl group, ν^{KBr} near 1655 cm^{-1} (Table II). The extended conjugation of a 5-aryl-2,4-pentadien-1-one is supported by ultraviolet spectra typical of this chromophore; an intense band is found near 370 mμ (Table II).[11,12] The nmr spectra of cyclohexenones **6a**, **b**, **d**, and **e** (Table III) agree with the structures assigned. A satisfactory alternate synthesis of cyclohexenone **6b** is described by Heilbron.[7]

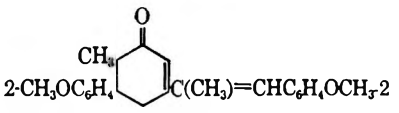
A useful extension of the styryl methyl ketone condensation would employ α-alkylstyryl methyl ketones (**7**).[13] 1-(2-Methoxyphenyl)-2-methyl-1-buten-3-one

$$ArCHO + RCH_2COCH_3 \xrightarrow{H^+} \underset{\mathbf{7}}{ArCH{=}C(R)COCH_3} + H_2O$$

(**8**) was prepared by condensation of 2-methoxybenzaldehyde with 2-butanone employing hydrogen chloride catalyst (77–81% yield).[14] Heating **8** in ethanolic

$$2\ 2\text{-}CH_3OC_6H_4CH{=}C(CH_3)COCH_3 \xrightarrow[\text{EtOH, reflux}]{\text{NaOEt}}$$

8



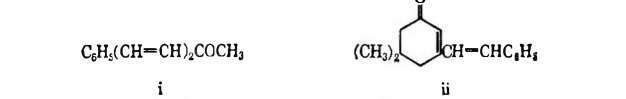
9

sodium ethoxide led to cyclohexenone **9** (34% yield) The infrared and ultraviolet spectra of the product resemble the spectra of other cyclohexenones (Table II). The nmr spectrum (Table III) reveals the expected characteristic cyclohexenone C-2 vinyl singlet at τ 3.69, a side chain vinyl methyl singlet at 7.95, and a 7-Hz C-6 methyl doublet at 9.03.

Self-Condensation of Styryl Ethyl Ketones.—The base-catalyzed intermolecular condensation of styryl ethyl ketones has not previously been studied systematically. Styryl ethyl ketones are readily formed by condensation of an aromatic aldehyde with 2-butanone in ethanolic or aqueous ethanolic sodium hydroxide solution.[3,5] There are two reported 1:1 condensation products derived from styryl ethyl ketones generated *in situ*. Gheorghiu condensed 2-methoxybenzaldehyde with 2-butanone (ethanolic sodium hydroxide) to produce a yellow crystalline material, mp 178–179°, which he described as a dimer of 2-methoxystyryl ethyl ketone, $C_{24}H_{28}O_4$ (*ca.* 29% yield).[8] His elemental analyses support this molecular formula, but no structure was suggested for the compound. Gheorghiu and Arwentiew[9] reported the formation, in small yield, of a colorless compound, mp 194° (assigned molecular formula $C_{24}H_{28}O_4$), by condensation of 4-methoxybenzaldehyde with 2-butanone (equimolar quantities), using aqueous ethanolic sodium hydroxide catalyst. Following the reported procedure for this latter reaction we were unable to isolate the reported compound, or any crystalline solid from the reaction mixture.

We have repeated Gheorghiu's condensation of 2-methoxybenzaldehyde with 2-butanone (ethanolic sodium hydroxide) and obtained a yellow crystalline material, mp 186–187°, after recrystallization from ethanol (yield, 64%). Elemental analysis and molecular weight data indicate a molecular formula $C_{24}H_{26}O_3$ rather than $C_{24}H_{28}O_4$, reported by Gheorghiu. Only by using pure reagents and a nitrogen atmosphere was it possible to obtain a pure sample of the product which gave satisfactory analyses. We believe our condensation product and Gheorghiu's compound to be samples of the same compound. Impurities, possibly water and/or oxidation products, in Gheorghiu's sample may account for its lower melting point and unsatisfactory elemental analyses.

(11) Related dienones are i [(a) A. L. Wilds, L. W. Beck, W. J. Close, C. Djerassi, J. A. Johnson, Jr., T. L. Johnson, and C. H. Shunk, *J. Amer. Chem. Soc.*, **69**, 1985 (1947); (b) R. Kuhn and H. A. Staab, *Ber.*, **87**, 262 (1954)] and ii [(c) G. R. Ensor and W. Wilson, *J. Chem. Soc.*, 4068 (1956)].



i λ_{max}^{EtOH} 234 mμ (ε 6750), 319 (36,400)

ii λ_{max}^{EtOH} 235 mμ (ε 7800), 324 (27,300)

(12) Alkoxy phenyl substituents in compounds listed in Table II are responsible for the expected *ca.* 50-mμ bathochromic shift in the long wavelength band relative to a phenyl substituent: C. N. R. Rao, "Ultraviolet and Visible Spectroscopy," Butterworth and Co., Ltd., London, 1961, pp 40–48. We found 1-(2-methoxyphenyl)-1-penten-3-one to have uv absorptions at λ_{max}^{EtOH} 284 mμ (ε 12,500) and 331 (8500). Compare the spectrum of 1-phenyl-1-penten-3-one: λ_{max}^{MeOH} 220 mμ (ε 11,000), 286 (23,400) [M. Stiles, D. Wolf, and G. V. Hudson, *J. Amer. Chem. Soc.*, **81**, 628 (1959)].

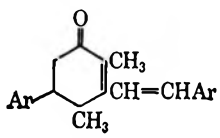
(13) M. T. Bogert and D. Davidson, *ibid.*, **54**, 334 (1932).

(14) E. H. Woodruff and T. W. Conger, *ibid.*, **60**, 465 (1938).

Employing our procedure we have condensed 2,4-, 2,5-, and 3,5-dimethoxybenzaldehydes, 2,4,5- and 3,4,5-trimethoxybenzaldehydes and 4-dimethylaminobenzaldehyde with 2-butanone to yield yellow, crystalline 1:1 condensation products derived *in situ* from the resulting styryl ethyl ketones (compounds **11b–g**, Table I). Yields of these products (12–50%) were all lower than that of **11a** obtained from 2-methoxybenzaldehyde (64%), but generally higher than yields of products **6a–e** derived from styryl methyl ketones (8–18%). Several other aromatic aldehydes failed to yield crystalline condensation products with 2-butanone using a variety of procedures.

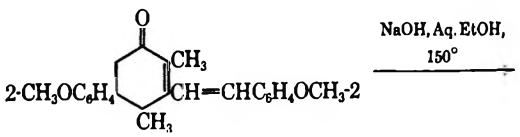
The self-condensation products derived from styryl ethyl ketones (**10**) are believed to be 5-aryl-2,4-dimethyl-3-styryl-2-cyclohexen-1-ones (**11**) (eq 2). The structures of compounds **11a–g** were in complete agreement with their infrared, ultraviolet, and nmr spectra, their elemental analyses, and molecular weight data (see Tables I, II, and III).

$$2\mathrm{ArCH{=}CHCOCH_2CH_3} \xrightarrow[\mathrm{EtOH}]{\mathrm{NaOH}} \underset{\mathbf{10}}{} \qquad + \ \mathrm{H_2O} \qquad (2)$$

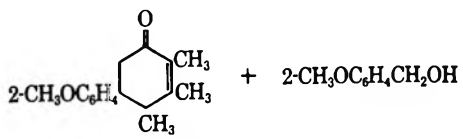


11

Chemical evidence supporting structure **11a** (Gheorghiu's compound) was provided by retroaldol cleavage in aqueous ethanolic sodium hydroxide at 150° (17 hr). The principal products, separated by distillation and vpc, were 2-methoxybenzyl alcohol (44% yield) and epimeric 5-(2-methoxyphenyl)-2,3,4-trimethyl-2-cyclohexen-1-ones (**12a** and **b**; total yield *ca.* 18%).



11a, Gheorghiu's compound



12a (C-4 axial CH_3)

b (C-4 equatorial CH_3)

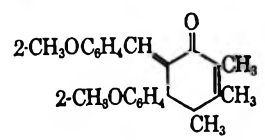
2-Methoxybenzyl alcohol was identified by comparison of its infrared spectrum and 1-naphthylurethan derivative with an authentic sample. Neither 2-methoxybenzaldehyde nor 2-methoxybenzoic acid could be detected or isolated as cleavage products; spectra and the material balance suggest that they were not final products. The vigorous reaction conditions required for retroaldol cleavage evidently reduced the initially formed 2-methoxybenzaldehyde by a hydride-transfer process involving solvent ethanol. Milder reaction conditions failed to effect cleavage of **11a**.

Spectra of epimers **12a** and **b** agree with the structures assigned. Elemental analyses and molecular weight data support the molecular formulas, $C_{16}H_{20}O_2$. Nmr spectra indicate an epimer product ratio of **12a**:**12b** of *ca.* 2:1. Epimer **12b** could be separated and purified by vpc. Its nmr spectrum (deuteriochloroform solvent) showed four aryl protons as a complex multiplet at τ 2.5–3.3, a methoxyl singlet at 6.16, four ring-proton multiplets at 6.4–7.9, two vinyl methyl singlets at 7.98, 8.17, and a 7-Hz methyl doublet at 9.18. Its infrared and ultraviolet spectra indicate an α,β,β-trialkyl substituted α,β-unsaturated ketone: ν^{KBr} 1640 $\mathrm{cm^{-1}}$; $\lambda_{\mathrm{max}}^{\mathrm{EtOH}}$ 244 mμ (ε 11,300).[15] Epimer **12a** could not be obtained free of **12b** by vpc. However, a chromatographed sample which contained *ca.* two-thirds **12a** had infrared and ultraviolet spectra identical with pure epimer **12b**. The nmr spectrum of this sample indicated epimer **12a** to differ from **12b** principally in the chemical shifts of the C-3 and C-4 methyl signals; for **12a**, there was a singlet at τ 8.07 and a 7-Hz doublet centered at 8.82. The C-2 methyl singlet appeared at *ca.* τ 8.17 in both epimers. Assuming the C-5 2-methoxyphenyl group to remain equatorial in both isomers, it appears reasonable that they are C-4 epimers. The lower field C-4 methyl signal of epimer **12a** suggests that its C-4 methyl is pseudo-axial and deshielded by the closely adjacent aryl group.[16] Dreiding models show a pseudo-equatorial C-4 methyl in **12b** to be rather far removed from the C-5 aryl group.

The 2,4-dinitrophenylhydrazones of both epimers of **12** were prepared. That of **12a** had mp 159–161° and uv bands at $\lambda_{\mathrm{max}}^{\mathrm{EtOH}}$ 258 mμ (ε 15,000), 385 (23,000); that of **12b** had mp 201.5–202.5° and uv bands at $\lambda_{\mathrm{max}}^{\mathrm{EtOH}}$ 260 mμ (ε 13,000), 386 (21,000).[17]

An attempt to resynthesize cyclohexenone **11a**, or **11a′**, by reaction of 2-methoxybenzaldehyde with epimer mixture **12a** and **b** containing *ca.* two-thirds **12a** (lithium amide, tetrahydrofuran, 150°) led to ketone **13**, mp 190–191°, by aldol condensation on the ring methylene group. Structure **13** is supported by its spectra: ν^{KBr} 1670 (C=O), 1640 $\mathrm{cm^{-1}}$ (C=C); $\lambda_{\mathrm{max}}^{\mathrm{EtOH}}$ 328 mμ

$$2\text{-}\mathrm{CH_3OC_6H_4CHO} + \mathbf{12a} \xrightarrow[150^\circ]{\mathrm{LiNH_2,\ THF}}$$



13

(ε 11,800), 278 (11,100), 273 (10,700), 244 (10,400).[18] The nmr spectrum of **13** closely resembles that of **12a**: C-4 methyl doublet at τ 8.82 (7-Hz), C-2 methyl singlet at 8.22, C-3 methyl singlet at 8.10. Two methoxy singlets appear at τ 6.13, 6.22; aryl and vinyl protons (9) were at τ 2.5–3.3. Comparison of this nmr spectrum

(15) α,β,β-Trialkyl-substituted α,β-unsaturated ketones have a uv band at $\lambda_{\mathrm{max}}^{\mathrm{EtOH}}$ 247 ± 5 mμ: R. B. Woodward, *J. Amer. Chem. Soc.*, **64**, 76 (1942). For example, $(CH_3)_2C{=}C(CH_3)COCH_3$ has a uv band at $\lambda_{\mathrm{max}}^{\mathrm{EtOH}}$ 247 mμ (ε 7900): R. Mecke and K. Noack, *Angew. Chem.*, **68**, 150 (1956).

(16) In substituted 2- and 4-methylcyclohexanones the axial methyl signal is always observed at lower field (by *ca.* τ 0.1–0.2) relative to the signal for the corresponding equatorial methyl isomer: F. Johnson, N. A. Starkovsky, and W. D. Gurowitz, *J. Amer. Chem. Soc.*, **87**, 3492 (1965); F. Nerdel, D. Frank, and K. Rehse, *Chem. Ber.*, **100**, 2978 (1967).

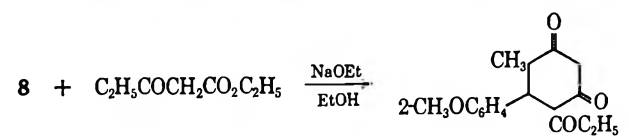
(17) Mesityl oxide 2,4-dinitrophenylhydrazone has a uv band at $\lambda_{\mathrm{max}}^{\mathrm{EtOH}}$ 379 mμ (ε 23,000): J. D. Roberts and C. Green, *J. Amer. Chem. Soc.*, **68**, 214 (1946).

(18) *trans*-2-Benzal-4,4-dimethyl-1-tetralone has uv bands at $\lambda_{\mathrm{max}}^{\mathrm{MeOH}}$ 307 mμ (ε 16,500) and 227 (11,400); the *cis* isomer has bands at $\lambda_{\mathrm{max}}^{\mathrm{MeOH}}$ 311 mμ (ε 11,300), 269 (9300), and 234 (9700): D. N. Kevill, E. D. Weiler, and N. H. Cromwell, *J. Org. Chem.*, **29**, 1276 (1964); *cf.* A. Hassner and T. C. Mead, *Tetrahedron*, **20**, 2201 (1964).

with that of **12a** and **b** suggests an equatorial C-5 aryl, axial C-4 methyl in **13** (condensation product derived from **12a**).[16] It is not clear from our spectral data whether the aryl of the 6-benzal group in **13** is *cis* or *trans* to the carbonyl.[18]

Formation of **13** by aldol condensation is atypical since all reported reactions of aromatic aldehydes with 3-methyl-2-cyclohexen-1-ones (ethanolic sodium ethoxide, 25°, several days) favor a thermodynamically controlled product derived by aldol condensation on the C-3 methyl group, with formation of a 3-styryl derivative.[11c,19] No reaction, to form either **11a**, **11a'** or **13**, occurred between 2-methoxybenzaldehyde and **12** in ethanolic sodium ethoxide, or with potassium *t*-butoxide in tetrahydrofuran, at 25° or at reflux temperatures. Attack at the C-3 methyl (*i.e.*, on the appropriate **12** anion) may be severely hindered by the adjacent C-2 and C-4 methyl groups, as well as by the *ortho* methoxyl group in the aldehyde. The formation of **13** rather than **11a** or **11a'** in our experiment could be a result of rapid irreversible formation of a high concentration of the enolate anion of **12** derived by removal of the most acidic C-6 proton, a process favored by the reaction conditions employed.[20] Also, use of tetrahydrofuran solvent and lithium amide minimizes retroaldol reaction.

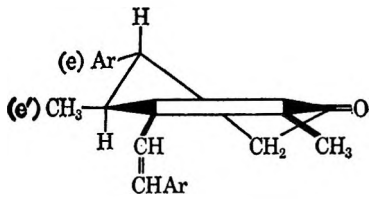
An attempt to synthesize ketone **12** by condensation of 1-(2-methoxyphenyl)-2-methyl-1-buten-3-one (**8**) with ethyl propionyl acetate (ethanolic sodium ethoxide) led to a triketone, believed to be an enolic form of **14** (36% yield). Spectral data agree with this



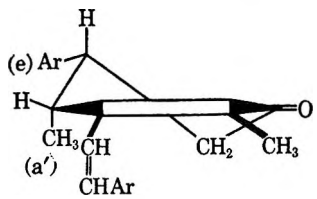
14

structure; see Experimental Section. Intramolecular Claisen condensation is favored over aldol cyclization in this example.[21] Attempted condensation of 1-(2-methoxyphenyl)-1-penten-3-one with ethyl α-methylacetoacetate also failed to yield **12** (reactant styryl ketone recovered).

The stereochemistry of the 5-aryl-2,4-dimethyl-3-styryl-2-cyclohexen-1-ones **11a–g** is of interest. Assuming in each compound an equatorial aryl group at C-5, epimer pairs should differ in configuration of the methyl group at C-4. Epimerization of the 2-methoxyphenyl derivative **11a**, mp 186–187°, by equilibration in aqueous ethanolic sodium bicarbonate at 180° for 2 hr, led to an 8% conversion into epimer **11a'**, mp 118–120°, with 76% recovery of **11a**. The infrared and ultraviolet spectra of these epimers are virtually identical (Table II). Differences were observed in solubility and nmr spectra. The low melting form is much more soluble in ethanol; it was crystallized from hexane. A difference was observed in the chemical shift of the C-4 methyl doublets which appeared at τ 9.04 in **11a** and at 8.53 in **11a'**, a situation also found with the derived cyclohexenone epimer pair **12a** and **b**. Epimer **11a'** having the lower field C-4 methyl signal is believed to have a pseudo-axial C-4 methyl.[16] The cyclohexenone methylene proton signals in **11a** agree with the assigned stereochemistry: the equatorial proton at C-6 at τ 7.52 (dd, $J_{ae} \cong 5$ Hz and $J_{gem} \cong 18$ Hz), the axial C-6 proton at 6.97 (dd, $J_{aa} \cong 15$ Hz, and $J_{gem} \cong 18$ Hz). The axial C-5 proton at 6.05 and the pseudo-axial C-4 proton at 6.58 each appear as distinct multiplets with splittings characteristic of their assigned stereochemistry.



11a, mp 186–187°



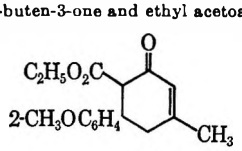
11a', mp 118–120°

Chemical behavior in basic media agrees with the configuration assignments for **11a** and **11a'**. The lower melting epimer (**11a'**) was found to be partially destroyed under the reaction conditions (53% recovery of **11a'** after 114 hr). With more vigorous conditions (ethanolic sodium ethoxide, 150°, 3 hr) destruction of **11a'** was *ca.* 90% complete, only 10% of **11a'** being recovered. *No significant epimerization of* **11a'** *to the higher melting, less soluble epimer* **11a** *was found in these experiments.* Epimer **11a** is much more stable in basic media and is only slowly epimerized to **11a'** even at 180°. It remained unchanged after refluxing in aqueous sodium hydroxide–tetrahydrofuran for 25 hr (100% recovery). These results suggest a slow axial attack in **11a** (proton removal from C-4) and more rapid equatorial attack in the common intermediate carbanion (protonation at C-4 leading to epimer **11a'**).[22] The converse situation is believed to be true in epimer **11a'** which undergoes a relatively rapid proton removal from C-4 by equatorial attack, followed by destruction of the intermediate carbanion, which evidently occurs much more rapidly than axial protonation required to form **11a**. The accumulation of retroaldol product **12a** (axial C-4 methyl) in favor of **12b** is in agreement with

(19) (a) G. Kabas, *Tetrahedron*, **22**, 1213 (1966); (b) J.-M. Conia and U. O'Leary, *Compt. Rend.*, **249**, 1002 (1959); (c) G. Renzi, A. Steuer, and V. Dal Piaz, *Ann. Chim.*, **57**, 279 (1967); (d) J. Dewar, D. R. Morrison, and J. Read, *J. Chem. Soc.*, 1598 (1936).

(20) H. O. House, *Rec. Chem. Progr.*, **28**, 98 (1967).

(21) The course of this type of reaction evidently depends on substituents. 1-(2-Methoxyphenyl)-1-buten-3-one and ethyl acetoacetate lead to i (or the 4-carbethoxy derivative) by aldol cyclization (aqueous ethanolic sodium hydroxide): T. A. Forster and I. M. Heilbron, *J. Chem. Soc.*, **125**, 340 (1924).



i

(22) We believe this interesting example to parallel that found in 2-phenyl-1-nitrocyclohexanes wherein equatorial, relative to axial, attack at C-1 (proton abstraction or insertion) is favored by rate factors of 200–550:1; F. G. Bordwell and M. M. Vestling, *J. Amer. Chem. Soc.*, **89**, 3906 (1967); F. G. Bordwell, W. J. Boyle, Jr., J. A. Hautala, R. H. Imes, K. C. Lee, and E. C. Steiner, Abstracts, 155th National Meeting of the American Chemical Society, San Francisco, Calif., April 1–5, 1968, p R-10.

these observations. The intermediate carbanion derived from **12** is more stable than that of **11a**. It leads, by equatorial C-4 protonation, to **12a**.

In each condensation leading to cyclohexenones **11a–g** (Table I) only one epimer was isolated. In all compounds the nmr peaks for the C-4 methyl doublet are centered at *ca.* τ 9.03, with the exception of the 4-dimethylamino compound **11g** (τ 8.57). It is suggested that compounds **11a–f** all have a pseudo-equatorial C-4 methyl; **11g** may have a pseudo-axial C-4 methyl.[16]

The exclusive formation of one epimer with *trans* C-4—C-5 stereochemistry may be a consequence of at least three factors favoring the isolated product: (1) its lower solubility and facile crystallizability, (2) its greater stability under the reaction conditions, and (3) its more rapid rate of formation in an irreversible process. As shown with **11a′** one factor is not an equilibration of products which favors one epimer. A more rapid cyclization to the epimer with C-4–C-5 *trans* stereochemistry (believed to be favored thermodynamically) would account for its formation, since the cyclization is irreversible under the reaction conditions. A mixture of equilibrating epimers of precursor diketone **2** would lead to only one product, if rate-limiting cyclization rates leading to product epimers differed sufficiently. Alternatively, and probably less likely, one product would result if only one epimer of **2** were formed initially, or favored at equilibrium.

Scope of the Reaction.—The self-condensation of styryl alkyl ketones to 5-aryl-3-styryl-2-cyclohexen-1-ones is a reaction quite limited in scope. Styryl methyl and styryl ethyl ketones having certain electron-releasing aryl substituents (alkoxy, methylenedioxy, dialkylamino) have been shown to undergo the reaction.

The reaction has been examined with respect to two principal structural features in the reactant ketone ($ArCH{=}CHCOCH_2R$), *i.e.*, the nature of (1) the alkyl group R and (2) the substituents in the aryl group, including type, ring position, and number of substituents. Reaction conditions were limited to catalysts (sodium hydroxide or sodium ethoxide), solvents (water, ethanol, or aqueous ethanol), and temperatures from −15° to reflux (*ca.* 80–90°). The method of isolation of products restricted successful results to formation of products insoluble in aqueous acetone or aqueous ethanol which elected to crystallize from the reaction mixture after standing at −15–25° for periods up to several months. To some degree this simplified isolation procedure has limited the observed reaction scope, but not its major features.

The reaction is clearly limited to styryl methyl and styryl ethyl ketones. Styryl alkyl ketones having larger alkyl groups and suitable aryl substituents undergo Michael cyclization to 4-alkanoyl-2-alkyl-3,5-diarylcyclohexanones (**3**) under similar reaction conditions. It is the failure of intermediate acyclic diketone **2** to undergo aldol cyclization, when R is larger than methyl, which limits the reaction.

Only aryl substituents having negative Hammett σ_{para} substituent constants[23] permit a successful condensation to a cyclohexenone. Condensations were achieved with methoxy, propoxy, methylenedioxy, and dimethylamino substituents in the phenyl group. However, certain other styryl methyl and styryl ethyl ketones with electron-releasing aryl substituents failed to produce crystalline condensation products. Failures resulted with phenyl substituents ethoxy, amino, diethylamino, methyl, isopropyl, and hydroxy, as well as with 2-, 3-, and 4-pyridyl aryl groups. No successful condensation to a cyclohexenone resulted from benzaldehyde itself.[24] Aldehydes with electron-withdrawing substituents (2-chloro- and 2-nitrobenzaldehydes) failed to form a cyclohexenone by reaction with 2-butanone.

The condensation of styryl alkyl ketones (**1**, R larger than methyl) to cyclohexanones (**3**) also is favored by electron-releasing aryl substituents, and disfavored by electron-withdrawing substituents such as nitro. However, the range of electronegativity of substituents allowed for Michael cyclization to **3** is larger, and includes alkoxy, amino, and alkyl substituents as well as chloro, which has a positive σ_{para} substituent constant.

The ring position and number of aryl substituents affect the cyclohexenone forming reaction. *ortho* and *para* substituents favor the reaction relative to *meta*, although *meta* substitution does not prevent reaction. Although 2-methoxystyryl ethyl ketone gave the highest yield of a cyclohexenone, the 3- and 4-methoxystyryl ethyl ketones did not form one; surprisingly, 2-methoxystyryl methyl ketone also failed to react. Only one other monosubstituted ketone was found to react—4-dimethylaminostyryl ethyl ketone. Most dimethoxy and trimethoxystyryl methyl and ethyl ketones underwent reaction rather well. Interesting anomalies were 3,4-dimethoxy and 3,4-methylenedioxy styryl ethyl ketones which failed to produce cyclohexenones, whereas the corresponding methyl ketones did react.

It is of interest to compare the effects of the ring positions and total number of aryl substituents on the two cyclization reactions (paths 1 and 2 leading from diketone **2**). One striking difference is the fact that *ortho* substituents prevent Michael cyclization (Scheme I, path 1) leading to cyclohexanone **3**, but distinctly favor aldol cyclization to **4**. Also, Michael cyclization is often quite successful with a single electron-withdrawing substituent in the *para* position; aldol cyclization occurs best with two or three electron-withdrawing substituents. These observations suggest that electron-releasing effects of aryl substituents are of greater importance in favoring the aldol cyclization (path 2) than in the Michael cyclization.

Experimental Section[25]

Procedure A. Condensation of 2,4,5-Trimethoxybenzaldehyde with Acetone. Formation of 3-(2,4,5-Trimethoxystyryl)-5-(2,4,5-trimethoxyphenyl)-2-cyclohexen-1-one (6e).—A mixture of 1.96 g (0.01 mol) of 2,4,5-trimethoxybenzaldehyde, 15 ml (11.7 g, 0.2 mol) of acetone, 10 ml of water, and 0.4 ml of 10% aqueous sodium hydroxide solution was warmed slightly on the steam bath to secure a clear solution. The glass-stoppered flask was allowed to stand at room temperature (nitrogen atmosphere) for

(23) G. B. Berlin and D. D. Perrin, *Quart. Rev.* (London), **20**, 75 (1966); H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).

(24) Styryl ethyl ketone itself is the only styryl methyl or styryl ethyl ketone which we have found to form a cycloalkanone (**3**, R = CH_3; yield only 1%).[6]

(25) Melting points were determined on a Kofler block and are corrected. Ultraviolet spectra were determined on a Cary Model 11 spectrophotometer, infrared spectra were obtained on a Perkin-Elmer Model 137 spectrophotometer, and nmr spectra were obtained on a Varian A-60 spectrometer (10–20% solutions in deuteriochloroform). Magnesium sulfate was employed as a drying agent.

6 days (crystals slowly deposited during this time), and in the refrigerator (5°) for 2 months. The orange-yellow prisms (0.22 g, 9.6%) were removed by filtration, mp 190–193°. Recrystallization from ethyl acetate gave small prisms which deposited slowly, mp 191–193°. The prolonged reaction time at 5° could be shortened, since most of the product appeared to crystallize from the reaction mixture within *ca.* 2 weeks.

The above procedure was effective in the condensation of piperonal with acetone to yield cyclohexenone **6d** (Table I). The crude product isolated was mixed with a gummy material from which it could be separated by crystallization from ethyl acetate–ethanol.

The procedure of Heilbron[7] was repeated with 3,4-dimethoxybenzaldehyde (0.05 mol) and acetone (same as above procedure, but with *ca.* one-half the relative amount of acetone). The crude product (5.2 g) which separated, mp 105–145°, was crystallized from ethyl acetate to yield cyclohexenone **6b** (1.75 g, 18%), mp 168–169° (lit.[7] mp 168°; yield, 20%[7]).

Attempts to apply procedure A to the preparation of cyclohexenones from certain other aromatic aldehydes and acetone led to styryl methyl ketones which separated from the reaction mixture. The following known styryl methyl ketones were obtained in this manner; substituents, melting points of crude products, and yields (in parentheses) are listed: 4-dimethylamino, mp 133.5–136.5 (91%) (lit.[5g,26] mp 134–135°); 2-methoxy, mp 34–49° (65%) (lit.[26] mp 50°); 4-hydroxy-3-methoxy, mp 123–128° (77%) (lit.[27] mp 128–129°); 2,4-dimethoxy, mp 54–57° (80%) (lit.[28] mp 62°). Benzaldehyde with excess acetone yields styryl methyl ketone itself in 65–78% yield with aqueous sodium hydroxide catalyst.[4] Modification of procedure A by replacement of most or all of the water with ethanol, to increase solubility of styryl methyl ketone intermediates, sometimes gave clear solutions but usually precipitated the styryl methyl ketones from the reaction solution in low yields (<10%). No crystalline cyclohexenones could be isolated subsequently after the solutions had been diluted with water and chilled; oils and/or styryl methyl ketones resulted.

Procedure A gave unidentified oily products (possibly containing low-melting styryl alkyl ketones) when aplied to acetone condensations with substituted benzaldehydes having the following substituents: 3-methoxy, 4-methoxy, 2-ethoxy, 4-diethylamino, 2,3-dimethoxy, 2,5-dimethoxy, 3,5-dimethoxy, and 3,4,5-trimethoxy.

Procedure B. Condensation of 2-Methoxybenzaldehyde with 2-Butanone. Formation of Gheorghiu's Compound, 2,4-Dimethyl-5-(2-methoxyphenyl)-3-(2-methoxystyryl)-2-cyclohexen-1-one (11a).[8]—To a solution of 30.0 g (0.22 mol) of freshly distilled 2-methoxybenzaldehyde in 225 ml of 95% ethanol was added 30 g (0.416 mol) of 2-butanone and 15 ml of 10% aqueous sodium hydroxide solution. By external cooling the temperature was kept below 32°. After the initial reaction had subsided the yellow solution was allowed to stand in an atmosphere of nitrogen, in the dark, for 18 hr at 25°. The yellow crystals which formed were separated (11.1 g, mp 183–187°); chilling the filtrate at 0° for several weeks deposited 15.5 g of additional material, mp 181–185°, to give a total yield of 26.6 g (64%). Recrystallization of the first crop from ethanol gave 8.5 g of yellow prisms, mp 186–187°.

The above procedure, employing a 1- to 2-week reaction time, was effective in condensation of the following substituted benzaldehydes with 2-butanone to yield cyclohexenones **11b–11g** listed in Table I: phenyl substituents, 2,4-dimethoxy, 2,5-dimethoxy, 3,5-dimethoxy, 2,4,5-trimethoxy, 3,4,5-trimethoxy, and 4-dimethylamino. In some instances it was necessary to warm the reaction mixture initially in order to dissolve the reactant aldehyde. The crude cyclohexenone product was usually mixed with some styryl alkyl ketone. Purification was readily achieved by crystallization from ethanol or ethyl acetate. With 4-dimethylaminobenzaldehyde a 3-week reaction time was employed resulting in a crude product containing much 4-dimethylaminostyryl ethyl ketone;[5g] the cyclohexenone (**11g**) was isolated with some difficulty by fractional crystallization from ethanol.

Procedure B with 2-butanone and 4-diethylaminobenzaldehyde gave principally an oily product from which a 3% yield of 4-diethylaminostyryl ethyl ketone could be isolated by crystallization from ethanol, mp 71–72°.

Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05; mol wt, 231.33. Found: C, 77.75; H, 9.16; N, 6.30; mol wt, 233.

Procedure B with 2-butanone gave oily or gummy products, from which no crystalline product could be isolated, with benzaldehydes having the following substituents: 2-methyl, 4-methyl, 2,3-dimethoxy, 3,4-methylenedioxy, 4-isopropyl, and 3-methoxy.

Procedure B with 2-butanone gave clear solutions from which no product separated, with benzaldehydes having the following substituents: 2-chloro, 2-ethoxy, 4-hydroxy-3-methoxy, 2-amino, 4-hydroxy, 2-nitro, 3,4-dimethoxy, as well as with 2-, 3-, and 4-pyridinecarboxaldehyde. Attempted condensation of 2-pentanone with 2-methoxybenzaldehyde also gave a clear solution with procedure B. Dilution of these solutions with water and/or acidification failed to yield crystalline cyclohexenones.

Attempts to apply procedure B to condensations of aldehydes with acetone failed to yield cyclohexenones. Benzaldehyde and 2-ethoxybenzaldehyde gave gummy products and no crystalline material. Vanillin and 3,4-dimethoxybenzaldehyde gave low yields (<10%) of the styryl methyl ketones. 2-Methoxybenzaldehyde gave *ca.* 15% of di-2-methoxybenzalacetone; the crude product had mp 115–125° (lit.[29] mp 125°).

1-(2-Methoxyphenyl)-2-methyl-1-penten-3-one.—Procedure B applied to condensation of 2-methoxybenzaldehyde with 3-pentanone (reaction time, 11 days; 25°) gave an oil, bp 95–115° (0.1 mm), which was crystallized from hexane to yield the styryl alkyl ketone, mp 39–41° (62% yield). Recrystallization from hexane gave long prisms: mp 42–43°; ν 1670 cm^{-1} (C=O) (measurement on supercooled liquid).

Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90; mol wt, 204.26. Found: C, 76.63; H, 7.93; mol wt, 210.

1-(2,4-Dimethoxyphenyl)-1-buten-3-one.—A mixture of 2,4-dimethoxybenzaldehyde (8.3 g, 0.05 mol), 30 ml of acetone, 10 ml of water, and 10 ml of 10% sodium hydroxide solution was heated under reflux for 15 min. The solution was chilled to yield 9.55 g (93%) of the styryl ketone, mp 55–60°. Recrystallization from ethanol gave pale yellow needles, mp 62–63 (lit.[28] mp 62°).

Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84; mol wt, 206.23. Found: C, 70.04; H, 7.02; mol wt, 205.

Procedure C. Self-Condensation of 1-(2,4-Dimethoxyphenyl)-1-buten-3-one to 3-(2,4-Dimethoxystyryl)-5-(2,4-dimethoxyphenyl)-2-cyclohexen-1-one (6a).—To a solution of 8.1 g of 1-(2,4-dimethoxyphenyl)-1-buten-3-one in 20 ml each of acetone and ethanol, and 40 ml of water was added 2 ml of 10% sodium hydroxide solution. After standing at room temperature for 1 week and in the refrigerator for 6 weeks, the crystalline cyclohexenone **6a** (0.71 g, 9.1%) was removed by filtration, mp 161–162°. Recrystallization from ethyl acetate gave prisms, mp 169–170°.

The above procedure could not be applied successfully to the preparation of a cyclohexenone from 4-dimethylaminostyryl methyl ketone;[5g,26] 38% of the reactant ketone was recovered. 2-Methoxystyryl methyl ketone[26] gave only an oily product. An unsuccessful attempt was made to improve the yield of cyclohexenone **11g** (Table I) by applying the above procedure to self-condensation of 4-dimethylaminostyryl ethyl ketone;[5g] only recovered ketone (*ca.* 75%) and gummy material could be isolated.

Procedure D. Self-Condensation of 1-(2-Methoxyphenyl)-2-methyl-1-buten-3-one (8) to 5-(2-Methoxyphenyl)-3-[1-methyl-2-(2-methoxyphenyl)vinyl]-6-methyl-2-cyclohexen-1-one (9).—A 3.8-g (0.02 mol) sample of 1-(2-methoxyphenyl)-2-methyl-1-buten-3-one (**8**), mp 23–26°,[14,30] was dissolved in 10 ml of absolute ethanolic sodium ethoxide (prepared from 0.1 g of sodium). The

(26) I. M. Heilbron and J. S. Buck, *J. Chem. Soc.*, **119**, 1500 (1921).

(27) A. Ya. Berlin and S. M. Sherlin, *Zh. Obshch. Khim.*, **18**, 1386 (1948); *Chem. Abstr.*, **43**, 2185 (1949).

(28) (a) 2,4-Dimethoxystyryl methyl ketone, mp 62°, has been prepared in 14% yield by Friedel–Crafts acylation of 1,3-dimethoxybenzene with 1-chloro-1-buten-3-one employing stannic chloride catalyst: A. N. Mesmeyanov, N. K. Kochetkov, and L. R. Matov, *Dokl. Akad. Nauk SSSR*, **92**, 85 (1953); *Chem. Abstr.*, **48**, 10665 (1954). (b) The compound, prepared by condensation of 2,4-dimethoxybenzaldehyde with acetone and aqueous sodium hydroxide catalyst, is described as an oil, bp 185–190° at 2 mm (no elemental analyses given): A. Ya. Berlin and T. P. Sycheva, *Zh. Obshch. Khim.*, **22**, 1998 (1952); *Chem. Abstr.*, **47**, 8681 (1953). We have repeated this preparation and find mp 62–63° for 2,4-dimethoxystyryl methyl ketone.

(29) A. Baeyer and V. Villiger, *Ber.*, **35**, 3013 (1902).

(30) Woodruff and Conger[14] report ketone **8** as a liquid, bp 162–163° (12 mm). We determined the nmr spectrum of **8** ($CDCl_3$): τ 2.25 (s, 1, CH=), 2.5–3.2 (m, 4, aryl, CH), 6.22 (s, 3, CH_3O), 7.62 (s, 3, CH_3CO), 8.02 (d, 3, J = 1 Hz, CH_3C=); ν_{neat} 1640 cm^{-1} (C=O).

solution was allowed to stand at 25° for 16.5 hr, then heated on the steam bath for 2 hr. The reddish solution was concentrated to remove ethanol and the residue was treated with saturated potassium carbonate solution. The mixture was extracted with methylene chloride, and the extracts were dried and concentrated to remove solvents. The residue was crystallized from ethanol to yield 1.25 g (34%) of cyclohexenone **9**, mp 126–128°. Recrystallization from ethanol gave 1.0 g of nearly colorless prisms, mp 132–133°. Spectral data are given in Tables II and III.

Anal. Calcd for $C_{24}H_{26}O_3$: C, 79.53; H, 7.23; mol wt, 362.45. Found: C, 79.62; H, 7.31; mol wt, 360.

Procedure D was applied to 1-(2-methoxyphenyl)-2-methyl-1-penten-3-one (preparation described above). A gummy product was obtained, soluble in ethanol or benzene. An amorphous solid, mp 125–140°, which could not be obtained in crystalline form, separated on dilution of the benzene solution with heptane.

Condensation of 1-(2-Methoxyphenyl)-2-methyl-1-buten-3-one (8) with Ethyl Propionylacetate.—A solution of 3.80 g (0.02 mol) of ketone **8**[14,30] and ethyl propionylacetate (2.88 g, 0.02 mol) in 20 ml of absolute ethanolic sodium ethoxide (prepared from 0.46 g of sodium) was heated under reflux for 1.5 hr. The solution was concentrated to remove most of the ethanol and the residue was diluted with water and extracted twice with ether. The dried ether extracts gave 2.4 g (63%) of recovered ketone **8** (analysis by vpc on 10 ft × 0.25 in. Chromosorb W-20% Apiezon L at 200°; retention time and infrared spectrum identical with authentic **8**). The aqueous alkaline part was treated with hydrochloric acid to deposit 2.17 g (36%) of crude **5-(2-methoxyphenyl)-6-methyl-4-propionyl-1,3-cyclohexanedione** (**14**), mp 155–160°. Recrystallization from benzene gave small prisms, mp 160–170° dec; ethanolic ferric chloride gave a red color: ν^{Nujol} 2400–2600 (enolic OH), 1710 (C=O, nonconjugated), and 1590 and 1530 cm^{-1} (bands due to enolic 1,3-diketone).[31] The nmr spectrum was determined in D_2O–potassium carbonate: τ 2.5–3.5 (m, 3, aryl CH), 6.30 (s, 3, CH_3O), 9.13 (d, 3, CH_3CH), 9.08 (t, 3, CH_3CH_2–), 6.02 (q, 2, CH_3CH_2–), and 5.5–6.0 (m, 1); ring protons (3) which did not appear in the spectrum were exchanged by deuterium in the alkaline medium. The analytical sample was dried at 100° (0.05 mm).

Anal. Calcd for $C_{17}H_{20}O_4 \cdot H_2O$: C, 66.65; H, 7.24; mol wt, 306.35. Found: C, 66.34; H, 7.38; mol wt, 306.

The above procedure was applied, with slight modifications, to the condensation of 1-(2-methoxyphenyl)-1-penten-3-one[8] and ethyl α-methylacetoacetate to yield principally recovered styryl ketone.

1,5-Bis(2-methoxyphenyl)-2-methyl-1,4-pentadien-3-one.—To a solution of 13.6 g (0.1 mol) of 2-methoxybenzaldehyde and 3.6 g (0.05 mol) of 2-butanone in 60 ml of ethanol was added 10 ml of 10% aqueous sodium hydroxide solution. After standing 4 days at room temperature the gummy crystals which deposited were filtered (4.6 g) and recrystallized from ethanol to yield 2.1 g (22%) of cyclohexenone **11a**, mp 183–186°. Chilling the mother liquor gave a low-melting solid which was crystallized from dilute ethanol to yield 1.15 g (7.5%) of the dienone: mp 93–95° (another recrystallization raised the melting point to 94–96°); ν^{KBr} 1645 (conjugated C=O) and 1620 cm^{-1} (conjugated C=C); neither another carbonyl absorption nor a hydroxyl band was present; λ_{max}^{EtOH} 239 mμ (ε 14,900) and 345 (20,800).

Anal. Calcd for $C_{20}H_{20}O_3$: C, 77.90; H, 6.54; mol wt, 308.3. Found: C, 78.37; H, 6.68; mol wt, 308.

Retroaldol Cleavage of 2,4-Dimethyl-5-(2-methoxyphenyl)-3-(2-methoxystyryl)-2-cyclohexen-1-one (11a). Formation of Epimeric 5-(2-Methoxyphenyl)-2,3,4-trimethyl-2-cyclohexen-1-ones (12a and b).—A mixture of 7.24 g (0.02 mol) of cyclohexenone **11a**, sodium hydroxide (2.0 g), 100 ml 95% ethanol, and 10 ml of water was heated in a 300-ml capacity, stainless steel bomb at 150° for 17 hr. After cooling, the clear orange solution was concentrated under reduced pressure to remove the ethanol. The residue was extracted with ether, and the extracts were washed with 10% aqueous sodium hydroxide solution. The combined, dried extracts were concentrated to yield 7.23 g of yellow viscous oil which was fractionally distilled under reduced pressure.

The first fraction was 2-methoxybenzyl alcohol: 1.22 g (44%); bp 68–70° (0.1 mm); $n^{25}D$ 1.5440 (lit. $n^{25}D$ 1.5428,[32] $n^{21}D$ 1.5470).[33] An authentic sample (Aldrich) had an index of refraction of $n^{25}D$ 1.5450; its infrared spectrum was identical with authentic sample, ν^{neat} 3200 cm^{-1} (OH); carbonyl absorption was absent. The 1-naphthylurethan derivative was crystallized from cyclohexane and had mp 135–136° which was not depressed when mixed with an authentic sample of 2-methoxybenzyl alcohol 1-naphthylurethan, mp 136–137° (lit.[34] mp 135–136°).

The second fraction (1.7 g), bp 126–130° (0.2 mm), was chromatographed on a 4 ft × 0.25 in. Teflon–5% silicone oil column at 215°. Two major peaks appeared. The first (45% of total) was an unidentified mixture: ν 3300 (OH, weak), 1690 (C=O, weak), and 1640 cm^{-1} (C=O, strong). The last peak (**12a** and **b** mixture, 55% of total, ν^{neat} 1640 cm^{-1}) was used for elemental analysis.

Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25; mol wt, 244.32. Found: C, 78.94; H, 8.50; mol wt, 243.

Rechromatography of the **12a** and **b** mixture permitted a separation of epimer **12b** (last material to leave the column); **12a** could not be completely freed of **12b** (analysis, based on nmr spectra, is discussed in the text). Epimer **12b** formed a 2,4-dinitrophenylhydrazone: dark-red, flat plates; mp 201.5–202.5°; τ ($CDCl_3$) 2.5–3.3 (m, aryl), 6.15 (s, 3, CH_3O), 6.3–9.0 (m, 4, cyclohexene ring protons), 7.97 (s, 3, CH_3C=), 7.98 (s, 3, CH_3C=), 9.22 (d, 3, J = 7 Hz, CH_3CH).

Anal. Calcd for $C_{22}H_{24}N_4O_5$: C, 62.25; H, 5.70; N, 13.20. Found: C, 62.43; H, 5.55; N, 13.06.

Fractional crystallization of 2,4-dinitrophenylhydrazones prepared from the mixture of **12a** and **b** afforded the derivative of **12a**. It was purified by chromatography on alumina (elution with benzene), and recrystallization from ethanol gave dark red prisms, mp 159–161°.

Anal. Calcd for $C_{22}H_{24}N_4O_5$: C, 62.25; H, 5.70; N, 13.20. Found: C, 62.32; H, 5.89; N, 13.18.

The residue from the distillation (4.15 g) failed to yield crystalline material from ethanol or hexane. The aqueous alkaline residue remaining from the ether extractions was acidified with concentrated hydrochloric acid to yield traces of gummy material from which no crystalline material could be isolated.

Condensation of 5-(2-Methoxyphenyl)-2,3,4-trimethyl-2-cyclohexen-1-one (12) with 2-Methoxybenzaldehyde to 6-(2-Methoxybenzal)-5-(2-methoxyphenyl)-2,3,4-trimethyl-2-cyclohexen-1-one (13).—A mixture of a 0.55-g sample of the above unchromatographed fraction 2 (containing *ca.* 0.2 g of **12a** and 0.1 g of **12b**), 0.33 g of 2-methoxybenzaldehyde, 0.05 g of lithium amide, and 2 ml of tetrahydrofuran was heated in a sealed glass tube at 150° for 5 hr. The cooled solution was concentrated to remove the solvent and the residue was extracted with hexane. Ketone **13** separated from the extracts: 22.3 mg, mp 170–185°, and 39.0 mg, mp 185–187°; total yield 61.3 mg, 19% based on assay of **12a** present. Recrystallization from ethanol gave small, pale yellow prisms, mp 190–191°; when mixed with a sample of cyclohexenone **11a** (mp 186–187°) the melting point was depressed to 160–170°. Condensation of 2-methoxybenzaldehyde with crude **12** in parallel experiments, employing ethanolic sodium ethoxide or potassium *t*-butoxide in tetrahydrofuran at 25° or at reflux temperature (16–20 hr), failed to yield **13** or any other crystalline product. Spectra of **13** are discussed in the text.

Anal. Calcd for $C_{24}H_{26}O_3$: C, 79.53; H, 6.93. Found: C, 79.60; H, 7.02.

Epimerization of 2,4-Dimethyl-5-(2-methoxyphenyl)-3-(2-methoxystyryl)-2-cyclohexen-1-one 11a to 11a′.—A mixture of 3.62 g (0.01 mol) of cyclohexenone **11a**, mp 186–187°, 100 ml of 95% ethanol, 50 ml of water, and 0.84 g of sodium bicarbonate was heated in a 300-ml stainless steel bomb at 180° for 2 hr. The cooled mixture deposited 2.75 g (76%) of recovered epimer **11a**, mp 182–186°. The filtrate was concentrated under reduced pressure to remove the ethanol and the residue was extracted with ether. From the ether extracts there was isolated 0.73 g of oil which was extracted with hot hexane. The chilled extracts deposited 0.27 g (8%) of epimer **11a′**, mp 115–120°. Recrystallization from hexane gave 0.14 g of pale yellow prisms, mp 118–120°; see Tables I–III for elemental analyses and spectral data.

Cyclohexenone **11a** was recovered (93%) when a 1.0-g sample was heated under reflux for 28 hr with a solution of 20 ml of ethanol, 10 ml of water, and 1 ml of 10% aqueous sodium hydroxide solution. Heating a 0.51-g sample of **11a** under reflux for 25 hr with a solution of 20 ml of tetrahydrofuran, 2 ml of

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(32) E. J. Cragoe, Jr., and A. M. Pietruszkiewicz, *J. Org. Chem.*, **22**, 1338 (1957).

(33) R. Grice and L. N. Owen, *J. Chem. Soc.*, 1947 (1963).

(34) V. T. Bickel and H. E. French, *J. Amer. Chem. Soc.*, **48**, 747 (1926).

water, and 1 ml of 10% aqueous sodium hydroxide solution gave recovered **11a** (100%), mp 183–185°.

A 44.5-mg sample of epimer **11a'**, mp 115–120°, in 2.0 ml of absolute ethanol containing 10 mg of sodium methoxide was heated in a sealed glass tube at 150° for 3 hr. After removal of the ethanol the residue was extracted with hot hexane; the cooled extract deposited 4.4 mg of recovered **11a'**, mp 116–118°; no other crystalline product could be isolated. In a second experiment with 50 mg of **11a'** in 5 ml of 95% ethanol and 0.5 ml of 10% aqueous sodium hydroxide, the solution was allowed to stand at room temperature for 114 hr. From the reaction mixture there was obtained 26.4 mg of recovered **11a'**, mp 116–120°, as the only crystalline product.

Registry No.—**6a**, 16831-37-1; **6b**, 16831-33-7; **6d**, 16831-34-8; **6e**, 16831-35-9; **9**, 16859-74-8; **11a**, 16831-38-2; **11a'**, 16831-39-3; **11b**, 16831-36-0; **11c**, 16831-40-6; **11d**, 16831-41-7; **11e**, 16831-42-8; **11f**, 16831-43-9; **11g**, 16831-44-0; **12a**, 16831-45-1; 2,4-dinitrophenylhydrazone of **12a**, 16831-07-5; **12b**, 16830-99-2; 2,4-dinitrophenylhydrazone of **12b**, 16831-00-8; **13**, 16831-01-9; **14**, 16831-02-0; 4-diethylaminostyryl ethyl ketone, 16831-03-1; 1-(2-methoxyphenyl)-2-methyl-1-penten-3-one, 16831-04-2; 1-(2,4-dimethoxyphenyl)-1-buten-3-one, 16831-05-3; 1,5-bis-(2-methoxyphenyl)-2-methyl-1,4-pentadien-3-one, 14164-68-2.

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The Conformational "Size" of the Methyl Group in 4-, 5-, and 6-Methyl-2-carbomethoxytetrahydropyrans

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The conformational preferences of the methyl group in 4-, 5-, and 6-methyl-2-carbomethoxytetrahydropyran were found to be 1.70, 1.27, and 1.70 kcal/mol, respectively. The value at the 5 position is smaller because of the smaller size of the oxygen with its unshared electron pairs compared to a methylene group. The conformational preference of the carbomethoxy group in 2-carbomethoxy-6-*t*-butyltetrahydropyran was found to be larger than in cyclohexane (1.6 *vs.* 1.1 kcal/mol). This effect is attributed to a dipole–dipole interaction.

Recently Eliel and Knoeber[1] have reported that a series of 2-alkyl-5-*t*-butyl-1,3-dioxanes, where alkyl is methyl, ethyl, isopropyl, and *t*-butyl, show the same equilibrium *cis/trans* ratio. In each case, the *cis* isomer was less stable than the *trans* isomer by 1.4–1.5 kcal/mol. It was concluded that in each *cis* isomer the various 2-alkyl groups must be in equatorial conformations; thus the 5-*t*-butyl group must be in an axial conformation. This is a unique situation for the bulky *t*-butyl group which prefers the equatorial conformation in cyclohexane systems by *ca.* 5.6 kcal/mol.[2] In fact the cyclohexane ring is forced into a skew boat conformation, which is unfavorable compared to the chair by 5.3 kcal/mol, rather than have the *t*-butyl axial in the chair conformation.[3]

The 1,3-dioxane chair form has been estimated as 2.2 kcal/mol[4] more stable than the skew boat form although more recently arguments have been advanced in favor of a larger estimate, greater than 3 kcal/mol.[5] Although a boat 1,3-dioxane (even at 3 kcal/mol) may seem to be an energetically feasible alternative explanation to an axial *t*-butyl group, Eliel and Knoeber[1] concluded from an interpretation of nmr coupling constants that the above substituted 1,3-dioxanes must be in chair conformations. The small value of the conformational preference of the 5-*t*-butyl group in the 1,3-dioxane system compared to that in cyclohexane was ascribed to the smaller steric bulk of the unshared electron pairs on the ring oxygens compared to the *syn, axial* hydrogens in cyclohexane. A 5-methyl group was observed to have a 0.80-kcal/mol preference for the equatorial conformation in the 1,3-dioxane system.

We have been investigating conformational effects in tetrahydropyran derivatives[6] and were also interested by the steric consequences of the ring oxygen. In order to assess the conformational preference of the methyl group in methyltetrahydropyrans, an epimerizable group is needed which is of steric size comparable to the methyl group. (Otherwise the data are inaccurate as can be shown in the calculation below.) The 2-carbomethoxy group can be epimerized conveniently with sodium methoxide in methanol.

The 2-carbomethoxy-5-methyl- and 2-carbomethoxy-6-methyl-tetrahydropyrans could be obtained in poor yield (2–5%) from the Diels–Alder reaction[7] of methacrolein or methyl vinyl ketone and methyl acrylate. None of the desired 4-methyl product could be obtained from crotonaldehyde and methyl acrylate. A better preparative procedure was found to be the treatment of the alkyldihydropyran with amylsodium followed by treatment with carbon dioxide[8] which yielded, after acidification, hydrogenation, and esterification, the appropriate 2-carbomethoxyalkyltetrahydropyran. The alkyldihydropyrans were obtained by distillation of the corresponding 2-isobutoxymethyltetrahydropyran[6,9] in the presence of toluenesulfonic acid. The respective 2-isobutoxyalkyltetrahydropyrans were obtained by Diels–Alder reaction of isobutyl vinyl ether with crotonaldehyde, methacrolein, or methyl vinyl

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(2) E. L. Eliel, N. J. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," John Wiley and Sons, Inc., New York, N. Y., 1965, p 44.

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(4) See ref 2, p 249.

(5) J. E. Anderson, F. G. Riddell, and M. J. T. Robinson, *Tetrahedron Lett.*, 2017 (1967).

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(9) W. E. Parham and H. E. Holmquist, *J. Amer. Chem. Soc.*, **73**, 913 (1951).

ketone.[10] In all cases elementary analysis was on the mixture of isomers obtained from the preparative procedure, which in some cases was purely one isomer. The other isomer was obtained by equilibration. Subsequently the *cis* and *trans* isomers were separated preparatively by gas chromatography.

The respective *cis* and *trans* isomers were identified by their nmr spectra which are partially listed in Table I. Axial 2 protons are found at higher field than the equatorial 2 protons.[11] Some of the isomers are not conformationally fixed, and consequently the chemical shift and multiplicity are time averages. The resonances for axial protons are quartets and those for equatorial protons are unresolved multiplets of smaller width.

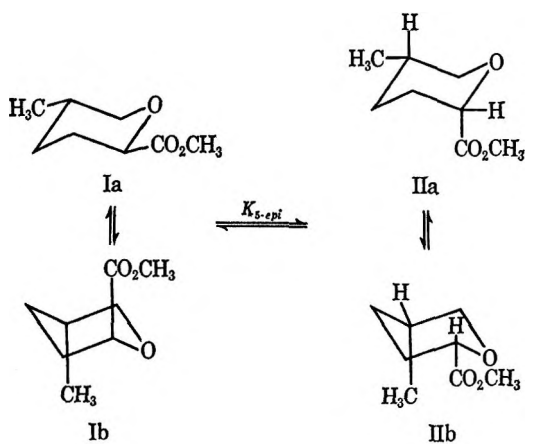
TABLE I

NMR SPECTRA[a] OF ALKYL-SUBSTITUTED 2-CARBOMETHOXYTETRAHYDROPYRANS[b]

2-Carbomethoxytetrahydropyran derivative	Isomer	Conformation	H_2 (τ)	J_{ae}, cps	J_{aa}, cps	CO_2CH_3, τ
6-*t*-Butyl	*cis*	e,e	6.17	2.5	10.5	6.34
6-*t*-Butyl	*trans*	e,a	5.55			6.26
6-Methyl	*cis*	e,e	6.18	2.4	10.4	6.34
6-Methyl	*trans*	e,a $\rightleftarrows$ a,e	5.70			6.32
5-Methyl	*cis*	e,a $\rightleftarrows$ a,e	5.88			6.31
5-Methyl	*trans*	e,e	6.27	2.3	10.8	6.34
4-Methyl	*cis*	e,e	6.23	2.2	11.2	6.35
4-Methyl	*trans*	e,a $\rightleftarrows$ a,e	5.73			6.32

[a] All spectra were taken of solutions 10 mol % of solute in carbon tetrachloride. Spectra were taken on both a Varian A-60 and HA-100 nmr spectrometers using tetramethylsilane as an internal reference. [b] The registry numbers are given in consecutive order: 16831-08-6, 16831-09-7, 16831-10-0, 16831-11-1, 16831-12-2, 16831-13-3, 16831-14-4, 16831-15-5.

Four chair conformers of 2-carbomethoxy-5-methyltetrahydropyran are possible (Ia and b and IIa and b) at equilibrium.



The diaxial *trans* isomer (Ib) can be excluded on the basis of an *a priori* conformational analysis in which the energy difference between Ia and Ib is estimated as half the *A* value of methyl (1.7/2 kcal/mol[2]) and the *A* value of carbomethoxy (1.1 kcal/mol[2]) or 1.95 kcal/mol which means there should be 96.5% of Ia and 3.5% of Ib. (Actually if the correct conformational preference of the 2-carbomethoxy group in tetrahydropyran (*vide infra*) is used, the free energy difference becomes 2.65 kcal/mol.) Therefore only Ia, IIa, and IIb need be considered in the epimerization equilibrium as shown in eq 1. The ratio [IIa]/[Ia] is the conformational

$$K_{5\text{-}epi} = \frac{[\text{IIa}] + [\text{IIb}]}{[\text{Ia}]} = \frac{[\text{IIa}]}{[\text{Ia}]} + \frac{[\text{IIb}]}{[\text{Ia}]} \quad (1)$$

preference of the 2-carbomethoxy group ($K_{2\text{-COOMe}}$). The ratio [IIb]/[Ia] is the conformational preference of the methyl group which is drawn in the 5 position ($K_{5\text{-Me}}$) (eq 2a and b). Therefore, the relationships for

$$K_{5\text{-}epi} = K_{2\text{-COOMe}} + K_{5\text{-Me}} \quad (2a)$$

$$K_{5\text{-Me}} = K_{5\text{-}epi} - K_{2\text{-COOMe}} \quad (2b)$$

the 2-carbomethoxy-4-methyltetrahydropyran and 6-methyltetrahydropyran are exactly analogous.

The compositions of the equilibrium mixtures of the various compounds studied are listed in Table II. In each case equilibrium was approached from the side of *cis* as well as from the side of the *trans* isomer at 25°. In the solution, substrate concentration was 1.1 *M* and the sodium methoxide catalyst concentration was 0.6 *M*. Mixtures were analyzed by gas chromatography directly after neutralization of the base. The mixtures were also "worked-up" by neutralization of the base with hydrochloric acid followed by extraction with ether–water. Analysis of such "worked-up" solutions gave nearly the same results as the first procedure. Direct injection of the basic methanol solution into the gas chromatograph gave substantial isomerization (or possibly preferential hydrolysis) in the chromatograph. Response ratios for the isomers were determined with mixtures of composition similar to the equilibrium mixtures.

In order to obtain the conformational preference of the 2-carbomethoxy group, 2-carbomethoxy-6-*t*-butyltetrahydropyran was prepared *via* the *t*-butyl dihydropyran as outlined above. The compound, *ca.* 1 *M*, was equilibrated in dried methanol with *ca.* 0.6 *M* sodium methoxide at 25° under the same conditions as the other esters. The equilibrium constant for epimerization of the 2-carbomethoxy-6-*t*-butyltetrahydropyran was found to be 0.064. Using the values in Table II, the constant for the equilibrium between an equatorial and axial methyl group in the 5 position may be calculated: $K_{5\text{-Me}} = 0.179 - 0.064 = 0.115$. This corresponds to a free energy difference of −1.27 kcal/mol. Analogous calculations for both the 4 and 6 positions give K_{Me} as 0.056 and the free energy differences as −1.7 kcal/mol.

It is a little surprising that methyl groups at the 4 and 6 positions have the same conformational preference, and also that they have the same conformational preference as methyl on cyclohexane (−1.7 kcal/mol)[2] although the range of values reported is 1.5–2.1 kcal/mol. This suggests that the geometry of the tetrahydropyran ring is practically identical with that of cyclohexane. If a Dreiding molecular model of tetrahydropyran is examined, it is evident that this cannot be the case. Because of the shorter C–O bonds, the 2–6 distance (2.34 Å) is shorter than the 2–4 or 4–6 distances (2.54 Å), and so an axial methyl group at position 6 would be expected to have a larger steric interaction with a *syn*, axial hydrogen than would a methyl group at position 4. However it should be also noted that there is considerable torsional strain in the

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(11) R. U. Lemieux, R. K. Kullnig, M. J. Bernstein, and W. G. Schneider, *ibid.*, **80**, 6098 (1958).

TABLE II

EQUILIBRATIONS OF 2-CARBOMETHOXY ALKYLTETRAHYDROPYRANS AT 25° IN METHANOL

Tetrahydropyran	e,a isomers, %	K^c	K_{Me}	$-\Delta G_{Me}$, kcal/mol
2-Carbomethoxy-4-methyl	10.7 ± 0.4[a] (12)[d]	0.120 ± 0.005[b]	0.056 ± 0.010[b]	−1.70 ± 0.10
2-Carbomethoxy-5-methyl	15.2 ± 0.4 (16)	0.179 ± 0.006	0.115 ± 0.011	−1.27 ± 0.05
2-Carbomethoxy-6-methyl	10.7 ± 0.4 (11)	0.120 ± 0.005	0.056 ± 0.010	−1.70 ± 0.10
2-Carbomethoxy-6-*t*-butyl	6.0 ± 0.4 (8)	0.064 ± 0.005		

[a] Errors are average deviations of several measurements. [b] Error is maximum error calculated from error in per cent e,a isomer. [c] K is defined as e,a isomers/e,e isomer. [d] Value in parentheses is the equilibration value obtained by ether extraction work-up. The better value is without work-up.

model especially between atoms 3–4 and 4–5. This might be alleviated by altering some of the interior ring angles. A crystallographic study of glucose[12] gave the C_5–O_5–C_1 angle at 113.1 ± 0.5°, the C_4–C_5–O_5 angle as 115.5 ± 0.6° and the others within one degree of tetrahedral. Bond lengths were C_5–O_5, 1.455 ± 0.009 Å, and O_5–C_1, 1.437 ± 0.009 Å; and the others were within experimental error of 1.54 Å except for C_3–C_4 which was 1.517 ± 0.010 Å. (One wonders whether the large angle at C-5 is due to the presence of the hydroxymethyl substituent.) In this structure the C_5–C_1 distance (corresponding to the 6–2 distance in tetrahydropyran) is 2.43 Å; the C_1–C_3 (2–4) distance is 2.49 Å; and the C_3–C_5 (4–6) distance is 2.50 Å. With these distances one would expect nearly the same steric interactions for large groups at tetrahydropyran positions 2, 4, and 6. Thus if individual tetrahydropyran derivatives have slightly different geometries in order to accommodate the shorter C–O bonds and to accommodate various substituents, it is not so surprising that a methyl group experimentally is found to have the same conformational preference whether at position 4 or 6. At the same time, this means that methyls may possibly have somewhat different conformational preferences in differently substituted tetrahydropyrans.

In contrast, the conformational preference of the 5-methyl is markedly smaller than that of the 4- or 6-methyl. As Eliel has suggested,[1] this decreased instability of the axial conformation may be due to the smaller "space requirements of the axial (?) electron pairs" on oxygen compared to the "larger space requirements of the axial hydrogens in cyclohexane." Presumably this results in a smaller van der Waals repulsion with the ring oxygen compared to a ring methylene. It is also possible that van der Waals attractive forces might be larger between the axial methyl group and a ring oxygen than between the axial methyl group and a ring methylene group because the unshared pairs of electrons are more polarizable than those shared in bonds.

If the interaction of the 5-methyl on the tetrahydropyran ring with one axial hydrogen is 0.85 kcal/mol, then the other interaction with the unshared electron pair must be 1.27 − 0.85 or 0.42 kcal/mol. Twice this interaction is 0.8 kcal/mol which is exactly that observed by Eliel for the 2-alkyl-5-methyl-1,3-dioxane (0.8 kcal/mol). It appears then that the 1,3 *syn*-axial methyl–hydrogen interaction and the 1,3-*axial* methyl–oxygen interactions are additive within the experimental errors. (The errors given in Table II are maximum errors, and thus are undoubtedly too large.) It is interesting to note that this effect in 5-methyltetrahydropyran is of nearly the same size as the 3-methyl ketone effect. For example, an axial 3-methyl group in a 3-methylcyclohexanone was found to be 0.6 kcal less unfavored than in cyclohexane.[13]

The conformational "size" of the unshared electron pair on nitrogen or oxygen has been the subject of considerable interest recently. Situations where the size of the unshared pair may be an important conformational factor are the conformational preference of the hydroxyl or amino groups on cyclohexane (A value), the conformational preference of the proton (or the unshared electron pair) on the nitrogen in piperidine, and the conformational preference of substituents in certain positions on nitrogen or oxygen heterocycles (*e.g.*, tetrahydropyrans, dioxanes as discussed above). The A values for the hydroxyl, amino, and methyl groups are 0.7, 1.2, and 1.7 kcal/mol,[2] respectively, in aprotic solvents. This is just the order of number of protons on the group, and thus the steric order suggests that hydrogens are larger in "size" than unshared electron pairs. Allinger and coworkers have concluded that in piperazines[14] the proton on nitrogen is predominately but not entirely equatorial from dipole moment measurements. However, from nmr studies, Lambert[15] has come to the opposite conclusion, that the N proton is almost entirely axial in piperidine. It has been suggested that two other effects may be operative besides steric size, namely, preferential solvation of the unshared electron pair and hyperconjugative effects on the equatorial unshared electron pair. Allinger[16] has very recently argued that the hydrogen on nitrogen should not necessarily prefer the equatorial conformation because van der Waals repulsive forces between *syn, axial* hydrogens should be negligible, and furthermore repulsive forces with the 2 and 6 hydrogens should favor the axial conformation.

An interesting result in Table II which has been neglected so far is the much larger preference of the 2-carbomethoxy group for the equatorial conformation (1.62 ± 0.05 kcal/mol) over what is "normal" in cyclohexane systems (1.1 kcal/mol).[2] The difference of 0.5 kcal/mol between them is probably to be attributed to a "reverse" anomeric effect (reverse because it favors the equatorial conformation). The anomeric effect, which is the preference of electronegative substituents α to the ring oxygen in pyranose derivatives for the axial conformation, has been shown to be the consequence of dipole–dipole interactions within the molecule.[6,17] Lemieux has noted a "reverse" anomeric effect in a

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(14) N. L. Allinger, J. G. D. Carpenter, and F. M. Karkowski, *ibid.*, **87**, 1232 (1965).

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(16) N. L. Allinger, J. A. Hirsch, and M. A. Miller, *Tetrahedron Lett.*, 3729 (1967).

(17) J. T. Edward, *Chem. Ind.* (London), 1102 (1955); see ref 2, p 376.

glucopyranosyl pyridinium salt.[18] The "reverse" anomeric effect in the 2-carbomethoxytetrahydropyran can be attributed perhaps then to the greater distance between positive ends of bond dipoles at the carboxyl carbon and the 6 position of the tetrahydropyran ring when the carbomethoxyl is equatorial.

Experimental Section

2-Carbomethoxy-4-methyltetrahydropyran.—Amylsodium (0.18 mol, 85% yield assumed) was prepared by the method of Paul and Tchelitcheff[8] using 9.5 g of sodium and 22.3 g of *n*-amyl chloride in a 500-ml, round bottom, three-necked creased flask fitted with a Cole-Parmer "Stir-O-Vac" model high speed stirrer. The flask was cooled in a carbon tetrachloride Dry Ice bath at −10°. A solution containing 15.6 g of 4-methyldihydropyran prepared by the method of Parham[9] in 50 ml of petroleum ether (bp 30–60°) was added dropwise over a 15-min period. After stirring at −10° for 1 hr, the reaction mixture was allowed to warm to room temperature and then poured over 50 g of Dry Ice. After the Dry Ice had evaporated, the resulting paste was dissolved in 100 ml of water. The aqueous layer was extracted three times with 100 ml of ether, acidified with 20 ml of concentrated hydrochloric acid, and extracted five times with 100 ml of ether. The ether extract was dried and evaporated leaving 5.6 g of a viscous sour-smelling liquid which when dissolved in 50 ml of ethyl acetate and hydrogenated for 2 days at atmospheric pressure over 3 g of 10% palladium on charcoal yielded 4.8 g of a bad-smelling yellowish viscous liquid. The acid was dissolved in 50 ml of methanol with a crystal of toluenesulfonic acid and refluxed for 18 hr. After the methanol was distilled off, 4.8 g (21%) of a sweet-smelling liquid remained. Vacuum distillation yielded a clear liquid which was found to be 100% pure by gas chromatographic analysis at 100° on a 2 m × 0.25 in. column of 30% 3-methyl-3-nitropimelonitrile on Chromosorb W nonacid washed (retention time 24 min). The esters hydrolyze very easily, but the acids do not come through the gas chromatograph except after very long times. The sample was further purified by gas chromatography at 100° on a 1 m × 0.5 in. column of 20% Carbowax 4000 (retention time 13.0 min) and then distilled, bp 99–100° (10 mm), $n^{25}D$ 1.4413.

Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.84; H, 8.87.

A solution of 1.28 g of the above *cis* isomer and 6.75 ml of 0.7 *M* sodium methoxide in dried methanol was sealed in an ampoule and heated at 100° for 4 days. The solution was acidified with concentrated hydrochloric acid and purified by gas chromatography at 100° (5 psi) on a 0.5 m × 0.5 in. column of 10% Carbowax 4000 on Chromosorb W (retention times: *cis* 12.9 min, *trans* 8.1 min). The *trans* isomer was 100% pure by gc, $n^{25}D$ 1.4403.

2-Carbomethoxy-5-methyltetrahydropyran.—A mixture of 123.7 g of methacrolein and 239.6 g of methyl acrylate was heated in an autoclave for 2 hr at 190°. The resulting yellow liquid was distilled. At atmospheric pressure 206 g distilled below 80°. Under reduced pressure 58 g of 2,5-dimethyl-2H-3,4-dihydropyran-2-carboxaldehyde, bp 55° (5 mm), and an 18.6-g fraction, bp 61–86 (5 mm), were obtained. The last fraction was found by gas chromatography on a 0.5 m × 0.5 in. column of 10% Carbowax on Chromosorb W at 110° to be 36% the dimer of methacrolein and 64% the desired 2-carbomethoxy-5-methyl-2H-3,4-dihydropyran. This represents a 4% yield of ester and 52% of methacrolein dimer. This mixture was hydrogenated for 12 hr over a 10% palladium-on-carbon catalyst in 95% ethanol. After filtration and removal of solvent, the residual liquid was distilled yielding 6.5 g of liquid, bp 70.5–74° (5 mm), which gas chromatography indicated was *ca.* 95% the desired compound, 2-carbomethoxy-5-methyltetrahydropyran. The ester was purified by preparative gas chromatography and distilled: bp 70.5–71.0° (5 mm); $n^{25}D$ 1.4427. Nmr spectral analysis showed the product to be the pure *cis* isomer. No *trans* isomer was found.

Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.53; H, 9.21.

A solution of 0.89 g of the above *cis* isomer and 4.0 ml of 0.7 *M* sodium methoxide in dried methanol was sealed in a flask with a serum cap and allowed to stand 3 weeks at 25°. The solution was acidified with 10 ml of 0.05 *M* hydrochloric acid and extracted with ether. Preparative gas chromatography at 96°, 10 psi on a 0.5 m × 0.5 in. column of 10% Carbowax 4000 on Chromosorb W (retention times: *cis* 5.8 min, *trans* 8.3 min), yielded a fraction which was 94% *trans* and 6% *cis*, $n^{25}D$ 1.4438.

2-Carbomethoxy-6-methyltetrahydropyran.—A mixture of 86.6 g of methyl vinyl ketone and 159.1 g of methyl acrylate was heated in an autoclave for 2 hr at 180°. The resulting yellow liquid was distilled to obtain an 87-g fraction with bp 80–84° and a 32.7-g fraction with bp 65–90° (7.3 mm). The tarry residue was discarded. Gas chromatographic analysis at 100° on a 0.5 m × 0.5 in. column of 10% Carbowax 4000 on Chromosorb W indicated a composition in the latter fraction of 62% 2-acetyl-6-methyl-2H-3, 4-dihydropyran (dimer of methyl vinyl ketone) and 30% of 2-carbomethoxy-6-methyl-2H-3,4-dihydropyran. The yield is then 6% of the desired ester and 27% in the ketone.

The fraction boiling at 65–90° was hydrogenated for 2 hr over 10% palladium-on-carbon in 75 ml of 95% ethanol. After filtering and removing the solvent, the residue was distilled yielding 14.3 g with bp 58–59° (5 mm) and 4.5 g with bp 79–81 (5 mm). The lower boiling fraction was shown to be 2-acetyl-6-methyltetrahydropyran by retention time in gas chromatography and the ir and nmr spectra of the collected peak. It was 97% pure by peak area. The higher boiling fraction was 96% pure 2-carbomethoxy-6-methyltetrahydropyran. Nmr spectral measurements indicated the compound was the *cis* isomer. The ester was purified by preparative gc on a 0.5 m × 0.5 in. column of 10% Carbowax 4000 on Chromosorb W at 116° (retention time 10.9 min), and then distilled: bp 63–64° (3.5 mm) (lit.[19] bp 205–210°); $n^{25}D$ 1.4432.

Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.61; H, 9.15.

The compound was also prepared by oxidation of the hydrogenated dimer of methyl vinyl ketone, 2-acetyl-6-methyltetrahydropyran, with bromine and aqueous sodium hydroxide as described by Alder and coworkers.[19] This product was found to be 99% *cis* and 1% *trans*.

A solution of 2.21 g of the pure *cis* isomer an 10 ml of 0.7 *M* sodium methoxide in dried methanol was sealed in a flask with a serum cap and let stand 3 weeks at 25°. The solution was acidified with 10 ml of 1 *M* hydrochloric acid and extracted with ether. The extract was purified by preparative gas chromatography at 100° and 10 psi on a 1 m × 0.375 in. column of 30% 3-methyl-3-nitropimelonitrile (retention times: *cis* 14.1 min, *trans* 7.9 min; $n^{25}D$ 1.4386).

6-*t*-Butyl-2-isobutoxy-2H-3,4-dihydropyran.—A mixture of 68.0 g of *t*-butyl vinyl ketone[20] and 91.0 g of isobutyl vinyl ether was heated in an autoclave for 2 hr at 185°. The resulting solution was distilled yielding 51.1 g (yield 40%) of colorless material, bp 77–82° (4 mm). Gas chromatographic analysis on a 3 m × 0.25 in. column of 20% Carbowax 4000 on Chromosorb W at 100° showed the product to be *ca.* 97% one component by peak area (retention time 21 min). A small portion was purified by preparative gas chromatography followed by distillation, bp 71–72° (3.5 mm), $n^{25}D$ 1.4424. Nmr spectral analysis confirmed the compound as 6-*t*-butyl-2-isobutoxy-2H-3,4-dihydropyran; these nmr values follow: a triplet at τ 5.09 with a coupling constant of 3.0 cps integrating for one proton, a quartet at 5.50 with coupling constants of 2.9 and 4.9 cps integrating for one proton, an octet at 6.64 integrating for two protons, a group of broad signals at *ca.* 8 integrating for five protons, a singlet at 8.95 integrating for nine protons, and a doublet at 9.10 with a coupling constant of 6.5 cps integrating for six protons.

Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39. Found: C, 73.36; H, 11.16.

6-*t*-Butyl-2-isobutoxytetrahydropyran.—A high pressure hydrogenation apparatus equipped for shaking was charged with 49.6 g of 6-*t*-butyl-2-isobutoxy-2H-3,4-dihydropyran, 250 ml of 95% ethanol, and 2 g of 10% palladium-on-charcoal. The hydrogenation was conducted over 5 days at a pressure of 900–1100 psi. Hydrogenation failed at lower pressures. After removal of the catalyst and solvent, the residue was distilled, bp 76–84° (3 mm), yielding 29.1 g (58% yield). Gas chromatographic analysis using a 2 m × 0.5 in. column of 20% Carbowax 4000 on Chromosorb W at 100° showed the product to be 12% *trans*- (retention time 11.8 min) and 86% *cis*-6-*t*-butyl-2-isobutoxytetrahydropyran

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(retention time 15.0 min.). The two isomers were separated by preparative-scale gas chromatography. The *cis* isomer was further purified by distillation: bp 82.5° (5 mm); n^{25}D 1.4072.

Anal. Calcd for $C_{13}H_{26}O_2$: C, 72.85; H, 12.22. Found: C, 73.15; H, 12.36.

The nmr spectrum of the *cis* isomer showed a quartet for the anomeric proton at τ 5.58 (J = 2.3 and 7.8 cps). The *trans* isomer, n^{25}D 1.4342, showed a broad unresolved signal for the anomeric proton at τ 5.31 with a half-width of 6 cps. As further evidence for the isomeric nature of these compounds, both isomers were equilibrated 0.1 M in acetonitrile with 0.001 M tosylic acid to the same mixture of isomers: 63.6% *trans* from pure *trans* isomer and 63.2% *trans* from pure *cis* isomer.

2-*t*-Butyl-2H-3,4-dihydropyran.—A catalytic amount of toluenesulfonic acid was added to 22.1 g of 6-*t*-butyl-2-isobutoxytetrahydropyran in a vacuum distillation apparatus connected to a receiver cooled in a Dry Ice–acetone bath. The liquid was heated with stirring at 3 mm of pressure for 5 hr using an oil bath at 65–75°. A yield of 19.8 g of colorless liquid was collected. Gas chromatographic analysis on a 3 m × 0.25 in. column of 20% Carbowax 4000 at 97° showed the distillate to be 46% isobutyl alcohol (retention time 5.3 min) and 54% 2-*t*-butyl-2H-3,4-dihydropyran (retention time 7.4 min) thus indicating a 97% yield. The isobutyl alcohol was separated by distillation. Redistillation gave pure material: bp 157.0–157.5°; n^{25}D 1.4455. The nmr spectrum showed the following: a broad doublet at τ 3.72 (J = 6.0 cps, integrating for one proton), a broad signal at 5.48 (half-width 14 cps, one proton), a quartet at 6.69 (J = 2.5 and 10.0 cps, one proton), a broad group of signals at about 8 (four protons), and a singlet at 9.08 (nine protons).

Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 77.23; H, 11.69.

6-*t*-Butyl-4H-5,6-dihydropyran-2-carboxylic Acid.—Amylsodium (0.093 mol) was prepared by the method of Paul and Tchelitcheff[8] as above at −10° but using 6.3 g of sodium and 14.1 g of *n*-amyl chloride (70% yield). A solution of 50 ml of petroleum ether (30–60°) and 13.5 g of 2-*t*-butyl-2H-3,4-dihydropyran (containing 4% isobutyl alcohol as an impurity) was added dropwise over a 10-min period. The reaction solution was stirred for 1 hr, was allowed to warm, and was poured onto 75 g of Dry Ice. After warming to room temperature, the light gray slurry was poured into 100 ml of water, and the mixture was stirred until both layers became clear. The organic phase was separated, and the aqueous layer was extracted twice with 50-ml portions of ether, yielding 4.8 g of unreacted 2-*t*-butyl-2H-3,4-dihydropyran. To the remaining aqueous solution was added 20 ml of concentrated hydrochloric acid whereupon a white solid precipitated. The acidic aqueous solution was extracted five times with 100-ml portions of ether. After the solid in ether and the extracts were dried over magnesium sulfate, the ether was evaporated leaving 5.3 g (49% yield) of a white solid, mp 118–120°. Recrystallization from 20% benzene–cyclohexane gave pure products, mp 123–124°. Nmr spectral analysis showed a singlet resonance at τ −1.29 (integrating for one proton), a triplet at 3.84 (J = 3.2 cps, one proton), a quartet at 6.57 (J = 2.5 and 10.7 cps, one proton), a group of signals at 7.5–8.7 (four protons), and a sharp singlet at 9.00 (nine protons).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.76. Found: C, 65.46; H, 8.98.

6-*t*-Butyltetrahydropyran-2-carboxylic Acid.—Unrecrystallized 6-*t*-butyltetrahydropyran-2-carboxylic acid (5.1 g) was hydrogenated for 3 days at atmospheric pressure in 50 ml of ethyl acetate with 3 g of 10% palladium-on-charcoal. After filtration and removal of the solvent, 4.1 g (80% yield) of a white solid remained, mp 56–62°. Ir and nmr analysis showed no evidence of unreacted starting material. The nmr spectrum showed the following signals: a singlet at τ −0.82, a quartet at 6.12 (J = 2 and 9 cps, one proton), a quartet at 7.01 (J = 2 and 10 cps, one proton), a broad set of signals at 7.8–8.7 (six protons), and a singlet at 9.08 (nine protons). The fact that no other signals were detected near that for the anomeric proton (τ 6.12) indicates that only one isomer is obtained, and that it must be the *cis* isomer because the signal is a quartet.

***cis*-6-*t*-Butyl-2-carbomethoxytetrahydropyran.**—A solution of 2.02 g of unrecrystallized 6-*t*-butyltetrahydropyran-2-carboxylic acid, 40 ml of absolute methanol, and three drops of concentrated hydrochloric acid was refluxed for 12 hr. The solution was neutralized and concentrated. The product *cis* ester was purified by preparative gas chromatography using a 1 m × 0.5 in. column of 20% Carbowax 4000 on Chromosorb W at 100° (retention time 12.9 min). The fruity smelling ester was distilled after collection yielding 1.42 g (68% yield): bp 85–86° (2.3 mm); n^{25}D 1.4375. The nmr spectrum showed the following signals: a quartet at τ 6.17 (J = 2.5 and 10.5 cps, one proton), a singlet at 6.34 (three protons), a quartet at 7.10 (J = 1.8 and 10.7 cps, one proton), a group of signals between 7.8 and 8.7 (six protons), and a singlet at 9.10 (nine protons).

Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 66.12; H, 10.28.

Mixture of *cis*- and *trans*-6-*t*-Butyl-2-carbomethoxytetrahydropyran.—A solution of 844 mg of pure *cis*-6-*t*-butyl-2-carbomethoxytetrahydropyran and 3.5 ml of 0.6 M sodium methoxide in dried absolute methanol was sealed in a glass tube and heated for 3 days at 100°. The solution was neutralized with methanolic hydrogen chloride and concentrated. Gas chromatographic analysis on a 2 m × 0.25 in. column of 30% 3-nitro-3-methylpimelonitrile on Chromosorb W at 100° showed peak area percentages of 83.1% *cis* (retention time 18.2 min) and 16.9% *trans* (retention time 12.8 min). The product was put through a 0.5 m × 0.5 in. column of 10% Carbowax 4000 at 100° and the two esters were collected together. Then this mixture, 468 mg, having the same composition as before, was partially separated using a 1 m × 0.375 in. column of 30% 3-nitro-3-methylpimelonitrile on Chromosorb W at 100°. A mixture of isomers enriched in *trans* was obtained, n^{25}D 1.4447, and found to be 64% *cis* and 36% *trans*. Nmr spectral analysis, using a time averaging computer to improve the spectrum, showed the following signals which were assigned to the *trans* isomer: an unresolved multiplet at τ 5.55 of half-width 4.1 cps, assigned to axial H_2; a singlet at 6.26, assigned to the methoxy group; a quartet at 6.72 (J = 2.5, 9.7 cps) assigned to axial H_6; and a singlet at 9.13 assigned to the equatorial *t*-butyl group. The signals at τ 5.55 and 6.72 integrated identically and roughly a third of that at 6.26.

Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 66.03; H, 10.00.

Equilibration Method.—A 0.7 M solution of sodium methoxide in methanol was prepared from dried absolute methanol and sodium metal. The concentration was measured by titration. A typical reaction was 1.1 M ester substrate and 0.6 M sodium methoxide in dried methanol, prepared in a dried flask. The flask was closed with a serum cap and kept at 25°. Aliquots of this solution (50 μl) were removed with a syringe at various times over 2–3 weeks and quenched by adding methanolic hydrogen chloride to acidify the aliquot. This acidic solution was analyzed by gc. Basic solutions were found to isomerize upon gc analysis while acidic solutions did not. Response ratios were determined for *cis* and *trans* isomers and were found to be identical within experimental error. For example, 2-carbomethoxy-5-methyltetrahydropyran which was 75.7% *trans* by weight gave a peak area ratio of 75.9 ± 0.5% *trans*.

Registry No.—6-*t*-Butyl-2-isobutoxy-2H-3,4-dihydropyran, 16831-16-6; *cis*-6-*t*-butyl-2-isobutoxytetrahydropyran, 16822-20-1; *trans*-6-*t*-butyl-2-isobutoxytetrahydropyran, 16831-17-7; 2-*t*-butyl-2H-3,4-dihydropyran, 16765-52-9; 6-*t*-butyl-4H-5,6-dihydropyran-2-carboxylic acid, 16831-19-9; 6-*t*-butyltetrahydropyran-2-carboxylic acid, 16831-20-2.

Medium-Sized Cyclophanes. VII. 4,14-Disubstituted [2.2]Metacyclophanes[1]

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The stereoselective syntheses of 4,14-dimethyl- and 4,14-dimethoxy[2.2]metacyclophanes have been achieved by the modified Wurtz dimerization reaction carried out under extremely mild conditions. A series of further 4,14-disubstituted [2.2]metacyclophanes have been derived from the dimethyl derivative **4**. The nmr spectra of these compounds were examined in relation to the electronic and long-range effects of the substituents to the aryl and methylene signals. The chemical shift difference in protons *meta* to the substituent was correlated with Hammett σ_m constant; $-\rho_{6,12\text{-H}} = 28.2$ cps/σ_m and $-\rho_{8,16\text{-H}} = 14.5$ cps/σ_m. Whereas 1,2-methylene protons, especially those in the equatorial position, deviated largely, good linear relations were observed in 9,10-methylene absorption; $-\rho_{9,10\text{-ax}} = 6.88$ cps/σ_p and $-\rho_{9,10\text{-eq}} = 14.4$ cps/σ_p.

As the results of improvement[2,3] in the synthesis of [2.2]metacyclophane (**1**), a number of structural, spectroscopic, and chemical studies were carried out.[3] However, only a little is known about the chemistry of its derivatives. Attempts to introduce a functional group by means of electrophilic substitution reactions all failed and were led to the formation of 4,5,9,10-tetrahydropyrene or its derivatives.[2,4,5] Attempted reactions of **1** with various reagents, including alkyl metal, halogen, and oxidants, have also failed, so far, to introduce functionality into the side chain.[3] These results may be compared with the *para* counterpart in which nuclear[6] as well as side-chain[7] substitution reactions have been successfully applied to obtain a number of the derivatives.

Boekelheide and his coworkers have prepared 8,16-dimethyl[2.2]metacyclophane[8] and its derivatives[9] either by the bimolecular Wurtz method or by using multistepped reactions taking advantage of an efficient cyclization reaction of 3,3′-bis(bromomethyl)bibenzyl derivatives. They have also prepared[10] 5,13-dimethyl and -dimethoxy derivatives **2** (R = CH_3 or CH_3O) in 7 and 2.5% yields, respectively, by the dimerization of appropriate bis(bromomethyl) compounds, whereby noticing a marked decrease in the yields especially in the case of the preparation of **2** with electronegative substituents.

Isomeric 4,12- or 4,14-disubstituted [2.2]metacyclophanes may also be prepared by the similar dimerization method. An attempted reaction of 2,4-bis(bromomethyl)toluene with sodium and tetraphenylethylene, however, has resulted in the formation of trimer or tetramer.[11]

This paper will describe the preparation of these unknown isomers, and particularly the stereochemistry of the syntheses of 4,14-dimethyl and -dimethoxy derivatives **4** and **6** and 4,12-dimethoxy derivative **7** and nmr spectra of these as well as several derivatives derived from dimethyl compound **4**. A part of the results have already appeared in a preliminary form.[12]

Stereoselective Syntheses of 4,14-Disubstituted [2.2]-Metacyclophanes.—The chloromethylation[13] under forced conditions of toluene or anisole afforded the corresponding bis(chloromethyl) derivatives **3**. Bimolecular Wurtz condensation reaction of **3** may be conceived to afford 4,14 (**4** or **6**) and 4,12 derivatives (**5** or **7**). The reaction of **3** (R = CH_3) with disodium tetraphenylethane in a tetrahydrofuran solution after the method of Müller and Röscheisen[14] was carried out under high-dilution conditions which were realized by the slow addition of the halide (68 hr) at −60 to −70° to the condensing agent. By distillation under reduced pressure of the reaction mixture, a crystalline material, mp 68–69°, was obtained. Molecular weight determination and elemental analyses supported the formula $C_{18}H_{20}$.

The structural determination was achieved by the nmr spectral studies. As is shown in Figure 1 the compound showed a methyl proton signal as a singlet at δ 2.36 and intraannular aryl protons at δ 4.22 as a doublet (J = 1.8 cps) together with the rest of aryl proton signals at about δ 7.0 as an ABX pattern (not shown). The appearance of the doublet at an unusually high field is indicative of the generation of the [2.2]metacyclophane structure, since the intraannular protons (8,16 protons), which are extended over the diametrical benzene ring, should experience shielding by the diamagnetic ring current. It has already been shown that the ten-membered ring in **1** exists in a rigid-chair conformation as is evidenced by the appearance of an A_2B_2 type signal,[4,15,16] which is not affected over a wide range of temperatures between *ca.* −80 and 190°,[1,12] arising from axial and equatorial protons in the methylene group. In such compounds as **4**, in which two substituents are located in both of the *ortho* positions of one of the ethylene bridges, the methylene signals should be composed of two sets of A_2B_2 pattern, while in the *trans* compound such as **5** they would no longer be a simple A_2B_2 type but an ABCD type. An examination of the nmr spectra of the dimethyl derivative (Table II) re-

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(3) R. W. Griffin, Jr., *Chem. Rev.*, **63**, 45 (1963).
(4) N. L. Allinger, M. A. Da Rooge, and R. B. Hermann, *J. Amer. Chem. Soc.*, **83**, 1974 (1961); N. L. Allinger, B. J. Gordon, S.-E. Hu, and R. A. Ford, *J. Org. Chem.*, **32**, 2272 (1967).
(5) T. Sato, M. Wakabayashi, Y. Okamura, T. Amada, and K. Hata, *Bull. Chem. Soc. Jap.*, **40**, 2363 (1967).
(6) For recent papers see D. J. Cram and H. P. Fischer, *J. Org. Chem.*, **30**, 1815 (1965); D. J. Cram and A. C. Day, *ibid.*, **31**, 1227 (1966); B. E. Norcross, D. Becker, R. I. Cukier, and R. M. Schutz, *ibid.*, **32**, 220 (1967); S. C. Dickerman and N. Milstein, *ibid.*, **32**, 852 (1967).
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(8) W. S. Lindsay, P. Stokes, L. G. Humber, and V. Boekelheide, *ibid.*, **83**, 943 (1961).
(9) V. Boekelheide and J. B. Phillips, *ibid.*, **85**, 1545 (1963); **89**, 1695 (1967); J. B. Phillips, R. J. Molyneux, E. Sturm, and V. Boekelheide, *ibid.*, **89**, 1704 (1967); V. Boekelheide and T. Miyasaka, *ibid.*, **89**, 1709 (1967).
(10) V. Boekelheide and R. W. Griffin, Jr., unpublished work cited in ref 3.
(11) R. W. Griffin, Jr., and C. R. Slator, unpublished work cited in ref 3.
(12) T. Sato, S. Akabori, M. Kainosho, and K. Hata, *Bull. Chem. Soc. Jap.*, **39**, 856 (1966).
(13) R. C. Fuson and C. H. McKeever, *Org. Reactions*, **1**, 63 (1942).
(14) E. Müller and G. Röscheisen, *Chem. Ber.*, **90**, 543 (1957).
(15) D. J. Wilson, V. Boekelheide, and R. W. Griffin, Jr., *J. Amer. Chem. Soc.*, **82**, 6302 (1960).
(16) H. S. Gutowsky and C. Juan, *J. Chem. Phys.*, **37**, 120 (1962).

TABLE I

PHYSICAL PROPERTIES OF 4,12- AND 4,14-DISUBSTITUTED DERIVATIVES

Compd	Mp, °C	Formula	Mol wt Calcd	Mol wt Found	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found
4	68–69	$C_{18}H_{20}$	236.34	236[a] 235[b]	91.47	91.34	8.53	8.34
6	132–134	$C_{18}H_{20}O_2$	268.34	268[a] 266[b]	80.56	80.60	7.51	7.45
7	182	$C_{18}H_{20}O_2$	268.34	268[a]				
8	170	$C_{18}H_{18}Br_2$[c]	394.16	394[a]	54.85	54.61	4.60	4.33
9	>300	$C_{18}H_{16}O_4$	296.31		72.96	72.60	5.44	5.51
10	117–120	$C_{18}H_{16}O_2$	264.31		81.79	80.99	6.10	5.98
12	196–197	$C_{18}H_{14}N_2$	258.31		83.69	83.36	5.46	5.78

[a] Determined by mass spectrometry. The measurements were carried out with Hitachi RMU-6D high-resolution mass spectrometer using an electron current of either 40 or 70 eV. The authors are grateful to the members of Naka works of Hitachi Co. for providing us with the data. [b] Determined by the Rast method. [c] Calcd: Br, 40.55. Found: 40.42.

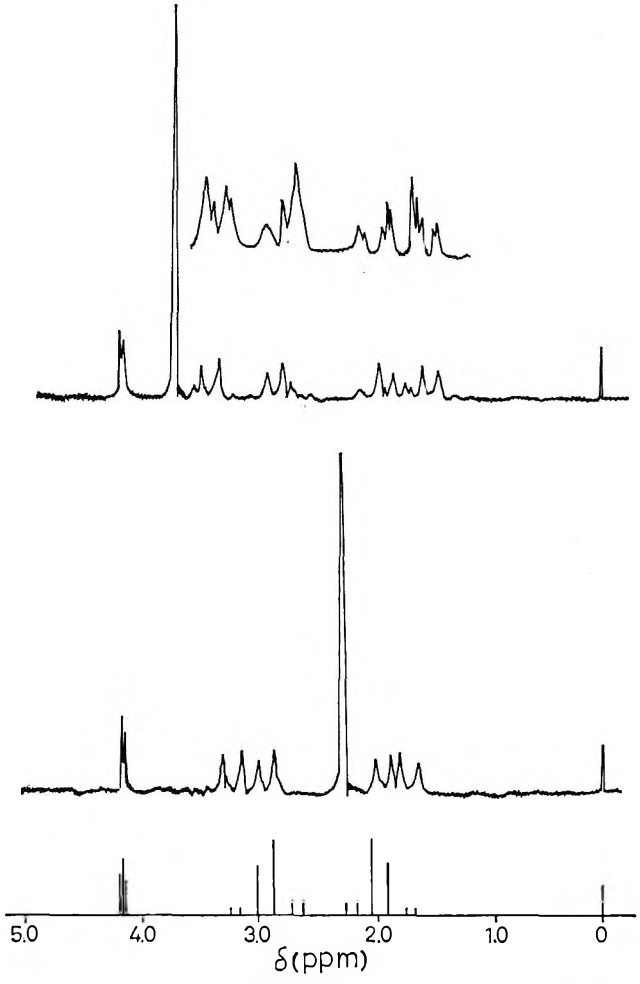


Figure 1.—Nmr spectra of 4,12-dimethoxy[2.2]metacyclophane (**7**), 4,14-dimethoxy[2.2]metacyclophane (**6**), and 4,14-dimethyl-[2.2]metacyclophane (**4**) from top to bottom. For comparison a line spectrum of [2.2]metacyclophane (**1**) is also shown.

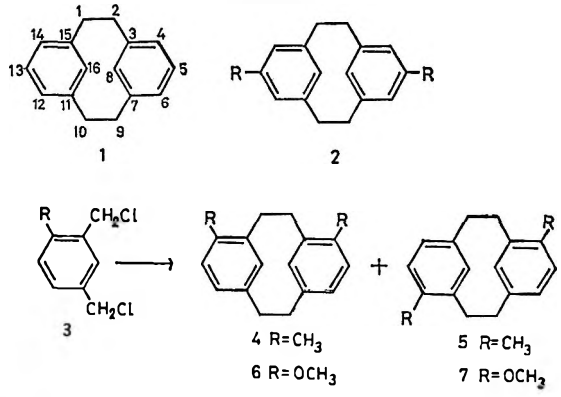
vealed that the methylene region absorption could be analyzed as an overlap of an A_2B_2 pattern similar to **1** occurring at δ 2.99 and 1.99 (unsubstituted side, 9,10-H) and an $A'_2B'_2$ pattern at δ 3.28 and 1.76 (substituted side, 1,2-H). The structure **4** was thus assigned to the compound, which was formed in a 21% yield. A more direct evidence in favor of the structure was obtained by the optical resolution of **4**[1,12,17] which was achieved by a complex formation with the Newman's reagent.[18]

(17) Due to restricted inversion of a ten-membered ring in the [2.2]metacyclophane system, 4,14-disubstituted derivatives and also other suitably substituted compounds may exist as racemic molecules.

Careful examination of the reaction product either by alumina column chromatography or by gas chromatography[19] using SE-30 on Chromosorb W, Carbowax 20M on Chromosorb W, or neopentyl glycol adipate on Chromosorb G column revealed that the material was uniform.

The stereoselectivity observed in the formation of **4** was further experienced in the synthesis of dimethoxy analogs **6** and **7**. A similar condensation reaction of **3** (R = CH_3O) which was carried out over 184 hr at −20 to −40° furnished two products by chromatography on alumina. *n*-Hexane first eluted a minor compound, mp 182°, which was followed by the major product, mp 132–134°, both having expected analytical values and molecular weight as dimethoxy[2.2]metacyclephane (Table I). The low-melting isomer, formed in a 9% yield, was assigned the structure 4,14-dimethoxy compound (**6**)[20] from nmr spectrum (Figure 1) which consisted of signals at δ 6.92, 6.70 (ABX-type absorption, 5,6,12,13-H), 4.25 (doublet, J = 1.8 cps, 8,16-H), 3.80 (singlet, CH_3O) together with two sets of A_2B_2 patterns at δ 2.94 and 2.00 (9,10-H) and δ 3.50 and 1.59 (1,2-H). On the other hand, the high-melting isomer showed a complex absorption in the methylene region as is shown in Figure 1 indicating that the compound be isomeric 4,12-dimethoxy compound **7** (Scheme I).

SCHEME I



(18) M. S. Newman and W. B. Lutz, *J. Amer. Chem. Soc.*, **78**, 2469 (1956).

(19) The authors are grateful to Dr. N. Ikekawa of the Institute for Physical and Chemical Research for the measurements.

(20) As a possible clue to the structure, the dipole moment was measured in a benzene solution at 20° and was found to be μ = 0.79 D. The value, although compatible with structure **6**, may not, however, be used positively for the distinction between **6** and **7**, since the dipole moment of the *trans* compound **7** may not necessarily be zero due to conformational mobility of the methoxyl group. For detailed studies on the conformation of methoxyl group in several condensed ring systems deduced from dipole moment data see: K. B. Everard and L. E. Sutton, *J. Chem. Soc.*, 2312 (1949); 16 (1951).

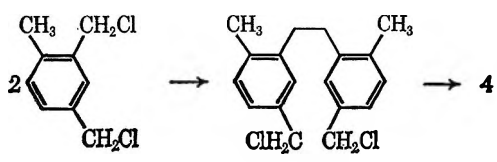
TABLE II

NMR DATA FOR [2.2]METACYCLOPHANE (1) AND 4,14-DISUBSTITUTED DERIVATIVES[a]

		Aryl protons					Methylene protons			
							9,10-H[d]		1,2-H[d]	
Compd	Substituent	5,13-H[b]	6,12-H[b]	$J_{8,6(12,13)}$	8,16-H[c]	$J_{8,6(12,16)}$	Equatorial	Axial	Equatorial	Axial
6	OCH_3	402.1	415.5	9.0	255.0	1.8	176.1	119.7	210.3	95.6
4	CH_3	424.5	411.3	8.0	252.9	1.8	179.5	119.5	197.0	105.6
1	H	430.8[e]	418.2[e,f]	8.0	254.8	1.8	182.9	122.7	182.9	122.7
8	CH_2Br	431.4	419.7	8.0	260.1	1.8	184.0	122.6	211.3	137.3
9	COOH	450.7	432.3	8.0	264.7	1.8	189.0	124.6	218.3	121.3
12	CN	451.2	434.0	8.0	264.0	1.8	196.2	128.6	225.0	133.4
10	CHO	477.6	440.8	8.0	261.0	1.8	199.0	131.2	277.3	108.7

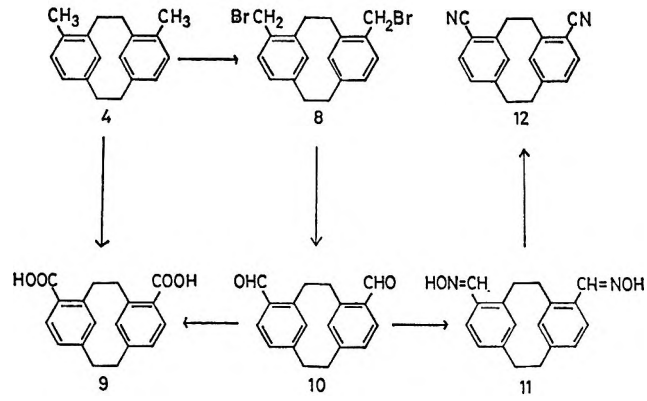
[a] The spectra were recorded with a Varian A-60 spectrometer on a *ca.* 10% (w/v) carbon tetrachloride solution except for **9** which was dissolved in an alkaline deuterium oxide solution. Chemical shifts are expressed in cycles per second (cps) relative to internal TMS as zero. [b] An ABX-type absorption having 6(12)-H weakly coupled with 8(16)-H. [c] Appeared as a doublet except for **1** which showed a triplet. [d] An A_2B_2-type absorption analyzed by AB approximation. [e] An AB_2X-type absorption. [f] Signal for 4,14-H included.

The bimolecular condensation reaction of **3** under extremely mild conditions was thus shown to be highly stereoselective. A combination of low temperature and slow addition is assumed to provide the minimum of the reaction conditions which permit a guiding of the product formation in the desired direction. Especially by using low temperature, a sufficient difference in the activation energies and hence the reactivities between the *o*- and *p*-chloromethyl groups could be realized. The first stage of the condensation of **3** then would afford symmetrical bis(chloromethyl)bibenzyl in preference to the unsymmetrical one no matter which chloromethyl group is more reactive than the other. Further condensation reaction of the intermediate would produce *cis* structure such as **4** or **6**. The relative reactivities of *o*- and *p*-chloromethyl groups were examined by carrying out the competitive Wurtz reaction between *o*- and *p*-methylbenzyl chlorides. Disodium tetraphenylethane solution was added to an equimolar mixture of the methylbenzyl chlorides at −40 to −50°, and the resulting mixture was analyzed by gas chromatography using 5% silicone gum XE-60 on Chromosorb W column. By comparing retention time with the standard samples, the mixture was found to contain 2,2′-dimethylbibenzyl as the major product but not any 4,4′-dimethylbibenzyl. Although the peak was not symmetrical, probably owing to the presence of 2,4′-dimethyl isomer, it was clearly demonstrated that *o*-chloromethyl group was more reactive compared with *p*-chloromethyl group. It may therefore be concluded that the dimerization of 2,4-bis(chloromethyl)toluene would first result in the condensation between *o*-chloromethyl groups to give 5,5′-bis(chloromethyl)-2,2′-dimethylbibenzyl which is then cyclized to the cyclophane **4**.



A series of 4,14-disubstituted [2.2]metacyclophanes bearing various substituents has been prepared for the nmr spectral studies starting from dimethyl compound **4** as is shown in Scheme II. The treatment of **4** with 2 mol of NBS in a carbon tetrachloride solution furnished bis(bromomethyl) derivative **8** in a 60% yield. The preferential bromination of methyl group over methylene group, in contrast to the usual reactivity

SCHEME II



order, may be ascribed to the inertness of the latter group due to inherent steric restriction that the bridging methylene group is deviated from the plane of benzene ring to discourage the usual charge stabilization associated with a benzyl methylene group.[3] Dialdehyde **10** was obtained either by the Sommelet reaction[21] of **8** in a 57% yield or preferably by the reaction with 2-nitropropane and sodium ethoxide in DMSO[22] in a 89% yield. Dicarboxylic acid **9**, which was obtained with difficulty and only in a poor yield by the direct oxidation of **4** due to the accompanying side reaction,[23] was formed in a high yield by the oxidation of **10** with potassium permanganate. The treatment of **10** with hydroxylamine hydrochloride gave dioxime **11** as a mixture of geometrical isomers, which on dehydration by heating with acetic anhydride afforded dinitrile **12**, the over-all yield from **10** being 37%. The results of molecular weight determinations and elemental analyses for these compounds are summarized in Table I. Infrared spectra were consistent with the structure assigned, and further, nmr spectra (Table II) which showed an intraannular 8,16-proton signal as a doublet (J = 1.8 cps) at δ 4.3–4.4 together with other typical signals, indicated that during these transformations the [2.2]metacyclophane structure was not affected.

Nmr Spectra Studies.—The molecular geometry of **1** was elucidated by Brown[24] in 1953 using X-ray measurements and was reported to have a steplike arrangement in which two slightly distorted benzene rings lie on

(21) S. J. Angyal, *Org. Reactions*, **8**, 197 (1954).
(22) B. H. Klanderman, *J. Org. Chem.*, **31**, 2618 (1966).
(23) Attempted reactions of **1** with various oxidizing reagents are summarized in ref 3.
(24) C. J. Brown, *J. Chem. Soc.*, 3278 (1953).

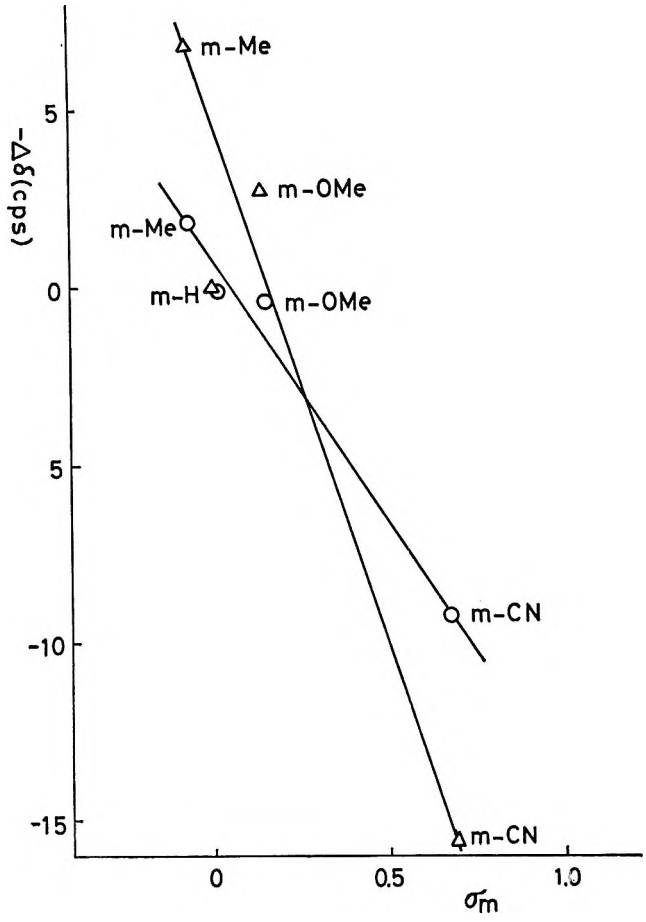


Figure 2.—Plot of chemical shift difference Δδ (cps) against Hammett σ_m: O, 8,16-H; Δ, 6,12-H.

parallel planes. As a consequence the ten-membered ring in **1** exists as a rigid-chair form, intraannular 8,16-hydrogens being extended over, or even into, the π-electron cloud of the opposite benzene ring. These structural features have been shown to be well reflected in the nmr spectra.[25] In an effort to test ring current theory, Boekelheide and his coworkers[15] have examined the nmr spectra of **1** and also several derivatives. Their results indicated that shielding predicted on the basis of ring current anisotropy alone is not adequate to account for the observed shifts such as those between the nonequivalent methylene protons or AB_2-type aryl protons. They could, however, provide a qualitative explanation for the unusual upfield shift of almost 3 ppm exhibited by 8,16 protons, by assuming an induced diamagnetic ring current, which predicted a shift of 2.82 ppm. The ethylene bridge protons showed a typical A_2B_2 pattern consisting of two sets of multiplets, each of which was symmetrical about the midpoint of the spectrum. The most prominent peaks in each of the multiplets appeared as doublet. Owing to a rather large difference in the AB chemical shift, which amounted to almost 60 cps, the analysis of the ethylene bridge signal as a simple AB-type absorption seemed to be feasible. In fact, the calculated values[26] obtained in this way, $\delta_A = 2.04$ and $\delta_B = 3.05$, were in good agreement with those obtained by Boekelheide, *et al.*,[15] $\delta_A = 2.03$ and $\delta_B = 2.99$. Thus the analyses of the ethylene bridge proton signals of 4,14-disubstituted derivatives were achieved by this approximation. The main peaks used for the calculations were tabulated in Table III. The difference of 1.01 ppm in the chemical shift

TABLE III
THE MAIN PEAKS OF A_2B_2 AND $A'_2B'_2$ SYSTEMS

	9,10-H (A_2B_2)				1,2-H ($A'_2B'_2$)			
Compd	Equatorial		Axial		Equatorial		Axial	
6	115.3	123.4	172.3	180.5	91.5	100.0	206.1	214.9
4	115.0	123.0	175.9	184.0	100.7	110.2	192.4	202.0
1	118.0	126.5	179.1	187.1				
8	118.2	126.4	180.3	188.5	132.9	141.4	207.2	216.0
9	120.5	128.5	186.2	194.5	116.5	125.5	214.0	223.0
12	128.8	137.5	182.2	200.5	124.8	132.7	221.0	230.0
10	125.0	134.2	195.2	203.2	105.7	115.7	270.2	279.9

between the methylene protons of **1** is far greater than expected since the calculated value assuming ring current anisotropy was only 0.28 ppm.[15] It is considered, however, that the value is underestimated by neglecting ring-current effect of the second benzene ring to which the methylene group is not directly attached. An examination of the molecular model of **1** indicated that the particular methylene group is situated within the influence of the ring current of both of the benzene rings due to the rigid nature of the molecule. The sum of these two terms estimated from the Johnson–Bovey table[27] was found to be 0.50 ppm. Even regarding approximate nature of the ring-current theory, the difference between the observed and the estimated values, which was as large as 0.51 ppm (1.01 − 0.50), indicated the importance of other contributing factors such as methylene–methylene, ring–methylene,[28] and double bond anisotropy terms.

That the spectral features of derivatives of **1** are reminiscent of those of the parent hydrocarbon has been well established.[25] Since the authors have prepared a series of 4,14-disubstituted derivatives bearing electron-releasing as well as electron-withdrawing substituents, the nmr spectra of these compounds were examined in relation to the electronic and long-range shielding effects of the substituents to the aryl and methylene proton signals. These derivatives appeared to be particularly suited to study the effect of anisotropy of the substituent, separately from other terms, on each of the axial and equatorial proton signals of conformationally locked methylene group at the *ortho* position. The spectral data, which are summarized in Table II, were determined[29] in a 10% (w/v) carbon tetrachloride solution except for **9**, which was measured in an alkaline deuterium oxide solution using a Varian A-60 spectrometer, and were expressed downfield from TMS in cycles per second or δ (parts per million) units. Aryl protons showed two groups of signals: The outer aryl protons at 5,6(12,13) positions showed an ABX-type absorption, of which assignment was unequivocal since 6(12) protons coupled weakly ($J = 1.8$ cps) with intraannular 8(16) protons. The latter protons appeared as a doublet at unusually high field of 253–265 cps, thus serving as a diagnostic purpose of the genera-

(25) B. H. Smith, "Bridged Aromatic Compounds," Academie Press Inc., New York, N. Y., 1964, p 407.
(26) 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 119.
(27) C. E. Johnson and F. A. Bovey, *J. Chem. Phys.*, **29**, 1012 (1958).
(28) Diamagnetic term due to ring-methylene anisotropy may cause an upfield shift of 0.20 ppm as is estimated from McConnel's equation.
(29) The authors are indebted to Mr. M. Kainosho of Ajinomoto Co., Inc., for the measurements.

tion and transformation of the metacyclophane structure.

Both the 6 and 8 protons are situated in the *meta* position of the 4 substituent just as the 12,16 protons are for the 14 substituent. It has been well established[30,31] that the Hammett σ constant could be correlated with chemical shifts of *meta* and *para* protons in substituted benzene derivatives. In Figure 2, a plot of the chemical shift difference of the 8,16 and 6,12 protons against σ_m[32] is shown. Except for compounds **9** and **10**, there were obtained good linear correlations whereby

$$-\rho_{6,12\text{-H}} = 28.2 \text{ cps}/\sigma_m \text{ and } -\rho_{8,16\text{-H}} = 14.5 \text{ cps}/\sigma_m$$

A rather large difference has been shown to exist between these two values indicating that the effect of the substituents on 8,16 proton signals are less pronounced as compared with the 6,12 proton case. This may indicate that the 8,16 protons, which are much more shielded compared with the usual aryl protons by being extended over the π-electron cloud of the opposite benzene ring, are influenced by the nature of the *meta* substituent in a more or less equalized manner.

The assignment of the bridge methylene protons are summarized in Table II. Of the nonequivalent methylene protons in **1**, one at the high field was ascribed to be due to axial, and one at the low field to equatorial protons. Since 4,14-disubstituted derivatives have no plane of symmetry about the plane bisecting both of the benzene rings, they would show two sets of axial and equatorial proton signals, which, actually, were observed as an overlap of two sets of A_2B_2 patterns. One of these occurring at an approximately similar position to **1** was assigned to be due to the methylene protons of the unsubstituted side, namely the 9,10 protons. The chemical shift difference, $\delta_{ax} - \delta_{eq}$, was found to be kept around 1 ppm as in the parent compound. The 9,10-methylene proton signals were affected in a minor degree by changing the substituent. The presence of an electron-withdrawing group caused a downfield shift, whereas an electron-releasing group exhibited an upfield shift. Except for dialdehyde **10**, a good linear correlation was observed between the chemical shift difference and the Hammett σ_p, affording $-\rho_{9,10\text{-ax}} = 9.96 \text{ cps}/\sigma_p$ and $-\rho_{9,10\text{-eq}} = 20.1 \text{ cps}/\sigma_p$. This calculation may, however, be oversimplified by neglecting the contribution from the substituent in the opposite benzene ring, since the benzyl methylene grouping at the 9 or 10 position is regarded also as the β-methylene group in the phenethyl moiety. Thus by taking into account the $-\rho$ value of methyl protons[31] for *para*-substituted toluenes (12.5 cps/σ_p) as well as that for *para*-substituted ethylbenzenes (6.76 cps/σ_p), the substituent effect was correlated with better precision by using a modified Hammett relationship $\delta_R - \delta_H = \rho(\sigma_p - 6.76/12.5\sigma_p)$ instead of the usual Hammett equation used above. The calculated values, $-\rho_{9,10\text{-ax}} = 6.78 \text{ cps}/\sigma_p$ and $-\rho_{9,10\text{-eq}} = 14.4 \text{ cps}/\sigma_p$ (Figure 3), not only had higher consistency and less deviation but are more compatible with $-\rho$ of *para*-substituted toluenes, in which the methyl protons are conformationally equalized. The difference in ρ_{ax} and ρ_{eq} indicates that axial protons, which are more shielded than equatorial ones and make an angle of about 60° with a benzene plane, are less sensitive to the electronic effect than the equatorial ones which lie approximately in the plane of benzene ring. The cause of the phenomena, which is not explainable on the basis of ring-current effect, may be due partly to the σ–π interaction between the rear lobe of the sp^3 orbital of the bridge carbon used in the bonding with equatorial hydrogen and the π-electron system of the aromatic ring as in the case of the anti proton at C-9 of substituted benzonorbornenes.[33]

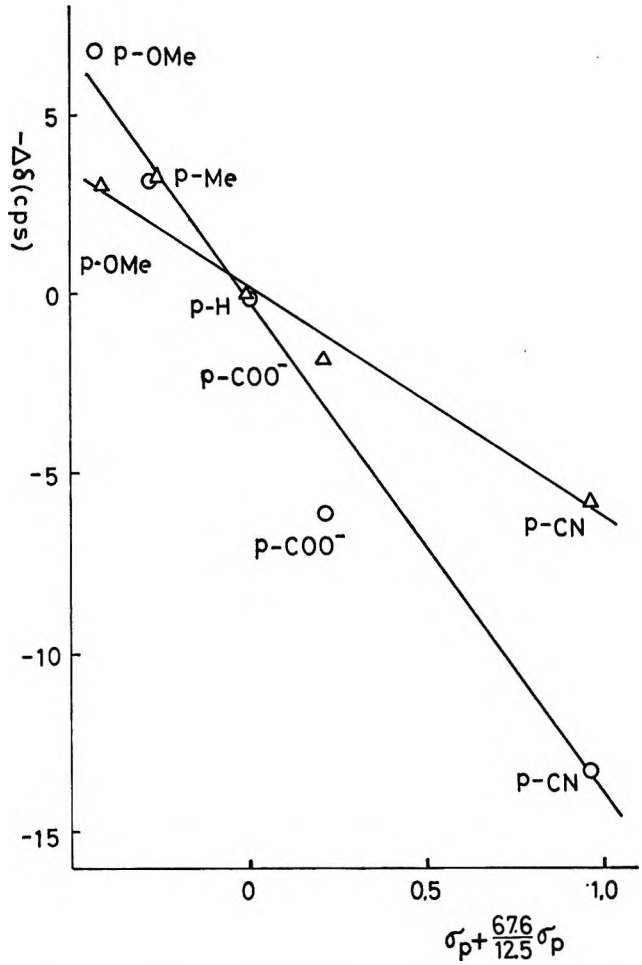


Figure 3.—Plot of chemical shift difference $\Delta\delta$ (cps) of 9,10-methylene protons against Hammett $\sigma_p + 6.76/12.5\ \sigma_p$: ○, equatorial H; △, axial H.

In Figure 4, chemical shifts of axial and equatorial protons at 1,2 positions relative to various substituents are illustrated. If the chemical shift is only dependent on the inductive and mesomeric effect of the substituents, a linear correlation similar to the 9,10 proton case may be expected. It was found, however, that the difference in the chemical shift between the axial and equatorial protons increased and varied widely. For example, the difference reached 114.7 and 168.6 cps in dimethyl ether **6** and dialdehyde **10**, respectively. Although the axial proton did not suffer from a large deviation, except for **6** and **10**, the equatorial proton experienced a marked downfield shift which amounted to

(30) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High-Resolution Nuclear Magnetic Resonance Spectroscopy," Pergamon Press, Ltd., London, 1966, p 752.

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(32) L. P. Hammett, *J. Amer. Chem. Soc.*, **59**, 96 (1937).

(33) N. Inamoto, S. Masuda, K. Tori, K. Ando, and H. Tanida, *Can. J. Chem.*, **45**, 1186 (1967).

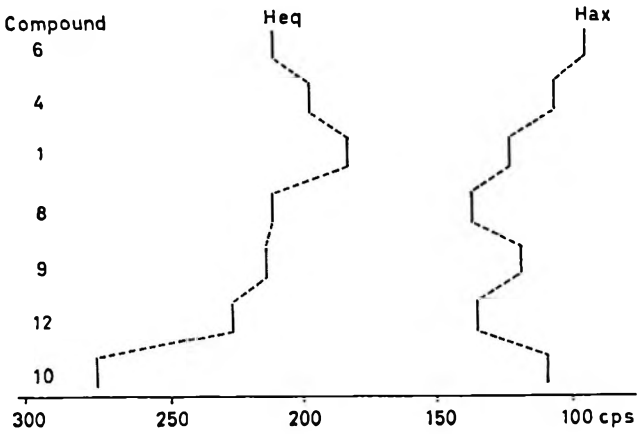

Figure 4.—Chemical shifts (cycles per second downfield from TMS) of axial (H_{ax}) and equatorial (H_{eq}) protons of 1,2-methylene group in [2.2]metacyclophane and its 4,14-disubstituted derivatives.

24.2 and 78.3 cps in the case of **6** and **10** (the chemical shift difference between $1,2_{eq}$ and $9,10_{eq}$ protons). These deviation may be caused by long-range shielding effects which are governed by the conformational preference of the substituent and the anisotropy terms of benzene ring and the substituent group.

Experimental Section[34]

4,14-Dimethyl[2.2]metacyclophane (4).—According to the method of Müller and Roscheisen,[14] disodium tetraphenylethane solution was prepared from 5 g (excess) of sodium and 3.5 g (0.011 mol) of tetraphenylethylene in 300 ml of absolute tetrahydrofuran (THF). To the above mixture was added, with stirring, a solution of 12 g (0.064 mol) of 2,4-bis(chloromethyl)toluene[35] [bp 146–160° (14–15 mm), mp 43–45° (from hexane)] dissolved in 500 ml of tetrahydrofuran at −60 to −70° through a specially designed dropping funnel over a period of 68 hr, the whole operation being conducted under a current of nitrogen. After the addition was completed a small amount of ethanol was added, and the reaction mixture was filtered. The concentrated mixture was then extracted with ether. The distillation of extract at 183° (12 mm) gave 1.56 g of colorless oil, which crystallized as colorless needles: mp 68–69°; $\lambda_{max}^{C_6H_{12}}$ 276 mμ (ε 673); ν_{max}^{KBr} 2900, 2810, 1490, 1170, 812, and 742 cm^{-1}.

The crude distillate was examined carefully by gas chromatography. By using a 5-ft column of 2.0% CNSi on Anakrom U with a nitrogen flow rate of 36 cc/min or a 6-ft column of 1.5% SE-30 on Anakrom U with a nitrogen flow rate of 80 cc/min only a sharp peak due to **4** was detectable: retention times for each column were 8.1 and 5.6 min, respectively.[19] It was also examined by several other columns including 10% SE-30 on Chromosorb W (6 ft), 10% Carbowax 20M on Chromosorb W (6 ft), and 4% neopentyl glycol adipate on Chromosorb G (6 ft). In no case was another peak due to isomeric **5** detectable.

The Competitive Wurtz Reaction of *o*-Methylbenzyl Chloride and *p*-Methylbenzyl Chloride.—A mixture of 1.24 g (9.1 mmol) of *o*-methylbenzyl chloride and 1.14 g (8.3 mmol) of *p*-methylbenzyl chloride was dissolved in 250 ml of tetrahydrofuran. In another vessel a solution of sodium–tetraphenylethylene adduct was prepared from 2.0 g (0.087 g-atom) of sodium in 200 ml of THF. The solution of condensing agent was added, with stirring and under a nitrogen current, into the competing mixture in the course of 13 hr, while the reaction temperature was maintained at −40 to −50°. The analysis of the reaction mixture by gas chromatography (Hitachi K-53 gas chromatography with a hydrogen flame ionization detector) using 5% silicone gum XE-60 on a Chromosorb W (60–80 mesh) column operated at 130° with a flow rate of 50 cc/min of nitrogen showed the presence of a material having a retention time of 23.6 min. The gas chromatography of the standard sample under the same conditions revealed that 4,4′-dimethylbibenzyl, mp 82–83° (lit.[36] mp 82–83°), and 2,2′-dimethylbibenzyl, mp 65–66° (lit.[37] mp 66–67°), had retention times of 21.4 and 23.4 min, respectively. Hence the main product was deduced to be 2,2′-dimethylbibenzyl.

4,14- and 4,12-Dimethoxy[2.2]metacyclophanes (6 and 7).—A solution of 40 g (0.20 mol) of 2,4-bis(chloromethyl)anisole,[38] bp 130–150° (2 mm), mp 64–66° (from petroleum ether (bp 30–60°)), in 760 ml of tetrahydrofuran was added dropwise, in the course of 184 hr, to a solution of the condensing agent, which was prepared from 16 g of sodium added to 5.0 g (0.015 mol) of tetraphenylethylene in 300 ml of absolute tetrahydrofuran at −40 to −20° under a current of nitrogen. After working up as described for the methyl analog, ether extract was subjected to vacuum sublimation at 100–130° (0.3–0.7 mm), thus obtaining 3.7 g of colorless crystalline material, which was then passed through an alumina column using *n*-hexane as an eluent. Tetraphenylethylene and tetraphenylethane came out first, followed by a compound which was found to be **7** as evidenced by its nmr spectrum (see Figure 1): mp 182° (recrystallized from ethanol); ν_{max}^{KBr} 1239, 1099, and 810 cm^{-1}.

The next few fractions contained a mixture of **6** and **7**. Then compound **6**, which was isolated in a 9.2% yield, followed: colorless needles; mp 132–134°; $\lambda_{max}^{C_6H_{12}}$ 290 mμ (ε 3380); ν_{max}^{KBr} 1238, 1088, and 796 cm^{-1}; dipole moment μ = 0.79 D (benzene solution at 20°).

Gas chromatography, carried out using a 1-m column of 5% silicone XE-60 on Chromosorb W, could not distinguish between **6** and **7** since both compounds had equal retention times (6.2 min).

4,14-Bisbromomethyl[2.2]metacyclophane (8).—To a solution of 2.6 g (0.011 mol) of **4** in 40 ml of carbon tetrachloride was added 4.0 g (0.023 mol) of N-bromosuccinimide and a few milligrams of benzoyl peroxide. After being kept at reflux for 8 hr, the mixture was filtered and the filtrate was concentrated to about 10 ml. A crude material, mp 161–166°, was obtained as colorless needles, which on repeated recrystallizations from carbon tetrachloride melted at 170°. An optimum yield of 60% was obtained by this method: ν_{max}^{KBr} 2940, 2840, 1600, 1580, and 1430 cm^{-1}.

[2.2]Metacyclophane-4,14-dicarbaldehyde (10). A.—A mixture of 2.4 g (6.1 mmol) of **8**, 2 ml of water, 40 ml of glacial acetic acid, and 2.0 g (0.014 mol) of hexamethylenetetramine was heated under reflux for 2 hr. An additional 25 ml of water was added and reflux was continued for 15 min. The reflux was further continued for 5 min by adding 2 ml of concentrated hydrochloric acid. After being diluted with water, the whole was extracted with several portions of ether. A crude material, mp 110–120°, was obtained in a 57% yield. Three recrystallizations from ethanol afforded colorless powder, mp 117–120°.

B.—A sodium ethoxide solution made by adding 0.46 g (0.02 g-atom) of sodium to 30 ml of ethanol, containing 3.0 g (0.034 mol) of 2-nitropropane, was added to a solution of 3.3 g (8.5 mmol) of **8** dissolved in 50 ml of DMSO in the course of 30 min. After the reaction mixture was kept at room temperature for 4 hr under stirring, it was diluted with 200 ml of water and allowed to stand overnight in the refrigerator. A crude material, mp 110–120°, which totaled 1.99 g (89% yield), was obtained as colorless powder by filtration of mixture. Final purification was achieved either by repeated recrystallizations or by column chromatography on alumina: mp 117–120°; $\lambda_{max}^{C_6H_{12}}$ 266 mμ (ε 19,200), and 300 (3250); ν_{max}^{KBr} 1688 cm^{-1}.

4,14-Dicyano[2.2]metacyclophane (12).—A mixture of 100 mg (0.38 mmol) of **10**, 70 mg (1 mmol) of hydroxylamine hydrochloride, and 3 ml of ethanol was warmed at 30–40° for 20 hr. On concentration a white solid separated, which consisted of oxime **11** (ν_{max}^{KBr} 3535 and 930 cm^{-1}) containing a small amount of dinitrile **12** which exhibited an additional absorption at 2200 cm^{-1}. Without further purification, the material was refluxed with 3 ml of acetic anhydride for 2 hr. On cooling a crystalline material, 33 mg (34% yield), found to be **12**, mp 185°, was separated. A purified material, mp 196–197°, was obtained as colorless needles on recrystallization from ethanol or acetic anhydride: λ_{max}^{EtOH} 286 mμ (ε 2330) and 245 (sh); ν_{max}^{KBr} 2200 cm^{-1}.

(34) All melting and boiling points are uncorrected. The authors are grateful to Mr. S. Hayashi of Nihon University for providing uv data.

(35) M. G. Blanc, *Bull. Soc. Chim. Fr.*, [4] **33**, 313 (1923).

(36) E. I. du Pont de Nemours and Co., British Patent 583,634; *Chem. Abstr.*, **41**, 2749*d* (1947).

(37) J. Meisenheimer, O. Beisswenger, H. O. Rauffman, U. V. Rummer, and J. Link, *Ann.*, **468**, 216 (1929).

(38) R. Quelet and M. Anglade, *Bull. Soc. Chim. Fr.*, [5] **3**, 2200 (1936).

[2.2]Metacyclophane-4,14-dicarboxylic Acid (9). A.—A mixture of 250 mg (1.1 mmol) of 4, 900 mg (5.7 mmol) of potassium permanganate, and 10 ml of water containing 1 ml of sulfuric acid was heated under reflux for 1 hr. The reflux was further continued for 30 min by adding additional 500 mg of potassium permanganate. After being made acidic with hydrochloric acid, the mixture was extracted continuously with benzene. A small amount of 9, which did not melt below 300°, was obtained by extraction with a sodium hydroxde solution, ν_{max}^{KBr} 1680 cm^{-1}.

B.—To a solution of 200 mg (0.76 mmol) of 10 in 7.5 ml of acetone, 8 ml of 3.2% potassium permanganate solution was added with stirring during the course of 1 hr at 50–80°. After filtration, the filtrate was made acidic and 192 mg (86% yield) of a crystalline material was collected. It was recrystallized from acetic acid as colorless plates: mp >300°; λ_{max}^{EtOH} 250 mμ (sh), 286 (ε 2330), and 355 (43); ν_{max}^{KBr} 1680 cm^{-1}.

Registry No.—1, 2319-97-3; 4, 16620-99-8; 6, 10125-36-7; 7, 16621-01-5; 8, 16621-02-6; 9, 16621-03-7; 10, 16621-04-8; 12, 16621-05-9.

Acenaphthene Chemistry. IX.[1,2] The Synthesis and Epoxidation of 2a,3,4,5-Tetrahydroacenaphthylene

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2a,3,4,5-Tetrahydroacenaphthylene (I) was synthesized. This compound, when treated with *m*-chloroperbenzoic acid, formed *trans*-1-(2-hydroxy-2a,3,4,5-tetrahydroacenaphthyl) *m*-chlorobenzoate, *via* the intermediate epoxide. Hydrolysis of the ester formed *trans*-1,2-dihydroxy-2a,3,4,5-tetrahydroacenaphthene.

Only two attempts to epoxidize an acenaphthylene are described in the literature. In 1939, Wittig and Henkel[4] treated 1,2-diphenylacenaphthylene with perbenzoic acid in chloroform but were only able to isolate 1,8-dibenzoylnaphthalene. Bartlett and Brown[5] found the reaction to lead to the formation of a complex mixture from which they isolated 1,2-diphenylacenaphthylene glycol, 1,2-diphenyl-1,2-dichloroacenaphthene, 1,1-diphenylacenaphthenone, and 1,8-dibenzoylnaphthalene.

It is possible that, in acenaphthylene, delocalization of the electrons of the double bond is sufficient to reduce its nucleophilic character such that the molecule is sensitive to gross oxidative effects such as radical attack, but insensitive toward less electrophilic systems. This is reasonable in view of the fact that Bartlett and Brown found, among their products, 1,2-dichloro-1,2-diphenylacenaphthene which could arise from radical breakdown of the solvent chloroform.

We treated acenaphthylene with the nitrile–hydrogen peroxide system described by Payne,[6] but the starting material was recovered nearly quantitatively. 1,2-Diphenylacenaphthylene was similarly unreactive.

Base-catalyzed elimination of HX from *trans* halohydrins offers another possible route to epoxides. Even though the halohydrin formed by addition of hypohalite to acenaphthylene could not assume a *trans* coplanar arrangement, since the bridge substituents are in an eclipsed conformation, the possibility that HX elimination would proceed to give an epoxide could not be excluded. The treatment of acenaphthylene with a solution of "hypochlorous acid"[7] resulted in no change.

The properties of acenaphthylene[8] suggest that the double bond is not epoxidized since it is part of an essentially aromatic system. The 2a,3,4,5-tetrahydroacenaphthylene ring system, however, resembles the readily epoxidized indene and thus we visualized a synthesis of acenaphthylene oxide through its tetrahydro derivative.

Only one example of a 2a,3,4,5-tetrahydroacenaphthene ring system is reported in the literature. Buchta and Maar[9] described the synthesis of the 1,2-diphenyl-2a,3,4,5-tetrahydroacenaphthylene (II). We find that, when this compound was treated with benzonitrile–50% hydrogen peroxide, buffered with solid potassium bicarbonate, for 142 hr, 90% of the starting material was recovered. When II was treated with *m*-chloroperbenzoic acid, a yellowish oil was recovered. Chromatography of this oil gave a yellow glass. An infrared (ir) spectrum of the glass indicated that the tetrahydro ring was still intact, but no chemical entity could be isolated.

Attention was then directed toward the synthesis of an unsubstituted tetrahydroacenaphthylene. Utilizing a procedure similar to that of Buchta and Maar, we prepared 1,2,3,4-tetrahydronaphthyl-1-acetic acid (III) by the condensation of α-tetryl chloride and diethyl sodiomalonate, followed by hydrolysis and decarboxylation. Ring closure was effected in high yield by briefly heating the acid in polyphosphoric acid. The resulting 1-oxo-2a,3,4,5-tetrahydroacenaphthene (IV) was reduced with sodium borohydride to the alcohol V and then treated with phosphorous tribromide to form 1-bromo-2a,3,4,5-tetrahydroacenaphthene (VI). The bromide was found to be unstable as a marked discoloration appeared after 3 days at room temperature.

(1) Paper VIII: H. J. Richter, R. L. Dressler, and S. F. Silver, *J. Org. Chem.*, **30**, 4078 (1965).

(2) This work was supported by U. S. Public Health Service Research Grant CA 02997-8,9 from the National Cancer Institute, National Institutes of Health.

(3) Taken from a portion of the dissertation submitted to the Graduate School of the University of Colorado in partial fulfillment of the requirements for the Ph.D. degree, 1966.

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(5) P. D. Bartlett and R. F. Brown, *J. Amer. Chem. Soc.*, **62**, 2927 (1940).

(6) G. B. Payne, P. H. Deming, and P. H. Williams, *J. Org. Chem.*, **26**, 659 (1961); G. B. Payne, *Tetrahedron*, **18**, 763 (1962).

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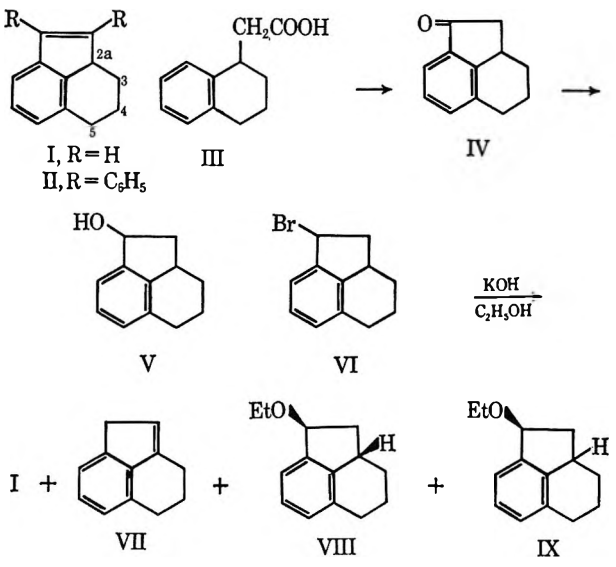
(8) R. H. Boyd, R. L. Christensen, and R. Pua, *J. Amer. Chem. Soc.*, **87**, 3554 (1965).

(9) E. Buchta and H. Maar, *Ber.*, **95**, 1826 (1962); E. Buchta and H. Maar, *Ann.*, **674**, 129 (1964).

Base-catalyzed dehydrohalogenation in refluxing alcoholic potassium hydroxide and extraction with benzene yielded a residue which distilled between 94 and 110° at 0.8-mm pressure. A vpc analysis of the distillate indicated four components in approximately equal amounts. The first two components were shown to be the isomeric hydrocarbons I and VII. The latter two components were separated as one fraction by preparative vpc. An elemental analysis required $C_{14}H_{18}O$. The nmr spectrum of the mixture was very complex but was consistent with $C_{14}H_{18}O$ and the isomeric ether structures VIII and IX.

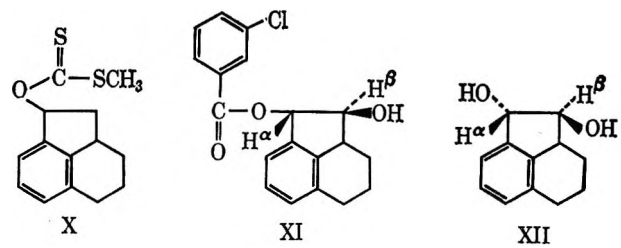


When a solution of the bromide VI was refluxed in pyridine, only one product could be isolated in low yield. An elemental analysis indicated the formula $C_{12}H_{12}$. An nmr spectrum of the compound exhibited a quintet at δ 5.82 (J = 2.0 cps, 1 H) and a quartet at 3.15 (J = 2.0 cps, 2 H). Over-all integration was consistent with the formula $C_{12}H_{12}$. Structure VII, 3,4-trimethyleneindene, provides the most reasonable interpretation of the observed splitting patterns and the proton integration values. A pyrolytic method such as xanthate pyrolysis appeared attractive.

The sodium salt of V was prepared by refluxing a solution of V in ether with powdered sodium. The xanthate X was prepared by the addition of carbon disulfide followed by methyl iodide. It was not isolated but decomposed directly to give a pale yellow oil which distilled at 59–61° at 0.18-mm pressure. The nmr spectrum was characteristic of compound I. Vinyl proton absorption occurred as an AB quartet at δ 6.57 (J = 5 cps), that had been split into an octet (J = 2 cps) by the proton at the 2a position. Over-all integration of the proton absorption peaks was consistent with the formula $C_{12}H_{12}$. A great deal of difficulty was experienced in removing small amounts of sulfur from the distillate. The normal procedure involving storage over sodium wire could not be used because of the acidity of the hydrocarbon. When a solution of the xanthate decomposition product in ether was vigorously stirred with mercury, all but trace amounts of sulfur were removed. Satisfactory elemental analysis could not be obtained owing in part to residual sulfur but chiefly because the material readily decomposed at room temperature. Both olefins I and VII were readily convertible into acenaphthylene by the action of 2,3-dichloro-5,6-dicyanobenzoquinone. When a mixture of 2a,3,4,5-tetrahydroacenaphthylene (I) and tetraphenylcyclopentadienone was strongly heated, an adduct was formed.

When a solution of I in chloroform was treated with *m*-chloroperbenzoic acid at room temperature, a yellow oil was formed. Trituration with petroleum ether produced a white solid which was purified by chromatography on alumina to afford white needles melting at 160.5–162.5°. The substance gave a positive test for halogen and elemental analysis required $C_{19}H_{17}O_3Cl$. Its ir spectrum exhibited hydroxyl and doublet carbonyl absorption. The position of the ester moiety was established by a comparison of nmr chemical shifts[10] observed for the benzylic proton (H^α) in XI (δ 5.97), the diol XII (4.64), benzyl benzoate (5.34),[11a] and benzyl alcohol (4.58).[11b]

The similarity in the chemical shifts of H^α in both XI and benzyl benzoate, and again the correspondence in the hydrolysis products, XII and benzyl alcohol, allow



the conclusion that the ester moiety exists at position 1 as shown in XI. The additional downfield shift in both XI and XII can be attributed to both ring strain and a shielding effect from the vicinal hydroxyl group.

Hydrolysis of the hydroxy ester XI gave colorless needles of *trans*-1,2-dihydroxy-2a,3,4,5-tetrahydroacenaphthene (XII), mp 142–143.5°. A solution of 18 mg of XII in 15 ml of carbon tetrachloride exhibited a single peak at 3710 cm^{-1}. Since intramolecular hydrogen-bonding peaks are present even in very dilute solutions of *cis*-diols the possibility of a *cis*-diol is eliminated since no intramolecular hydrogen-bonding peak was observed.

The intermediacy of an epoxide is confirmed since only a *trans*-diol could be isolated upon hydrolysis of the hydroxy ester. Since hydrolysis of esters with a strong base results in acyl–oxygen cleavage, the configuration about the carbon bearing the ester moiety is retained and thus the configuration of XII is *trans*. Therefore an epoxide is an intermediate in the hydroxybenzoylation of 2a,3,4,5-tetrahydroacenaphthene.

Experimental Section

All melting points were taken in capillary tubes on a Thomas–Hoover apparatus. The ir spectra were recorded by a Beckman

(10) Because of the lack of solubility of the compounds XI and XII in solvents amenable to nmr, no discrete splitting patterns were observed.

(11) (a) Varian Nmr Spectra Catalog, Varian Associates, Palo Alto, Calif., no. 627; (b) no. 181.

Model IR-5 spectrophotometer and the details are given in ref 3. The nmr spectra were determined on a Varian A-60 spectrometer.

1-Keto-2a,3,4,5-tetrahydroacenaphthene (IV).—1-(Diethylmalonyl)-1,2,3,4-tetrahydronaphthalene[12] (186.7 g) was hydrolyzed on being refluxed with a solution of 160 g of potassium hydroxide in 1 l. of methanol for 1 hr. The separated solid was removed by filtration and the filtrate was evaporated to dryness *in vacuo*. The combined solids from above were dissolved in 1 l. of water and the solution was filtered and extracted with ether to remove unreacted ester. The aqueous layer was heated on a steam bath to remove dissolved ether, cooled to room temperature, and acidified with 15% hydrochloric acid with vigorous stirring. The precipitated solid was extracted with ether and, upon removal of the ether *in vacuo*, 165 g of solid material was obtained.

The solid material was not purified but was heated in an oil bath at 200–220° until gas evolution stopped. There was obtained 114 g of crude 1,2,3,4-tetrahydronaphthyl-1-acetic acid (III).

The acid III was heated with stirring on a steam bath with 780 g of polyphosphoric acid to an internal temperature of 85°. The dark green mixture was hydrolyzed with 2 l. of ice water, the separated solid was dissolved in benzene, and the aqueous portion was extracted four times with benzene. The combined benzene extracts were washed successively with water, 5% sodium hydroxide solution, water, 3% acetic acid solution, 10% sodium bicarbonate solution, and water. The benzene extracts were dried over anhydrous magnesium sulfate. Removal of the solvent *in vacuo* yielded 88.0 g of crude solid (91% of the theoretical yield). Crystallization from ethanol–water gave white crystals, mp 101.5–103.5° (lit.[13] mp 100–101.5°).

1-Hydroxy-2a,3,4,5-tetrahydroacenaphthene (V).—To a cooled solution of 88.0 g of 1-keto-2a,3,4,5-tetrahydroacenaphthene in 900 ml of 95% ethanol, 10.0 g of sodium borohydride was added portionwise with good stirring. The reaction mixture was allowed to stand overnight. The heterogeneous mixture was then heated to boiling, water was added to incipient cloudiness, and the mixture was allowed to cool to room temperature. The solid that separated was removed by filtration and crystallized from 2 l. of Skellysolve B (bp 60–70°) to give 83 g (93%) of white crytals, mp 97.5–98.5°. A portion was sublimed *in vacuo* at 110° and used as an analytical sample. An nmr spectrum of the alcohol in acetonitrile exhibited a singlet at δ 7.32, a complex multiplet between 7.66 and 6.82, a multiplet centered at 5.17, and a doublet at 3.35.

Anal. Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.63; H, 8.00.

1-Bromo-2a,3,4,5-tetrahydroacenaphthene (VI).—To a solution of 6.0 g of V in 50 ml of anhydrous ether, cooled in an ice bath, was added 1.23 ml of phosphorous tribromide. The mixture was allowed to stand for 0.5 hr. The mixture was then hydrolyzed with ice–water, the layers were separated, and the benzene layer was washed successively with water, 10% sodium bicarbonate solution, and water. The benzene solution was dried over anhydrous magnesium sulfate. Removal of the solvent *in vacuo* resulted in a crude solid which was digested with 20 ml of Skellysolve B and filtered, yield 6.95 g (86%) of white crystals, mp 73–75°. Recrystallization from Skellysolve B gave white crystals, mp 77.5–79.5°.

Anal. Calcd for $C_{12}H_{13}Br$: C, 60.75; H, 5.53. Found: C, 60.83; H, 5.51.

Formation of the Olefin. Method A. Treatment of 1-Bromo-2a,3,4,5-tetrahydroacenaphthene (VI) with Ethanolic Potassium Hydroxide.—Thirty grams of VI was refluxed for 3 hr with 250 ml of a 10% ethanolic potassium hydroxide solution. The solution was evaporated to semidryness *in vacuo* and then diluted with 500 ml of cold water. The resulting heterogeneous mixture was extracted twice with benzene and the benzene extracts were washed with dilute hydrochloric acid solution and water. The benzene extracts were dried over anhydrous magnesium sulfate and the benzene was removed *in vacuo*. The residue was distilled from an oil bath at 130–145°, bp 94–110° (0.64–0.80 mm). Vapor phase chromatography of a dilute acetone solution of the distillate on an SE-30 column at 133° and a flow rate of 30 ml/min showed the distillate to be composed of four components with retentions of 4.09, 5.07, 10.9, and 12.9 in. (chart speed, 1 in./min). The first two components were identified as the 1,7- and 3,4-trimethylenindene by comparison of the nmr spectra and vpc retention times of independently prepared samples. The latter two components were separated as one fraction and were composed of the isomeric 1-ethoxy-2a,3,4,5-tetrahydroacenaphthenes (VIII and IX). An nmr spectrum of the mixture of ethers was quite complex. It showed aromatic absorptions centered at δ 6.50, a quartet at 4.78 (J = 3.7 cps), a doublet at 4.50 (J = 5 cps), a quintet at 3.45 (J = 7 cps), and a complex pattern of peaks between 2.7 and 0.9. Integration of the proton absorption peaks was consistent with $C_{14}H_{18}O$.

Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 82.87; H, 8.63.

Method B. Treatment of 1-Bromo-2a,3,4,5-tetrahydroacenaphthene (VI) with Pyridine.—A solution of 11.9 g of VI in 100 ml of pyridine was refluxed for 20 hr. Three-fourths of the pyridine was removed *in vacuo* and the remaining pyridine solution was poured into 250 ml of cold water and extracted twice with 125-ml portions of benzene. The benzene extracts were washed three times with 200 ml of water, twice with 10% acetic acid solution, and twice with 200 ml of water. The benzene solution was dried over anhydrous magnesium sulfate and the solvent was removed *in vacuo*. The dark oil remaining was distilled at 62–63° and 0.2-mm pressure (oil bath at 90–95°), to give 1.53 g (20%) of 1,7-trimethylenindene, a white semisolid, as the only product. The nmr spectrum showed aromatic absorptions centered at δ 6.99 (3 H), a quintet at 5.82 (1 H, J = 2 cps), a quartet at 3.15 (2 H, J = 2 cps), a multiplet at 2.60 (4 H), and a multiplet centered at 1.80 (2 H).

Anal. Calcd for $C_{12}H_{12}$: C, 92.26; H, 7.74. Found: C, 92.18; H, 7.82.

Method C. Xanthate Pyrolysis.—All apparatus was dried in an oven overnight at 110°. In a 500-ml, three-necked Morton flask with a Herschberg stirrer, a dropping funnel, and a reflux condenser (protected with calcium chloride drying tubes) was placed a solution of 13.0 g of 1-hydroxy-2a,3,4,5-tetrahydroacenaphthene in 200 ml of anhydrous ether. To this solution 1.75 g of powdered sodium was added and the mixture was stirred vigorously at room temperature for 42 hr. Carbon disulfide (5.0 ml) was then added portionwise and the yellow solution (containing a small amount of unreacted sodium) was stirred at room temperature for 3 hr. Methyl iodide (9.8 ml) was then added and the reaction mixture was allowed to stir overnight. More methyl iodide (4 ml) was then added and stirring was continued for 1 hr. The insoluble material was filtered off and washed well with ether and the ether was removed by distillation from a steam bath. The residue from the ether solution was placed in 50-ml flask equipped with a Dean–Stark trap and reflux condenser and heated on a steam bath at a pressure of 0.30 mm for 2 hr until no gas was evolved as judged by an external bubbler. The residue distilled at 59–61° at 0.18 mm to give 7.45 g (64%) of a pale yellow oil.

An nmr spectrum exhibited an AB quartet centered at δ 6.57 (J = 5 cps) that had been split into an octet (J = 2 cps). Integration of the proton absorption peaks was consistent with $C_{12}H_{12}$.

An unsatisfactory elemental analysis was obtained and believed to be due to the presence of trace amounts of sulfur and to the instability of the product.

The olefins obtained by methods B and C were dehydrogenated with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ). Thus, a solution of 0.5 g of 2a,3,4,5-tetrahydroacenaphthylene prepared by method A dissolved in 25 ml of anhydrous benzene was refluxed for 0.5 hr with 0.8 g of DDQ after which an additional 1.2 g of DDQ was added and refluxing was continued for 2 hr. The dark green solution was cooled to room temperature, diluted (50 ml of Skellysolve B), and filtered. The filtrate was chromatographed on alumina. Elution with Skellysolve B and removal of the solvent *in vacuo* gave 0.25 g of acenaphthylene, mp 90–91° after two crystallizations from ethanol–water. There was no depression of a mixture melting point with an authentic sample.

1,7-Trimethylenindene, obtained by treating 1-bromo-2a,3,4,5-tetrahydroacenaphthene with pyridine (method B), was also dehydrogenated with DDQ to give acenaphthylene.

Tetracyclone Adduct of 2a,3,4,5-Tetrahydroacenaphthalene.—Tetraphenylcyclopentadienone (0.5 g) and 0.5 g of 2a,3,4,5-tetrahydroacenaphthylene contained in a test tube were heated with a microburner to an internal temperature of 300°. The reddish mass was cooled, treated with a small amount of ethanol,

(12) M. Protiva, J. O. Jilek, Z. J. Vejdelek, and P. Finglova, *Chem. Listy*, **47**, 584 (1953).

(13) W. S. Johnson and H. J. Glenn, *J. Amer. Chem. Soc.*, **71**, 1087 (1949).

and filtered. The solid was crystallized from ethanol–water to give the adduct as pale yellow microcrystals, mp 125–129°.

Anal. Calcd for $C_{40}H_{32}$: C, 93.70; H, 6.29. Found: C, 93.96; H, 5.88.

trans-1-(2-Hydroxy-2a,3,4,5-tetrahydroacenaphthyl) *m*-Chlorobenzoate (XI).—To a cooled solution of 4.25 g of 2a,3,4,5-tetrahydroacenaphthylene in 100 ml of chloroform, 5.66 g of 83% *m*-chloroperbenzoic acid was added in portions with good stirring. The mixture was allowed to stir at room temperature for 6 hr. At that time 97% of the peracid had been consumed as determined by iodometric titration. The reaction mixture was filtered and the chloroform solution was washed with water. The solution was dried over anhydrous magnesium sulfate and the solvent was removed *in vacuo* to give a light yellow oil. The oil solidified when rubbed with a glass rod in the presence of approximately 15 ml of Skellysolve B to give 1.73 g of a white solid. The crude solid was chromatographed on alumina (Merck, no. 71707). Elution with 250 ml of benzene gave a yellowish oil, which was not characterized. Elution with 750 ml of ethyl acetate followed by crystallization from benzene–Skellysolve B gave 1-(2-hydroxy-2a,3,4,5-tetrahydroacenaphthyl) *m*-chlorobenzoate as white needles, mp 160.5–162.5°. The substance gave a positive Beilstein test for halogen and a positive test with ferric hydroxamate for ester. An nmr spectrum of an acetone solution exhibited a singlet at δ 5.97 and a doublet at 4.13 (J = 5 cps).

Anal. Calcd for $C_{14}H_{17}O_3Cl$: C, 69.40; H, 5.21; Cl, 10.78. Found: C, 69.53; H, 5.30; Cl, 10.26.

trans-1,2-Dihydroxy-2a,3,4,5-tetrahydroacenaphthene (XII).—1-(2-Hydroxy-2a,3,4,5-tetrahydroacenaphthyl) *m*-chlorobenzoate (2.62 g) was refluxed with 100 ml of 3 *N* sodium hydroxide for 3 hr. The heterogeneous mixture was cooled, filtered, and diluted with 1 l. of cold water. The aqueous solution was extracted five times with 200-ml portions of ether. Removal of the ether *in vacuo* gave 0.76 g of *trans*-1,2-dihydroxy-2a,3,4,5-tetrahydroacenaphthene, mp 142–143.5° after crystallization from benzene. A sample in carbon tetrachloride (18 mg/15 ml) exhibited a single peak in the infrared at 3710 cm^{-1}. An nmr spectrum of the material in acetonitrile showed a singlet at δ 7.55, aromatic absorption peaks centered about 7.06, a singlet at 4.64, and a doublet at 4.28 (J = 4 cps).

Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.62; H, 7.44.

Registry No.—I, 16897-56-6; V, 16897-57-7; VI, 16897-58-8; VIII, 16897-59-9; IX, 16897-60-2; 1,7-trimethylenindene, 16897-56-6; tetracyclone adduct of 2a,3,4,5-tetrahydroacenaphthalene, 16897-62-4; XI, 16897-63-5; XII, 16897-64-6.

Organolithium Compounds and Acetylenes. IV.[1] Sequence of Addition–Metalation in the Reaction of Organolithium Compounds with Diphenylacetylene

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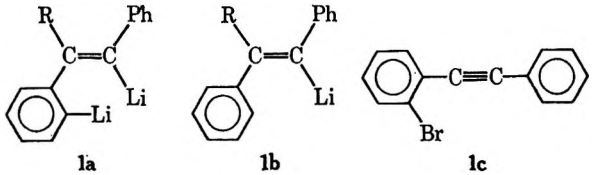
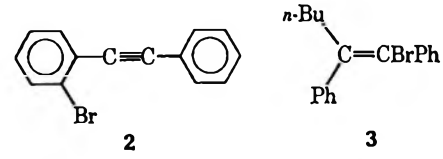
Products from the reaction of *n*-butyllithium and/or lithium metal with *o*-bromodiphenylacetylene (2) and 1-bromo-1,2-diphenyl-1-hexene (3) have been identified. The results lead to the conclusion that *n*-butyllithium reacts with diphenylacetylene by addition followed by metalation. In the course of the work the stereochemistry of the isomeric 2,3-diphenyl-2-heptenoic acids has been determined by stereoselective decarboxylation to the corresponding α-*n*-butylstilbenes.

In previous papers[1] reactions of organolithium compounds and acetylenes have been described. The reaction of diphenylacetylene (DPA) with an excess of primary organolithium compounds yields deuterolysis or carbonation products arising very largely from the dilithiated intermediate **1a**. Only very small amounts of **1b** and **1c** were present in the reaction mixture.[3] Furthermore, although the stereochemistry of **1a** was proven, the carbonation product of **1b** was not obtained in sufficient purity or quantity to allow a stereochemical assignment.



1a **1b** **1c**

To determine whether addition to DPA precedes and/or promotes metalation or *vice versa*, and to determine the stereochemistry of **1b**, *o*-bromodiphenylacetylene (2) and 1-bromo-1,2-diphenyl-1-hexene (3)

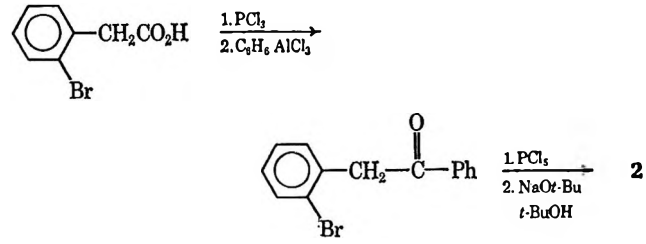


2 **3**

were synthesized, and reactions of these compounds with *n*-butyllithium and/or lithium metal were examined.

Results

o-Bromodiphenylacetylene was synthesized by a different procedure from that reported in the literature. The method used in this work is shown briefly.



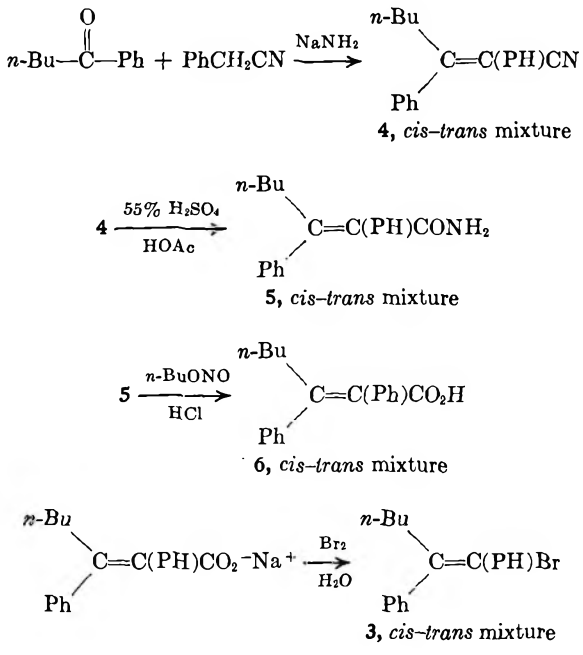
(1) Research supported by AFOSR(SRC)-OAR, U.S.A.F. Grant No 720-65 and 720-67.

(2) NASA Predoctoral Fellow, 1964–1966.

(3) J. E. Mulvaney, Z. G. Gardlund, S. L. Gardlund, and D. J. Newton, *J. Amer. Chem., Soc.*, **88**, 476 (1966).

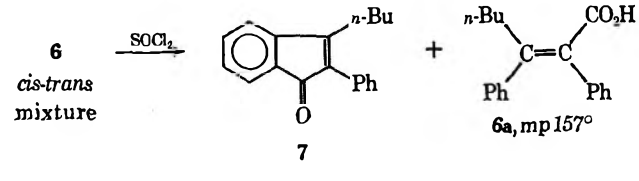
Because a number of vinylic bromides have been synthesized, although in low yields, by treating 1,1-dibromo compounds with a mixture of triphenylphosphine, potassium *t*-butoxide, and a ketone,[4] we treated valerophenone with benzal bromide–triphenylphosphine and potassium *t*-butoxide in an attempt to obtain **3** directly. However, only starting materials were recovered. The synthesis of **3** was accomplished starting with valerophenone and proceeding as shown in Scheme I.

SCHEME I



Compounds **4**, **5**, **6** and **3** were all shown to be *cis–trans* mixtures by a number of criteria, particularly the nmr spectra which in the region τ 7–8 showed two distinct multiplets for the allylic protons. Pure stereoisomers (see below) gave only one multiplet for the allylic protons.

To learn the stereochemistry of **1b** it was desirable to isolate and distinguish between the *cis* and *trans* forms of **6**. One pure geometrical isomer of **6**, mp 157° (**6a**), was obtained when the *cis–trans* mixture was treated with thionyl chloride to yield 55% of 2-phenyl-3-*n*-butylindone (**7**) and 43% of a crystalline sharp melting

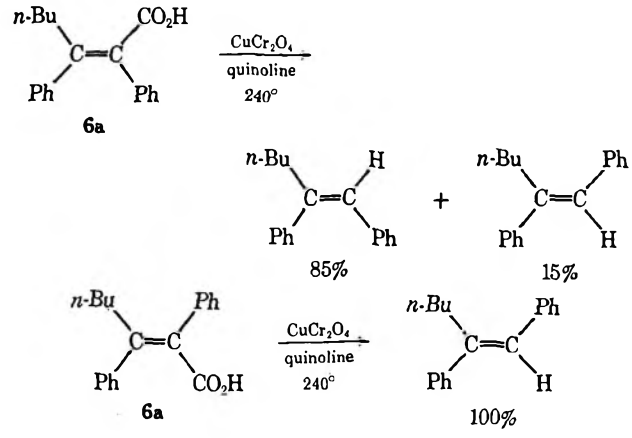


compound **6a** which showed only one allylic proton multiplet in its nmr spectrum and was assigned the *cis* structure (see below). The other stereoisomer **6b**, mp 127°, was obtained by the treatment of **3** with *n*-butyllithium as described in succeeding paragraphs.

(4) J. W olinsky and K. L. Erickson, *J. Org. Chem.*, **30**, 2208 (1965).

α,β-Unsaturated carboxylic acids are said to decarboxylate with retention of configuration to the corresponding olefins when treated with copper chromite in refluxing quinoline.[5] Isomer **6a** was decarboxylated under these conditions to give a quantitative yield of a mixture consisting of 85% *cis*-α-*n*-butylstilbene and 15% *trans*-α-*n*-butylstilbene. Under the same conditions isomer **6b** gave a quantitative yield of only *trans*-α-*n*-butylstilbene (Scheme II).

SCHEME II



It may be concluded that **6a** is *cis*-2,3-diphenyl-2-heptenoic acid and that **6b** is the *trans* isomer.

It is worth noting in passing that **6b** is converted to indone **7** in 75% yield with thionyl chloride as would be expected, but **6a** is also converted to **7** under the same conditions albeit in 25% yield. The point is that ring closure of a cinnamic acid derivative with thionyl chloride to an indone does not necessarily allow one to designate the stereochemistry of the cinnamic acid.[6]

Reactions of **2** and **3** with *n*-butyllithium in diethyl ether at room temperature for 22 hr produced the results indicated in Scheme III.

It should also be pointed out that treatment of 1.0 mol of **3** with 2.2 g-atoms of lithium in diethyl ether resulted in the formation of a 77% yield of the *trans* acid **6b**.

Discussion

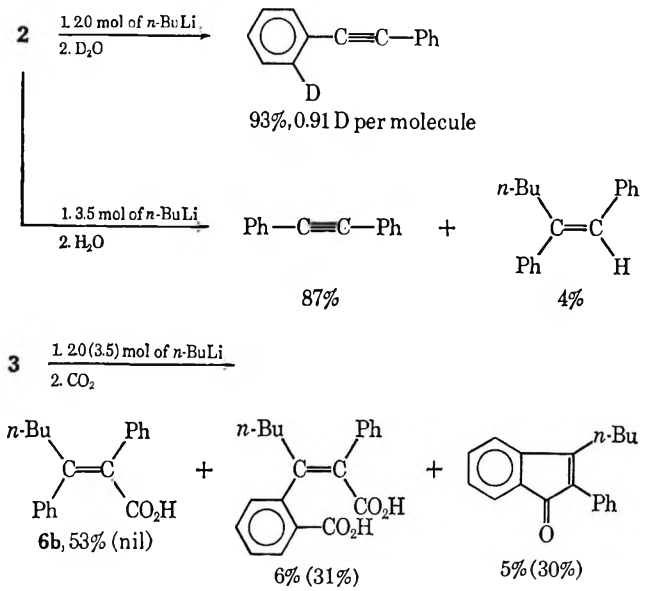
From Chart I and from ref 3 it is apparent that the reaction of *n*-butylithium with *o*-bromodiphenylacetylene (**2**) produces the *o*-lithiated intermediate **1c** in at least 90% yield and that this intermediate, in fact, reacts with *n*-butyllithium more slowly than does DPA itself. (The 4% yield of *trans*-α-*n*-butylstilbene obtained when a 3.5:1 molar ratio of RLi to **2** was used may have arisen by addition followed by metalation.) In contrast treatment of **3** (Scheme III) with *n*-butyllithium followed by carbonation indicates in the first example that approximately 20% of the product is dilithiated and that, within the limits of detection, all of the product is *dilithiated at the 3.5:1 ratio of RLi to* acetylene (**3**).

(5) D. Y. Curtin and E. E. Harris, *J. Amer. Chem. Soc.*, **73**, 2716 (1951), and references cited therein.

(6) (a) See also J. A. Kampmeier and R. M. Fautzier, *ibid.*, **88**, 1959 (1966); (b) J. E. Mulvaney, L. J. Carr, Z. G. Gardlund, and S. L. Gardlund, in preparation.

The course of reaction of primary organolithium compounds with DPA must proceed very largely then by addition followed by metalation. It may be pointed out that when **3** is treated with an excess of lithium metal only monolithiated product is obtained. Apparently the vinyl carbanion derived from **3** is not sufficiently basic to remove an *o*-hydrogen of a phenyl ring, but *n*-butyllithium can.

SCHEME III



A possible explanation as to why the addition product is metalated to form a dicarbanion-like intermediate is discussed in the preceding paper in this series.[1]

A few other observations seem pertinent. The addition of *n*-butylithium to the acetylenic bond of DPA is irreversible inasmuch as no DPA was obtained from reaction of **3** with *n*-butyllithium or lithium metal.

The *trans* stereochemistry of the products does not necessarily reflect the initial mode of addition across the triple bond. Treatment of **3**, which from its nmr spectrum is a 70:30 mixture of geometrical isomers, with Li metal or *n*-butyllithium gives after carbonation or hydrolysis only the *trans*-stilbenyl derivatives. This indicates that the *cis*-stilbenyllithium intermediate isomerizes to the *trans*, a result in accord with the work of Curtin and Koehl concerning the parent stilbenyllithium itself.[7a] It has been shown that carbonation of vinylic lithium compounds proceeds with retention of configuration.[7b]

Experimental Section

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Nuclear magnetic resonance spectra were determined on a Varian Model A-60 spectrometer (at 60 MHz) using tetramethylsilane as an internal standard; ultraviolet spectra were determined in 95% ethanol on a Cary 11 recording spectrometer. A Beckman IR-4 spectrometer was used to determine infrared spectra; a polystyrene film was used to calibrate the instrument.

Microanalyses were performed by the Micro-Tech Laboratories, Skokie, Ill., and by C. F. Geiger, Ontario, Calif. Deuterium analyses were made by Mr. J. Nemeth, Urbana, Ill., using the falling drop method. Vapor phase chromatography was carried out on a F & M Model 609 flame ionization instrument. For analytical glpc determinations, correction factors for weight ratio–area ratio data were determined with standards containing the same compounds as in the unknown mixture.

Ligroin (bp 30–60°) was purified by stirring overnight with 95% sulfuric acid, washing with distilled water, drying over magnesium sulfate, and refluxing for 24 hr over sodium prior to final distillation.

n-Butyllithium was synthesized in the usual manner[8] and its concentration determined by the double titration method.[9] All organolithium reactions were run under a helium atmosphere in a flame-dried apparatus protected by drying tubes.

α-(*o*-Bromophenyl)acetophenone was prepared according to a procedure used in the synthesis of α-(*p*-nitrophenyl)acetophenone.[10] A stirred solution containing phosphorus trichloride (65.0 ml) and *o*-bromophenylacetic acid[11] (116.5 g, 0.542 mol) was heated at 90° for 2 hr, followed by addition of 150 ml of thiophene-free benzene. The solution was decanted from the yellow phosphorus acid and added slowly to anhydrous aluminum chloride (95.2 g, 0.712 mol) in 250 ml of benzene. After refluxing for 2.5 hr, the solution was poured into a 4-l. beaker containing 2 kg of ice and 350 ml of 12 *M* hydrochloric acid.

The benzene solution was separated and extracted with 200 ml of 10% sodium hydroxide. After drying over anhydrous sodium sulfate, benzene was removed under reduced pressure. There remained 158.3 g of yellow oil which solidified on standing. Recrystallization from 95% ethanol yielded 129.0 g (86.5%) of colorless needles: mp 69.5–70.0°; nmr (10% in $CDCl_3$), τ 1.83–2.00 (2, multiplet), 2.19–3.06 (7, multiplet), 5.56 (2, singlet); $\nu_{max}^{CHCl_3}$ 1695 cm^{-1}.

Anal. Calcd for $C_{14}H_{11}OBr$: C, 61.11; H, 4.03; Br, 29.04. Found: C, 61.32; H, 4.04; Br, 28.92.

α-(*o*-Bromophenyl)acetophenone forms a 2,4-dinitrophenylhydrazone derivative having mp 202.5–203.0° after two recrystallizations from 95% ethanol–benzene.

o-Bromodiphenylacetylene (2).—α-(*o*-Bromophenyl)acetophenone (129.0 g, 0.472 mol) and phosphorus pentachloride (107.0 g, 0.600 mol) were mixed and ground into a fine powder. After heating at 75–80° for 0.5 hr, the mixture liquefied with rapid evolution of hydrogen chloride. The yellow melt was stirred for an additional 2 hr at 85°. Distillation yielded 120.3 g of light yellow oil, bp 167–171° (1.6 mm). This oil was added immediately to a rapidly stirred solution of 313 g (3.26 mol) of sodium *t*-butoxide in 1800 ml of *t*-butyl alcohol and refluxed for 17 hr. The resulting orange solution was diluted with 4 l. of water and extracted with two 250-ml portions of diethyl ether. After drying over anhydrous sodium sulfate, solvent was removed under reduced pressure. There remained 87.8 g of red oil. Distillation gave 75.3 g (62.1%) of pale yellow *o*-bromodiphenylacetylene, bp 129–130° (0.40 mm) [lit.[12] bp 155–160° (0.70 mm)], $n^{26.5}D$ 1.6684.

2,3-Diphenyl-2-heptenenitrile (4).—2,3-Diphenyl-2-heptenenitrile was prepared by the procedure used in the synthesis of 2,3-diphenyl-2-pentenenitrile.[13] To a stirred suspension of 39.0 g (1.00 mol) of commercial sodamide in 500 ml of xylene was added one-fifth of a total of 117 g (1.00 mol) of commercial phenylacetonitrile. The mixture was heated to reflux, and the remainder of the phenylacetonitrile was added as rapidly as the exothermic reaction permitted. To this α-sodiophenylacetonitrile, an insoluble green sludge, 162.0 g (1.00 mol) of commercial valerophenone was added rapidly. The mixture turned deep red and pasty. After refluxing for 4 hr, the solution was cooled to room temperature. Glacial acetic acid (60 ml) in 200 ml of water was added slowly and the mixture stirred for 2 hr. Diethyl ether (600 ml) and 50 ml of 12 *M* hydrochloric acid in 150 ml of water were added and the layers separated. After drying the organic layer over anhydrous sodium sulfate, the solvents and starting materials were removed by heating to 100° under reduced pressure

(7) (a) D. Y. Curtin and W. J. Koehl, *J. Amer. Chem. Soc.*, **84**, 1967 (1962); (b) D. Seyferth and L. G. Vaughn, *ibid.*, **86**, 883 (1964).

(8) R. G. Jones and H. Gilman, *Org. Reactions*, **6**, 352 (1951).

(9) H. Gilman and A. H. Haubein, *J. Amer. Chem. Soc.*, **86**, 1515 (1944).

(10) E. J. Corey and J. P. Schaefer, *ibid.*, **82**, 918 (1960).

(11) H. Gilman and O. L. Marrs, *J. Org. Chem.*, **30**, 325 (1965), and references cited therein.

(12) R. L. Letsinger, T. J. Saveriede, and J. R. Nazy, *ibid.*, **26**, 1273 (1961).

(13) K. Rorig, *J. Amer. Chem. Soc.*, **73**, 1290 (1951).

(0.50 mm). The remaining dark semisolid was added to 300 ml of rapidly stirred pentane at 0° and filtered; the crude solid phenylacetamide (15 g) was discarded.

Distillation of the pentane solubles gave 163 g (62.5%) of a pale yellow mixture of *cis*- and *trans*-2,3-diphenyl-2-heptenenitrile (**4**): bp 152–159° (0.70 mm); $\nu_{max}^{CHCl_3}$ 2225 cm^{-1}; nmr (10% in CCl_4), τ 2.55 and 2.89 (10), 7.07 (1.3, triplet), 7.42 (0.7, triplet), 8.40–8.83 (4, multiplet) and 9.09 (3, triplet, J = 5 cps).

Anal. Calcd for $C_{19}H_{19}N$: C, 87.33; H, 7.33; N, 5.36. Found: C, 87.61; H, 7.03; N, 5.33.

In 15 ml of pentane was dissolved 2.0 g of this mixture of *cis*- and *trans*-2,3-diphenyl-2-heptenenitrile. After cooling at −18° for 1 week, filtration gave 1.59 g of white solid, mp 34–37°. The nitrile had mp 50.5–51.0° after three recrystallizations from pentane at −18°. This solid is presumed to be *trans*-2,3-diphenyl-2-heptenenitrile: nmr (10% in CCl_4), τ 2.89 (10, singlet), 7.07 (2, triplet, J = 8 cps), 8.40–8.83 (4, multiplet), and 9.09 (3, triplet, J = 5 cps).

2,3-Diphenyl-2-heptenamide (5).—A mixture of *cis*- and *trans*-2,3-diphenyl-2-heptenenitrile (50.0 g, 0.192 mol), 250 ml of 55% sulfuric acid, and 700 ml of glacial acetic acid were stirred at 100° for 40 hr. The reaction mixture was cooled to 20°; diluted with 2 l. of water, and filtered. The tan solid was triturated in 150 ml of warm 10% sodium hydroxide; this process was repeated until the basic filtrate was colorless. The tan solid was washed with water and dried in a vacuum oven to give 62.3% of a crude mixture of *cis*- and *trans*-2,3-diphenyl-2-heptenamide (**5**). After two recrystallizations from acetonitrile, the white powdery amide had mp 135–136°; $\nu_{max}^{CHCl_3}$ 3550, 3400, and 1685 cm^{-1}; nmr (5% in $CDCl_3$), τ 2.30 and 2.60 (10), 7.12 (1.6, triplet, J = 8 cps), 7.56 (0.4, triplet, J = 7 cps), 8.37–8.89 (4, multiplet) and 9.12 (3, triplet, J = 7 cps).

Anal. Calcd for $C_{19}H_{21}NO$: C, 81.68; H, 7.58; N, 5.01. Found: C, 81.49; H, 7.68; N, 4.88.

2,3-Diphenyl-2-heptenoic Acid (6a, b).—The following procedure was based on a method reported by Sperber, Papa, and Schwenk for the synthesis of tri-*n*-butylacetic acid.[14] Anhydrous hydrogen chloride was bubbled slowly for 30 min into a stirred solution of 27.9 g (0.1000 mol) of 2,3-diphenyl-2-heptenamide in 265 ml of dioxane. Freshly distilled *n*-butylnitrite[15] (28.3 g, 0.275 mol) was added dropwise over a period of 2 hr. After the addition of *n*-butylnitrite was completed, the deep red solution was stirred at room temperature for 17 hr and then on a steam bath for an additional 3 hr. The solvent was removed under reduced pressure, and the residual oil was dissolved in 100 ml of diethyl ether. The ether solution was extracted with three 50-ml portions of 2% sodium hydroxide. The combined basic extracts were acidified wih 6 *N* hydrochloric acid and extracted with diethyl ether. After drying over anhydrous sodium sulfate, the ether was removed under reduced pressure, leaving 16.1 g of crude 2,3-diphenyl-2-heptenoic acid (**6a, b**).

The crude neutral material, predominantly *n*-butyl 2,3-diphenyl-2-heptenoate, was hydrolyzed by refluxing for 4 hr in a solution containing 10 ml of 50% aqueous sodium hydroxide and 40 ml of absolute alcohol. Acidification gave 9.60 g of crude **6a, b**.

The acidic fractions (25.7 g) were combined, triturated in 50 ml of cold pentane (0°), and filtered to give 20.40 g (73.0%) of a mixture of *cis*- and *trans*-2,3-diphenyl-2-heptenoic acid (**6a, b**): mp 115–118° after two recrystallizations from hexane (the two isomers were not separable by fractional recrystallization from hexane); $\nu_{max}^{CHCl_3}$ 1695 cm^{-1}; nmr (10% in CCl_4), τ 2.68 and 2.98 (10, doublet and singlet), 7.22 (1.1, triplet, J = 8 cps), 7.69 (0.9, triplet, J = 7 cps), 8.41–9.33 (7, multiplet).

Anal. Calcd for $C_{19}H_{20}O_2$: C, 81.40; H, 7.19; neut equiv, 280. Found: C, 81.31; H, 7.24; neut equiv, 279.

Refluxing a solution of commercial valerophenone (16.2 g, 0.10 mol), phenylmalonic acid (36.0 g, 0.20 mol), piperidine (17.0 g, 0.20 mol), and pyridine (125 ml) under nitrogen for 24 hr yielded no 2,3-diphenyl-2-heptenoic acid.

The reaction of 2,3-diphenyl-2-heptenoic acid with thionyl chloride was run according to the method of Koelsh.[16] A mixture of *cis*- and *trans*-2,3-diphenyl-2-heptenoic acid (2.0 g, 7.1 × 10^{-3} mol) was dissolved in 20 ml of anhydrous carbon tetrachloride. Thionyl chloride (1.28 ml, 1.78 × 10^{-2} mol) was added in one portion and the mixture refluxed for 6 hr. The yellow reaction mixture was allowed to cool to room temperature and poured into a solution of 10 ml of concentrated hydrochloric acid in 125 ml of water. The stirred mixture was boiled on a steam bath for 1 hr and then cooled to 15°. Diethyl ether was added and the layers were separated. The ether solution was extracted with two 50-ml portions of 2% aqueous sodium hydroxide. The neutral solution was dried and solvent was removed under reduced pressure to yield 1.03 g (55.3%) of red 2-phenyl-3-*n*-butylindone (**7**). After two recrystallizations from ethyl acetate–95% ethanol, the 2,4-dinitrophenylhydrazone derivative of the indone had mp 178.0–179.0° (lit.[3] mp 176–178°). An infrared spectrum of the indone was identical with that of an authentic sample.[3]

The combined basic extracts were acidified with 10% hydrochloric acid and extracted with diethyl ether. Evaporation of the dried ether solution yielded 0.69 g (42.5%) of a solid acid, mp 154–155°. After two recrystallizations from hexane, the acid had mp 7157.0–157.5°; $\nu_{max}^{CHCl_3}$ 1695 cm^{-1}; λ_{max} 254 mμ (ϵ 8950) 223 (12,700); nmr (10% in $CDCl_3$), τ 2.53 (1),0, singlet 7.00, (2, triplet, J = 8 cps), 8.34–8.83 (4, multiplet), and 9.12 (3, triplet, J = 6 cps). This isomer of 2,3-diphenyl-2-heptenoic acid has been assigned the *cis* configuration (see Results).

Anal. Calcd for $C_{19}H_{20}O_2$: C, 81.40; H, 7.19; neut equiv, 280. Found: C, 81.20; H, 7.28; neut equiv, 279.

Treatment of *cis*-2,3-diphenyl-2-heptenoic acid with thionyl chloride under the above reaction conditions yielded 2-phenyl-3-*n*-butylindone in 25% yield.

Preparation of 1-Bromo-1,2-diphenyl-1-hexene (3).—The procedure used is similar to the one reported by Price and Berman for the preparation of *cis*- and *trans*-α-bromostilbenes from the corresponding isomeric α-phenylcinnamic acids.[17] A mixture of *cis*- and *trans*-2,3-diphenyl-2-heptenoic acid (16.10 g, 0.0575 mol) was dissolved in a solution of 2.36 g (0.0625 mol) of sodium hydroxide in 90 ml of water. Bromine (10.0 g, 0.0625 mol) was added dropwise to the rapidly stirring solution at 58–60°. The yellow heterogeneous solution was stirred for 1 hr at 60° before cooling to room temperature and extracting with diethyl ether. The ether solution was extracted twice with 50-ml portions of 2% sodium hydroxide and dried over anhydrous sodium sulfate. After removal of the ether under reduced pressure, the remaining viscous yellow oil (20.37 g) was distilled to give 14.30 g (79.1%) of a mixture of straw-yellow *cis*- and *trans*-1-bromo-1,2-diphenyl-1-hexene (**3**): bp 142–144° (0.80 mm); $n^{27.0}D$ 1.5888; nmr (10% in CCl_4), τ 2.63–2.95 (10), 7.19 (1.4, triplet, J = 7 cps), 7.78 (0.6, triplet, J = 6 cps), 8.33–8.89 (4, multiplet), and 9.05 (3, triplet, J = 6 cps).

Anal. Calcd for $C_{18}H_{19}Br$: C, 68.57; H, 6.03. Found: C, 68.18; H, 5.98.

Both *trans*-2,3-diphenyl-2-heptenoic acid and *cis*-2,3-diphenyl-2-heptenoic acid, when treated with bromine under the above conditions, gave an inseparable mixture of the isomeric bromides.

The following procedure was attempted in order to prepare the desired bromide (**3**) directly from valerophenone. To a stirred solution of triphenylphosphine (30.0 g, 0.111 mol), potassium *t*-butoxide (30.6 g, 0.111 mol) and 250 ml of heptane at 0° were added over a period of 30 min to freshly distilled commercial benzal bromide (27.7 g, 0.111 mol) in 200 ml of heptane. The resulting yellow suspension was concentrated to *ca.* 100 ml under reduced pressure. Valerophenone (16.2 g, 0.100 mol) in 100 ml of heptane was added and the mixture heated at 50° for 3 hr. Distillation under reduced pressure gave 15.8 g of valerophenone (97.8% recovered).

***n*-Butyllithium and 1-Bromo-1,2-diphenyl-1-hexene (3). 1. Reaction with *n*-Butyllithium (2 Mol).**—To a stirred solution of a freshly distilled mixture of *cis*- and *trans*-1-bromo-1,2-diphenyl-1-hexene (6.30 g, 0.020 mol) in 8 ml of anhydrous diethyl ether at −78° was added rapidly 0.020 mol of *n*-butyllithium in 14 ml of diethyl ether. The solution was stirred for 15 min at −78° before an additional 0.020 mol of *n*-butyllithium in 14 ml of diethyl ether was added. The yellow solution was allowed to warm to room temperature and stirred for 22 hr. The solution, which contained a small amount of yellow precipitate, was cooled to −50° and decanted onto a large excess of powdered Dry Ice. After standing for 9 hr, the product was acidified with

(14) N. Sperber, D. Papa, and E. Schwenk, *J. Amer. Chem. Soc.*, **70**, 3091 (1948).

(15) W. A. Noyes, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p 108.

(16) C. F. Koelsh, *J. Amer. Chem. Soc.*, **54**, 2487 (1932).

(17) C. C. Price and J. D. Berman, *ibid.*, **79**, 5474 (1957).

10% hydrochloric acid and the organic layer separated. The ether solution was extracted with two 50-ml portions of 2% sodium hydroxide. The combined basic extracts were acidified with hydrochloric acid and extracted with several portions of ether. After drying over sodium sulfate, the ether was removed under reduced pressure leaving 4.07 g of yellow solid. Trituration with cold (0°) pentane removed 0.74 g of valeric acid. The remaining 3.33 g of white solid, mp 120–121°, was added to 250 ml of boiling hexane. After stirring for 15 min, the hot hexane solution was filtered to yield 0.27 g (5.7%) of insoluble *trans*-2-phenyl-3-(*o*-carboxyphenyl)-2-heptenoic acid, mp 170–175°. Two recrystallizations from acetonitrile afforded white needles, mp 177.5–178.5° (lit.[3] mp 176–177°). A mixture melting point with an authentic sample showed no depression, and the infrared spectra were identical.

The hexane filtrate was concentrated to give 2.96 g (52.9%) of *trans*-2,3-diphenyl-2-heptenoic acid (**6b**), mp 123–124°. Two recrystallizations from hexane produced a pure product: mp 126.5–127.0°; $\nu_{max}^{CHCl_3}$ 1695 and 1625 cm^{-1}; λ_{max} 242 mμ (ε 11,000); nmr (10% in $CDCl_3$), τ 2.41 and 2.50 (10), 6.37 (2, triplet, J = 8 cps), 8.60–9.09 (4, multiplet) and 9.30 (3, triplet, J = 7 cps).

Anal. Calcd for $C_{19}H_{19}COOH$: C, 81.40; H, 7.19; neut equiv, 280. Found: C, 81.08; H, 7.19; neut equiv, 276.

2-Phenyl-3-*n*-butylindone (7) was prepared in 80% yield by refluxing for 6 hr a solution containing 0.50 g (1.78×10^{-3} mol) of *trans*-2,3-diphenyl-2-heptenoic acid, 0.32 ml (4.45×10^{-3} mol) of thionyl chloride, and 5.0 ml of anhydrous carbon tetrachloride.

The neutral layer from the carbonation reaction of **3** with *n*-butyllithium was dried over sodium sulfate. Removal of the ether under reduced pressure left 2.61 g of red oil. The crude neutral oil produced a solid 2,4-dinitrophenylhydrazone derivative which had mp 176–178° after one recrystallization from ethyl acetate–95% ethanol. A mixture melting point with the 2,4-dinitrophenylhydrazone derivative of 2-phenyl-3-*n*-butylindone showed no depression.

2. Reaction with *n*-Butyllithium (3.5 Mol).—To a stirred solution of 0.070 mol of *n*-butyllithium in 39 ml of diethyl ether at −10° was added dropwise 6.03 g (0.020 mol) of a mixture of *cis*- and *trans*-1-bromo-1,2-diphenyl-1-hexene in 6 ml of anhydrous diethyl ether. After allowing the solution to warm to room temperature, an exothermic reaction occurred, followed by the precipitation of a yellow solid. The solution was stirred for 22 hr at room temperature, then cooled to −78° and decanted onto a large excess of powdered Dry Ice. After standing overnight, 250 ml of 5% hydrochloric acid and 200 ml of ether were added to the orange carbonation mixture; the mixture was stirred to dissolve the solids. The ether layer was separated and extracted with two 100-ml portions of 5% sodium hydroxide. The combined basic extracts were acidified with 6 *N* hydrochloric acid and extracted with two 50-ml portions of ether. After drying over sodium sulfate, the ether was removed under reduced pressure, leaving 3.94 g of yellow semisolid. Trituration with 5 ml of cold (0°) pentane removed 1.92 g of valeric acid. There remained 2.02 g (31.2%) of solid *trans*-2-phenyl-3-(*o*-carboxyphenyl)-2-heptenoic acid, mp 170–171°. After two recrystallizations from acetonitrile, the acid had mp 178.5–179.5° (lit.[3] mp 176–177°). A mixture melting point with an authentic sample showed no depression.

The neutral ether solution was dried and the ether removed under reduced pressure. There remained 4.01 g of orange red oil. Distillation yielded 30.5% of 2-phenyl-3-*n*-butylindone, bp 170–180° (0.30 mm) [lit.[3] bp 170° (0.30 mm)]. The indone formed a 2,4-dinitrophenylhydrazone derivative, mp 177–178° after one recrystallization from ethyl acetate–95% ethanol. A mixture melting point with an authentic sample showed no depression.

Decarboxylation of *trans*-2,3-Diphenyl-2-heptenoic Acid (6b).—*trans*-2,3-Diphenyl-2-heptenoic acid (0.50 g, 1.8×10^{-3} mol) was added to a suspension of 0.075 g of copper chromite in 1.0 ml of quinoline. The black mixture was heated at 240° for 10 min. After the addition of diethyl ether and filtration extraction with acid and base there remained 0.42 g (100%) of a dark neutral oil. Vapor phase chromatography (5-ft GE-SE-30; 190°) and nuclear magnetic resonance spectroscopy indicated that this oil was *trans*-α-*n*-butylstilbene:[3] nmr (10% in CCl_4), τ 2.69 (10), 3.36 (1), 7.33 (2), 8.41–8.91 (4), and 9.19 (3).

Decarboxylation of *cis*-2,3-Diphenyl-2-heptenoic Acid (6a).—*cis*-2,3-Diphenyl-2-heptenoic acid (0.50 g) was decarboxylated under the same conditions described above for *trans*-2,3-diphenyl-2-heptenoic acid. A dark oil (0.42 g) was obtained which contained 85% *cis*-α-*n*-butylstilbene[3] and 15% *trans*-α-*n*-butylstilbene as shown by vapor phase chromatography and nuclear magnetic resonance spectroscopy: nmr (10% in CCl_4), τ 2.78 and 3.02 (10), 3.36 (0.15), 3.61 (0.85), 7.53 (2), 8.64 (4), and 9.11 (3).

Lithium Metal and 1-Bromo-1,2-diphenyl-1-hexene (3).—To a suspension of small freshly cut lithium metal pieces (0.29 g, 0.0418 mol) in 10 ml of anhydrous diethyl ether under helium, there was added dropwise over a period of 15 min a mixture of *cis*- and *trans*-1-bromo-1,2-diphenyl-1-hexene (6.0 g, 0.019 mol) in 5 ml of diethyl ether. Occasional external cooling (ice bath) was necessary to maintain the reaction temperature at 31–33°. After stirring at room temperature for 23 hr, the black solution was cooled to −30° and decanted onto a large excess of powdered Dry Ice.

After standing overnight, 100 ml of 6 *N* hydrochloric acid and 50 ml of diethyl ether were added. The ether layer was separated and extracted with two 30-ml portions of 2% sodium hydroxide. The combined basic extracts were acidified and extracted with diethyl ether. The ethereal solution was separated, dried, and the solvent removed under reduced pressure. There remained 4.10 g (77.0%) of *trans*-2,3-diphenyl-2-heptenoic acid, mp 124–125°.

***n*-Butyllithium and *o*-Bromodiphenylacetylene (2). 1. Reaction with *n*-Butyllithium (2 Mol). A. Termination of Reaction by Deuteriolysis.**—To a stirred solution of *o*-bromodiphenylacetylene (2.86 g, 0.015 mol) in 8 ml of anhydrous diethyl ether at −20° was added 0.0150 mol of *n*-butyllithium in 10.5 ml of diethyl ether. After stirring at −20° for 15 min, the yellow solution was warmed to 0°. An additional 0.0150 mol of *n*-butyllithium was added, and the mixture was allowed to warm to room temperature. After stirring for 22 hr the mixture was cooled to 0° and 5 ml of deuterium oxide was added slowly. The solution was stirred at room temperature for 2 hr, followed by the addition of 20 ml of water. The ether layer was separated, dried, and concentrated to yield 2.91 g of yellow oil, which solidified on standing. Two recrystallizations from 95% ethanol gave white needles of deuterated diphenylacetylene in 93% yield, mp 58.5–59.0°.

Anal. Calcd for $C_{14}H_9D$: D, 10.0 atom %. Found: D, 9.10 atom %.

Glpc indicated no *trans*-α-*n*-butylstilbene.

B. Termination of Reaction by Carbonation.—To a solution of *o*-bromodiphenylacetylene (10.3 g, 0.040 mol) in 15 ml of anhydrous diethyl ether at −78° was added 0.040 mol of *n*-butyllithium in 28 ml of diethyl ether. After stirring at −78° for 15 min, the solution was warmed to room temperature. An additional 0.040 mol of *n*-butyllithium in 28 ml of diethyl ether was added, and the yellow reaction mixture stirred for 22 hr. After cooling to −78°, the reaction mixture was decanted onto a large excess of powdered Dry Ice and let stand overnight. The product was acidified with 10% hydrochloric acid and the ether layer separated. The ethereal solution was extracted with two 100-ml portions of 2% aqueous sodium hydroxide. The combined basic extracts were acidified and extracted with ether. After drying over sodium sulfate, the ether was removed under reduced pressure, leaving 4.64 g (52.3%) of crude *o*-carboxydiphenylacetylene, mp 127–129°. Two recrystallizations from heptane afforded pure product: mp 128.0–129.0° (lit.[18] mp 126° from acetic acid–heptane).

The neutral ether solution from the basic extractions was dried and the ether removed under reduced pressure. There remained 4.60 g of a dark red oil. Elution chromatography gave 46% by weight of diphenylacetylene (over-all yield, 30%). Vapor phase chromatography of the crude neutral product gave four peaks corresponding to *n*-butyl bromide, *n*-octane, diphenylacetylene, and *o*-bromodiphenylacetylene.

2. Reaction with *n*-Butyllithium (3.5 Mol).—To a stirred ethereal solution of 22.5 ml of 1.96 *M* (0.0441 mol) of *n*-butyllithium at −20° was added rapidly 3.23 g (0.0126 mol) of *o*-bromodiphenylacetylene in 5 ml of anhydrous diethyl ether. A yellow precipitate formed after 1 min of stirring. The solution was stirred for an additional 15 min at −20° and then allowed to warm to room temperature. After stirring for 22 hr, the yellow mixture was cooled to −40°, and 20 ml of water was added

(18) R. L. Letsinger, E. N. Offedahl, and J. R. Nazy, *J. Amer. Chem. Soc.*, **87**, 742 (1965).

slowly. The ether solution was separated, dried, and concentrated to yield 2.57 g of yellow oil. Heating the oil to 100° under reduced pressure (35 mm) removed 0.80 g of *n*-butyl bromide. The residual oil, which solidified on standing, was dissolved in 5 ml of pentane and cooled to −18° for 3 hr. Filtration gave white needles of diphenylacetylene (61.5%), mp 57–58°.

Vapor phase chromatography (2-ft GE-SE-30; 190°) showed that the crude product contained by weight 59% diphenylacetylene, 3.3% of *trans*-α-*n*-butylstilbene, 1.2% starting material, 28.4% *n*-butyl bromide, 5.3% *n*-octane, and 3.4% *n*-butyl alcohol. This corresponds to an over-all yield of 89.3% diphenylacetylene, 3.8% *trans*-α-*n*-butylstilbene, and 1.2% *o*-bromodiphenylacetylene.

Registry No.—Diphenylacetylene, 501-65-5; *cis* **3**, 16897-91-9; *trans* **3**, 16915-88-1; *cis* **4**, 16897-92-0; *trans* **4**, 16915-89-2; *cis* **5**, 16897-93-1; *trans* **5**, 16897-94-2; **6a**, 16897-95-3; **6b**, 16897-96-4; α-(*o*-bromophenyl)acetophenone, 16897-97-5; 2,4-dinitrophenylhydrazone of α-(*o*-bromophenyl)acetophenone, 16915-90-5; deuterated diphenylacetylene, 16897-98-6.

Small-Ring Epoxides. II. 2,2,6,6,7,7-Hexamethyl-1,5-dioxadispiro[2.0.2.1]heptane[1a]

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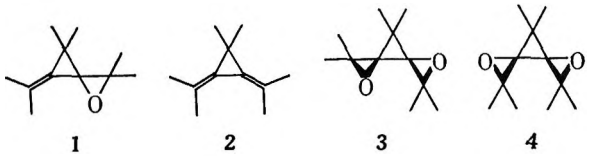
2,2,6,6,7,7-Hexamethyl-1,5-dioxadispiro[2.0.2.1]heptane (**3**) has been prepared by epoxidation of its dimethylenecyclopropane precursor **2**. Thermolysis of the diepoxide gives two ketones, 2,2,5,5,6,6-hexamethyl-4-oxo-1-oxaspirohexane (**5**) and a compound tentatively assigned as 3,5,5-trimethyl-2-(1-hydroxy-1-methylethyl)cyclopent-2-enone (**6**). Acid-catalyzed rearrangement yields 2,2,4,4,5,5-hexamethylcyclopentane-1,3-dione (**14**) and 3,3,4,4,5,5-hexamethylcyclopentane-1,2-dione (**15**), probably by way of **5** as an intermediate. The rearrangement of **3** with diethylamide produces 2,5-dimethyl-4-isopropylidene-5-hydroxyhex-2-en-3-one (**17**). The mechanistic details of these transformations are discussed.

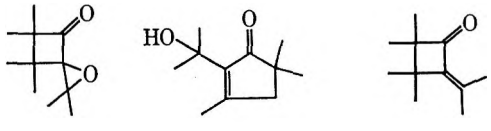
We have recently reported on the preparation and some of the reactions of the interesting oxaspiropentane derivative **1**.[2] Reaction of the precursor dimethylenecyclopropane **2** with an excess of peracetic acid leads, as expected, to the diepoxidation product, 2,2,6,6,7,7-hexamethyl-1,5-dioxadispiro[2.0.2.1]heptane (**3**), in good yield. The present paper is concerned with some of the properties of diepoxide **3**.

The assignment of the *anti* structure **3** as opposed to *syn* structure **4** is based on a 100-MHz spectrum of the homogeneous epoxidation product which shows three equivalent sharp methyl peaks rather than the four types of methyls expected for **4**. The predominance of epoxide **3** can probably be attributed to unfavorable dipole–dipole interactions in the transitions state leading to the *syn* diepoxide.[3]



1 **2** **3** **4**

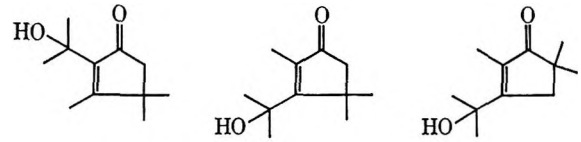
Pyrolysis of **3** in a vacuum pyrolysis system at 400° gave two major compounds. The predominant product (75%) was identified as 2,2,5,5,6,6-hexamethyl-4-oxo-1-oxaspirohexane (**5**), and the minor product (13%) is tentatively assigned as 3,5,5-trimethyl-2-(1-hydroxy-1-methylethyl)cyclopent-2-enone (**6**).



5 **6** **7**

Compound **5** displays a strong band at 5.63 μ indicative of a cyclobutanone carbonyl,[4] and its 100-MHz nmr spectrum shows six different methyl groups. Confirmation of structure **5** was effected by alternate preparation from the *m*-chloroperbenzoic acid epoxidation of ketone **7**.[2]

The structure of compound **6** is assigned on the basis of its spectroscopic properties. The infrared spectrum of **6** displays carbonyl absorption (5.95 μ), a conjugated double bond (6.13 μ), and an alcohol group (2.92 μ). These data, along with ultraviolet absorption at 232 mμ, are in agreement with other examples of 2-cyclopentenones.[5] The nmr spectrum of **6** shows a two-proton quartet (J = 1.0 Hz) at τ 7.68 and a three-proton triplet (J = 1.0 Hz) at 7.83. The chemical shift of the olefinic methyl is as expected for a methyl β to the carbonyl group.[6] Possible alternate structures **8**, **9**, and **10** are therefore not compatible with the observed coupling patterns and chemical shifts.[7] The remainder of the spectrum shows six-proton singlets



8 **9** **10**

(1) (a) Supported by Research Grant GP-6610 from the National Science Foundation. (b) National Institutes of Health Predoctoral Fellow 1966–1968.

(2) J. K. Crandall and D. R. Paulson, *J. Org. Chem.*, **33**, 991 (1968).

(3) See, for example, N. S. Crossley, A. C. Darby, H. B. Henbest, J. J. McCullough, B. Nicholls, and M. F. Stewart, *Tetrahedron Lett.*, 398 (1961), and references cited therein.

(4) R. T. Conley, "Infrared Spectroscopy," Allyn and Bacon, Inc., Boston, Mass., 1966, p 141.

(5) A. I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products," The Macmillan Co., New York, N. Y., 1966, p 66.

(6) The methyl resonance of 3-methylcyclopent-2-enone appears at τ 7.9.

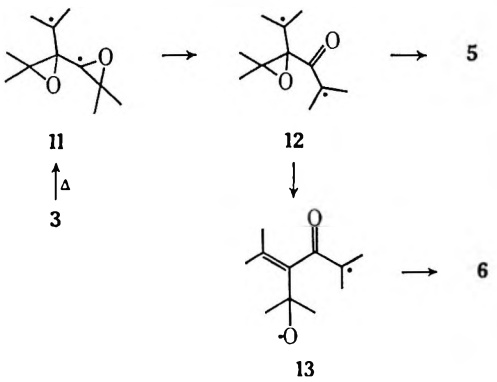
(7) The methyl group in the 2 position of i appears at τ 8.30 while the methyl group in the 2 position of ii appears at τ 8.28: W. E. Doering, M. R. Wilcott, and M. Jones, *J. Amer. Chem. Soc.*, **84**, 1224 (1962).

i ii

at 8.65 [$C(CH_3)_2OH$] and 8.97 [$C(CH_3)_2CO$] in addition to a hydroxyl proton.

The pyrolytic rearrangement of diepoxide **3** can be described as shown in Chart I. This transformation is

CHART I



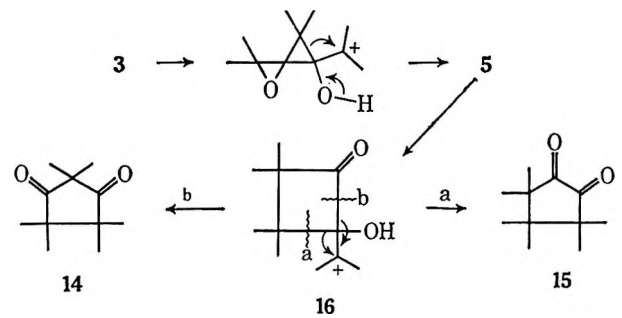
initiated by bond breakage in the more strained cyclopropyl ring which is followed by rearrangement of the epoxy radical moiety of **11** to α-keto radical **12**.[8] Radical coupling then gives epoxy ketone **5** directly. Subsequent rearrangement of **12** could give **13** which is probably the precursor of cyclopentenone **6**.[9]

Acid-catalyzed reaction of **3** in acetic acid containing sulfuric acid generated two new compounds in a 1:2 ratio. The minor component was identified as 2,2,4,4,-5,5-hexamethylcyclopentane-1,3-dione (**14**) by its characteristic spectral properties.[10] The major material, an orange crystalline solid, is assigned as 3,3,4,4,5,5-hexamethylcyclopentane-1,2-dione (**15**). The nmr spectrum of **15** displays singlets at τ 9.05 and 8.86 in the ratio of 1:2, and the infrared spectrum shows a strong carbonyl at 5.72 μ with a characteristic overtone at 2.91 μ. Finally the ultraviolet spectrum displays weak absorption at 516 and 493 mμ. Taken together, these data clearly support the nonenolizable α-diketone structure **15**.[11] When epoxy ketone **5** was subjected to the conditions used in the acid-catalyzed rearrangement of **3**, compounds **14** and **15** were again obtained in a 1:2 ratio.

The acid-catalyzed transformations are visualized (Chart II) as involving protonation at one of the oxygen atoms, followed by bond heterolysis and preferential pinacolic migration to give **5**. Epoxy ketone **5**, which was not isolated from this reaction but which gave the same products under the reaction conditions, is most probably an intermediate species. Thus, protonation at the epoxy group and ring opening gives intermediate **16**. Pinacolic rearrangement of **16** by migration of bond a leads to **15** while acyl migration (bond b) leads to **14**.[12]

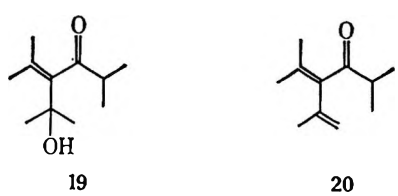
The final aspect of the chemistry of **3** to be examined was its base-promoted transformation. Thus treatment of **3** with an ethereal solution of lithium diethylamide resulted in the formation of a mixture of two

CHART II



compounds. The relative ratio of these two products could be greatly varied by changing the reaction conditions. Treatment of this crude mixture with potassium hydroxide solution resulted in the formation of 2,5-dimethyl-4-isopropylidene-5-hydroxyhex-2-en-3-one (**17**) in good yield. The infrared spectrum of **17** shows hydroxyl absorption and a conjugated carbonyl at 6.04 μ. The nmr displays a six-proton singlet at τ 8.66 for the dimethylmethylol group, olefinic methyl singlets at 8.52 and 8.08, and an additional methyl on a double bond at 8.16 coupled weakly to the individual terminal methylene protons (4.20, 4.09), in addition to the hydroxyl proton. The ultraviolet spectrum displays a maximum at 218 mμ.[13] It was readily shown that **17** is one of the two products present in the diethylamide reaction product. When **3** was treated with lithium diethylamide containing an excess of diethylamine, the other compound noted above was obtained as the major product. This material is tentatively assigned as 1-(N,N-diethylamino)-2,5-dimethyl-4-isopropylidene-5-hydroxyhexan-3-one (**18**) on the basis of its spectral properties (see Experimental Section) and its conversion into **17** by aqueous base.

Attempted hydrogenation of **17** in methanol at atmospheric pressure was unsuccessful, but proceeded smoothly in methanolic hydroxide solution to give 2,5-dimethyl-4-isopropylidene-5-hydroxyhexan-3-one (**19**) in high yield. Treatment of **18** under the same conditions also gave **19** in high yield. The nmr spectrum (see Experimental Section) demonstrates that the isopropenyl group of **17** has been selectively satu-



rated, while the infrared spectrum provides visible support for retention of the hydroxyl and conjugated carbonyl groups. Acid dehydration of keto alcohol **19** gave the known ketone **20**[2] in almost quantitative yield, thereby providing solid confirmation of the above assignments.

The lithium diethylamide catalyzed rearrangement of **3** is interpreted as being initiated by β elimination[14] and subsequent ring opening as shown in Chart III.

(8) T. J. Wallace and R. J. Gritter, *Tetrahedron*, **19**, 657 (1963).

(9) Precedent for the **12** → **13** conversion can be found in E. C. Sabatino and R. J. Gritter, *J. Org. Chem.*, **28**, 3437 (1963). A six-center intramolecular hydrogen abstraction followed by ring-closure completes the pathway to **6**.

(10) H. V. Hostettler, *Tetrahedron Lett.*, 1941 (1965).

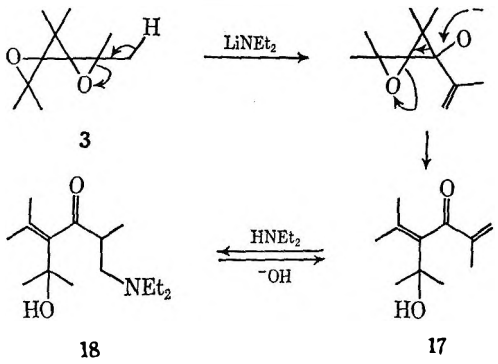
(11) N. J. Leonard and P. M. Mader, *J. Amer. Chem. Soc.*, **72**, 5388 (1950); R. S. Rasmussen, D. D. Tunnicliff, and R. R. Brattain, *ibid.*, **71**, 1068 (1949).

(12) Rearrangements of this type have been well studied. See for example: H. O. House and R. L. Wasson, *ibid.*, **79**, 1488 (1957).

(13) Other examples of highly substituted conjugated systems with anomalously low wavelength maxima are known. See, for example, W. F. Forbes, R. Shilton, and A. Balasubramanian, *J. Org. Chem.*, **29**, 3527 (1964); R. Criegee, U. Zirngibl, H. Furrer, D. Seebach, and G. Freund, *Chem. Ber.*, **97**, 2942 (1964).

(14) J. K. Crandall and L. H. Chang, *J. Org. Chem.*, **32**, 435 (1967).

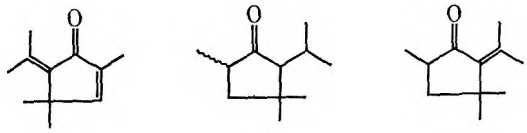
CHART III



3 18 17

Amino compound **18** is postulated as arising *via* Michael-type addition of diethylamine to the initial product **17**.

An interesting rearrangement occurs upon treatment of **17** with acid. A clean transformation product was isolated in 87% yield and identified as 2,4,4-trimethyl-5-isopropylidene-2-cyclopentenone (**21**). Again infrared bands at 5.92 and 6.16 μ are indicative of the cyclopentenone moiety.[6] This structure is supported by its nmr spectrum which shows a six-proton singlet at 8.72, a three-proton doublet (J = 1.5 Hz) at 8.28, three-proton singlets at 8.04 and 7.74, and a one-proton quartet (J = 1.5 Hz) at 3.39.[6] Confirmation of the five-membered ring structure proposed for the acid-catalyzed dehydration product **21** was secured by exhaustive hydrogenation. Three products were obtained from this treatment, two of which were collected as a mixture and shown to have a 5.77-μ carbonyl band as expected for a mixture of the epimeric saturated cyclopentanones **22**.[4] The remaining product is apparently the half-hydrogenated ketone **23** as determined from its spectroscopic properties (see Experimental Section). A possible formulation for this cyclization involves ionization of the hydroxyl group and cyclization of the resultant cation at the terminal methylene carbon.



21 22 23

Experimental Section

General.—Infrared spectra were obtained with Perkin-Elmer Model 137 and 137-G infracord spectrophotometers and unless otherwise specified were taken in carbon tetrachloride solution. Nuclear magnetic resonance (nmr) spectra were obtained on Varian Associates A-60 and HR-100 spectrometers in carbon tetrachloride solution. Chemical shifts are given as τ values. Mass spectra were obtained with an AEI MS-9 mass spectrometer at 70 eV; ultraviolet spectra (uv) were taken on a Cary 14 spectrophotometer. Gas chromatography (glpc) was performed on Aerograph Model 600, Model 1200 (analytical, hydrogen flame detector), and A700 (preparative). Chromatographs and percentage composition data were estimated by peak areas (uncorrected). Melting points were determined in sealed capillary tubes. Anhydrous magnesium sulfate was used for all drying operations. Microanalyses were performed by Midwest Microlabs Inc., Indianapolis, Ind.

2,2,6,6,7,7-Hexamethyl-1,5-dioxadispiro[2.0.2.1]heptane (3). To an ice-cold, mechanically stirred mixture of 1.80 g of **2** and 16.8 g of powdered, anhydrous sodium carbonate in 50 ml of methylene chloride was added dropwise 7.12 g of 40% peracetic acid which had been pretreated with a small amount of anhydrous sodium acetate. The mixture was stirred until the methylene chloride solution gave a negative test with moist starch–iodide paper. The solid salts were removed by suction filtration and washed well with additional solvent. The methylene chloride was removed from the filtrate by flash evaporation to give 2.17 g (95%) of **3** shown by glpc to contain only one significant component. Glpc collection gave pure **3**: ir (neat), 10.7 and 11.4 μ;[15] 100-MHz nmr, τ 8.86 (s, 6), 8.68 (s, 6) and 8.59 (s, 6). A precise mass spectrometric determination on the molecular ion of **3** gave m/e 182.1305 (calcd for $C_{11}H_{18}O_2$: 182.1307). Repeated attempts to obtain a satisfactory combustion analysis were unsuccessful.

Pyrolysis of 3.—A 100-mg sample of **3** was pyrolyzed in a flow system at 400° (0.25 mm)[2] to give 86 mg (86%) of a crude oil. Glpc analysis of this product showed two major compounds as 75 and 13% of the volatile material. No other component accounted for more than 2% of the mixture.

The major material was 2,2,4,4,5,5-hexamethyl-6-oxo-1-oxaspiro[2.3]hexane (**5**): ir, 5.63 (cyclobutanone)[4], 11.0, and 11.3 μ (epoxide);[15] 100-MHz nmr, τ 8.94 (s, 3), 8.89 (broad s, 6), 8.80 (s, 3), 8.65 (s, 3), and 8.59 (s, 3); uv max (hexane), 214 mμ (ϵ 865) and 336 (32).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.50; H, 10.02.

The minor product is assigned as 3,5,5-trimethyl-2-(1-hydroxy-1-methylethyl)cyclopent-2-enone (**6**): ir, 2.93, 5.92 and 6.14 μ; nmr, τ 8.97 (s, 6), 8.63 (s, 6), 7.83 (t, 3, J = 1 Hz), 7.68 (q, 2, J = 1 Hz), and 5.59 (s, 1); uv max (hexane), 232 mμ (ϵ 8750).

Acid-Catalyzed Rearrangement of 3.—To a solution of 1.5 g of **3** in 25 ml of glacial acetic acid was added a solution of 25 drops of concentrated sulfuric acid in 10 ml of glacial acetic acid. The resulting mixture was stirred at room temperature for 3 hr, poured into 100 ml of water, and extracted with five 25-ml portions of pentane. The pentane extracts were washed with two 25-ml portions of saturated sodium bicarbonate solution and dried. The solvent was removed by flash evaporation to give 1.3 g of crude product. Two compounds were isolated by glpc as 66 and 33% of the volatile reaction product.

The minor product is identified as 2,2.4,4,5,5-hexamethylcyclopentane-1,3-dione (**14**): ir, 5.80, 7.9, and 9.4 μ; nmr, τ 8.96 (s, 12) and 8.85 (s, 6); uv max (hexane), 215 mμ (ϵ 227) and 290 (27). These data agree in detail with those reported by Hostettler.[10]

The major product, an orange crystalline solid of mp 105–110°, is identified as 3,3,4,4,5,5-hexamethylcyclopentane-1,2-dione (**15**): ir, 2.91 (weak) and 5.75 μ; nmr, τ 9.05 (s, 6) and 8.86 (s, 12); uv max (hexane), 516 mμ (ϵ 25.5) and 493 (28.6).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.66; H, 10.04.

Acid-Catalyzed Rearrangement of 5.—A 45-mg sample of **5** was stirred with 15 ml of glacial acetic acid containing four drops of concentrated sulfuric acid for 4 hr, the mixture was poured into water and extracted with several portions of pentane. After drying the combined extracts, the solvent was removed to give a crude oil which was shown by glpc analysis to contain two components in the ratio of 1:2. Glpc isolation demonstrated that these were **14** and **15**, respectively.

2,2,4,4,5,5-Hexamethyl-6-oxo-1-oxaspiro[2,3]hexane(5).—To a solution of 100 mg of **7**[2] in 10 ml of methylene chloride was added 0.19 g of *m*-chloroperbenzoic acid and the resulting solution was refluxed for 6 days. The reaction mixture was washed with 10 ml of saturated sodium bicarbonate solution and dried. The methylene chloride was removed by flash evaporation to give 80 mg of crude **5**. Collection by glpc gave the major component (90%) which was identical with the material obtained from the pyrolysis of **3**.

Rearrangement of 3 by Lithium Diethylamide.—To a predried flask, cooled to 0°, and under a nitrogen atmosphere, was added 75 ml of anhydrous ether, 1.50 g of anhydrous diethylamine, and 12.2 ml of 1.6 *N* *n*-butyllithium solution in hexane. After stirring for 15 min, the ice bath was removed, 1.00 g of **3** was added, and the reaction mixture was heated to reflux for 12 hr. After pouring into 100 ml of water, the layers were separated and the aqueous layer was washed with three 50-ml portions of ether. The combined ethereal portions were washed with 100 ml of saturated sodium chloride solution and dried. The solvent was removed to give 0.95 g of a crude oil. Glpc analysis showed

(15) Reference 4, p 130.

one major product as over 80% of the volatile reaction mixture, and nmr analysis of the crude material showed essentially the same spectrum as glpc-collected product. This was identified as 2,5-dimethyl-4-isopropylidene-5-hydroxyhex-2-en-3-one (**17**): uv max (hexane), 218 mμ (ε 6900), 262 (390), and 340 (11); ir, 2.84 (OH), 6.04 (conjugated carbonyl) and 10.6 μ; nmr, τ 8.66 (s, 6), 8.52 (s, 3), 8.16 (m, 3), 8.08 (s, 3), 4.20 (m, 1), and 4.09 (m, 1).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.25; H, 9.98.

When the above reaction was conducted at room temperature for 30 min or for 24 hr at reflux with an excess of diethylamine, a mixture of **17** and a new substance possessing a diethylamino function was obtained. This material was purified by extraction from ethereal solution with 1% hydrochloric acid solution followed by careful neutralization with saturated sodium bicarbonate solution to give a 60% yield of 1-(N,N-diethylamino)-2,5-dimethyl-4-isopropylidene-5-hydroxyhexan-3-one (**18**), the Michael addition product of diethylamine and **17**. Compound **18** displays the following spectral data: ir, 3.0, 5.92, 7.95, 8.4, 9.3, and 10.7 μ; 100 MHz nmr, τ 8.98 (d, 6, J = 6.1 Hz), 8.98 (t, 6, J = 6.6 Hz), 8.60 (s, 3), 8.51 (s, 3), 8.43 (s, 3), 8.24 (s, 3), 7.46 (apparent overlapping quartets, 4), 7.09 (m, 2), and 7.80 (m, 1). Examination of the nmr spectrum of the crude reaction product showed about a 6:1 ratio of **18** and **17**.

Stirring 100 mg of **18** in 25 ml of 20% potassium hydroxide solution for 2 hr followed by extraction with ether gave 45 mg (62%) of **17**.

Catalytic Hydrogenation of 17.—A solution of 0.30 g of **17** in 50 ml of 20% potassium hydroxide in methanol was hydrogenated at atmospheric pressure using 5% palladium-on-charcoal as catalyst. Exhaustive hydrogenation resulted in the uptake of 1 equiv of hydrogen. The resulting mixture was filtered to remove the catalyst, and the filtrate was poured into 100 ml of water and extracted several times with 25-ml portions of ether. The ethereal extracts were combined and dried, and the ether was removed to give 0.29 g (97%) of keto alcohol **19** which was further purified by glpc: ir, 2.95 (OH), 5.95 (conjugated carbonyl), and 6.10 μ (conjugated C=C); 100 MHz nmr, τ 8.95 (d, 6, J = 6.9 Hz), 8.55 (s, 6), 8.48 (s, 3), 8.21 (s, 3), 7.46 (s, 1), and 7.28 (septet, 1, J = 6.9 Hz).

Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.46; H, 10.95.

Catalytic Hydrogenation of 18.—Catalytic hydrogenation of 3.0 g of **18** in the same manner as the hydrogenation of **19** gave **14** in 85% yield.

Dehydration of 2,5-Dimethyl-4-isopropylidene-5-hydroxyhexan-3-one (19).—An 0.29-g sample of **19** was stirred in 25 ml of glacial acetic acid containing ten drops of concentrated sulfuric acid for 30 min. The reaction mixture was poured into 50 ml of water and extracted with three 25-ml portions of pentane. The combined pentane extracts were washed with 50 ml of saturated sodium bicarbonate solution and dried, and the pentane was removed to give 0.24 g of crude **20** which was purified by glpc and shown to be identical with an authentic sample.[2]

Acid-Catalyzed Rearrangement of 17.—The reaction was carried out on an 0.180-g sample in essentially the same manner as the acid-catalyzed rearrangement of **3**. The crude product (0.140 g) was shown by glpc to be 94% one compound. Glpc purification gave 2,4,4-trimethyl-5-isopropylidenecyclopent-2-enone (**21**): ir, 5.92 and 6.16 μ; nmr, τ 8.72 (s, 6), 8.28 (d, 3, J = 1.5 Hz), 8.04 (s, 3), 7.74 (s, 3) and 3.39 (s, 1, J = 1.5 Hz).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.36; H, 9.88.

Catalytic Hydrogenation of 21.—A solution of 140 mg of **21** in 50 ml of methanol was exhaustively hydrogenated at atmospheric pressure using 5% palladium-on-charcoal as catalyst. The reaction mixture was filtered to remove the catalyst, and the filtrate was poured into 100 ml of water and extracted several times with 50-ml portions of pentane. The pentane extracts were combined and dried, and the pentane was removed to give 120 mg of crude product. Glpc analysis showed three compounds as 63, 18, and 19% of the volatile reaction product. The 19% product was isolated by glpc collection and the other two products were collected together since they could not be effectively separated by preparation glpc.

The 19% product is tentatively assigned as 2,4,4-trimethyl-5-isopropylidenecyclopentanone (**23**) on the basis of the following spectroscopic evidence: ir, 5.85 and 6.16 μ; nmr, τ 8.98 (d, 3, J = 6.5 Hz), 8.77 (s, 3), 8.69 (s, 3), 8.09 (s, 3), and 7.82 (s, 3). The methylene and methine protons are obscured by the olefinic methyl resonances.

The other two products are assigned as the *cis* and *trans* isomers of 2,4,4-trimethyl-5-isopropylcyclopentanone (**22**): ir, 5.77 μ (strong, cyclopentanone).[4] The 100-MHz nmr spectrum of this mixture was very complicated in the methyl region as expected for a mixture of the two isomers of **18**.

Registry No.—**3**, 16980-16-8; **5**, 16980-17-9; **6**, 16980-18-0; **15**, 16980-19-1; **17**, 16980-20-4; **18**, 16980-21-5; **19**, 16980-22-6; **21**, 16980-23-7; 23, 16980-24-8.

A One-Step Procedure for the Preparation of Tertiary α-Ketols from the Corresponding Ketones

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Received February 27, 1968

Steroidal ketones having a tertiary α-hydrogen react at −25° with oxygen and a trialkyl phosphite in the presence of a strong base to yield the corresponding α-ketols. The method is especially useful for the introduction of a 17α-hydroxyl group into 20-keto steroids, yields of 65% being obtained in many cases. The scope and limitations of the reaction are discussed.

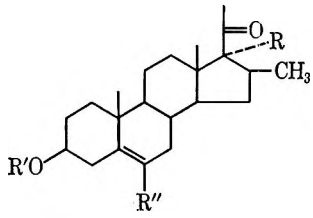
The preparation of 17α-hydroperoxypregnan-20-ones and their reduction to the corresponding 17α-hydroxy compounds has been reported by Barton and coworkers.[2] The introduction of the 17α-hydroperoxy function was accomplished by treatment of the pregnan-20-one with oxygen in the presence of *t*-alkoxide in the corresponding *t*-alkyl alcohol, and, after isolation, the hydroperoxide was reduced to the alcohol, zinc dust in acetic acid being the preferred reagent.

Some years ago we employed this procedure to introduce a 17α-hydroxyl into compound **1** and obtained **2** in only 22% yield.[3] We encountered two difficulties in the conversion. Preparation of the hydroperoxide at ambient temperature, as advocated in the original procedure, gave yields of less than 50% on a 0.5-g scale, and on a 50 to 100 g scale none of the desired product could be isolated. Secondly, the yield of **2** (46%) on zinc dust reduction of the hydroperoxide was disappointing, and the product always contained traces of an impurity that was hard to

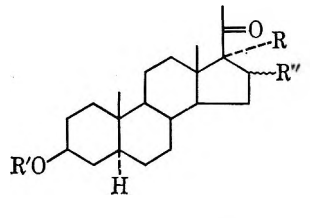
(1) Author to whom correspondence should be addressed at Hoffmann-La Roche Inc., Nutley, N. J. 07110.

(2) E. J. Bailey, D. H. R. Barton, J. Elks, and J. F. Templeton, *J. Chem. Soc.*, 1578 (1962).

(3) J. N. Gardner, F. E. Carlon, C. H. Robinson, and E. P. Oliveto, *Steroids*, **7**, 234 (1966).



1, R = H; R′ = Ac; R″ = CH_3
2, R = OH; R′ = H; R″ = CH_3
5, R = H; R′ = Ac; R″ = H
6, R = OH; R′ = H; R″ = H



3, R = H; R′ = Ac; R″ = β-CH_3
4, R = OH; R′ = H; R″ = β-CH_3
7, R = H; R′ = Ac; R″ = H
8, R = OH; R′ = H; R″ = H
17, R = H; R′ = Ac; R″ = α-CH_3
18, R = OH; R′ = Ac; R″ = α-CH_3
19, R = OH; R′ = Ac; R″ = β-CH_3

remove. These difficulties prompted us to seek an alternative system for the autoxidation which would permit operation at low temperatures, and an improved reducing agent.

In the period since the completion of our work, the autoxidation of pregnan-20-ones at 0° in tetrahydrofuran–*t*-butyl alcohol has been described,[4] as has reduction of hydroperoxides with trialkyl phosphites.[5] The nature of the difficulty in autoxidations at ambient temperature has been indicated also by demonstration of the ease of degradation of 17α-hydroperoxypregnan-20-ones to androstan-17-ones on warming with alkali.[6]

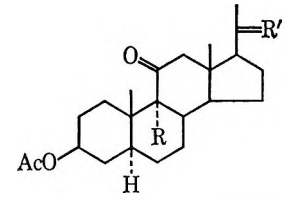
Our initial investigations quickly established that treatment of the 17α-hydroperoxide derived from **1** in an inert solvent with triethyl phosphite leads to a high yield of **2**. The triethyl phosphate formed in the reduction is easily removed from the steroid by washing with water. We then turned our attention to the search for an improved solvent system for the autoxidation, and decided to try the dimethylformamide–*t*-butyl alcohol mixture which has been used for the autoxidation of picolines.[7] A few experiments sufficed to reveal that down to approximately −25° rapid autoxidation occurred, and hydroperoxides could be isolated in high yield. Furthermore, the yields were not diminished if the reactions were allowed to continue for several hours, or were run on a 50 to 100 g scale, and because of the low temperature a 3β-acetoxy group could be preserved during the reaction. The experimental details for this procedure have been reported.[8]

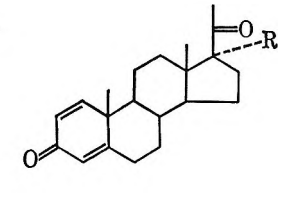
As it is known that trialkyl phosphites are not rapidly oxidized by molecular oxygen at ambient temperature,[9] we decided to try to combine the autoxidation and reduction into a one-step procedure. When **1** was allowed to react with oxygen and a slight excess of triethyl phosphite in sodium *t*-butoxide–*t*-butyl alcohol–dimethylformamide and the product was subjected to hydrolysis, the desired alcohol **2** was obtained in 65% yield. Likewise, **3** gave **4** in 62% yield, and we were thus led to investigate the range of suitable experimental conditions, and the limitations imposed by the structure of the substrate on the procedure.

Dimethylformamide–*t*-butyl alcohol was found to be the solvent of choice as it results in the shortest reaction times, but tetrahydrofuran–*t*-butyl alcohol can be employed, although in this solvent it takes about twice as long for the hydroxylation of **3** to go to completion. Dimethyl sulfoxide–*t*-butyl alcohol can be used also, but temperatures below 0 to 15° result in crystallization of the solvent, and at these higher temperatures lower yields are obtained. The need for a solvent with a low freezing point (our best results have been obtained in the temperature range of −20 to −25°) imposes a considerable limitation on the range of materials one might employ, but any inert polar liquid which meets this criterion is potentially satisfactory.

Using the dimethylformamide–*t*-butyl alcohol–*t*-butoxide system, 17α-hydroxyl groups were introduced into compounds **1**, **3**, **5**, and **7**, the yields being in the 60–70% range. In the case of **7**, the concentration of *t*-butoxide employed was double that used in the first three examples. This reflects the fact that the rate of the reaction is sensitive to the concentration of base and the best results with **7** were obtained using the higher concentration. It is significant that **7** does not contain a 16β-methyl group which has been reported to promote formation of the 17α-hydroperoxide.[2]

That this method of hydroxylation is not restricted to the 17 position is shown by the formation of **10** from **9**, where the more hindered position of the entering





9, R = H; R′ = $-OCH_2CH_2O-$
10, R = OH; R′ = O

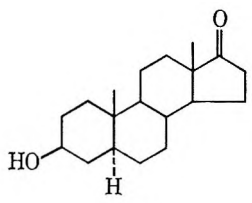
11, R = H
12, R = OH

hydroxyl group may well account for the reduced yield (30%). The obtention of **12**[10–13] from **11** shows that the $\Delta^{1,4}$-3-keto system can survive the reaction conditions, but this is not true of the Δ^4-3-keto moiety. When an attempt was made to prepare 17α-hydroxyprogesterone from progesterone, the gummy product was found by thin layer chromatography to contain several materials, and the ultraviolet spectrum[14] indicated that at least partial oxidation of the A ring had occurred.

Despite their instability, the isolation of secondary α-hydroperoxy ketones has been described.[15] How-

(4) G. V. Baddeley, H. Carpio, and J. A. Edwards, *J. Org. Chem.*, **31**, 1026 (1966).
(5) R. Joly, J. Warnant, J. Jolly, and J. Mathieu, *C. R. Acad. Sci., Paris*, **258**, 5669 (1964).
(6) J. B. Siddall, G. V. Baddeley, and J. A. Edwards, *Chem. Ind.* (London), 25 (1966).
(7) W. Bartok, D. D. Rosenfeld, and A. Schriesheim, *J. Org. Chem.*, **28**, 410 (1963).
(8) J. N. Gardner, F. E. Carlon, and O. Gnoj, *ibid.*, **33**, 1566 (1968).
(9) K. Smeykal, H. Baltz, and H. Fisher, *J. Prakt. Chem.*, **22**, 186 (1963).
(10) There is some conflict in the literature[11–13] regarding the physical constants of **12**. We have prepared an authentic sample from 17α-hydroxyprogesterone, as described in the Experimental Section.
(11) M. Nishikawa and K. Morita, German Patent 1,079,630 (1960); *Chem. Abstr.*, **55**, 23600 (1961).
(12) S. Wada, *Yagugaku Zasshi*, **79**, 120 (1959); *Chem. Abstr.*, **53**, 10296 (1959).
(13) G. Rosenkranz, J. Pataki, St. Kaufmann, J. Berlin, and C. Djerassi, *J. Amer. Chem. Soc.*, **72**, 4081 (1950).
(14) B. Camerino, B. Patelli, and R. Sciaky, *Gazz. Chim. Ital.*, **92**, 693 (1962).
(15) See references cited in ref 2.

ever, when hydroxylation of **13** and **14** was attempted, no reaction could be detected. The same was true of



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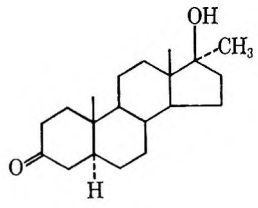
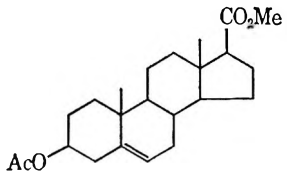
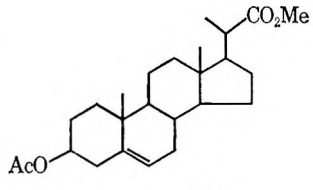


14

the esters **15** and **16**, but we do not know if this results



15



16

from a failure to enolize, or a failure of the hydroperoxide to form.

The original workers failed[2] to obtain a 17α-hydroperoxide from a 16α-methylpregnan-20-one. We attempted the hydroxylation of **17** under various conditions and were able, almost always, to detect traces of **18** by thin layer chromatography. We were not able, however, to obtain more than a very small conversion into products and **18** was isolated in only 1% yield. This result is very probably due to steric hindrance by the 16α-methyl group.

In conclusion, it may be noted that the principle of autoxidation and reduction occurring sequentially in the one reaction requires only that the reducing agent be stable in the presence of oxygen under the specified conditions. For reasons of solubility and ease of removal, the lower trialkyl phosphites are particularly favorable for use with steroids. However, another example of a suitable reducing agent is sodium methylsulfinate. Using this, salt **19** was obtained from **3** in 45% yield, using the solvent system dimethylformamide–tetrahydrofuran–dimethyl sulfoxide–*t*-butyl alcohol. This choice of solvents was necessitated by the poor solubility of the sodium salt.

Experimental Section

Ultraviolet data refer to solutions in methanol, and rotations to approximately 1% solutions in the solvents indicated. Melting points were determined on a Kofler hot-stage microscope except where another instrument is specified. With the exception of compound **10**, all the products reported were identified unambiguously by comparison (thin layer chromatography, infrared spectrum, and rotation) with authentic samples. (For many of these materials the melting point is an unreliable means of identification as it varies greatly with the apparatus used for the determination.)

Sodium hydride refers to the 50% suspension in oil. The course of the hydroxylation reactions was conveniently monitored by thin layer chromatography on silica gel coated microscope slides. Prior to development, the slides were dried for 10 min at 60° in a current of air to free them of dimethylformamide. In most instances, the system benzene–methanol (99:1) was used to develop the slides.

3β,17α-Dihydroxy-6,16β-dimethyl-5-pregnen-20-one (2).—Sodium hydride (0.15 g) was dissolved in *t*-butyl alcohol (2 ml) and dimethylformamide (3 ml), and to the solution were added dimethylformamide (5 ml) and triethyl phosphite (0.5 ml). The mixture was cooled to −25°, oxygen was passed through it, and a solution of **1** (1.09 g) in tetrahydrofuran (8 ml) was added. Passage of oxygen was continued for 22 hr, when a solution of sodium hydroxide (0.5 g) in methanol–water (2:1, 15 ml) was added; the mixture was stirred at ambient temperature for 1 hr. After acidification with acetic acid, the product was precipitated by addition of water, isolated by filtration, and dried. Crystallization from methanol–ethyl acetate gave **2** (662 mg), mp 175–182°. A second crop of 104 mg had mp 170–178° (lit.[3] mp 180–186°).

3β,17α-Dihydroxy-16β-methyl-5α-pregnan-20-one (4).—Sodium hydride (7.5 g) was dissolved in a mixture of *t*-butyl alcohol (100 ml) and dimethylformamide (150 ml) at ambient temperature, approximately 1 hr being taken to effect solution. Dimethylformamide (100 ml) and triethyl phosphite (25 ml) were added and, after cooling the solution to −25°, oxygen was passed through it. A solution of **3** (50 g) in tetrahydrofuran (120 ml) was added over 5 to 10 min and the passage of oxygen was continued for a further 45 min while maintaining −25°. The oxygen was then replaced by nitrogen and a solution of sodium hydroxide (5 g) in methanol (100 ml) and water (50 ml) was added. After agitation for 70 min at ambient temperature, followed by addition of acetic acid (10 ml), the mixture was poured into water (4000 ml). The precipitate was isolated by filtration, washed with water, and dried in an air draft at 100° to yield crude **4** (47 g). This material was dissolved in methanol (1500 ml) and ethyl acetate (500 ml) and the solution was concentrated to half its initial volume. Ethyl acetate (500 ml) was added and the solution was cooled to yield **4** (29.4 g): mp 255–260° (Kofler hot bench); $[\alpha]_D$ +45.6° (dioxane) (lit.[2] mp 214–216°; $[\alpha]_D$ +44° (dioxane)).

3β,17α-Dihydroxy-16β-methyl-5-pregnen-20-one (6).—Compound **5** (5 g) was hydroxylated as described for compound **3** (reaction time 2.5 hr) to yield **6** (3.15 g), $[\alpha]_D$ −20.4° (tetrahydrofuran) (lit.[16] $[\alpha]_D$ −33° (dioxane)).

3β,17α-Dihydroxy-5α-pregnan-20-one (8).—Compound **7** (15 g) was hydroxylated as described for compound **3** except that the amount of sodium hydride was doubled. Crystallization of the crude product gave **8** (10.1 g): mp 250–258°; $[\alpha]_D$ +36.3° (ethanol) (lit.[2] mp 251–256°; $[\alpha]_D$ +35° (ethanol)).

3β-Acetoxy-9α-hydroxy-5α-pregnane-11,20-dione (10).—Sodium hydride (0.3 g) was dissolved in *t*-butyl alcohol (1 ml) and dimethylformamide (5 ml) at ambient temperature. Triethyl phosphite (0.5 ml) was added, the mixture was cooled to −25°, and oxygen was passed through it. A solution of 9[17] (0.5 g) in tetrahydrofuran (4 ml) was added and the passage of oxygen was continued for 50 min. After addition of sodium hydroxide (2 g) in water (10 ml) and methanol (20 ml), the mixture was stirred at ambient temperature for 1 hr, then poured into dilute acetic acid. The precipitate was isolated, dried, and acetylated in excess pyridine–acetic anhydride at 100° for 20 min. The product was precipitated with water and adsorbed on Florisil (15 g) in hexane. Elution with hexane–ether mixtures yielded 3β-acetoxy-5α-pregnane-11,20-dione (100 mg) followed by crude **10** (109 mg). The latter was purified by preparative thin layer chromatography on silica gel in the system chloroform–ethyl acetate (3:1) and two crystallizations from acetone–hexane to yield pure material (58 mg): mp 208–211; $[\alpha]_D$ +101 (chloroform) (lit.[18] mp 209–211°; $[\alpha]_D$ +105° (acetone)).

Anal. Calcd for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.70; H, 8.70.

17α-Hydroxy-1,4-pregnadiene-3,20-dione (12). A. From 11.—Sodium hydride (0.3 g) was dissolved in *t*-butyl alcohol (1 ml) and dimethylformamide (4 ml). To the solution were added dimethylformamide (4 ml) and triethyl phosphite (0.5 ml). After cooling the mixture to −20°, oxygen was bubbled through it and **11** (0.5 g) in dimethylformamide (5 ml) was added. After 45 min the reaction mixture was acidified with acetic acid and poured into water, and the precipitate was isolated. This material was dried and chromatographed in ligroin–toluene–propylene glycol on Chromosorb W (50 g), the proportion of toluene in the eluent being slowly increased from 0 to 100%. Compound **12** was detected in almost all the fractions. These were combined and crystallized from dichloromethane–acetone to

(16) R. Sciaky, *Gazz. Chim. Ital.*, **91**, 562 (1961).

(17) C. Djerassi, E. Batres, J. Romo, and G. Rosenkranz, *J. Amer. Chem. Soc.*, **74**, 3634 (1952).

(18) D. H. R. Barton, R. M. Evans, J. C. Hamlet, P. G. Jones, and T. Walker, *J. Chem. Soc.*, 747 (1954).

yield pure material (90 mg). A second crystallization gave an analytical sample: mp 240–260°; $[\alpha]_D$ +31° (chloroform).

Anal. Calcd for $C_{21}H_{28}O_3$: C, 76.78; H, 8.59. Found: C, 76.61; H, 8.34.

B. From 17α-Hydroxy-4-pregnene-3,20-dione.—17α-Hydroxy-4-pregnene-3,20-dione (1 g) and 2,3-dichloro-5,6-dicyanobenzoquinone (0.81 g) in dioxane (50 ml) were heated at reflux for 18 hr. A further 0.2 g of the quinone was added and heating was continued for 20 hr. The reaction mixture was diluted with dichloromethane and washed twice with 1 *N* sodium hydroxide and successively with saturated sodium bisulfite, 1 *N* sodium hydroxide, and water. The solution was dried over magnesium sulfate, and the solvent was evaporated. The residue on crystallization from dichloromethane–acetone gave **12** (472 mg), mp 220–256°. Two further crystallizations gave an analytical sample: mp 245–262°; λ_{max} 244 mμ (ε 15,000) with a slight shoulder at 295 mμ (presumably due to the presence of a trace of the $\Delta^{1,4,6}$-3-ketone); $[\alpha]_D$ +29° (chloroform).

Anal. Calcd for $C_{21}H_{28}O_3$: C, 76.78; H, 8.59. Found: C, 77.04; H, 8.30.

3β-Acetoxy-17α-hydroxy-16α-methyl-5α-pregnan-20-one (18).—Compound **17** (5 g) was hydroxylated as for compound **3**. The crude product was acetylated with excess pyridine–acetic anhydride at ambient temperature and chromatographed on Florisil (175 g) in hexane, eluting with gradually increasing proportions of ether. Hexane–ether (3:2) eluted material (58 mg) which, on crystallization from acetone–hexane, gave **18** (33 mg), mp 169–173° (lit.[19] mp 180–181°).

3β-Acetoxy-17α-hydroxy-16β-methyl-5α-pregnan-20-one (19).—Sodium hydride (0.2 g) was dissolved in dimethylformamide (4 ml) and *t*-butyl alcohol (3 ml) at ambient temperature. Dimethylformamide (4 ml) was added, the mixture was cooled on ice, and oxygen was passed through it. Solutions of sodium methylsulfinate (1 g) in dimethyl sulfoxide (5 ml) and **3** (1 g) in tetrahydrofuran (5 ml) were added simultaneously over 5 min, a slight precipitate forming in the reaction mixture. Passage of oxygen was continued for a further 30 min; the mixture was neutralized with acetic acid and poured into water. The product was extracted with ethyl acetate and crystallized from acetone–hexane to yield **19** (0.5 g), mp 152–155° (lit.[20] mp 161–163°).

Registry No.—**2**, 5618-40-6; **4**, 2543-24-0; **6**, 13900-61-3; **8**, 570-54-7; **10**, 16980-65-7; **12**, 2477-61-4; **18**, 16980-67-9; **19**, 2543-25-1.

(19) K. Heusler, J. Kebrle, C. Meystre, H. Uberwasser, P. Wieland, G. Anner, and A. Wettstein, *Helv. Chim. Acta*, **42**, 2043 (1959).

(20) R. Mickova and K. Syhora, *Collect. Czech. Chem. Commun.*, **30**, 2771 (1965).

Fluoroalkylquinonemethides

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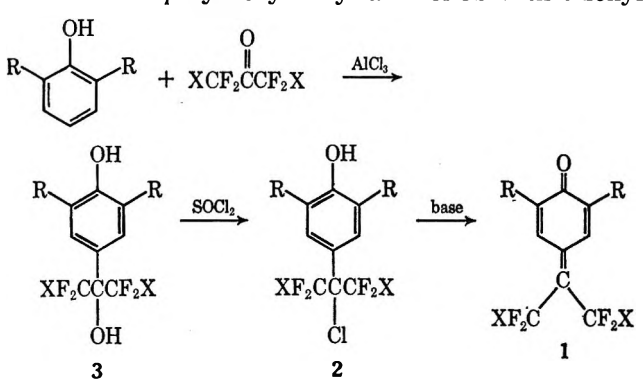
Received February 6, 1968

2,6-Dialkyl-7,7-bis(fluoroalkyl)quinonemethides were prepared in several steps from fluorinated ketones and 2,6-dialkylphenols. The quinonemethides, stabilized by the fluoroalkyl substituents at C-7, can be isolated and characterized, but they are reactive to nucleophilic attack, 1,6 polymerization, and addition of dienes and electron-rich olefins. *o*-Quinonemethides with 7,7-bis(fluoroalkyl) substituents were also prepared but could not be isolated pure; they were characterized by spectral properties and as the Diels–Alder adducts with styrene.

Quinonemethides, or 6-methylene-2,4-cyclohexadien-1-ones and 4-methylene-2,5-cyclohexadien-1-one, have long been of interest. Unfortunately, *p*-benzoquinonemethides are too unstable to isolate and characterize unless highly substituted both in the 2,6 and C-7 positions.[2] Recently, 2,6-di-*t*-butyl-7,7-dimethylquinonemethide,[3a] 2,6-di-*t*-butyl-7,7-dialkylquinonemethides,[3b] and 2,6-dimethyl-7,7-dicyanoquinonemethide[3c] were prepared and shown to be stable (but highly reactive) because of the sterically large or electronegative substituents. However, 2,6-di-*t*-butylquinonemethide with no C-7 substituents could be prepared only in dilute solution[2,4] and dimerized on attempted isolation. *o*-Benzoquinonemethides are less stable than the *para* isomers;[5] they have not been isolated[2b] but are proposed as intermediates in some reactions of substituted *o*-hydroxybenzyl alcohols.

Results and Discussion

A. *p*-Benzoquinonemethides. Synthesis.—Stable 2,6-dialkyl-7,7-bis(fluoroalkyl)quinonemethides, **1a**, **1b**, and **1c**, have been prepared in high yield (60–90%) by hydrogen chloride elimination from the *p*-hydroxybenzyl chlorides **2a** and **2c** with aqueous base or by treatment of *p*-hydroxybenzyl alcohol **3b** with thionyl chloride in pyridine. Benzyl chlorides **2a** and **2c** are readily prepared by condensation of fluorinated ketones with 2,6-disubstituted phenols to give the hydroxybenzyl alcohols **3a** and **3c**[6] which are then treated with thionyl chloride.



a, R = CH_3; X = F
b, R = $C(CH_3)_3$; X = F
c, R = CH_3; X = Cl
d, R = Br; X = F

(1) This work was presented at the Fourth International Fluorine Symposium, Estes Park, Colo., July 1967.

(2) (a) L. J. Filar and S. Winstein, *Tetrahedron Lett.*, **No. 25**, 9 (1960); (b) for a review of quinonemethide chemistry, see A. B. Turner, *Quart. Rev.* (London), **18**, 347 (1964).

(3) (a) C. D. Cook and B. E. Norcross, *J. Amer. Chem. Soc.*, **78**, 3797 (1956), *ibid.*, **81**, 1176 (1959); (b) A. Hubele, H. Suhr, and U. Heilmann, *Chem. Ber.*, **95**, 639 (1962); (c) H. H. Takimoto, G. C. Denault, and L. O. Krbechek, *J. Org. Chem.*, **29**, 1899 (1964).

(4) J. C. McClure, *ibid.*, **27**, 2365 (1962).

(5) (a) P. D. Gardner, H. Sarrafizadeh R., and R. L. Brandon, *J. Amer. Chem. Soc.*, **81**, 5515 (1959); (b) A. Merijan, B. A. Shoulders, and P. D. Gardner, *J. Org. Chem.*, **28**, 2148 (1963).

(6) (a) W. A. Sheppard, *J. Amer. Chem. Soc.*, **87**, 2410 (1965); (b) B. S. Farah, E. E. Gilbert, M. Litt, J. A. Otto, and J. P. Sibilia, *J. Org. Chem.*, **30**, 1003 (1965).

Condensation of hexafluoroacetone with 2,6-di-*t*-butylphenol requires hydrogen fluoride as catalyst; other catalysts such as aluminum chloride and boron trifluoride etherate or treatment of the hydroxybenzyl alcohol **3b** with excess thionyl chloride under acidic conditions caused partial loss or rearrangement of the *t*-butyl groups.

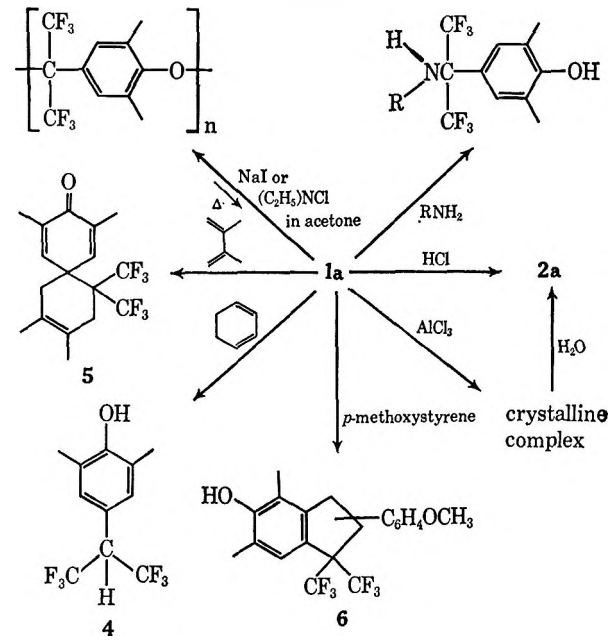
The stabilization by the CF_3 or CF_2Cl group in the C-7 position probably is derived from a combination of steric and electronic factors. Stabilization by the alkyl substituents in the 2,6 positions is needed since the hydroxybenzyl chloride with bromine substituents (**2d**) gave only polymer on treatment with base.

Physical and Spectral Properties.—The quinonemethides **1a**, **1b**, and **1c** are crystalline, orange solids with pungent spicy odors. The quinonemethide **1a** crystallizes in large needles and melts at 36° to an orange liquid which can be refluxed at 200° at atmospheric pressure without decomposition. The quinonemethide structure is clearly verified by spectral properties, as well as the chemical reactions discussed below. In the infrared spectra the strong, characteristic conjugated carbonyl absorption is at 1640 cm^{-1} as for other quinonemethides.[2,3] The intense bands in the ultraviolet spectra of compound **1a** in ethanol at λ_{max} 292 mμ (ε 28,600), of **1b** at λ_{max} 294 mμ (ε 26,700), and of **1c** at λ_{max} 307 mμ (ε 31,800) are similar to those observed for the other alkyl-substituted quinonemethides[2] but of higher energy and lower intensity than for the 7-cyano-substituted derivatives.[3c] The only direct spectral comparison is for compound **1b** [$\lambda_{max}^{isooctane}$ 295 mμ (ε 25,400) and $\lambda_{max}^{methanol}$ 295 mμ (ε 26,600)] with 2,6-di-*t*-butyl-7,7-dimethylquinonemethide [$\lambda_{max}^{isooctane}$ 314 mμ (ε 26,000), $\lambda_{max}^{methanol}$ 322 mμ)]. The energy increase in the ultraviolet absorption for compound **1b** reflects the destabilizing inductive influence of the fluoroalkyl groups on polar contributions in the electronically excited molecule. The proton nmr spectra are almost the same as for the starting phenols **2** but lacking the phenolic hydrogen resonance. As expected, the F^{19} resonance in compound **1a** shifts 15.6 ppm downfield from that of the starting phenol **2a** and shifts an additional 10.9 ppm downfield for the CF_2Cl group in compound **1c**.

The reduction potential of quinonemethide **1a** in acetonitrile is −0.35 eV. The reduction appears to be a two-electron process as is found in tetracyanoquinodimethane complexes. The reduction potential of this quinonemethide is 0.5 eV lower than that of tetracyanoquinodimethane (+0.15 eV)[7] under the same conditions. This lower potential is expected because of the poorer electron-withdrawing power of a trifluoromethyl group relative to a cyano group and the quinonemethide rather than quinodimethane structure. Formation of a stable ion radical appears unlikely because of the two-electron reduction and lower reduction potential. No evidence for ion radical was found, but complexing does occur with some reagents as indicated by the color on mixing; a stable adduct with aluminum chloride was isolated (see below).

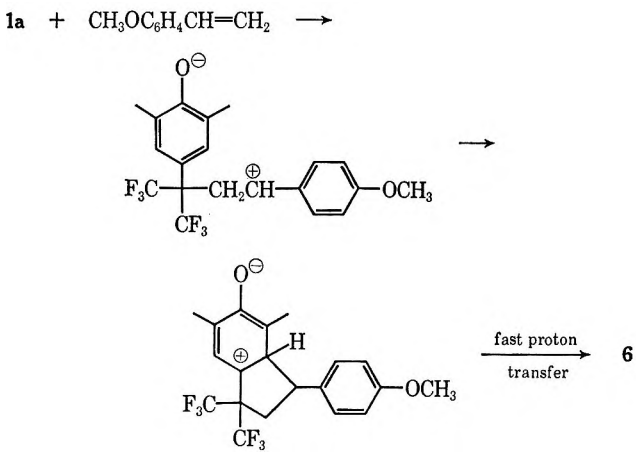
Chemical Reactions.—Most of the chemistry of the fluoroalkylquinonemethides was studied on compound **1a** as representative of the series. The reactions are outlined in Chart I. 1,6 addition of nucleophiles occurs readily as reported for other quinonemethides.[2,3c] Anhydrous hydrogen chloride in ether adds to give hydroxybenzyl chloride **2a**, but aqueous hydrochloric acid gives a mixture of phenols **2a** and **3a**. Ammonia, hydrazine, and primary aliphatic amines add easily, but alcohols are sluggish and phenols do not add in contrast to other quinonemethides.[2,3c] The steric repulsion of the trifluoromethyl groups appears greater than that of cyano or alkyl groups, and only relatively unhindered basic nucleophiles attack at C-7. Anions, however, can initiate polymerization (see below). 1,6 reduction to phenol **4** occurs when **1a** is heated with cyclohexadiene. Free-radical initiated polymerization of quinonemethide **1a** gives only very low molecular weight polymers, but anionic polymerization with sodium iodide or tetraethylammonium chloride in acetone gives a crystalline white polymer, mp 220°, that can be pressed into a brittle film at 200°. This polymer, of moderate molecular weight (almost 12,000), decomposes slowly to monomer above 200°. Spectral evidence strongly suggests a 1,6 polymerization. The quinonemethides **1** behave like other 7-substituted quinonemethides and do not show any tendency to dimerize.

CHART I

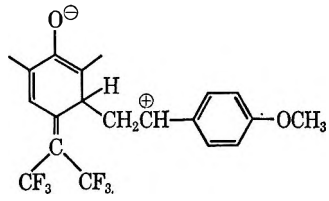


2,3-Dimethylbutadiene adds chiefly across the exocyclic double bond to give the spirane **5**, analogous to addition reactions of other quinonemethides.[4] However, butadiene gives as product an impure oil that is not easily purified; the main reaction appears to be the Diels–Alder addition to the exocyclic double bond. Electron-rich olefins such as *p*-methoxystyrene also react with the quinonemethide **1a**, to give an indanol such as **6**. The structure of the product was determined by spectral analysis; the position of the *p*-methoxyphenyl group was not proved but is suggested to be in the 1 position on the basis of spectra and possible mechanism of formation *via* attack of styrene on the terminal carbon of the exocyclic double bond (analogous to addition of nucleophiles). Alternatively, the

(7) D. S. Acker and W. R. Hertler, *J. Amer. Chem. Soc.*, **84**, 3370 (1962).



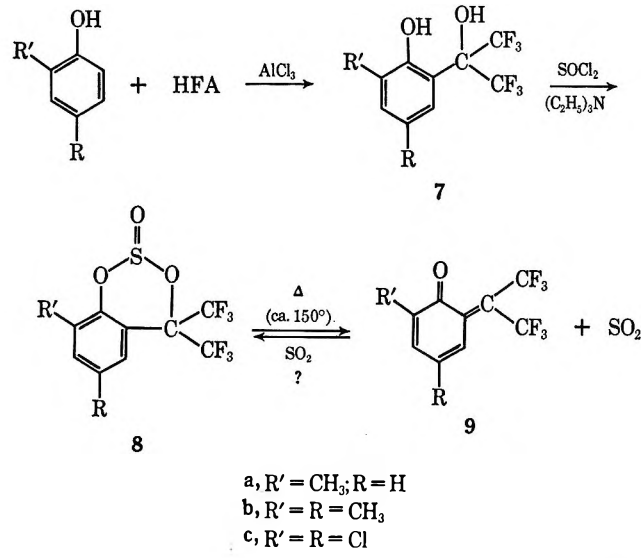
styrene could attack at the 3 position to give an intermediate



The indanol product would then have a *p*-methoxyphenyl group in the 2 position of the indan ring. Attack in this position would not be hindered by the steric repulsion of the trifluoromethyl groups, but this intermediate would not gain the favorable energy from aromatization. Some oily by-products from this reaction show a carbonyl absorption and may be cycloadducts. *t*-Butyl vinyl sulfide also gives an indanol product, but the spectral properties suggest that the *t*-butylmercapto group is not in the same position as the *p*-methoxyphenyl (the bulky *t*-butyl group may favor attack at the 3 position).

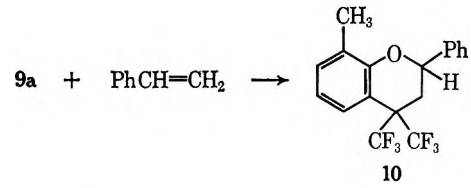
The quinonemethides **1** are not effective π acids, but **1a** forms a stable complex with aluminum chloride in methylene chloride. This complex has limited solubility in methylene chloride (dark green solution) and precipitates as a white solid when the solution is concentrated. The carbonyl absorption at 1640 cm^{-1} is weak and broad in the complex, and the proton nmr spectra are shifted approximately 0.5 ppm to lower field. Hydrolysis of the complex gives phenol **2a**.

B. *o*-Benzoquinonemethides.—When a phenol with an unsubstituted *ortho* position is treated with hexafluoroacetone with aluminum chloride catalyst, the *o*-hydroxybenzyl alcohol **7** is the main product.[8] Thionyl chloride treatment of **7** gives only the cyclic sulfite ester **8** in high yield.[9] The sulfite ester readily loses sulfur dioxide when heated to 150–200°, and the bright orange color of the *o*-quinonemethide quickly develops. Spectral measurements provide strong evidence for the presence of *o*-quinonemethide **9** [F^{19}



a, R′ = CH_3; R = H
b, R′ = R = CH_3
c, R′ = R = Cl

nmr—pair of quadruplets at lower field, 57.2 and 58.8 ppm (relative to CCl_3F) with J = 9 cps, compared to starting sulfite ester, at 73.7 and 77.3 ppm with J = 9.4 cps, and strong conjugated carbonyl at 1650–1660 cm^{-1} in infrared spectra]. However the *o*-quinononemethides **9** turn to resin when heated excessively; when isolated by distillation, they are mixed with the corresponding sulfite esters **8**. Compound **9a** was isolated in CCl_3F solvent by hydrolysis of the sulfite ester with aqueous base. Apparently these *o*-quinonemethides are much less stable than the *para* isomers and decompose almost as fast as they form. Possibly the quinonemethide complexes with the sulfite ester precursor as is observed for some *p*-quinonemethides.[3] Solutions of the *o*-quinonemethides decolorize readily when olefin is added, and the reaction of **9** with styrene gives the adduct **10**. The assignment of phenyl group posi-



tion is based on nmr spectral analysis and is predicted mechanistically. The adduct **10** was more conveniently prepared by refluxing the sulfite ester in *o*-dichlorobenzene solution containing styrene.

Experimental Section

Materials.—All standard chemicals and reagents were obtained from Eastman Kodak or other chemical supply houses. The hexafluoroacetone and 1,3-dichlorotetrafluoroacetone were obtained from Organic Chemicals Department, E. I. du Pont de Nemours and Co.

Quinonemethides.—All new compounds prepared in this work are listed in Table I with physical and spectral properties and analytical data. Representative procedures are given below. The methods of preparation and yields for each compound with reference to the Experimental Section are summarized in Table I with footnotes to describe any significant modifications of reaction conditions.

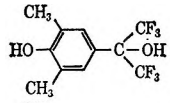
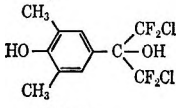
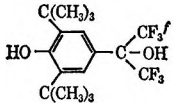
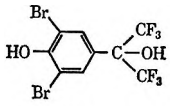
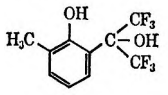
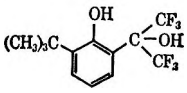
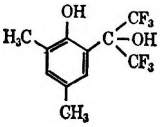
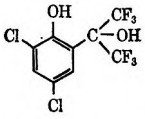
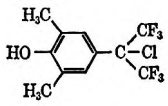
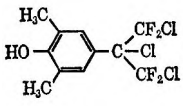
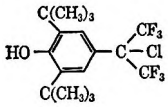
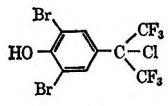
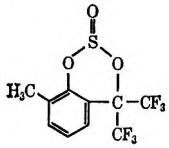
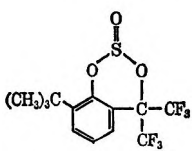
A. Synthesis.—The literature procedure[6] was used for the condensation of fluorinated ketones with phenols. The reactions with 1,3-dichlorotetrafluoroacetone were usually run at atmospheric pressure. In reactions with 2,6-di-*t*-butylphenol, the aluminum chloride caused isomerization involving the *t*-butyl group, but hydrogen fluoride was effective as a catalyst. The

(8) Aluminum chloride and *p*-toluenesulfonic acid are reported to give predominantly *ortho* orientation in hexafluoroacetone substitutions of phenols [see ref 6b and D. C. England, French Patent 1,325,204 (1963)], but hydrogen fluoride and boron trifluoride are reported to give almost exclusive *para* substitution (ref 6b and I. L. Knunyants, T.-Y. Chen, M. P. Gambaryan, and E. M. Rokhlin, *Zh. Vses. Khim. Obshchest.*, **5**, 114 (1960); *Chem. Abstr.*, **54**, 20962 (1960)).

(9) Formation of cyclic sulfite ester appears to be a diagnostic test for *ortho* substitution in phenols.

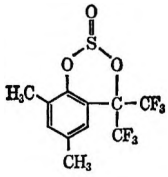
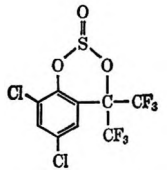
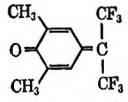
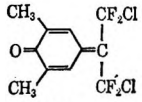
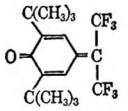
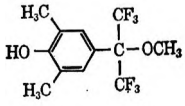
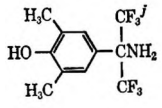
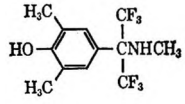
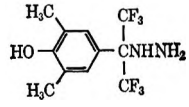
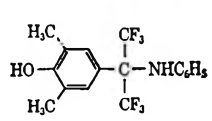
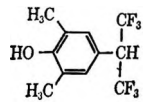
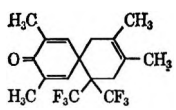
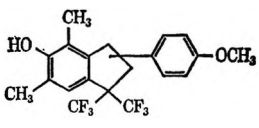
TABLE I

QUINONEMETHIDES, PRECURSORS, AND DERIVATIVES: PREPARATION AND PROPERTIES

Compd	Mp, °C, or $n^{25}D$	Bp, °C (mm)	Uv[a] λ, mμ	Uv[a] (ε)	Nmr, δ, ppm (rel intensity)[b] F^{19} (relative to CCl_3F)	Nmr, δ, ppm (rel intensity)[b] Proton (relative to tetramethylsilane)
			A. Precursors			
	90.5–91.8[d]	...	278 (E) 270 226	(900) (940) (7,120)	76.4	7.37 (2) 4.90 (1) 3.55 (1) 2.27 (6)
	95.6–96.8[e]	...	279 (E) 270 230	(800) (895) (7,800)	60.4	7.38 (2) 4.92 (1) 3.78 (1) 2.26 (6)
	95.5–96.5	...	276 (E) 269 227	(980) (1,000) (7,800)	76.4	7.58 (2) 5.48 (1) 3.33 (1) 1.50 (18)
	85.5–87.1	...	285 (I) 278	(2,200) (1,900)	76.7	7.87 (2) 6.17 (1) 3.57 (1)
	84.0–85.4	...	278 (E) 215	(2,770) (6,440)	76.2, doublet, J = 1.1 cps	6.7–7.3 (3) 7.1–7.3 (OH-2) 2.23 (3)
	125–127	...	280 (E) 221 216	(2,400) (7,340) (7,500)	76.2, doublet, J = 1.0 cps	7.3 (1), 6.43 (1) } OH 7.47 (1) 7.09 (2) AB pattern with additional splitting 1.27 (9)
	91.8–92.0	95 (3.0)	285 (E) 220	(2,910) (6,710)	76.2, doublet, J = 1.1 cps	7.41 (1, OH) 7.21 (2) 6.68 (1, OH) 2.30, 2.25 (6)
	101.8–103.4	...	293 (E) 232 222	(3,130) (5,630) (7,140)	75.9	7.48 (2) 6.81 (*ca.* 2) (broad)
	96.2–97.2	...	277 (A) 268 232	(900) (1,280) (6,680)	70.8, triplet, J = 0.8 cps	7.42 (2) splitting not defined; 3.5 cps width at half-peak height 4.97 (1) 2.23 (6) triplet, J = 0.5 cps
	105 (0.4)				54.9, 54.2 doublets, J = 8 cps with additional fine splitting	7.46 (2) 4.92 (1) 2.25 (6)
	126–127	...	295 (I) 276 268 231	(120) (930) (1,160) (6,340)	70.8, triplet J = 0.8 cps	7.67 (2) 5.43 (1) 1.47 (18)
	72–73	...	284 (E) 276	(2,030) (2,030)	71.0, triplet J = 0.7 cps	7.98 (2) 6.23 (1)
	44–45 1.4485	57 (0.6)	275 270	(1,170) (1,210)	73.7 (1), 77.3 (1) quadruplets, J = 9.4 cps secondary splitting of ~1 cps	6.9–7.5 (3) 2.13 (3)
	1.4479	70 (0.2)	382 (I) 279 271	(122)[h] (1,110) (1,200)	73.0 (1), 76.5 (1) quadruplets, J = 9.5 cps	7.64–7.0 (1) AB but complex on one side with additional peak ~7.6 1.33 (3)

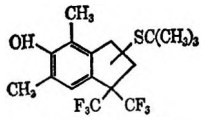
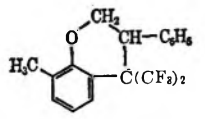
Method of preparation[c] (% yield), recrystallization solvent	Formula	Registry no.	Analysis, % Carbon Calcd	Carbon Found	Hydrogen Calcd	Hydrogen Found	Fluorine Calcd	Fluorine Found	Others Calcd	Others Found
			A. Precursors							
A1 (71), CCl_4 or hexane	$C_{11}H_{10}F_6O_2$	2950-32-5					39.6	39.4		
A1 (43), CCl_4 or hexane	$C_{11}H_{10}Cl_2F_4O_2$	2093-02-9	41.2	41.2	3.14	3.26	23.7	22.7 23.6	Cl, 22.1	21.4 22.0
A1[f] (59), pentane	$C_{17}H_{22}O_2F_6$	16867-83-7	54.8	54.9	5.96	5.95	30.6	30.1		
A1 (63), CCl_4	$C_9H_4Br_2F_6O_2$	16867-84-8	25.9	26.0	0.96	0.86	27.3	26.9	Br, 38.2	39.2
A1 (70), CCl_4, prec. with pentane	$C_{10}H_8F_6O_2$	3015-33-6	43.8	43.8	2.94	3.19	41.6	42.7		
A1[g] (48), hexane	$C_{13}H_{14}F_6O_2$	16878-08-3	49.4		4.47		36.1	36.2		
A1 (20), hexane	$C_{11}H_{10}F_6O_2$	16867-86-0	45.8	45.7	3.50	3.50	39.6	39.5		
A1 (45), CCl_4 or hexane	$C_9H_4Cl_2F_6O_2$	16867-87-1	32.9	33.0	1.22	1.38	34.7	35.2	Cl, 21.6	21.5
A2 (91), CCl_4 or hexane	$C_{11}H_9ClF_6O$ 306.6	16867-80-4	43.1	43.1	2.96	3.27	37.2	36.8	Cl, 11.6	11.6
A2 (75)	$C_{11}H_9F_4Cl_3O$	16878-09-4					22.4	22.4		
B1a (84), sublimed	$C_{17}H_{12}F_6ClO$	16867-88-2					30.0	30.0		
A2 (99), pentane	$C_9H_8Br_2ClF_6O$	16867-89-3					26.1	26.5	Br, 36.6 Cl, 8.12	35.3 8.52
A2 (89)	$C_{10}H_6F_6O_3S$	16878-06-1	37.5	37.8	1.89	2.01	35.6	35.8	S, 10.0	10.1
A2 (97)	$C_{13}H_{12}F_6O_3S$	16867-67-7	43.1		3.34		31.5	31.5		

TABLE I (*Continued*)

Compd	Mp, °C, or $n^{25}D$	Bp, °C (mm)	Uv[a] λ, mμ	Uv[a] (ε)	Nmr, δ, ppm (rel intensity)[b] F^{19} (relative to CCl_3F)	Nmr, δ, ppm (rel intensity)[b] Proton (relative to tetramethylsilane)
	1.4544	82 (4.0)	282 (E) 275	(1,590) (1,620)	76.6 (1), 73.1 (1) quadruplets J = 9.4 cps	7.37 (2) 2.35, 2.27 (6)
	65–66	...	292 (A) 284 235 sh 204	(1,510) (1,530) (7,120) (42,400)	72.5 (1), 76.6 (1) quadruplets J = 9.6 cps	7.68 (1), doublet J = 2.1 cps 7.54 (1), complex
			B. Quinonemethides			
	35–36 1.4787	107 (50)	292 (E)	(28,600)	54.2 10-line symmetrical pattern, J = 0.6 cps	7.45 (1), 2.08 (3) poorly defined splitting, 3 to 4.5 cps width at half-peak height
	62.2–63.0	90–90.5 (1.6)	307 (E)	(31,800)	43.3 half-peak width of 3 cps	7.49 (1) 2.08 (3)
	50–51	...	455 (E) 294	(19) (26,700)	54.3, triplet J = 1.1 cps	7.37 (1) 1.28 (9)
			C. Reaction Products			
	98.5–98.7	...	277 (I) 268 266	(730) (790) (7,400)	76.4, quadruplet J = 0.9 cps	7.13 (2) 4.67 (1) 3.43 (3), quadruplet 2.26 (6)
	74–75	...				
	95.5–95.9	...	277 (I) 268 220	(760) (780) (7,500)	70.0 quadruplets J = 0.8 cps	7.32 (2) 4.8 broad (1) 2.4 broad, 2.27 sharp, 2.1 v. broad (10)
	162–162.5	...	279 (E) 270 228	(870) (980) (7,580)	68.9 (C)[b]	7.32 (2) 3 to 5 (4) 2.32 (6)
	83.5–84.2	...	288 (I) 278 273 231	(1,200) (2,300) (2,000) (17,100)	68.4	7.33 (2) 7.2 to 6.3 (6) 4.78 (1) 4.38 (1) 2.23 (6)
	62–63.8	...	277 (I) 272 269 217	(1,080) (990) (1,000) (8,200)	66.4, doublets J = 8.4 cps split into triplets J = 0.6 cps	7.11 (2) 4.78 (1, OH) 3.89 (1, heptuplet, J = 8 cps) 2.28 (6)
	85.5–87.0	...	338 (E) 238	(30) (13,800)	64.6	6.67 (2) 2.60 (2) 2.13 (2) 1.81 (6) 1.72 (3) 1.60 (3)
	128.5–129.1	...	283 (E) 278 275 227 sh	(2,890) (3,400) (3,270) (21,500)	72.6 (1), 70.6 (1) quadruplets J = 9.8 cps	See Experimental Section

Method of preparation[c] (% yield), recrystallization solvent	Formula	Registry no.	Analysis, % Carbon Calcd	Carbon Found	Hydrogen Calcd	Hydrogen Found	Fluorine Calcd	Fluorine Found	Others Calcd	Others Found
A2 (31)	$C_{11}H_8F_6O_3S$	16867-68-8	39.5	39.8	2.43	2.57	34.1	33.7	S, 9.60	8.43
A2 (79), hexane	$C_9H_2Cl_2F_6O_3S$	16867-69-9					30.4	30.6	S, 8.55	8.06
			B. Quinonemethides							
A3a (91)	$C_{11}H_8F_6O$	16915-87-0	48.9	49.0 49.0	2.99	3.13 3.09	42.2	42.5		
A3a (62)	$C_{11}H_8Cl_2F_4O$	16867-70-2	43.6	43.9	2.66	2.60	25.1	25.0	Cl, 23.4	23.4
A3a[i] (68), sublimed	$C_{17}H_{20}F_6O$	16867-71-3	57.6	56.8	5.69	5.76	32.2	32.3		
			C. Reaction Products							
B1c (93), hexane	$C_{12}H_{12}F_6O_2$	16867-72-4	47.7	47.6	4.01	4.01	37.7	37.6		
B1b (93), petroleum ether	$C_{11}H_{11}F_6NO$	14355-85-2	46.0	46.2	3.86	3.95	39.7	39.3	N, 4.88	4.72
B1b (87), hexane	$C_{12}H_{13}F_6NO$	16867-74-6	47.8	47.7	4.35	4.41	37.8	37.6	N, 4.65	4.73
B1b (90), hexane–benzene	$C_{11}H_{12}F_6N_2O$	16867-75-7	43.7	44.2	4.01	4.02	37.7	37.9	N, 9.27	9.27
B1b (94), hexane	$C_{17}H_{15}F_6NO$	16867-76-8	56.2	56.0	4.16	4.09	31.4	30.9	N, 3.86	3.87
B3 (39), hexane	$C_{11}H_{10}F_6O$	16867-77-9	48.7	48.9	3.35	3.81	42.1	41.9		
B4a (76), hexane	$C_{17}H_{18}F_6O$	16867-78-0	58.0	57.9 58.3	5.15	4.92 5.33	32.4	32.2		
B5a (42), cyclohexane	$C_{20}H_{18}F_6O_2$		59.4	59.6	4.49	4.72	28.2	27.8	Mol wt 363 369 (bp benzene)	404

TABLE I (*Continued*)

Compd	Mp, °C or $n^{25}D$	Bp, °C (mm)	Uv[a] λ, mμ	Uv[a] (ε)	Nmr δ, ppm (rel intensity)[b] F^{19} (relative to CCl_3F)	Nmr δ, ppm (rel intensity)[b] Proton (relative of tetramethylsilane)
	94.4–95.6	...	255	(8,210)	67.3, pentuplet J = 0.8 cps (from overlapping quadruplets?)	7.32 (2) 6.43 (2; AB, J = 16 cps, δ = 0.78 ppm) 4.94 (1, OH) 2.27 (6) 1.37 (9)
	89–90	...	283 (I) 276	(2,540) (2,520)	69.7 complex overlapping quadruplets? with J = ~9 cps with additional splitting	See Experimental Section

[a] Solvents used are E, ethanol; I, isooctane; and A, acetonitrile. [b] Proton nmr spectra obtained in CCl_4 or $CDCl_3$ with internal reference of tetramethylsilane, F^{19} nmr spectra obtained in CCl_3F as solvent and internal references, or if too low solubility in $CHCl_3$ with internal CCl_3F (designated by letter c). Concentration of 5–10% used for all spectra. [c] Letter and number refer to procedure listed in Experimental Section. [d] Lit.[6b] mp 93–104°. [e] Lit.[6b] mp 95°. [f] We are indebted to Dr. D. M. Gale of this laboratory for first preparing this compound. Anhydrous hydrogen fluoride is required as catalyst in this reaction. Both aluminum chloride and boron trifluoride–etherate cause rearrangement of *t*-butyl group. [g] Only product isolated when 2,6-di-*t*-butylphenol was condensed

products were purified by recrystallization usually followed by sublimation.

The *p*-hydroxybenzyl alcohol was dissolved in excess thionyl chloride and a small amount (few drops to 1 ml) of triethylamine was added. A mild reaction (gas evolution, exothermic) occurred, and the solution was heated at reflux overnight. The product was usually separated by pouring the reaction mixture into a large excess of ice–water to destroy the excess thionyl chloride, and the solid was suction filtered, washed with water, dried, and recrystallized from hexane, pentane, or carbon tetrachloride, or if a liquid, was extracted into methylene chloride, dried, and distilled. The product, in yields generally of 60–90%, from the *p*-hydroxybenzyl alcohol **3** was the benzyl chloride **2**, whereas from the *ortho* isomer **7** it was the sulfite ester **8**. The 2,6-di-*t*-butyl compound **3b** was partly decomposed and rearranged by this treatment. It was treated with thionyl chloride in pyridine and converted directly into quinonemethide.

The *p*-hydroxybenzyl chloride **2**, finely powdered, was stirred with excess 10% sodium carbonate or sodium hydroxide solution in water until all the white crystals had changed to an orange oil. This oil was separated by methylene chloride extraction, dried, and vacuum distilled.

The 2,6-di-*t*-butylquinonemethide **1b** was prepared by heating the *p*-hydroxybenzyl alcohol **3b** with thionyl chloride in pyridine solution at 80° for 15 min and separated by pouring the reaction mixture into ice–water.

The cyclic sulfite ester **8** was heated in a flask at *ca.* 150° until major gas evolution ceased. The product was distilled at reduced pressure. The distillate was found to be a mixture of recovered sulfite ester **8** with quinonemethide **9**; usually a considerable residue of a light-colored resin remained in the pot.

The sulfite ester **8a**, 7.3 g, was heated at 150–180° in a pot connected to a spinning-band distillation column. Sulfur dioxide evolution started at 150°, and the liquid turned orange. A total of 6.3 g of orange liquid [bp 94° (9.5 mm) to 111° (15 mm), $n^{25}D$ 1.4501–1.4481] was collected in six fractions. The F^{19} nmr spectra on a middle fraction showed the distillate contained about 90% of starting sulfite ester and 10% of quinonemethide **9a**.

A mixture was dissolved in trichlorofluoromethane and shaken with excess sodium hydroxide solution for several minutes. The trichlorofluoromethane solution was separated, dried, and used for spectral analysis: F^{19} nmr quadruplets at 57.2 and 58.8 ppm relative to CCl_3F with J = 9 cps (no other fluorine detected); proton nmr, equal intensity areas at δ 7.4 to 6.2 (complex) and 1.98 ppm (single) (10% impurity at 2.3 ppm). The quinonemethide was further characterized by the carbonyl absorption at 1660–1670 cm^{-1}. A 3.8-g sample of a mixture of quinonemethide **9a** and sulfite ester **8a** was added to 1.0 g of styrene in 10 ml of methylene chloride. The orange color of the quinonemethide faded to yellow after approximately 10 min, and the solution was colorless in a few hours. The methylene chloride was evaporated, and the residual oil was triturated with excess sodium hydroxide solution to hydrolyze and dissolve the sulfite ester. The white crystalline solid was filtered off and dried, 0.28 g, mp 89.0–90.0°, and recrystallized from hexane–pentane, mp 88.0–88.6°. The product (also prepared from *o*-quinonemethide **9a** that was purified and isolated for spectral measurements) was characterized as the Diels–Alder adduct **10** by analysis (see Table I), infrared spectra, F^{19} nmr (see Table I), and proton nmr spectra (δ in ppm with intensity in parentheses): complex aromatic 7.3–6.5 (8), tertiary hydrogen as doublet at 5.1 (1) with J = 10 cps, complex CH_2 2.8–2.2 (*ca.* 2, overlaps with methyl), CH_3 singlet 2.23 (3). The assignment of the phenyl α to the oxygen is based on the proton shift for the CH_2 group which should be approximately 1 ppm to lower field if in the other position, α to oxygen. Mechanistically both from steric and electronic considerations, the orientation for styrene addition is also expected to be as assigned.

The *o*-quinonemethide **9a** was generated and trapped *in situ* by refluxing a solution of 1.8 g of sulfite ester **8a** and 5 g of inhibited styrene in 20 ml of *o*-dichlorobenzene overnight. The solvent was removed under reduced pressure and the oily residue was extracted with pentane. The adduct **10a** crystallized from the pentane extract in a yield of 1.2 g (60%).

B. Reactions of 2,6-Dimethyl-α,α-bis(trifluoromethyl)quinomethides (1a). 1. Hydrogen Chloride Addition.—A solution of 2.0 g (7.4 mmol) of quinonemethide **1a** in 20 ml of ether was saturated with dry hydrogen chloride gas and allowed to stand in a stoppered flask. After about 1 hr, the orange color of the quinonemethide disappeared. The solution was evaporated under nitrogen, and a residue of white crystalline solid, 2.26 g, mp 97.6–98.4° (99.7% yield), was obtained. The product was shown by mixture melting point and spectral comparison to be 2,6-dimethyl-4-(2-chlorohexafluoroisopropyl)phenol (**2a**).

Reaction of the quinonemethide **1a** with concentrated hydrochloric acid gave a product that was shown by spectral analysis to be a mixture of **2a** and the corresponding benzyl alcohol **3a**, showing that water addition has also occurred.

2. Ammonia,[10] Amines, and Hydrazine Addition.—Anhydrous methylamine was bubbled into a solution of 2.4 g (0.010 mol) of quinonemethide **1a** in 25 ml of anhydrous ether at room temperature. The orange color of **1a** gradually faded to a pale yellow while passing in the amine. The solution was stoppered. After standing at room temperature for several hours, it became colorless and was evaporated to dryness. The crystalline residue was recrystallized from hexane to give 2.6 g (87%) of white crystalline solid, mp 95.5–95.9°, characterized by analysis and spectra as 3,5,N-trimethyl-4-hydroxy-α,α-bis(trifluoromethyl)benzylamine.

Ammonia was added in a similar manner. Hydrazine dissolved in ether was added to an ether solution of compound **1a**. The reaction was extremely exothermic, and part of the product

(10) We are indebted to Dr. C. G. Krespan of this laboratory for the experiment with ammonia.

Method of preparation[a] (% yield), recrystallization solvent	Formula	Registry no.	Analysis, % Carbon Calcd	Carbon Found	Hydrogen Calcd	Hydrogen Found	Fluorine Calcd	Fluorine Found	Others Calcd	Others Found
B5b (24), hexane	$C_{17}H_{20}F_6OS$		52.8	53.1 52.7	5.22	5.44 4.53	29.50	29.2	S, 8.3	8.3
See A3b	$C_{18}H_{14}F_6O$	16867-79-1	60.0	60.0	3.92	3.94	31.6	31.5		

with hexafluoroacetone in presence of boron trifluoride–etherate as catalysts at 100°. Product appeared to decompose during recrystallization. An isomer tetatively assigned *para* orientation of hexafluoroacetone to phenolic group has been reported,[6b] mp 63–71. [h] Product light orange color; absorption at 382 mμ may be due to impurity of quinonemethide formed during distillation. [i] By reaction of the hydroxybenzyl alcohols with thionyl chloride in pyridine. [j] See ref 10. This compound was first prepared by condensation of hexafluoroisopropylidenimine with 2,6-dimethylphenol: D. M. Gale and C. G. Krespan, *J. Org. Chem.*, **33**, 1002 (1968).

precipitated as white crystals during reaction. Aniline formed a wine red solution on mixing with the quinonemethide in ether; the adduct was isolated after standing overnight.

3. **Methanol Addition.**—The quinonemethide **1a** was dissolved in methanol, and a drop of concentrated sulfuric acid added. The orange color of the quinonemethide gradually faded, and the solution became colorless overnight. The methanol was evaporated, and the crystalline solid was washed with water and recrystallized.

4. **Polymerization.**—Quinonemethide **1a** and styrene reacted only when heated in the presence of benzoyl peroxide. The product appeared to be a low molecular weight polymer.

Attempts to prepare the anion radical of quinonemethide **1a** using a solution of sodium iodide in acetone gave only a white crystalline polymer. Thus, when 5 g of sodium iodide in 20 ml of acetone was mixed with a solution of 2.70 g (0.010 mol) of quinonemethide in 5 ml of acetone, the brown color of iodine developed immediately, and a white solid precipitated gradually. This white solid (1.92 g), mp 219–222°, was recrystallized from chloroform and was shown from spectral properties and analysis to be a polymer.

Anal. Calcd for $(C_{11}H_3F_6O)_x$: C, 48.9; H, 2.99; F, 42.2. Found: C, 49.4; H, 3.09; F, 41.4; ash content, 0.61%; mol wt (bp in benzene) 12,500, 11,840.

This material was pressed at about 200° into a brittle film, but some decomposition occurred (color and odor of monomer noted).

A series of polymerization experiments was carried out in an effort to prepare a higher molecular weight polymer. If the amount of sodium iodide was reduced below *ca.* 5–10%, the polymer did not form satisfactorily. The polymer of slightly lower melting point was also obtained with tetraethylammonium chloride in acetone. However, no polymers were obtained with sodium iodine or tetramethylammonium chloride in chloroform. Boiling the polymer in acetic anhydride increased the melting point slightly but did not improve the stability or the character of the pressed film. Heating in dimethyl sulfate also did not change the properties of the polymer.

A sticky gum was obtained in attempted polymerization experiments with sodium methoxide in alcohol or glyme. Oily products also obtained in these reactions may be the result of a nucleophilic attack by methoxide or alcohol on the quinonemethide but were not examined further.

5. **Reduction.**—A solution of 5.4 g (0.020 mol) of quinonemethide **1a** in 10 ml of 1,3-cyclohexadiene (80% purity) was refluxed overnight. The orange color of the quinonemethide faded to a pale yellow. The hydrocarbon was evaporated and residual solid sublimed at 100° (10–20 mm). A total of 2.06 g of white crystalline solid, mp 46–53°, was obtained. This product was recrystallized from hexane and resublimed, mp 62–63.8°. On the basis of analysis (see Table I) and spectral properties (OH in ir, tertiary hydrogen resonance split into a septuplet in nmr), the product was characterized as 2,6-dimethyl-4-(2H-hexafluoroisopropyl)phenol resulting from reduction of quinonemethide with the cyclohexadiene.

6. **With Dienes.**—A solution of 2.70 g (0.010 mol) of quinonemethide **1a** and 5 ml of 2,3-dimethylbutadiene was refluxed overnight. The orange color of the quinonemethide faded to a very pale yellow in a few hours. The excess diene was evaporated under nitrogen, and a residual white crystalline solid (3.42 g), mp 65–78°, was sublimed and recrystallized twice from hexane and resublimed, mp 85.5–87.0°. The analytical and spectral data are given in Table I. On the basis of the single F^{19} fluorine resonance, the simplicity of the proton nmr spectra, and the carbonyl frequency and carbon–carbon double bond at 1640 and 1680 cm^{-1} in the infrared spectrum, the spirane structure **5** (resulting from addition of the diene to the exocyclic double bond) was assigned.

A sealed Carius tube containing quinonemethide **1a** (9.1 g, 0.030 mol) and *ca.* 5 ml of butadiene was heated on a steam bath overnight. The orange color of the quinonemethide faded to pale yellow. The excess hydrocarbon was evaporated under nitrogen and the resulting oil was distilled, bp 108–115° (3.0 mm). The product, a colorless syrup, on the basis of analytical and spectral data (see Table I), was believed to contain approximately 75% of the spirane isolated from the 2,3-dimethylbutadiene reaction. The remainder is believed to be an isomeric adduct possibly contaminated with a 2:1 adduct.

Cyclopentadiene or hexachlorocyclopentadiene reacted with **1a** to give a black tar after extensive heating. 2,5-Diphenylisobenzofuran and **1a** in ethylene chloride formed a black complex, but no reaction could be detected.

7. **With Electron-Rich Olefins.**—A solution of 10.8 g (0.040 mol) of quinonemethide **3a** and 5.36 g (0.040 mol) of *p*-methoxystyrene (containing 0.1% hydroquinone) was heated at 100° under nitrogen overnight. The product was a viscous brown oil, and the orange color of the quinonemethide was no longer apparent. After cooling, the product was a glass which partly crystallized on standing. The oily material was extracted by trituration; the residue (10.5 g) was recrystallized once from methanol with hot filtration, mp 116–126°, and three times from cyclohexane. A total of 6.4 g of white crystalline solid, mp 128.5–129.1°, was obtained. On the basis of analysis (see Table I) and infrared (OH), ultraviolet, and nmr spectral properties, the indanol structure was assigned.

A solution of quinonemethide in excess vinyl ether was allowed to stand at room temperature. After *ca.* 2 weeks, the solution became a colorless syrup and could not be induced to crystallize. Nmr analysis indicated the product was complex. Further characterization was not carried out.

Heating at 100–125° overnight, 2.70 g (0.010 mol) of quinonemethide **1a** with 1.16 g (0.010 mol) of *t*-butyl sulfide gave a dark, viscous oil, from which *ca.* 1 g of light-colored crystals, mp 91–94°, was obtained by pentane trituration. This product was characterized as the indanol of structure **6** with a *t*-butylthio

group in place of *p*-methoxyphenyl, but possibly in the other position because of much smaller F^{19} chemical shift difference between the trifluoromethyl groups. The steric bulk of the *t*-butyl group could change the orientation in addition.

8. With Aluminum Chloride.—A solution of 2.70 g (0.010 mol) of quinonemethide **1a** in methylene chloride was added to 1.33 g (0.010 mol) of anhydrous aluminum chloride in 15 ml of methylene chloride. After about one-third of the quinonemethide solution was added, a dark green color developed, and a mild exothermic reaction was noted. After addition was complete, the solution was stirred for about 1 hr and filtered under nitrogen to separate a white precipitate, 0.88 g. The greenish black mother liquor was evaporated under nitrogen leaving 2.84 g of a tan solid streaked with green. The ir and nmr spectra of these two solids were almost identical and showed the same proton nmr spectra as the starting quinonemethide but with a chemical shift to lower field. In the ir spectra, the carbonyl absorption at 1640 cm^{-1} was weak and broad. The first precipitate above was hydrolyzed in water and extracted into methylene chloride; it was shown by melting point, mixture melting point, and infrared and nuclear magnetic resonance spectra to be the benzyl chloride **2a**.

Notes

Perhalo Ketones. XIV.[1] 7,7-Bis(trifluoromethyl)quinonemethide

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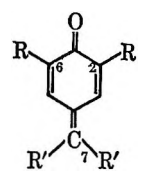
Although *p*-benzoquinonemethides (**1**) containing highly conjugated systems, such as **1i**, are stable,[2] those in which R′ is hydrogen or alkyl have required the presence of alkyl groups in the 2,6 positions to permit isolation in dilute solution. Thus, 2,6-di-*t*-butylquinonemethide with no C-7 substituents (**1a**) could be prepared only in dilute solution, and dimerized on

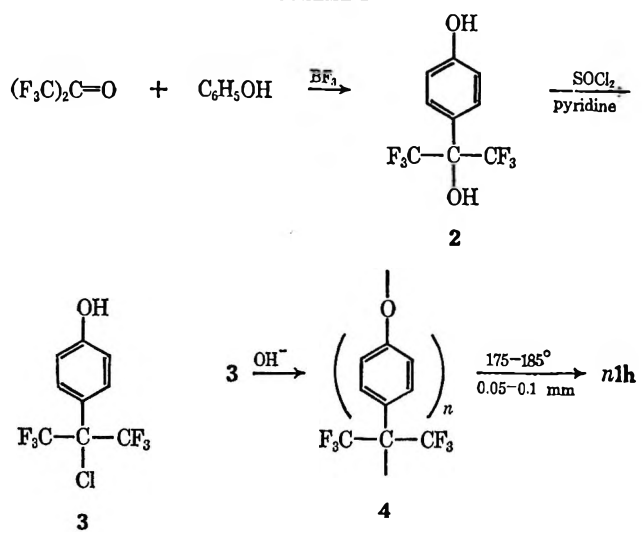


1a, R = *t*-butyl; R′ = H
b, R = *t*-butyl; R′ = alkyl
c, R = CH_3; R′ = CN
d, R = CH_3; R′ = CF_3
e, R = *t*-butyl; R′ = CF_3
f, R = CH_3; R′ = CF_2Cl
g, R = Br; R′ = CF_3
h, R = H; R′ = CF_3
i, R = H; R′ = C_6H_5

attempted isolation.[3] 2,6-Di-*t*-butyl-7,7-dialkylquinonemethides (**1b**)[4] and 2,6-dimethyl-7,7-dicyanoquinonemethide (**1c**)[5] have been isolated as stable compounds. Sheppard[6] has recently prepared fluoroalkylquinonemethides with R′ = $-CF_3$ or $-CF_2Cl$, and with R = CH_3 or *t*-butyl (**1d**, **e**, and **f**), and has found them to be stable at temperatures even considerably above room temperature. He concluded that the presence of alkyl substituents in the 2,6 positions was essential for stability. We wish to report the preparation and isolation of 7,7-bis(trifluoromethyl)quinonemethide (**1h**), a compound without 2,6 substitution but stable at room temperature in pure form for a short time, and for at least several weeks in solution.

Compound **1h** was prepared from phenol and hexafluoroacetone *via* **2**[7] and **3**[8] (Scheme I).

SCHEME I



The structure of 7,7-bis(trifluoromethyl)quinonemethide (**1h**) is quite clear from its infrared and nmr spectra. In carbon tetrachloride solution its infrared spectrum exhibited bands at 6.1 and 6.2 μ ascribed to the conjugated carbonyl group,[3,6] and strong C–F absorption in the 8–9-μ region.

Its nmr spectrum in carbon tetrachloride solution consisted of AA′BB′ spin pattern (of an AA′BB′X_3X_3' system) with A calculated δ 7.68 and B at δ 6.59 (J_{AB} = 10.5 Hz). The A portion shows fine structure due to coupling with the CF_3 groups: ($J_{AX} \cong J_{AX'} \cong J_{A'X} \cong$

(1) Perhalo Ketones. XIII: R. E. A. Dear, E. E. Gilbert, *J. Org. Chem.* **33**, 819 (1968).

(2) A. Bistrzycki and C. Herbst, *Ber.*, **36**, 2335 (1903).

(3) J. D. McClure, *J. Org. Chem.*, **27**, 2365 (1962); L. J. Filar and S. Winstein, *Tetrahedron Lett.*, **25**, 9 (1960).

(4) A. Hubele, H. Suhr, and U. Heilmann, *Ber.*, **95**, 639 (1962); C. D. Cook and B. E. Norcross, *J. Amer. Chem. Soc.*, **78**, 3797 (1956).

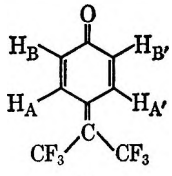
(5) H. H. Takimoto, G. C. Denault, and L. O. Krbechek, *J. Org. Chem.*, **29**, 1899 (1964).

(6) W. A. Sheppard paper presented at the Fourth International Fluorine Symposium, Estes Park, Colo., July 24–28, 1967.

(7) B. S. Farah, E. E. Gilbert, M. Litt, J. A. Otto, and J. P. Sibilia, *J. Org. Chem.*, **30**, 1003 (1965).

(8) I. L. Knunyants, C. Ching-Yun, N. P. Gambaryan, and E. M. Rokhlin, *Zh. Vses. Khim. Obshch.*, **5**, 114 (1960); *Chem. Abstr.*, **54**, 20962 (1960).

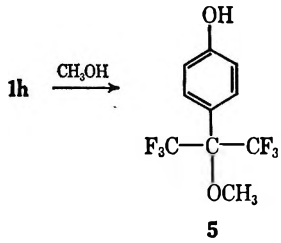
$J_{A'X'} \leq 2$ Hz) (width at approximately one-half peak height); $J_{AA'}$, $J_{BB'}$, $J_{AB'} \cong J_{A'B}$ were not calculated; $J_{BX} \cong J_{BX'} \cong J_{B'X} \cong J_{B'X'} \cong 0$. The ^{19}F nmr spec-



1h

trum of **1h** showed a partially resolved complex multiplet at 57.6 relative to $CFCl_3$ with spacings of 0.70 Hz. This reaction sequence, except for the last step, is the same as that employed by Sheppard for preparing compounds **1d**, **e**, and **f**, since those quinonemethides are stable in the presence of base. He observed, however, that only polymer resulted during an attempted similar preparation of **1g**; this was also noted by us in the attempted basic conversion of **3** into **1h**. We then found that polymer **4** could be thermally depolymerized to **1h** at low pressure, the product being trapped at liquid nitrogen temperature. This technique may be applicable to the preparation of other base-sensitive quinonemethides.

Compound **1h** is an orange-yellow solid at liquid nitrogen temperature, melting at room temperature to an orange liquid with a spicy odor, properties also characteristic of compounds **1d**, **e**, and **f**. At room temperature, pure **1h** soon polymerizes. As expected,[6] **1h** reacts with methanol at room temperature.

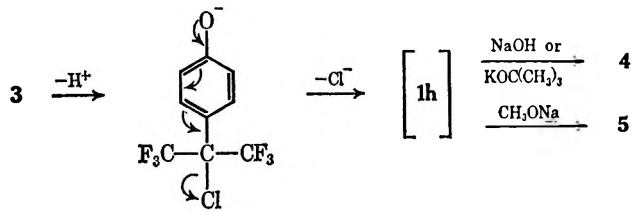


5

The mass spectrum obtained from the thermal decomposition of the polymer **4** at 200° showed a parent ion of *m/e* 242 $(\mathbf{1h})^+$ and a characteristic fragment ion of *m/e* 214, presumably 6,6-bis(trifluoromethyl)fulvene; corresponding to the loss of CO. Similar cracking patterns are reported for cyclic ketones such as anthraquinone and fluorenone.[9]

The conversion of **3** into **4** is thought to take the course given in Scheme II.

SCHEME II



The fate of **1h** is determined by the base used. Potassium *t*-butoxide forms polymer **4**, as does also aqueous sodium hydroxide. Sodium methoxide, on the other hand, yields **5** without any formation of polymer. The unusually high reactivity of the chlorine atom in **3** was shown by the fact that compound $C_6H_5C(CF_3)_2Cl$ (**6**) failed to form an analogous derivative, even under much more drastic conditions.

(9) J. H. Beynon, "Mass Spectrometry and Its Applications to Organic Chemistry," Elsevier Publishing Co., New York, N. Y., 1960, pp 259, 271.

Experimental Section

Melting and boiling points are uncorrected. The proton nmr spectra were obtained on a Varian A-60 spectrometer with tetramethylsilane as an internal reference; ^{19}F spectrum was run on a Hitachi Perkin-Elmer Model R-20 spectrometer at 56.4 Mc; the infrared spectrum was run on a Perkin-Elmer Model 521 spectrophotometer. The microanalyses were carried out in this laboratory's Analytical Department by Mr. G. Mohler and Schwarzkopf Microanalytical Laboratory.

Hexafluoroacetone and phenol–boron trifluoride complex were obtained from Industrial Chemicals Division, Allied Chemical Corp., Morristown, N. J.

1-(2-Hydroxyhexafluoro-2-propyl)-4-hydroxybenzene (**2**).—Phenol–boron trifluoride complex (128 g, comprising 1.0 mol of phenol and 0.5 mol of boron trifluoride) and toluene (100 ml) were mixed and hexafluoroacetone (bp −28°) was slowly admitted with efficient stirring as fast as reaction occurred; the presence of excess ketone was indicated by refluxing. The ketone (150 g, 0.90 mol) was introduced over 8 hr at 30–35°. The mixture was stirred at room temperature overnight, and then diluted with 600 ml of hexane. The crude dark brown residue was filtered, washed with *n*-hexane, and recrystallized from toluene (decolorizing carbon) to give 103 g (43%) of product, mp 120–123.5°. A second recrystallization from *n*-hexane gave **2**, mp 122–123.5° (lit. mp 127–130°,[7] 122.5–123.5°[8]).

1-(2-Chlorohexafluoro-2-propyl)-4-hydroxybenzene (**3**).—To a mixture of **2** (52 g, 0.20 mol) and pyridine (4 g) at room temperature was added excess thionyl chloride (80 g, 0.66 mol) dropwise (10 min). The mixture was then heated slowly to 105° over a period of 1 hr and maintained at 105 ± 1.0° for 45 min. Excess thionyl chloride was removed under reduced pressure and the resulting residue diluted with 1 l. of ice water to give 55.5 g (99%) of crude product. Two recrystallizations from carbon tetrachloride gave pure **3** as white needles, mp 107–111° (lit.[8] mp 112–112.5°).

Anal. Calcd for $C_9H_5F_6OCl$: C, 38.78; N, 1.79; Cl, 12.75. Found: C, 38.54; N, 1.92; Cl, 12.9.

Polymeric 7,7-Bis(trifluoromethyl)quinonemethide (**4**).—To a mixture of **3** (5.6 g, 0.02 mol) and potassium *t*-butoxide (2.5 g, 0.022 mol) at room temperature was added 40 ml of *t*-butyl alcohol. The resulting reaction mixture was refluxed 1 hr, cooled to room temperature, and filtered through a sintered glass filter. The crude product was washed with hot water overnight (Soxhlet apparatus) to remove potassium chloride, and air dried to give 4.8 g (99%) of crude **4** as an amorphous white powder. In a capillary tube it softened and melted between 175 and 185°.

Anal. Calcd for $C_9H_4F_6O$: C, 44.6; H, 1.60. Found: C, 44.4; H, 1.74.

7,7-Bis(trifluoromethyl)quinonemethide (**1h**).—Finely powdered polymer **4** (0.5 g, 0.002 mol) was outgassed by heating in a Wood's metal bath up to 175° at 0.05 mm. The temperature was then slowly raised to 190–195° and held there for 1 hr to effect depolymerization to **1h**, which was trapped as an orange-yellow solid at liquid nitrogen temperature. With maintenance of vacuum, the trap containing the crude **1h** was warmed to room temperature, whereupon **1h** is distilled into a second cold trap. Conversions to **1h** in several runs were 60–70%, with 0.15–0.20 g of solid distillation residue. For spectral study, it was briefly exposed to air as it was dissolved in carbon tetrachloride.

1-(2-Methoxyhexafluoro-2-propyl)-4-hydroxybenzene (**5**).—A mixture of **3** (1.4 g, 0.005 mol), sodium methoxide (1.1 g, 0.020 mol), and absolute methanol (20 ml) was heated at reflux with stirring for 2 hr (Drierite trap). After cooling to room temperature, 5 ml water was added. The clear solution was acidified with concentrated hydrochloric acid, diluted with 200 ml of ice water, stirred for 30 min and filtered to give 1.1 g (80%) of crude **5**. One recrystallization from petroleum ether, bp 30–60°, gave pure product, mp 79–83°.

Anal. Calcd for $C_{10}H_8F_6O_2$: C, 43.8; H, 2.92. Found: C, 43.74; H, 3.00.

The nmr spectrum (deuteriochloroform) displayed the characteristic signal for the methoxyl protons at δ 3.47 (three protons, J = 1 Hz, septet, tentative), a broad singlet at δ 5.28

(one proton), and the aromatic multiplet at δ 6.8–7.2 (four protons). Compound **5** was also prepared by dissolving **1h** in methanol and evaporating to dryness.

(2-Chlorohexafluoro-2-propyl)benzene (6).—A mixture of (2-hydroxyhexafluoro-2-propyl)benzene[10] (100 g, 0.41 mol), thionyl chloride (100 g, 0.83 mol), and pyridine (5 ml) was refluxed with stirring for 48 hr. After cooling to room temperature, 500 ml of ice water and 500 ml of 1 *N* potassium hydroxide were added. The lower organic layer was separated and the aqueous layer was extracted with 100 ml of methylene chloride. The organic layers were combined, dried over anhydrous magnesium sulfate, and distilled at atmospheric pressure to give 69.5 g (65%) of **6**, bp 159°.

Anal. Calcd for $C_9H_5F_6Cl$: Cl, 13.5. Found: Cl, 13.7.

Attempted Reaction of 6 with Sodium Methoxide.—A mixture of **6** (16 g, 0.061 mol), sodium methoxide (6.5 g, 0.12 mol), and 120 ml of absolute methanol was heated at reflux for 24 hr with stirring, cooled to room temperature, acidified with concentrated hydrochloric acid, and diluted with 1 l. of water. The lower organic layer was separated. The aqueous layer was extracted with 50 ml of methylene chloride and the two organic layers were combined. After drying over anhydrous magnesium sulfate, the solution was distilled at atmospheric pressure to give 9.6 g of unchanged **6**, bp 158–160°, with no evidence for the formation of the desired methoxyl compound.

Registy No.—**1h**, 16878-48-1; **5**, 16878-49-2; **6**, 16878-50-5.

Acknowledgment.—The author wishes to express his gratitude to Dr. E. E. Gilbert and Professors J. Meinwald and M. Litt for helpful discussions and to Dr. B. B. Stewart for his help in interpreting the nmr data.

(10) B. S. Farah, E. E. Gilbert, and J. P. Sibilia, *J. Org. Chem.*, **30**, 998 (1965).

Derivatives of Indeno[2,1-*b*]-1,4-benzothiazine

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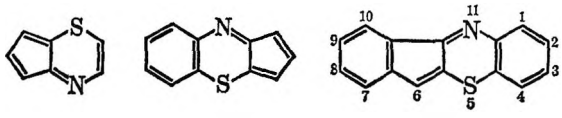
Inasmuch as the applicability of the Hückel $(4n + 2)$ π-electron rule[1] to fused heterocyclic systems is still unpredictable, synthesis of systems such as **1**, **2**, and **3**,

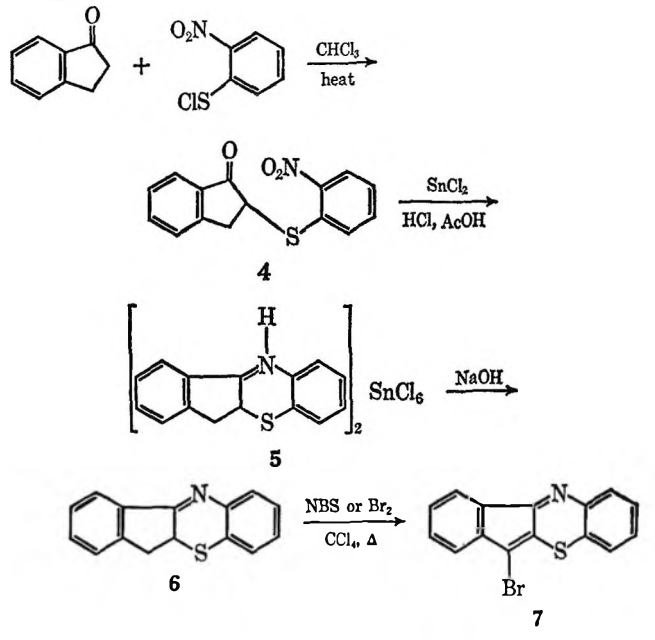


1 **2** **3**

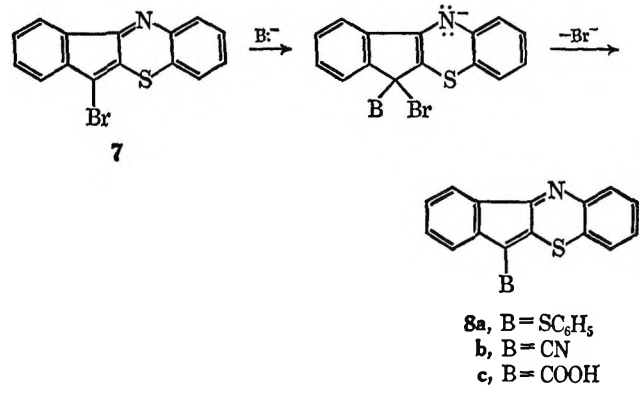
which obey the rule and may show nonclassical aromaticity, is of interest. Neither **1** nor **2** has been prepared to date. Recently, indeno[2,1-*b*]-1,4-benzothiazine (**3**) has been prepared[2] by the condensation of 1,2-indandione with *o*-mercaptoaniline, followed by dehydration. The present paper describes the preparation and properties of some derivatives of **3**.

Initially, the goal of this work was the preparation of the parent compound **3** by a different synthetic route. The approach, which used in part the Zincke procedure,[3] is outlined in Scheme I. Condensation of *o*-nitrophenylsulfenyl chloride with 1-indanone gave 2-(*o*-nitrophenylthio)indanone (**4**) in 66.3% yield. Treatment of **4** with stannous chloride in concentrated hydrochloric acid and glacial acetic acid resulted in reduction and condensation to form bis(5a,6-dihydroindeno-[2,1-*b*]-1,4-benzothiazinium) hexachlorostannate(IV) (**5**), in 80.1% yield. The tin complex salt **5**, when shaken with a 10% sodium hydroxide solution, gave a 94.2% yield of 5a,6-dihydroindeno[2,1-*b*]-1,4-benzothiazine (**6**). Dehydrogenation of **6** was effected by treatment with either bromine or N-bromosuccinimide in refluxing carbon tetrachloride. However, instead of obtaining the parent compound **3**, an 84.8% yield of the monobromo derivative, 6-bromoindeno[2,1-*b*]-1,4-benzothiazine (**7**), was obtained as a deep purple solid. This result also occurred using limited amounts of bromine or N-bromosuccinimide, **7** being obtained along with unreacted **6**.

SCHEME I



The location of the bromine atom in **7** was established by the ease with which it underwent nucleophilic aromatic substitution reactions and by the products obtained from these reactions. The 6 position should be activated toward nucleophilic aromatic substitution and a bromine atom located there should be easily replaced by typical nucleophiles. This was found to be the case.



8a, B = SC_6H_5
b, B = CN
c, B = COOH

(1) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., New York, N. Y., 1959, pp 412–419.
(2) D. Leaver, J. Smolicz, and W. H. Stafford, *J. Chem. Soc.*, 740 (1962).
(3) T. Zincke and H. Rose, *Ann.*, **406**, 103 (1914); T. Zincke and J. Baeumer, *ibid.*, **416**, 86 (1918).

TABLE I

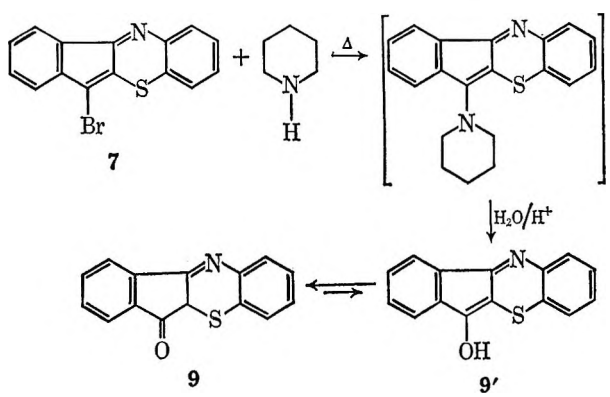
ULTRAVIOLET AND VISIBLE SPECTRA OF INDENO[2,1-*b*]-1,4-BENZOTHIAZINES[a]

Compd	(substituent)	Maxima, mμ (log ε)							
3[b]	H		250 (4.35)	257 (4.37)	292 (4.66)	357 (4.07)	374 (3.97)	519 (3.35)	
3′[b]	−H			276 (4.69)	299 (4.69)	365 (4.43)	381 (4.45)	514 (3.37)	572 (3.75)
6	2H	207 (4.38)			266 (4.34)	322 (3.92)		490 (2.00)	
9	=O	206 (4.42)	229 (4.45)		288 (3.00)				628 (3.00)
7	Br	214 (4.51)	250 (4.30)	257 (4.34)	297 (4.59)	357 (4.08)	373 (4.00)	515 (3.46)	
8a	SC_6H_5	205 (4.62)			301 (4.51)	363 (4.15)		534 (3.45)	
8b	CN	205 (4.30)	228 (4.34)	261 (4.11)	303 (4.34)		377 (3.97)	525 (3.36)	

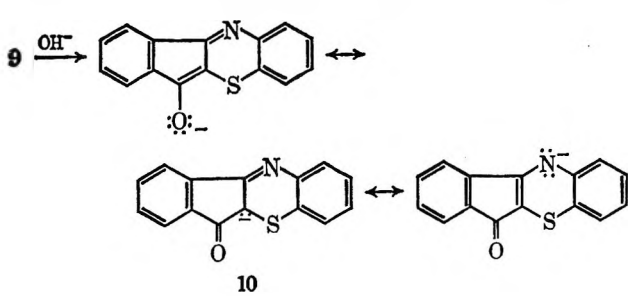
[a] Spectra of 6, 7, 8a, 8b, and 9 taken in 95% ethanol using a Beckman DB-G spectrophotometer. [b] Reference 2.

By refluxing **7** with sodium thiophenoxide in ethanol, a 73% yield of 6-phenylthioindeno[2,1-*b*]-1,4-benzothiazine (**8a**) was obtained. By refluxing **7** with cuprous cyanide in dimethylformamide,[4] a 96% yield of 6-cyanoindeno[2,1-*b*]-1,4-benzothiazine (**8b**) was obtained. The nitrile **8b** was converted, in low yield, into the carboxylic acid **8c** by acid hydrolysis. All of these compounds had the same deep purple color as **7** (and as **3**),[2] this color apparently being characteristic of this heterocyclic system.

When **7** was refluxed in a large excess of piperidine, the product isolated after the usual aqueous acid–base extraction techniques was not the expected 6-piperidino derivative, but was the hydrolysis product, 6-oxo-5a,6-dihydroindeno[2,1-*b*]-1,4-benzothiazine (**9**), a bluish green solid, obtained in 25% yield. The infrared spectrum of **9** showed no O–H or N–H absorption, but had a



strong carbonyl peak at 5.91 μ and a strong C=N peak at 6.10 μ. Compound **9** was soluble in dilute acid, giving a light blue solution, and in dilute base, giving a deep blue solution, presumably owing to the formation of the highly conjugated anion (**10**). The fact that this com-



pound exists in the keto (**9**) rather than the enol (**9′**) form indicates that the 5a,6 double bond provides very little (less than 5.5 kcal/mol)[5] stabilization energy to the aromatic system of **3** and its derivatives. This is not unusual for a centrally located double bond in a polycyclic aromatic system, however.

The location of the bromine atom in **7** at the 6 position would be expected by analogy with similar aromatic systems. Probably the bromine is incorporated *via* electrophilic substitution on the unsubstituted **3**, which is very likely formed by dehydrogenation of **6** during the reaction with bromine. The 6 position of the indeno-[2,1-*b*]-1,4-benzothiazine (**3**) ring system corresponds to the favored position in azulene and its heterocyclic analogs for electrophilic substitution.[6]

Since the dehydrogenation of **6** with bromine or N-bromosuccinimide led to the bromo derivative **7** instead of the desired parent compound **3**, another dehydrogenation procedure was attempted, in hope of obtaining pure **3**. This consisted of treating the dihydro derivative **6** with an equimolar quantity of benzoyl peroxide in a chloroform solution under ultraviolet radiation.[7] The product obtained was a dark reddish purple solid of questionable purity (mp up to 342°). Further examination indicated that this product was similar to that obtained[2] by Leaver, Smolicz, and Stafford, which they have shown[2] to be a mixture of **3** and its dimer (**3′**). Likewise, dehydrogenation of **6** with chloranil in refluxing xylene or with palladium on charcoal in refluxing xylene or reduction of bromo derivative **7** by zinc in acetic acid or by sodium borohydride in ethanol all led to similar products that appeared to be mixtures of **3** and **3′**.

Ultraviolet and visible spectra of the derivatives of **3** are compared with the published[2] spectral data for **3** and **3′** in Table I.

In summary, the indeno[2,1-*b*]-1,4-benzothiazine ring system, an 18-π-electron system, has been synthesized and shown to have some degree of aromaticity. However, the aromaticity must not be large, since the hydroxy derivative prefers the keto (**9**) rather than the enol (**9′**) form.

Experimental Section[8]

2-(*o*-Nitrophenylthio)indanone (4).—A solution of 42.0 g (0.222 mol) of *o*-nitrophenylsulfenyl chloride[9] and 29.3 g (0.222 mol) of

(4) L. Friedmann and H. Shechter, *J. Org. Chem.*, **26**, 2522 (1961).

(5) G. E. K. Branch and M. Calvin, "The Theory of Organic Chemistry," Prentice-Hall, Inc., New York, N. Y., 1941, pp 286 and 287.

(6) W. Keller-Schierlein and E. Heilbronner, "Non-Benzenoid Aromatic Compounds," D. Ginsburg, Ed., Interscience Publishers, Inc., New York, N. Y., 1959, pp 310–134 and references cited therein.

(7) These conditions are similar to bromine and N-bromosuccinimide dehydrogenation conditions.

(8) All melting points are uncorrected. Microanalyses were by Miss H. Beck. Infrared spectra were taken in potassium bromide pellets and measured on a Baird spectrophotometer. We wish to thank Dr. G. P. Hinds of the Shell Oil Co., Deer Park, Texas, for determination of the mass spectra.

(9) M. H. Hubacher, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p 455.

1-indanone[10] in 400 ml of dry chloroform was refluxed for 1.5 hr. After removal of the solvent *in vacuo*, the solid product was recrystallized from chloroform–hexane to give 42.0 g (66.3%) of **4**, mp 130–131°, as a yellow solid: ir, 5.88 (C=O), 6.28 (phenyl), 6.65, and 7.52 μ (NO_2).

Anal. Calcd for $C_{15}H_{11}NO_3S$: C, 63.16; H, 3.89. Found: C, 63.32; H, 3.73.

5a,6-Dihydroindeno[2,1-*b*]-1,4-benzothiazine (6).—To a boiling solution of 56.4 g (0.198 mol) of **4** in 500 ml of glacial acetic acid was slowly added with stirring a hot solution of 140 g (0.521 mol) of stannous chloride dihydrate in 150 ml of concentrated hydrochloric acid. After the addition was completed (about 15 min), the solution was boiled an additional 30 min before cooling. The golden yellow solid which had crystallized was washed with 95% ethanol followed by ether, then dried to give 64.0 g (80.1%) of bis(5a,6-dihydroindeno[2,1-*b*]-1,4-benzothiazinium) hexachlorostannate (**5**), mp 170° dec. As **5** was only sparingly soluble in water and organic solvents, it was not further purified but used directly in the next step: ir, ν 6.12 μ (C=N).

A mixture of 30.4 g (0.0376 mol) of **5** in 500 ml of 10% sodium hydroxide solution was shaken intermittently for 1 hr. The yellow-tan solid which formed was washed with dilute sodium hydroxide until free of tin salts, then with water until free of base. After drying, 16.8 g (94.2%) of **6** was obtained as a light tan solid. Recrystallization of a small portion of this solid from chloroform gave pure **6**: mp 100–105° dec; ir, 3.30 and 3.52 (C–H), 6.12 μ (C=N).

Anal. Calcd for $C_{15}H_{11}NS$: C, 75.93; H, 4.67. Found: C, 75.56; H, 4.81.

6-Bromoindeno[2,1-*b*]-1,4-benzothiazine (7).—To a solution of 16.0 g (0.0675 mol) of **6** in 200 ml of carbon tetrachloride was added slowly with swirling a solution of 21.6 g (0.135 mol) of bromine in 50 ml of carbon tetrachloride. A brown precipitate formed initially, but after one-third of the bromine was added, the mixture turned dark green. Hydrogen bromide evolution did not begin until over half of the bromine was added. The mixture was warmed and allowed to stand overnight at room temperature. The dark green solid (hydrobromide of **7**) which had precipitated was dried and added to 500 ml of 10% sodium hydroxide. After intermittent shaking for 1 hr, a deep purple solid formed. This was washed with water and dried to give 18.0 g (84.8%) of **7**, mp 205–206°. Compound **7** was soluble in concentrated hydrochloric acid, giving a green solution: ir, 3.37 (C–H), 6.26, 6.58, 7.01, 8.01, 8.17, 10.60, 13.1 (broad), and 13.3 μ (broad). The analytical sample was purified by sublimation, mp 205–206°.

Anal. Calcd for $C_{15}H_8BrNS$: C, 57.34; H, 2.57; N, 4.46. Found: C, 57.12; H, 2.59; N, 4.18.

The hydrobromide of **7** had mp 155° dec.

Anal. Calcd for $C_{15}H_9Br_2NS$: C, 45.57; H, 2.28; N, 3.54. Found: C, 45.58; H, 2.33; N, 3.28.

Nucleophilic Substitution Reactions of 7. A. 6-Phenylthioindeno[2,1-*b*]-1,4-benzothiazine (8a).—A solution of sodium thiophenoxide was prepared by adding a solution of 0.36 g (3.3 mmol) of thiophenol in 5 ml of absolute ethanol to a solution of 0.18 g (3.3 mmol) of sodium methoxide in 10 ml of absolute ethanol. To this solution was added a solution of 1.0 g (3.2 mmol) of **7** in 10 ml of absolute ethanol, and the mixture was refluxed overnight under nitrogen. Water was added to the cooled mixture to precipitate a purple solid, which was recrystallized from ethanol–water to give 0.8 g (73%) of **8a**: mp 114–116°; ir, 3.38 (C–H), 6.26, 6.36, 6.68, 6.81, 6.88, 7.01, 7.68, 8.01, 8.17, 13.4 (very broad), and 14.58 μ; mass spectrum (low ionizing voltage), 343.

Anal. Calcd for $C_{21}H_{13}NS_2$: C, 73.46; H, 3.82; N, 4.08. Found: C, 73.21; H, 3.85; N, 4.19.

B. **6-Cyanoindeno[2,1-*b*]-1,4-benzothiazine (8b).**—A mixture of 1.0 g (3.2 mmol) of **7**, 0.35 g (3.9 mmol) of cuprous cyanide, and 10 ml of dimethylformamide was refluxed for 4 hr.[4] After cooling, the mixture was poured into a ferric chloride–hydrochloric acid solution and warmed for 30 min. The precipitated solid was washed successively with dilute hydrochloric acid, dilute sodium hydroxide, and water, then dried to give 0.8 g (96%) of **8b**, mp 215–220°, as a deep purple solid: ir, 3.43 (C–H), 4.63 (C≡N), 6.29, 6.68, 6.92, 7.06, 7.68, 7.93, 8.12, 8.99, 13.1 (broad), and 13.3 μ (broad); mass spectrum, 260. The analytical sample was purified by sublimation, mp 215–220°.

Anal. Calcd for $C_{16}H_8N_2S$: C, 73.84; H, 3.10; N, 10.77. Found: C, 74.18; H, 3.17; N, 10.93.

C. **6-Oxo-5a,6-dihydroindeno[2,1-*b*]-1,4-benzothiazine (9).**—A solution of 1.0 g (3.2 mmol) of **7** in 30 ml (303 mmol) of piperidine was refluxed under nitrogen for 5 days. The excess piperidine was removed *in vacuo* and the residue was taken up in ether. The precipitated piperidinium bromide was removed by filtration (recovered 0.4 g, 75% of theoretical). The ethereal filtrate was extracted with dilute hydrochloric acid to give a blue aqueous solution. The purple ether layer containing unreacted **7** was discarded. The aqueous acidic solution was extracted with ether until all unreacted **7** was removed. When the solution was made basic with dilute sodium hydroxide, a deep blue solution was obtained, from which no organic material could be extracted with ether. However, when the solution was carefully neutralized by adding dilute hydrochloric acid, a greenish blue substance precipitated, which was extracted with ether. The ether solution was washed with water and dried over anhydrous sodium sulfate, and the ether was removed *in vacuo*. Recrystallization of the residue from ether–ethanol gave 0.2 g (25%) of **9**, mp 210–212°, as a blue-green solid. Compound **9** was readily soluble in dilute acid, giving a blue solution, and in dilute base, giving a deep blue solution: ir, 3.24 and 3.43 (C–H), 5.91 (C=O), 6.10 (C=N), 6.27, 6.35, 6.61, 6.83, 7.02, 7.32, 7.78, 8.26, 11.7, and 13.5 μ.

Anal. Calcd for $C_{15}H_9NOS$: C, 71.71; H, 3.61; N, 5.57. Found: C, 71.97; H, 3.71; N, 5.67.

Indeno[2,1-*b*]-1,4-benzothiazinyl-6-carboxylic Acid (8c).—A mixture of 0.50 g (1.9 mmol) of **8b** in 15 ml of glacial acetic acid, 15 ml of concentrated hydrochloric acid, and 5 ml of water was refluxed for 4 hr. The solvents were removed *in vacuo* and the residue was taken up in ether. The ether solution was extracted with dilute hydroxide until the extracts were colorless. The ether solution containing unreacted **8b** was discarded. The combined basic extracts were acidified with dilute hydrochloric acid, and the product was extracted with ether. After the ether washing layer was washed with water and dried over anhydrous sodium sulfate, the ether was removed *in vacuo* to give less than 0.1 g of **8c**, mp >250°, as a dark purple solid. Compound **8c** was soluble in dilute base: ir, 3.3–3.7 (COOH), 6.07 (conjugated C=O), 6.64, 6.85, 7.04, 7.63, 7.98, 8.13, 13.12, and 13.44 μ.

Anal. Calcd for $C_{16}H_9NO_2S$: N, 5.02. Found: N, 4.82.

Registry No.—**4**, 16888-88-3; **6**, 16888-89-4; **7**, 16888-90-7; **7** HBr, 16888-91-8; **8a**, 16888-92-9; **8b**, 16888-93-0; **8c**, 16888-94-1; **9**, 16888-95-2.

Acknowledgment.—This investigation was supported by Public Health Research Grant No. CA-07351 from the National Cancer Institute.

(10) K. L. Rinehart, Jr., and D. H. Gustafson, *J. Org. Chem.*, **25**, 1836 (1960).

Tishchenko Reaction of Chloral by Aluminum Haloalcoholates

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The Tishchenko reaction of trichloroacetaldehyde (chloral) by the usual aluminum alcoholate catalyst is very sluggish.[1,2] In this communication, we report our finding that some aluminum haloalcoholates cause a rapid Tishchenko reaction of chloral to produce trichloroethyl trichloroacetate. The results are sum-

$$Cl_3CCHO \longrightarrow Cl_3CCOOCH_2CCl_3 \quad (1)$$

(1) I. Lin and A. R. Day, *J. Amer. Chem. Soc.*, **74**, 5133 (1952).
(2) R. Dworzak, *Monatsch.*, **47**, 11 (1927).

marized in Table I. The catalyst activity is expressed in two ways, the reaction time (minutes) required for 30% conversion and the conversion per cent after 1 hr of reaction.

The results clearly demonstrate that $Al(OCH_2CCl_3)_3$ (I), $Al(OCH_2CBr_3)_3$ (II), and $Al[OCH(CH_2Cl_2)_2]_3$ (III) as well as alkylaluminum compounds are distinguished by high catalyst activity among aluminum compound catalysts in the Tishchenko reaction of chloral. $Al(OCH_2CHCl_2)_3$ and $Al(OCH_2CH_2Cl)_3$ are also aluminum haloalcoholates, but they are less active. The high catalytic activity of II has also been observed in the Tishchenko reaction of tribromoacetaldehyde (bromal).

The characteristic activities of I, II, and III in the Tishchenko reactions may be due, at least partly, to *their marked tendencies of dissociation into monomeric form in the presence of donors* such as carbonyl compounds (eq 2).

$$[Al(OR)_3]_n + nD \longrightarrow n\left[\begin{matrix} RO \\ RO \end{matrix}\!\!>\!Al\!<\!\begin{matrix} OR \\ D \end{matrix}\right] \quad (D, \text{donor}) \quad (2)$$

In our previous studies[3,4] the dissociation tendencies (which are quoted in Table I) of several aluminum alcoholates in the presence of carbonyl compound in hydrocarbon solvent were examined by nmr spectroscopy. The association of the usual aluminum alcoholates of unsubstituted alcohols is strong and is not broken even by strong donors.[3]

TABLE I
TISHCHENKO REACTION OF ALDEHYDES IN THE PRESENCE OF VARIOUS ALUMINUM CATALYSTS

	Catalyst	T_{30}, min[a]	% conversion after 1 hr	Structure in the presence of xanthone[b]
Cl_3CCHO[c]				
	$Al(OCH_2CCl_3)_3$	6	99	
	$Al(OCH_2CBr_3)_3$	3	50[d]	Dissociated
	$Al[OCH(CH_2Cl)_2]_3$	6	92	
	$Al(C_2H_5)_3$	5	84	
	$Al(C_2H_5)_2Cl$	5	94	...
	$Al(OC_2H_5)_3$	310	2	*e*
	$Al[OCH(CH_3)_2]_3$	30,600	0.06	Associated[f]
	$Al[OC(CH_3)_3]_3$		0	Associated
	$Al(OCH_2CHCl_2)_3$	150	7	Associated
	$Al(OCH_2CH_2Cl)_3$	1,420	0.67	
Br_3CCHO[g]				
	$Al(OCH_2CBr_3)_3$	2	98	Dissociated
	$Al(OC_2H_5)_3$	14,200	0 (4.6)[h]	Associated
n-C_3H_7CHO[i]				
	$Al(OCH_2CBr_3)_3$	2	92	Dissociated
	$Al[OCH(CH_3)_2]_3$	64	26	Associated

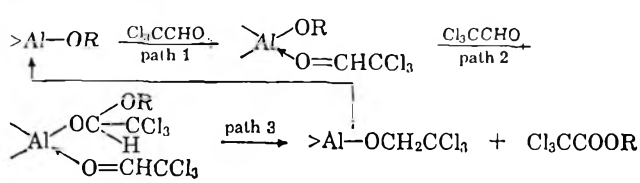
[a] T_{30} is the reaction time required for 30% conversion. [b] See ref 4. [c] Reaction conditions were Cl_3CCHO, 0.05 mol; aluminum compound, 0.0015 mol; benzene, 10 ml; naphthalene, 0.2 g; 30°. [d] The yield did not increase at a prolonged reaction time. [e] Insoluble (highly associated). [f] Acetone was used as a carbonyl compound: V. J. Shiner, Jr., and D. Whittaker, *J. Amer. Chem. Soc.*, **85**, 2337 (1963). [g] Reaction conditions were Br_3CCHO, 0.01 mol; aluminum compound, 0.0003 mol; benzene, 2 ml; dibenzyl, 0.2 g; 20°. [h] Reaction time, 46 hr. [i] Reaction conditions were n-C_3H_7CHO, 0.01 mol; aluminum compound, 0.0003 mol; benzene, 2 ml; diisopropylbenzene 0.2 ml; 20°.

$Al(OCH_2CHCl_2)_3$ and $Al(OCH_2CH_2Cl)_3$ are also strongly associated and, therefore, poor in catalytic activity. The superior catalytic activities of Al-$(C_2H_5)_3$ and $(C_2H_5)_2AlCl$ may be explained by the rapid reaction of the ethylaluminum group with chloral[5] to produce a trichloroethoxyaluminum species.

$$>AlC_2H_5 + Cl_3CCHO \longrightarrow >AlOCH_2CCl_3 + CH_2{=}CH_2 \quad (3)$$

According to the mechanistic scheme presented in our previous studies,[6,7] the Tishchenko reaction consists of three processes (Scheme I), the coordination of aldehyde with aluminum (path 1), the transfer of the alkoxyl group from aluminum to the aldehyde (path 2), and the transfer of hydride from the hemiacetal alcoholate to the aldehyde (path 3). After the first cycle of three processes, the so-called Tishchenko ester is continuously produced. The coordination of aldehyde

SCHEME I



with the aluminum alcoholate, which is essential in the Tishchenko reaction, has been demonstrated by infrared studies.[8] Thus, the dissociation tendency of aluminum alcoholates is directly related to the catalytic activity for the Tishchenko reaction.

The high catalytic activity of II is also observed in the Tishchenko reaction of unsubstituted aldehydes, *e.g.*, *n*-butyraldehyde (Table I). However, the effect of halogen in the alkoxyl group upon the catalyst activity is less conclusive. It may be explained by the difference in donating power between chloral and unsubstituted aldehyde. Chloral is a much weaker donor because of the electron-withdrawing nature of three chlorine atoms. *n*-Butyraldehyde is a stronger donor, which can coordinate even with aluminum alkoxide having no halogen in the alkoxyl group. Therefore, the coordination of chloral with aluminum catalyst is more facilitated by the ease of dissociation of catalyst. Further, as the reaction proceeds, the haloalkoxyl groups of the aluminum species are gradually replaced by the *n*-butoxyl group derived from *n*-butyraldehyde. The effect of haloalkoxyl groups of the initial catalyst is thus reduced.

Experimental Section

Catalysts.—Aluminum haloalcoholates were prepared and purified by the procedure described previously.[3,4]

Reaction of Aldehydes.—To a mixture of 1.5 mmol of aluminum catalyst and 10 ml of benzene containing naphthalene as the internal standard for glpc analysis (usually about 0.2 g), 50 mmol of anhydrous chloral was added with shaking while keeping the reaction mixture at 30°. At appropriate intervals, a small amount of reaction mixture was removed and analyzed by glpc using a combination of silicon DC 550 and PEG 20,000 columns.

(3) T. Saegusa and T. Ueshima, *Inorg. Chem.*, **6**, 1679 (1967).
(4) T. Ueshima and T. Saegusa, *Bull. Chem. Soc. Jap.*, in press.
(5) H. Meerwein, G. Hinz, and H. Majart, *J. Prakt. Chem.*, **147**, 236 (1937).
(6) J. Furukawa, T. Saegusa, and H. Fujii, *Makromol. Chem.*, **44/46**, 398 (1961).
(7) T. Saegusa, K. Hirota, E. Hirasawa, and H. Fujii, *Bull. Chem. Soc. Jap.*, **40**, 967 (1967).
(8) H. Fujii, T. Saegusa, and J. Furukawa, *Kogyo Kagaku Zasshi*, **65**, 695 (1962).

A similar procedure was used in the Tishchenko reactions of bromal and *n*-butyraldehyde.

Registry No.—Chloral, 75-87-6; bromal, 115-17-3; *n*-butylaldehyde, 123-72-8.

Aluminum Chloride Induced Cleavage and Alkylation of Ferrocene in Dichloromethane[1]

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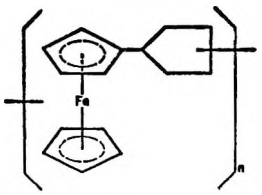
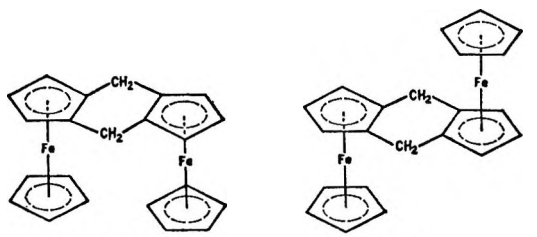
Nesmeyanov and coworkers[2] were the first to study the action of anhydrous aluminum chloride on ferrocene in boiling dichloromethane. The authors, using Lewis acid and metallocene in approximately equimolar quantities, obtained polynuclear alkylation products whose structures were assumed to comprise ferrocenylene units interlinked by a multiplicity of methylene bridges, these bridges being generated by action of the solvent as the alkylating species. However, no structural proof for any of the reaction products was established at that time. Later investigations[3] cast some doubt on these reports as one of the "alkylated" products from a related system involving 1,2-dichloroethane solvent[4] was found to arise in benzene solution as well and was identified[3b,c] as a diferrocenyldicyclopentyl. The proposed mechanism of formation involved Lewis acid induced cleavage of the metal–ring bond in the metallocene and intermediacy of cyclopentenyl and ferrocenyl cyclopentyl cations. Consistent with this concept of metal–ring bond fission, a reinvestigation[3c] of Nesmeyanov's earlier work[2] on the ferrocene–aluminum chloride–dichloromethane system revealed the presence of cyclopentylene groups in the polymeric products of this reaction, analytical results suggesting structure I.



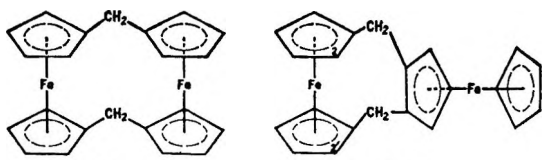
I

In a related investigation, Valot,[5] using a considerable Lewis acid excess, obtained polymers with an appreciably larger content of ferrocene cleavage products; the average repeat unit corresponded in composition to a ferrocenylenecyclopentylene skeleton plus three additional cyclopentenyl groups and one hydroxycyclopentyl moiety. No evidence of concurrent alkylation by the solvent as originally proposed[2] was found in these two later studies.[3c,5] In hopes of achieving the synthesis of [1.1]ferrocenophanes II,[6] of interest as prototype structures of double-bridged segments postulated in earlier polymer studies,[7] we have independently investigated the reaction of ferrocene with aluminum chloride in dichloromethane, using somewhat milder experimental conditions (12–24 hr, 0–25°) than previously employed. The results of this study have shown that, while the sequence of reactions based on metal–ring bond fission predominates, the alkylation of ferrocene by dichloromethane is, indeed, a competitive process. Consequently, the arising polymeric products possess structures appreciably more complex than originally[3b,c,5] assumed.

Typical experiments, employing equimolar quantities of ferrocene and aluminum chloride, resulted in the recovery of 50–60% ferrocene. Additionally, the following ferrocene derivatives were isolated: a dinuclear [1.1]ferrocenophane likely to possess



IIa IIb



IIc IId

structure IId (in addition to other unidentified isomers II);[8] 1,1′-(1,3-cyclopentylene)ferrocene (III);[9] 1,1′-(1-methyl-1,3-cyclopentylene)ferrocene (IV); diferrocenylmethane (V);[10] a 1,3-diferrocenylcyclopentane VI assumed previously[11] to possess the *cis* configuration; and a mixture, not further separated, essentially consisting of diferrocenylmethylcyclopentane isomers VII. In addition to these mono- and dinuclear com-

(1) Metallocene Polymers. XXIII. Part XXII: E. W. Neuse, *J. Macromol. Sci.*, in press. The denotation of the open bond on the left-hand side in structures I and VIII is the same as in previous parts of this series and implies attachment to the preceding recurring unit *via* any one position 2, 3, or 1′.

(2) A. N. Nesmeyanov, V. V. Korshak, V. V. Voevodskii, N. S. Kochetkova, S. L. Sosin, R. B. Materikova, T. N. Bolotnikova, V. M. Chibrikin, and N. M. Bazhin, *Dokl. Akad. Nauk SSSR*, **137**, 1370 (1961).

(3) (a) S. J. Goldberg, *J. Amer. Chem. Soc.*, **84**, 3022 (1962); (b) A. N. Nesmeyanov, N. S. Kochetkova, P. V. Petrovsky, and E. I. Fedin, *Dokl. Akad. Nauk SSSR*, **152**, 875 (1963); (c) S. G. Cottis and H. Rosenberg, *J. Polym. Sci., Part B-2*, 295 (1964); H. Rosenberg and S. G. Cottis, U. S. Patent 3,350,369 (1967).

(4) (a) A. N. Nesmeyanov and N. S. Kochetkova, *Dokl. Akad. Nauk SSSR*, **126**, 307 (1959); (b) A. N. Nesmeyanov, N. S. Kochetkova, and R. B. Materikova, *ibid.*, **136**, 1096 (1960); **147**, 113 (1962).

(5) H. Valot, *Double Liaison*, **130**, 775 (1966).

(6) The nomenclature and chemistry of ferrocenophanes has been reviewed most knowledgeably by W. E. Watts, *Organometal. Chem. Rev.*, **2**, 231 (1967).

(7) (a) E. W. Neuse and D. S. Trifan, *J. Amer. Chem. Soc.*, **85**, 1952 (1963); (b) E. W. Neuse and E. Quo, *J. Polym. Sci., Part A-3*, 1499 (1965).

(8) The all-heteroannular IIc was recently synthesized by W. E. Watts, *J. Organometal. Chem.*, **10**, 191 (1967). Also known is the 1,12-dimethyl derivative: W. E. Watts, *J. Amer. Chem. Soc.*, **88**, 855 (1966). We are most grateful to Dr. Watts for submitting copies of the ir, pmr, and mass spectra of both compounds for comparative purposes.

(9) (a) V. Weinmayr, *J. Amer. Chem. Soc.*, **77**, 3009 (1955); (b) S. G. Cottis and H. Rosenberg, *Chem. Ind.* (London), 860 (1963).

(10) (a) K. Schlögl and A. Mohar, *Monatsh. Chem.*, **92**, 219 (1961); (b) P. L. Pauson and W. E. Watts, *J. Chem. Soc.*, 3880 (1962); (c) E. W. Neuse and K. Koda, *Bull. Chem. Soc. Jap.*, **39**, 1502 (1966); (d) E. W. Neuse and E. Quo, *ibid.*, **39**, 1508 (1966).

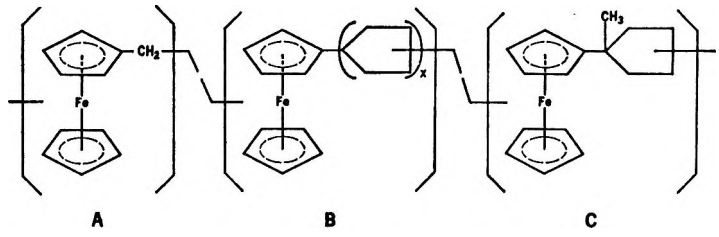
(11) E. W. Neuse, R. K. Crossland, and K. Koda, *J. Org. Chem.*, **31**, 2409 (1966).

TABLE I

Compound	Mp, °C	Mol wt[a]	Calcd, % C	Calcd, % H	Calcd, % Fe	Calcd, % CH_3	Found,[b] % C	Found,[b] % H	Found,[b] % Fe	Found,[b] % CH_3
IId	265–268	402	66.71	5.09	28.20		66.92	5.19	28.01	
IV	109–110	284	72.20	6.82	20.98	5.6	72.45	6.85	21.24	4.3
VII[c]	Liquid	465	69.06	6.24	24.70	3.3	69.29	6.32	24.25	2.7
VIIIa[d]	60–65	680	70.42	6.19	23.39	2.1	70.57	6.31	22.97	2.4
VIIIb[e]	90–115	1050	71.96	6.68	21.36		71.68	6.80	21.55	
VIIIc	90–110	2400	73.25	7.09	19.65		72.99	6.89	19.30	

[a] Average of two runs, by vapor pressure osmometry in CH_2Br_2. Calcd for II, 396; for IV, 266; for VII, 452. [b] Combustion analyses by G. I. Robertson, Florham Park, N. J. C-Methyl determinations by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. [c] Unseparated isomer mixture. [d] Essentially the same composition found for fraction VIIIa, M_n 810, mp 75–90°. [e] Essentially the same composition found for fraction VIIIb, M_n 1720, mp 90–120°.

pounds,[12] the reactions furnished several polymeric fractions with number-average molecular weight (M_n) 600–2400. The lower molecular fractions, with $M_n < 900$, essentially corresponded in elemental composition to the idealized structure VIIIa consisting of ferrocenylenecyclopentylene, ferrocenylenemethylene, and ferrocenylene(methyl)cyclopentylene segments randomly distributed in roughly equal proportions. Higher molecular fractions were found to contain additional cyclopentylene groups; in a simplified form, their structures may be depicted by VIIIb and c.



A B C

VIIIa, $x = 1$
b, $x = 2$
c, $x = 3$

The structural assignments of the new compounds IId, IV, VIII, the isomer mixture VII rest on microanalytical results (Table I) and spectroscopic data.

Compound IId gives an ir spectrum (KBr disks) closely resembling that[10] of V except that enhanced methylene stretch and deformation bands are shown. Furthermore, the 9,10-μ bands[13] and the peak at 7.1 μ all appear in decreased intensities relative to V (insufficient solubility prevented a quantitative determination). This suggests IId as the most probable structure, whereas IIa and IIb, possessing the same high (*i.e.*, 100%) homoannularity[7a] as V, are rendered highly unlikely as alternate candidates, and IIc,[8] identified by an entirely heteroannular bonding scheme, is altogether eliminated. The nmr spectrum (60 MHz, in $CDCl_3$; chemical shifts in τ values) is characterized by a complex multiplet, of fourteen ferrocene protons at 5.8–6.1 ppm, an apparent singlet of two ferrocene protons at 6.41 ppm, and an AB-type quartet (J_{AB} = 15 Hz; verified at 100 MHz), due to two pairs of methylene protons, centered at 6.73 ppm. This pattern, while inconsistent with both IIa and IIb,[14] is readily accommodated by IId,[15] in which protons 2 and 2′ are well within the shielding cone of the horizontal ferrocene unit, thus producing the signal at 6.41 ppm.[16] The mass spectrum (70 eV) exhibits an intense parent ion peak at *m/e* 396 and its prominent doubly charged counterpart at *m/2e* 198, and also both the $[M + 1]^+$ peak and the corresponding doubly charged species are of comparatively high intensity. Fragment ions of high abundances, deriving from the homoannularly linked ferrocene unit as the most vulnerable portion of the molecule, include $[M - 65]^+$ (loss of cyclopentadienyl), $[M - 66]^+$ (loss of cyclopentadiene following hydrogen transfer from the alkyl bridges[17]), $[M - 122]^+$ (elimination of ^{56}Fe from the preceding ion), and $[M - 78]^+$. The last-named species is probably a rearrangement product following loss of C_6H_6 as contended[17] for a similarly fragmentation-resistant ferrocene; the high-intensity peak at *m/e* 78 most likely due to the stable benzene cation[17] would seem to support this transition. In accord with IId (and inconsistent with IIa and IIb), no prominent peaks at *m/e* 266 or 264 corresponding to ions $[M - 130]^+$ (loss of 2 cyclopentadienyl rings) or $[M - 132]^+$ (loss of two cyclopentadiene units) are apparent. Of interest is the facile elimination of H_2 leading to the prominent $[M - 2]^+$ ion (*m/e* 394) and the doubly charged species (*m/e* 197); the fragments $[M - 2 - 65]^+$ with *m/e* 329 and $[M - 2 - 121]^+$ with *m/e* 273 are cor-

(12) In reactions conducted at −15°, diferrocenylcarbinol [ref 10a and R. L. Schaaf, *J. Org. Chem.*, **27**, 107 (1962)] was additionally separated. We are indebted to Dr. Schaaf for furnishing a sample of this carbinol for comparison.

(13) M. Rosenblum, Ph.D. Thesis, Harvard University, 1953; ref 10d.

(14) The methylene protons in IIa and b, located in the mutual deshielding zone of two essentially coplanar cyclopentadienyl rings, should give signals at approximately the same downfield position as shown by IIc (6.45 ppm). In addition, a singlet would be expected for the equivalent methylene protons in IIb. Similar considerations of the relative positions of the ring protons and resultant deshielding effects (in IIa) and combined deshielding and shielding effects (in IIb) would predict all ring-proton signals to arise to the low-field side of ~6 ppm in IIa and of ~6.2 ppm in IIb.

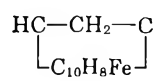
(15) Scale models show this "*trans*" form to be the less strained of the two possible configurations.

(16) (a) Furthermore, the remaining ring protons are neither especially shielded nor deshielded and, as part of a strain-free system, occupy positions essentially equally spaced from the respective Fe centers, giving a multiplet in the range typical of such methylene-bridged compounds as V or the isomeric diferrocylferrocenes.[16b] In contrast, the ferrocene proton signals shown by crude samples still containing other isomers[14] of II include broad envelopes, which extend downfield to 5.6 ppm and upfield to 6.2 ppm, and the methylene proton signals show satellites at 6.4–6.5 ppm. (b) E. W. Neuse, E. Quo, and W. G. Howells, *J. Org. Chem.*, **30**, 4071 (1965).

(17) H. Egger, *Monatsh. Chem.*, **97**, 602 (1966).

respondingly abundant. A species with *m/e* 394 and *m/2e* 197, aside from appearing in the spectrum IIc, was also found[8] to arise from 1,12-dimethyl[1.1]-ferrocenophane as one of the principal fragmentation products and precursor of *m/e* 329, which attests to the stability and importance of the methylidene-bridged ions (*m/e* 394) in the fragmentation pattern of [1.1]ferrocenophanes.

Compound IV gives an ir spectrum similar to that of III, showing the typical splitting of the 12.2-μ ferrocene CH out-of-plane deformation band into two band groups near 11.8 μ (multiplet) and 12.5 μ (sharp singlet) observed previously[11] with related hetero-bridged mononuclear ferrocenes;[18] in addition, a methyl band appears at 7.32 μ. The pmr spectrum shows ferrocenyl, methylidene, methylene, and methyl proton resonances in the calculated area ratio; the methyl signal emerges as a sharp singlet at 8.59 ppm, that is, in the region and multiplicity expected for a methyl group attached to tertiary carbon in α position to the cyclopentadienyl ring. The compactness of the bridged molecule, while causing highly intense *m/e* (266) and *m/2e* (133) molecular ion peaks, prevents high abundances of such fragments as $[M - 65]^+$ or $[M - 66]^+$, which appear to arise amply whenever cyclopentadienyl rings are available for ready primary cleavage at the iron–ring bond[17,19] or when, as in the case of $[M - 66]^+$, hydrocarbon side chains can provide a hydrogen atom for transfer to the ring.[17] Instead β cleavage is favored, as manifested by the prominent peaks at mass numbers corresponding to $[M - 14]^+$, $[M - 15]^+$, and $[M - 28]^+$. The most abundant ion in the *m/e* 100–252 range is $[C_5H_5Fe]^+$, *m/e* 121. The prominence of this peak, also apparent in III but unexpected in view of other reports[20] associating the $[C_5H_5Fe]^+$ ion with the presence of unsubstituted rings, obviously derives from the tendency of the odd-electron radical ion $[C_5H_4Fe]^+$ to pick up a side-chain hydrogen atom, thus converting into the more stable even-electron $[C_5H_5Fe]^+$ species. Consistent with the alicyclic position of the methyl group, the *m/e* 223 to *m/e* 224 abundance ratio is con-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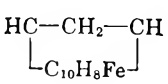
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siderably higher (1.27) than found in the spectrum of III (0.75). Furthermore, the spectrum of IV fails to show prominent peaks due to $[CH_3–C_5H_3Fe]^+$ (*m/e* 134) or $[CH_3–C_5H_4Fe]^+$ (*m/e* 135) in higher relative intensities than shown by III. A nuclear position of CH_3 would predict abundances at least as high as that of $[C_5H_5Fe]^+$, notably for *m/e* 135 whose proven stability[21] would seem to rule out rapid depletion by further fragmentation or rearrangement.

The isomer mixture VII gives an ir spectrum showing a methyl peak at 7.31 μ in addition to the typical features of diferrocenylcyclopentanes.[11] The pmr spectrum, closely related to that of VI and isomers,[11] exhibits ferrocene (5.8–6.1 ppm) and alicyclic methylidene (7.0–7.4 ppm) and methylene (7.6–8.5 ppm) proton signals; furthermore, a methyl proton singlet appears at 8.64 ppm, indicating attachment to alicyclic carbon.[22] Relative intensities are substantially in the calculated ratio. Additional weak absorption at 6.7–6.8 ppm suggests a minute percentage of methylene-bridged ingredients.

The polynuclear compounds VIII are characterized by ir spectra that can essentially be considered as composites of the spectra of I[3b,c,11] and the polymers $-[-C_{10}H_8Fe–CH_2-]_n$[7] of earlier studies. In addition, weak methyl absorption appears at 7.33 μ. The pmr spectra exhibit ferrocene and alicyclic (methylidene and methylene) proton multiplets in the same ranges (5.8–6.1 and 6.9–8.5 ppm) as shown by I and, additionally, display α-methylene and side-chain methyl proton signals near 6.7 and 8.6 ppm, respectively, all signal intensities being in the required ratio.

The occurrence of compounds II–VIII suggests a mechanism involving a multiplicity of cleavage and alkylation steps. Possible routes are depicted in Scheme I. The alkylation of ferrocene by dichloromethane to give V and, hence, the ferrocenophanes II *via* ferrocenylcarbinyl and ferrocylferrocenylcarbinyl cations is straightforward. Both V and IId (and other isomers II) undoubtedly undergo substantial dealkylation under the experimental conditions of this study.[23] The comparatively high yields in which IId was isolated relative to V reflect the appreciable probability of regeneration expected for a double-bridged [1.1]ferrocenophane in contrast to the single-bridged diferrocenylmethane. Formation of III and VI (and isomeric diferrocenylcyclopentanes undoubtedly present but not isolated in this study) clearly results from metal–ring bond cleavage and secondary reactions involving ensuing cyclopentenyl and ferrocenylcyclopentyl cations.[9,11] Less obvious is the formation of IV and isomers VII. From our failure to collect these compounds in reactions conducted in carbon tetrachloride solvent[24] we must conclude that the methyl substituent originates from dichloromethane. The mechanism shown in Scheme I,[25] which represents one of several possible routes, involves the intermediacy of methylcyclopentenyl and 3-ferrocenyl-3-methylcyclopentyl cations, the former arising by cleavage of methylferrocene. This chart also depicts the reaction paths likely to lead to the segment structures A, B, and C of VIII. Termination of the growing poly-

(18) Certain di- and polynuclear ferrocenes lacking hetero-bridged segments may also show this pattern, provided that free rotation of the rings in one of the ferrocene units is restricted sterically. The pattern, in such case, is superimposed by the regular, broad absorption near 12.2 μ associated with the unencumbered ferrocene groups. 1,1′-Diferrocylferrocene[16b] offers a case in point.

(19) C. Cordes and K. L. Rinehart, Jr., 150th National Meeting of the American Chemical Society, Atlantic City, N. J., 1965, Division of Organic Chemistry, Abstracts, p 37S.

(20) N. Maoz, A. Mandelbaum, and M. Cais, *Tetrahedron Lett.*, 2087 (1965).

(21) R. I. Reed and F. M. Tabrizi, *Appl. Spectros.*, **17**, 124 (1963).

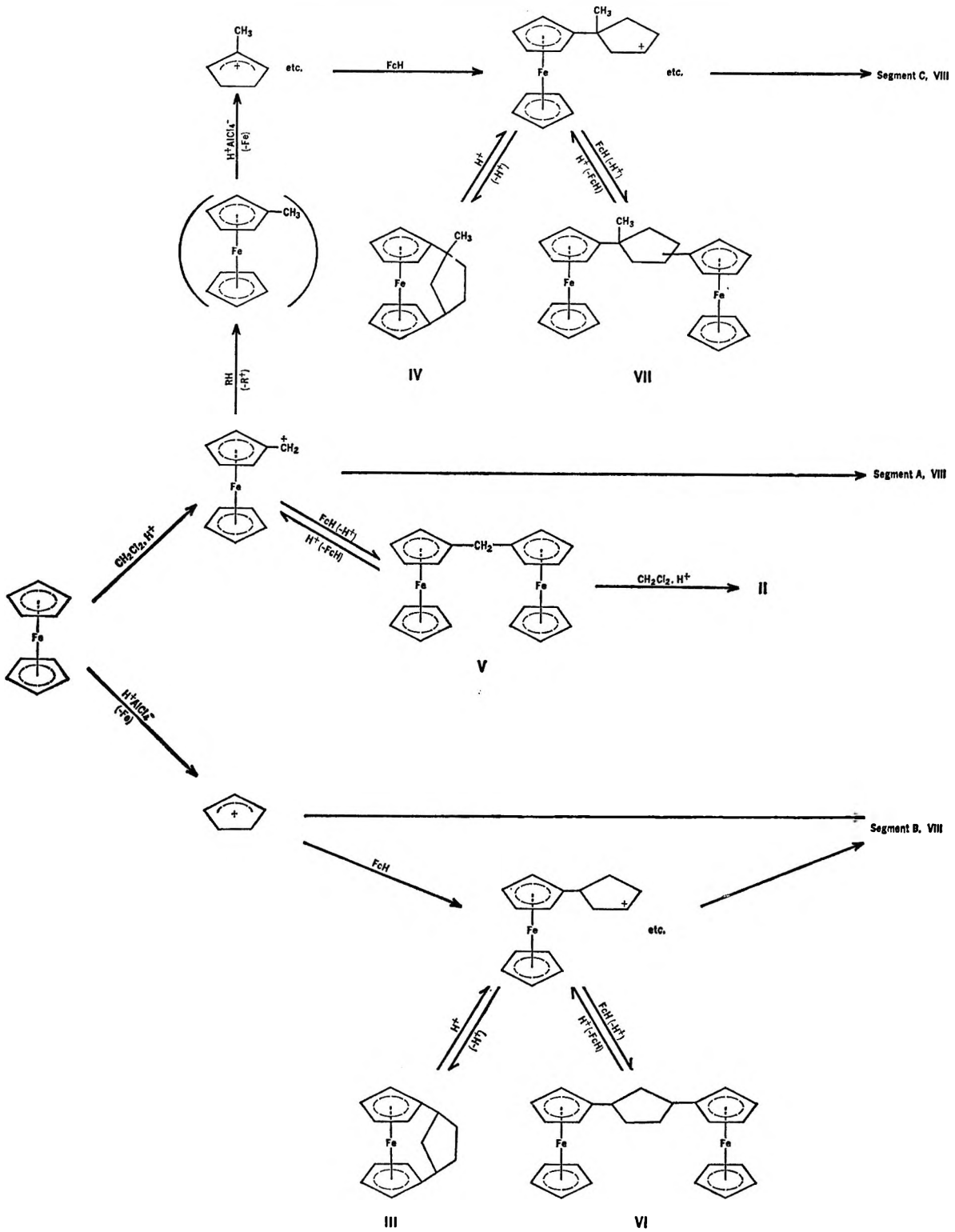
(22) Admixture of nuclearly methylated isomers, however, cannot be ruled out, as the respective signal might well be masked by methylene resonances near the expected 8-ppm position.

(23) Such dealkylation is suggested, for example, by the considerable quantities of ferrocene arising when V is substituted for ferrocene as the starting material.

(24) In addition to diferrocenyl ketone and polymeric compounds containing carbonyl and cyclopentylene bridges, reactions in CCl_4 furnished tetraferrocenylmethane, mp 202–204° (*Anal.* Found: C, 65.76; H, 5.01; Fe, 29.48. Pmr singlet at 5.87 ppm), and the stable diferrocenyldichloromethane, mp 209–211° (*Anal.* Found: Cl, 15.95; Fe, 24.50; mol wt, 440. Pmr signals at 5.10 ppm (four α protons) and 5.73 ppm (four β plus ten unsubstituted ring protons)].

(25) RH = solvent or ferrocenylalkane. The formation of diferrocenylcarbinol[13] from V may thus be explained.

SCHEME I
CLEAVAGE AND ALKYLATION OF FERROCENE (FcH = FERROCENE)



mer chains may proceed through electrophilic attack on ferrocene or a ferrocenyl unit of any of the products II–VII; self-substitution (cyclialkylation) with formation of end groups comprising, for example, the 1,1′-(1,3-cyclopentylene)ferrocene skeleton or its methyl-substituted counterpart is equally probable, although not readily detectable analytically.

Experimental Section

In an exemplifying experiment, ferrocene (0.1 mol), dissolved in dry dichloromethane (2.0 mol), was stirred under N_2 with anhydrous aluminum chloride (0.1 mol) for 3 hr at 0° and 20 hr at 25°. Following hydrolysis (0.05 mol of $SnCl_2$ added as reducing agent), the organic phase, worked up and dried in the usual manner, was evaporated *in vacuo*, and the residue was extracted with cyclohexane. Reprecipitation of the cyclohexane insolubles from benzene solution by 2-propanol gave orange-tan VIIIc, M_n 2400 (2.7%). The cyclohexane solubles were chromatographed on alumina, activity II; fast elution with hexane furnished four major zones. Rechromatography of the first zone (activity I) gave ferrocene (56% recovery), followed by III, mp 139–140° (0.8%), and IV, mp 108–109.5° (3.1%). The second zone, on rechromatography as before and laborious fractional crystallization from hexane, produced a ferrocenophane tentatively identified as IId, mp 265–268° (DTA endotherm 268°),

as the least soluble species (1.7%; in addition to impure fractions, mp 240–260°, containing other isomers), followed by V, mp 145–146° (0.3%), and a fraction that, when rechromatographed, was separated into VI, mp 102–105° (0.2%; wide melting point range indicates presence of other isomers), and the oily mixture VII (3.0%). The third zone, mechanically removed from the column, extracted with ether, and rechromatographed in cyclohexane, produced two bands. The lower one, reprecipitated from hexane by partial vacuum evaporation, gave VIIIa, M_n 680 (10.1%); similarly, the upper one gave VIIIa, M_n 810 (3.2%). From the fourth zone, worked up as in the preceding case, two fractions VIIIb were isolated; the lower molecular fraction (1.6%), reprecipitated from cyclohexane solution by methanol, had M_n 1050; the higher molecular fraction (6.6%), reprecipitated from benzene solution by methanol, had M_n 1720. Analytical data for all new compounds are collected in Table I. The identities of III, V, and VI were established by elemental analysis and comparison of melting point, X-ray diffraction pattern, and ir spectra with those of authentic samples.[9-11]

Registry No.—IId, 12271-18-0; III, 12088-07-2; IV, 12271-17-9; V, 1317-11-9; VI, 12271-19-1; VII, 12271-20-4; aluminum chloride, 7446-70-0; dichloromethane, 75-09-2; ferrocene, 102-54-5.

Acknowledgment.—The author is greatly indebted to Miss K. Koda and Mr. E. Quo for their excellent contribution to the experimental work. Mr. R. K. Crossland, University of Southern California, obligingly recorded the pmr spectra.

The Novel Reaction of 2-(2′,3′,4′-Trimethoxyphenyl)cycloheptyl Methanesulfonate with Dipotassium Mercaptoacetate

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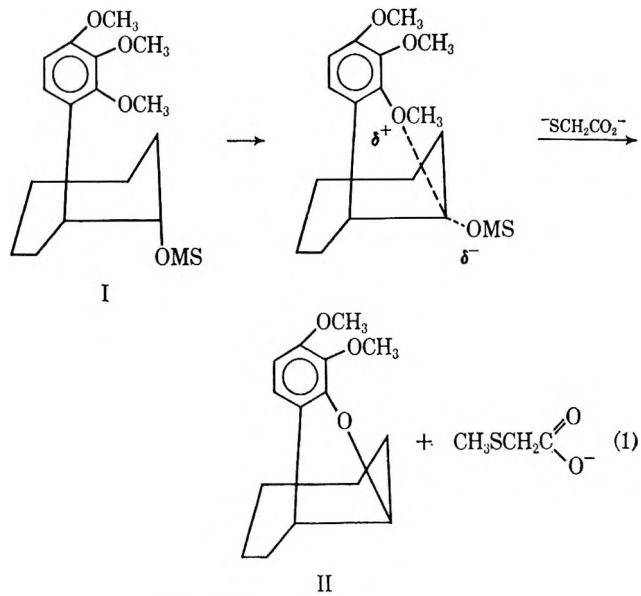
While studying the stereochemistry of 2-(2′,3′,4′-trimethoxyphenyl)cycloheptanemercaptoacetic acid obtained by the addition of mercaptoacetic acid to 1-(2′,3′,4′-trimethoxyphenyl)cycloheptene, it was necessary for the author to prepare *trans*-2-(2′,3′,4′-trimethoxyphenyl)cycloheptanemercaptoacetic acid. Because axial tosylates substituted in the axial 2 position by a phenyl group containing an electron-donating group in the *ortho* or *para* position retain their configuration when treated with nucleophilic reagents,[1] it was felt that in the present situation the desired compound could be obtained by treating *trans*-2-(2′,3′,4′-trimethoxyphenyl)cycloheptyl methanesulfonate with the dipotassium salt of mercaptoacetic acid.

Treatment of *trans*-2-(2′,3′,4′-trimethoxyphenyl)-cycloheptyl methanesulfonate with the dipotassium salt of mercaptoacetic acid yielded only a small amount of the desired product. The major fraction was sulfur free and insoluble in base. The nmr spectrum of the base insoluble material showed single-proton absorptions at τ 5.0 and 6.5. These single proton absorptions were not in the region of the olefinic protons of a conjugated or unconjugated cyclic system[2] and were not in the region of the ethylenic proton of 1-(2′,3′,4′-trimethoxyphenyl)cycloheptene which absorbed at τ 4.18. Absorptions at τ 6.08 and 6.17 integrated correctly for only six protons representing two methoxyl groups rather than the expected three methoxyl groups. Thus, a methyl group of one methoxyl group was evidently lost during the reaction. Since the infrared spectrum showed no absorption in the hydroxyl region for this compound, reaction 1 is believed to occur. The



structure of compound II is consistent with the nmr spectrum since the substitution pattern on the benzene ring remains unchanged, the seven-membered ring is intact, and the protons of one methoxy group are no longer present. The proton absorption at τ 5.0 is assigned to the hydrogen atom α to the oxygen of the cyclic ether. Although this value is approximately 0.57 ppm downfield from the absorption of the proton α to the ether oxygen in 2,3-dihydro-5-methoxybenzofuran (τ 5.57),[3] Fulmor, *et al.*, have assigned a proton absorption at τ 5.02 to a proton α to the cylic ether oxygen in the 6,14-*endo*-ethenotetrahydrothebaine system.[4] The proton absorption at τ 6.5 is assigned to the benzyl proton. Structure II is also consistent with the elemental analysis and the infrared spectrum. The isolation of S-methylmercaptoacetic acid also supports the postulated reaction.

Attempts to cleave the cyclic ether with gaseous hydrogen chloride at 80 and 100° were unsuccessful. Hydrogen bromide (48%) in refluxing glacial acetic acid (8 hr) cleaved the methoxyl groups but apparently failed to open the cyclic ether ring since the resulting phenolic ether could be successfully converted back into the starting compound by treatment with dimethyl sulfate and base.

Although it is generally postulated that the phenyl ring itself participates in anchimeric assistance, it has been suggested that the methoxyl group can participate directly in anchimeric assistance. Noyce[5] has postulated that the methoxyl group in 1,4-methoxycyclo-

(1) F. J. Lotspeich and S. Karickhoff, *J. Org. Chem.*, **31**, 2183 (1966).

(2) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press Inc., New York, N. Y., 1959, p 61.

(3) S. D. Darling and K. D. Wills, *J. Org. Chem.*, **32**, 2794 (1967).

(4) W. Fulmor, J. E. Lancaster, G. O. Morton, J. J. Brown, C. F. Howell, C. T. Nora, and R. A. Hardy, Jr., *J. Amer. Chem. Soc.*, **89**, 3322 (1967).

(5) D. S. Noyce and B. R. Thomas, *ibid.*, **79**, 755 (1957).

hexyl tosylate assists in the displacement of the tosylate through the boat-form intermediate. Allred and Winstein[6] recently reported the participation of the 5-methoxyl group in the lithium aluminum hydride reduction of 5-methoxyl-2-pentyl *p*-bromobenzene-sulfonate. In this case the oxygen atom of the methoxyl group was incorporated into the ring of 2-methyltetrahydrofuran which was formed in this reaction. Framework molecular models do not rule out the postulated reaction in the present case since they indicate that the *o*-methoxyl group of *trans*-2(2′,3′,4′-trimethoxyphenyl)cycloheptyl methanesulfonate is properly located for a backside displacement of the mesylate group. Further studies in this area are in progress.

Experimental Section

Melting points were taken using a Nalge–Axelrod melting point apparatus and are uncorrected. Infrared spectra were measured on a Perkin-Elmer Model 13-U spectrophotometer and nuclear magnetic resonance spectra were obtained on a Varian A-60 spectrometer in deuterated chloroform solutions (*ca.* 10%) using tetramethylsilane as an internal standard.

1-(2′,3′,4′-Trimethoxyphenyl)cycloheptanol was prepared according to the procedure of Ginsburg and Pappo[7] as modified by Lotspeich and Karickoff[1] for the preparation of 1-(2′,3′,4′-trimethoxyphenyl)cyclohexanol.

1-(2′,3′,4′-Trimethoxyphenyl)cycloheptene.—This preparation was achieved according to the procedure of Ginsburg and Pappo.[7]

***trans*-2-(2′,3′,4′-Trimethoxyphenyl)cycloheptanol.**—The procedure which was followed in this synthesis was that of Brown and Subba Rao.[8] 1-(2′,3′,4′-Trimethoxyphenyl)cycloheptene (23.6 g) gave 21.4 g of oil, bp 135–147° (0.04 mm). This oil (3 g) was chromatograped over 108 g of neutral aluminum oxide (Merk) prepared with hexane. Successive elution with the indicated solvents gave four fractions: (1) 120 ml of pentane–25% diethyl ether, 1.26 g of mainly 1-(2′,3′,4′-trimethoxyphenyl)-cycloheptene; (2) 400 ml of pentane–80% diethyl ether, nothing; (3) 160 ml of diethyl ether, 120 mg of 1-(2′,3′,4′-trimethoxyphenyl)cycloheptanol; (4) 200 ml of pentane–10% methanol, 1.44 g of *trans*-2-(2′,3′,4′-trimethoxyphenyl)cycloheptanol. Fraction 4 was distilled: bp 142–143° (0.05 mm); $n^{23}D$ 1.5380.

Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.57; H, 8.57. Found: C, 68.63; H, 8.62.

trans-2-(2′,3′,4′-Trimethoxyphenyl)cycloheptyl methanesulfonate was prepared by allowing 2.00 g (0.0071 mol) of the above alcohol to react with 0.96 g (0.0084 mol) of methanesulfonyl chloride in 5 ml of pyridine at 10° for 48 hr. The pyridine solution was worked up in the usual manner to give 1.6 g (63%) of white crystals which were recrystallized twice from methanol, mp 88–90°.

Anal. Calcd for $C_{17}H_{26}O_6S$: C, 56.98; H, 7.26. Found: C, 57.07; H, 7.22.

6H-3,4-Dimethoxybenzo[*b*]-5a,7,8,9,10,10a-hexahydrocyclohepta[*d*]furan.—*trans*-2-(2′,3′,4′-Trimethoxyphenyl)cycloheptyl methanesulfonate (5.5 g, 0.015 mol) was added to 100 ml of anhydrous methanol containing 3.00 g (0.018 mol) of potassium mercaptoacetate. The solution was heated a 55° for 60 hr and the methanol evaporated. Water (5 ml) was added and the material extracted with diethyl ether. The diethyl ether was washed with water and evaporated to yield 3.3 g of oil which solidified upon standing. The solid was crystallized from diethyl ether to yield 3.0 g of 6H-3,4-dimethoxybenzo[*b*]-5a,7,8,9,10,10a-hexahydrocyclohepta[*d*]furan, mp 70–71.5°. Attempts to reduce this compound with Raney nickel in methanol at 40 psi of hydrogen were unsuccessful. The compound also failed to react with potassium permanganate in acetone and to undergo hydroboration according to the procedure previously described. The infrared spectrum had bands at 3010, 2930, 2860, 1620, 1492, 1460, 1268, 1150, 1088, 1055, and 972 cm^{-1}. The nmr spectrum showed absorption bands at τ 3.4 (doublet, 2 H), 5.0 (broad, 1 H), 6.08 and 6.17 (6 H), 6.5 (broad, 1-H), 8.3 (10-H).

Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12; mol wt, 248. Found: C, 72.86; H, 7.92; mol wt, 255.

The basic solution was acidified with concentrated hydrochloric acid and extracted with diethyl ether. Evaporation of the ether after washing with water yielded 1.8 g of material. Distillation of this material yielded 0.9 g of oil, bp 64–68° (0.7 mm). This material was converted into the acid chloride and treated with aniline to yield the anilide of S-methylmercaptoacetic acid, mp 77–78° (lit.[9] mp 80°). This material did not depress the melting point of an authentic sample of the anilide of S-methylmercaptoacetic acid. The residue from the distillation was taken up in chloroform and the solid removed. The chloroform was evaporated and the liquid was taken up in a small amount of diethyl ether passed over a column (22 × 150 mm) containing 18 g of silicic acid. Elution with 20% diethyl ether in hexane yielded 0.40 g of an acidic oil which had an infrared and nmr spectra identical with the acid prepared by displacement of the *cis* tosylate.

The Reaction of 6H-3,4-Dimethoxybenzo[*b*]-5a,7,8,9,10,10a-hexahydrocyclohepta[*d*]furan with Hydrogen Bromide.—Hydrogen bromide (2.4 g of 48%), 5 ml of glacial acetic acid, and 2.0 g of 6H-3,4-dimethoxybenzo[*b*]-5a,7,8,9,10,10a-hexahydrocyclohepta[*d*]furan were refluxed for 8 hr. The solution was cooled, added to water, and extracted with diethyl ether. The ether extract was washed with 5% sodium bicarbonate solution and then water. Evaporation of the ether yielded 1.5 g of oil which solidified when treated with cold petroleum ether (bp 35–37°). This material melted at 160–166° after crystallization from methylene chloride–petroleum ether (bp 35–37°) (further recrystallization did not improve the melting point): nmr, τ 3.48 (center of two doublets), 4.55 (2-H), 4.48 (1-H), 6.50 (1-H), and 8.32 (10-H); the infrared spectrum (chloroform) had bands at 3633, 2925, 1641, 1486, 1013, and 1207 cm^{-1}.

Remethylation of 6H-3,4-Dihydroxybenzo[*b*]-5a,8,9,10,10a-hexahydrocyclohepta[*d*]furan.—6H-3,4-Dihydroxybenzo[*b*]-5a,-7,8,9,10,10a-hexahydrocyclohepta[*d*]furan (1.00 g, 0.0040 mol) and 0.80 g (0.020 mol) of sodium hydroxide were treated with 0.63 g (0.0050 mol) of dimethyl sulfate at 80°. After stirring for 10 min an additional 0.80 g (0.020 mol) of sodium hydroxide and 0.63 g (0.0050 mol) of dimethyl sulfate were added and the solution was refluxed for 2 hr. The resulting solution was cooled and extracted with diethyl ether. The ether extract was washed with water and the ether was evaporated to yield dark yellow crystals. These crystals were recrystallized from petroleum ether (bp 35–37°), mp 70–71.5°. They showed no depression in melting point when mixed with a sample of 6H-3,4-dimethoxybenzo[*b*]-5a,7,8,9,10-10a-hexahydrocyclohepta[*d*]furan.

Registry No.—I, 16958-54-6; free base of I, 16958-55-7; II, 16958-56-8; dipotassium mercaptoacetate, 16958-57-9.

Acknowledgments.—The author wishes to thank Dr. Charles McCarty, Chemistry Department, West Virginia University, for assistance with the proton magnetic resonance spectra. This investigation was supported by Public Health Service Research Grant (GM 09342) from the National Institutes of Health.

(6) E. L. Allred and S. Winstein, *J. Amer. Chem. Soc.*, **89**, 4008 (1967).
(7) D. Ginsburg and R. Pappo, *ibid.*, **75**, 1094 (1953).
(8) H. G. Brown and B. C. Subba Rao, *ibid.*, **81**, 6423 (1959).
(9) I. Heilbron, Dictionary of Organic Compounds, Vol. IV, Oxford University Press, New York, N. Y., 1953, p 2238.

Conformational Analysis of 1-Methylcyclohexanol

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The free-energy difference between the two chair forms of a monosubstituted cyclohexane is generally re-

(1) National Science Foundation Undergraduate Research Participant, summer, 1966.

ferred to as the conformational energy, $\Delta G°(x)$, where x represents the substituent on the ring. Although conformational energies of substituents are known to be sensitive to molecular environment,[2-6] their effects have often been additive[6,7] when two or more groups are placed on the same ring. Such additivity has been found, for example, in 1,4-disubstituted cyclohexanes and to a somewhat lesser extent in the 1,3 series.[2,8] The buttressing effect of adjacent groups will preclude additivity in 1,2-disubstituted cyclohexanes; however, it may be possible to correct for this.[9] This paper deals with the question of additivity in a 1,1-disubstituted cyclohexane. The available data, Table I, for such systems generally show satisfactory agreement between calculated and experimental values. The most serious deviation occurs with methylenecyclohexane oxide and undoubtedly it results from the severe decrease in the intersubstituent angle.

TABLE I
A COMPARISON OF CALCULATED AND EXPERIMENTAL CONFORMATIONAL ENERGIES IN 1,1-DISUBSTITUTED CYCLOHEXANES

Substituents [$\Delta G°(x)$][a]	Conformational free energies, kcal/mol: Predicted[b]	Observed	Ref
Methyl (1.7); chloro (0.4)	1.3	1.1	*c*
SR_2– (0.8); OR_2– (0.7)	0.1	*ca.* 0.0[d]	*d*
Hydroxy (0.6); ethynyl (0.2)[h]	0.4	0.6	*e*
Vinyl (1.1);[i] hydroxy (0.6)	0.5	0.64	*f*
Methyleneoxy–CH_2O (0.8 and 1.8)[j]	1.0	0.2[i]	*g*
Phenyl (3.1); $(CH_3)_2N$ (2.1)	1.0	0.5	*k*
Phenyl (3.1); $(CH_3)_2HN^+$ (2.4)	0.7	0.2	*k*
Methyl (1.7); CHO (1.35)[i]	0.35	0.14	*l*

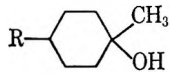
[a] These are the conformational energies suggested by E. L. Eliel [*Angew. Chem. Intern. Ed. Engl.*, **4**, 761 (1965)] for the substituents (x) in kilocalories/mole. [b] Values were obtained by subtraction of the $\Delta G°(x)$ values. [c] N. L. Allinger and C. D. Liang, *J. Org. Chem.*, **32**, 2391 (1967). [d] The observed value was obtained by equilibration of the *cis–trans* isomers of 4-*t*-butylcyclohexanone trimethylene monothioketal and the dimethylene monothioketal: E. L. Eliel, E. W. Della, and M. Rogic, *J. Org. Chem.*, **30**, 855 (1965); E. L. Eliel and L. A. Pilato, *Tetrahedron Lett.*, 103 (1962). [e] R. J. Ouellette, *J. Amer. Chem. Soc.*, **86**, 3089 (1964). [f] R. J. Ouellette, K. Liptak, and G. F. Booth, *J. Org. Chem.*, **31**, 546 (1966). [g] J. J. Uebel, *Tetrahedron Lett.*, 4757 (1967). [h] No independent value is available for this group. The listed value is for C≡N. [i] No independent value is available for this group. The listed value is for CO_2CH_3. A recent value of 1.35 kcal/mol has been suggested for –CHO by G. W. Buchanan and J. B. Stothers, *Chem. Commun.*, 179 (1967). [j] These are estimated values for OR and CH_2R groups. The observed value is for methylenecyclohexane oxide. [k] S. Sicsic and Z. Welvart, *Bull. Soc. Chim. Fr.*, 575 (1967). [l] G. W. Buchanan, J. B. Stothers, and S. T. Wu, *Can. J. Chem.*, **45**, 2955 (1967).

The conformational equilibrium of 1-methylcyclohexanol was investigated by nmr spectroscopy, using the chemical shifts of the hydroxyl protons, as a conformational probe.[10] The hydroxyl proton chemical shifts of 1-methylcyclohexanol (**1**) and the model compounds, 4-*t*-butyl-1-methylcyclohexanol (**2**) and 1,4-dimethylcyclohexanol (**3**), were measured in dimethyl sulfoxide[11] (DMSO) solution and are reported in Table II.

TABLE II
CHEMICAL SHIFTS OF HYDROXYL GROUPS[a]

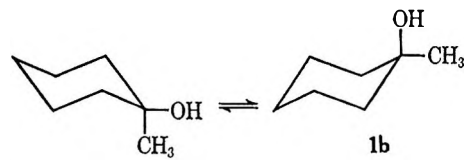
Compound	δ (OH),[b] Hz
trans-4-*t*-Butyl-1-methylcyclohexanol (*trans* **2**)	4.8 ± 0.2
cis-4-*t*-Butyl-1-methylcyclohexanol (*cis* **2**)	27.9 ± 0.1
trans-1,4-Dimethylcyclohexanol (*trans* **3**)	4.0 ± 0.4
cis-1,4-Dimethylcyclohexanol (*cis* **3**)	25.2 ± 0.3
1-Methylcyclohexanol (**1**)	13.1 ± 0.6

[a] The values are for 1 *M* solutions in DMSO at 35°. [b] Values are in cycles per second downfield from the low-field C-13-H satellite of DMSO. All spectra were taken at 60 MHz. The quoted errors are the average deviations of at least four independent measurements.



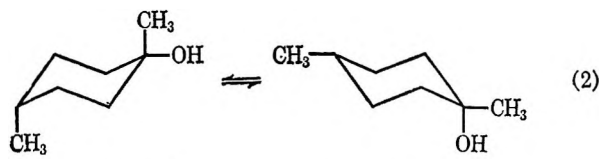
1, R = H
2, R = *t*-Bu
3, R = CH_3

Using the chemical-shift data obtained from compounds **1**, *cis* **2**, and *trans* **2**, a free energy of −0.35 kcal/mol was calculated[12] for equilibrium 1 in DMSO at

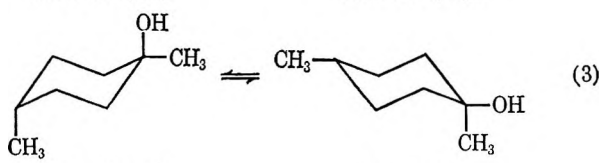


1a **1b** (1)

35°. The data (Table II) obtained from *cis* **3** and *trans* **3** support this free-energy value for equilibrium 1. Thus, if the remote 4-methyl group is regarded as a unit with a conformational preference for the equatorial position of $\Delta G°$ = 1.7 kcal/mol, and the geminal CH_3/OH groups are treated as another unit with $\Delta G°$ = 0.35 kcal/mol, then *trans* **3** would be predicted[13] to exist mainly in conformation **3b** and *cis* **3** predominantly in conformation *cis* **3b**.



trans **3a** (3%)[13] *trans* **3b** (97%) (2)

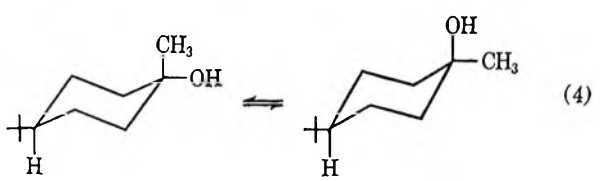


cis **3a** (10%)[13] *cis* **3b** (90%) (3)

(2) E. L. Eliel and T. J. Brett, *J. Amer. Chem. Soc.*, **87**, 5039 (1965).
(3) E. L. Eliel, S. H. Schroeter, T. J. Brett, F. J. Biros, and J. C. Richer, *ibid.*, **88**, 3327 (1966).
(4) R. D. Stolow, *ibid.*, **86**, 2170 (1964).
(5) D. H. R. Barton, F. McCapra, P. J. May, and F. Thudium, *J. Chem. Soc.*, 1297 (1960).
(6) N. L. Allinger, M. A. Miller, F. A. Van Catledge, and J. A. Hirsch, *J. Amer. Chem. Soc.*, **89**, 4345 (1967).
(7) E. L. Eliel, *J. Chem. Educ.*, **37**, 126 (1960).
(8) For a discussion of the factors which give rise to this generalization, see ref 6.
(9) For examples, see J. Sicher and M. Tichy, *Collect. Czech. Chem. Commun.*, **32**, 3687 (1967), and references therein.
(10) (a) R. J. Ouellette, *J. Amer. Chem. Soc.*, **86**, 3089 (1964); (b) R. J. Ouellette, *ibid.*, **86**, 4378 (1964); (c) J. J. Uebel and H. G. Goodwin, *J. Org. Chem.*, **31**, 2040 (1966).
(11) In DMSO proton exchange, processes involving alcoholic hydroxyl groups are generally slow: O. L. Chapman and R. W. King, *J. Amer. Chem. Soc.*, **86**, 1256 (1964); D. E. McGreer and M. M. Mocek, *J. Chem. Educ.*, **40**, 358 (1963).
(12) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformation Analysis," Interscience Publishers, Inc., New York, N. Y., 1965, p 152 ff.
(13) The percentages shown in parentheses for equilibria 2 and 3 are the expected conformational populations at 25°, assuming free-energy additivity.

As a result, the chemical shift of the hydroxyl proton of *trans* **3** (4.0 Hz) should be nearly identical with that of *trans* **2** (4.8 Hz) while that of *cis* **2** (25.2 Hz) should be close to *cis* **2** (27.9). This is indeed the case.

The experimental free energy of −0.35 kcal/mol for equilibrium 1 in DMSO is considerably smaller than the value of −1.1 kcal/mol, which would be expected assuming additivity of $\Delta G°$(x) values for the methyl (1.7 kcal/mol)[14] and hydroxyl (0.6 kcal/mol)[14,15] groups. This lack of additivity applies not only to equilibrium 1 but also to the analogous equilibrium between the isomers of 1-methyl-4-*t*-butylcyclohexanol—*cis* **2** and *trans* **2**. Each isomer was separately equilibrated in aqueous acetic acid containing sulfuric acid at 25°. Analysis of the equilibrated alcohols by gas chromatography on a Carbowax 20M column showed the presence of about 58.5% *trans* **2** and 41.5% *cis* **2**. This



(4)

cis **2** *trans* **2**

corresponds to a value of $-\Delta G° = 0.2$ kcal/mol for equilibrium 4. This value is in good agreement with that obtained by nmr spectroscopy in DMSO, but is in poor agreement with the calculated value, $-\Delta G° = 0.8$ kcal/mol (−1.7 + 0.9 = −0.8 kcal/mol). It should be noted that the calculated values for $-\Delta G°$ are different for the two experiments because of the solvent change from DMSO to aqueous acid. Available data suggest that $\Delta G°$(OH) is greater in H-bond-donating solvents (*ca.* 0.9 kcal/mol), than in either H-bond-accepting solvents or nonbonding solvents (*ca.* 0.6 kcal/mol).[15]

The leveling effect which geminal substitution has had on the conformational preference of the CH_3 and OH groups stands in contrast to most of the available data (Table I) on 1,1-disubstituted cyclohexanes. The reasons for the lack of additivity remain obscure[16] and probably can best be uncovered through a detailed analysis of the Westheimer type.[6,17]

Experimental Section[18]

Materials.—All nmr spectra were obtained on a Varian A-60 nmr spectrometer equipped with a variable-temperature probe. The reported spectral data are the result of several independent measurements, using different batches of solvent and sample. The water concentration in the DMSO varied from about 1% to less than 0.3%. The probe temperature was 35°.

DMSO was dried by heating over calcium hydride and distilling from calcium hydride under reduced pressure (bp *ca.* 80°) as previously described.[10c]

The three 1-methylcyclohexanols (**1**, **2**, and **3**) were all obtained by addition of an ether solution of the appropriate ketone to an ether solution of methylmagnesium iodide. The procedures for preparation and separation of isomers were modeled after those described by DePuy and King.[19] Cyclohexanone gave 1-methylcyclohexanol, bp 62–64° (15 mm) [lit.[20] bp 68 (24 mm) and 56.5 (10 mm)]. 4-Methylcyclohexanone gave a mixture of *cis*- and *trans*-1,4-dimethylcyclohexanol. Chromatography on activated alumina using hexane–benzene mixtures (0–100%) for development gave first samples of the *trans* isomer, mp 70–72° (lit.[21] mp 72.5), followed by the *cis* isomer as an oil (lit.[21] mp 24°). In a similar fashion from 4-*t*-butylcyclohexanone, *cis*-4-*t*-butyl-1-methylcyclohexanol, mp 88–91 (lit.[19] mp 97.5–98°), and *trans*-4-*t*-butyl-1-methylcyclohexanol, mp 72–74° (lit.[19] mp 70.5–71°), were obtained.

Equilibration Studies.—Separate samples of *cis*- and *trans*-4-*t*-butyl-1-methylcyclohexanol (10–30 mg) were dissolved in 2–4 ml of a solution containing concentrated sulfuric acid (20 ml), glacial acetic acid (20 ml), and water (10 ml). After 4 days at 25°, the equilibrated mixtures were diluted with an equal volume of 15% sodium hydroxide solution and extracted three times with 5–10 ml of ether. The ether solutions were washed with a few milliliters of 15% sodium hydroxide solution and concentrated at atmospheric pressure. The concentrated solutions were then analyzed by vpc on a 5% Carbowax 20M column at 130–140°. The response ratio (*trans*/*cis*) for the isomers was found to be 1.02 ± 0.02 with the *cis* isomer being eluted last. Starting with the *cis* isomer, K_{eq} was found to be 1.37 and from the *trans* isomer K_{eq} was 1.43. Therefore, K_{eq} was taken to be about 1.40 and $-\Delta G°$ (25°) = 0.20 kcal/mol. Control experiments demonstrated that this procedure did not fractionate known synthetic mixtures of the alcohols.

Registry No.—**1**, 590-67-0; *cis* **2**, 16980-56-6; *trans* **2**, 16980-55-5; *cis* **3**, 16980-60-2; *trans* **3**, 16980-61-3.

Acknowledgment.—We wish to thank Mr. Warren Cole for his assistance in the preparation of materials used in this work and to the National Science Foundation for a grant to purchase an nmr spectrometer.

(14) J. A. Hirsch in "Topics in Stereochemistry," Vol. I, N. L. Allinger and E. L. Eliel, Ed., Interscience Division, John Wiley and Sons, Inc., New York, N. Y., 1967, pp 199 ff.

(15) E. L. Eliel and S. H. Schroeter, *J. Amer. Chem. Soc.*, **87**, 5031 (1965).

(16) It should be pointed out that changes in the rotamer populations of substituents will occur in going from a mono- to a 1,1-disubstituted cyclohexane. The attending free-energy changes, while often small, are nevertheless not taken into account by a simple addition of free energies.

(17) J. B. Hendrickson, *ibid.*, **83**, 4537 (1961); J. B. Hendrickson, *ibid.*, **84**, 3355 (1962); J. B. Hendrickson, *ibid.*, **86**, 4854 (1964); K. B. Wiberg, *ibid.*, **87**, 1070 (1965).

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

(19) C. H. DePuy and R. W. King, *ibid.*, **83**, 2743 (1961).

(20) T. D. Nevitt and G. S. Hammond, *ibid.*, **76**, 4124 (1954); K. V. Anwers, R. Hintersuber, and W. Trippmann, *Ann.*, **410**, 257 (1915).

(21) G. Chiurdoglu, *Bull. Soc. Chim. Belges*, **47**, 241 (1938).

Conformational Analysis. LXIII. The 1-Methylcyclohexanol System[1,2]

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The conformational energies of simple groups on cyclohexane rings are now rather well known.[3,4] One of the questions which we are now in a position to consider concerns the degree of additivity which will result when two or more substituents are simultaneously present on the ring. If two substituents have a 1,2 relationship, their interaction is sizable.[5] If the relationship is 1,4, the interaction has long been assumed to be negligible,[6]

(1) Paper LXII: N. L. Allinger and W. Szkrybalo, *Tetrahedron*, in press.

(2) This research was supported by Grant GP 4290 from the National Science Foundation.

(3) J. A. Hirsch in "Topics in Stereochemistry," Vol. I, N. L. Allinger and E. L. Eliel, Ed., Interscience Division, John Wiley and Sons, Inc., New York, N. Y., 1967, p 199.

(4) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Division, John Wiley and Sons, Inc., New York, N. Y., 1965, p 436.

(5) Reference 4, p 50.

(6) S. Winstein and N. J. Holness, *J. Amer. Chem. Soc.*, **77**, 5562 (1955).

TABLE I

EQUILIBRATION OF 1-METHYL-4-*t*-BUTYLCYCLOHEXANOL

Temp, °K	Time, hr	K_2^{-1}		K_{av}
331	168	1.46	1.44	
		1.44	1.40	1.43 ± 0.03
		1.43	1.40	
348	24	1.43	1.44	
		1.44	1.40	1.43 ± 0.03
		1.42		
366	2	1.43	1.39	
		1.38	1.37	1.40 ± 0.03
		1.43		

TABLE II

EQUILIBRATION DATA FOR THE REACTION *trans*-4-*t*-BUTYL-1-METHYLCYCLOHEXANOL ⇌ 4-*t*-BUTYL-1-METHYLCYCLOHEXENE

Temp, °K	Olefin/alcohol
331	1.03
348	1.70
366	3.02

TABLE III

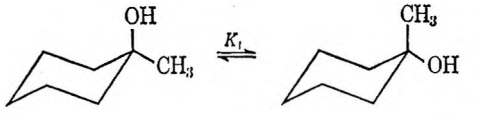
No.	Equilibrium Reactants	$\Delta G°_{343}$, kcal/mol	$\Delta H°$, kcal/mol	$\Delta S°$, eu
2	*trans* alcohol $\overset{K_2}{\rightleftharpoons}$ *cis* alcohol	+0.24 + 0.01	+0.14 ± 0.06	−0.30 + 0.18
3	*trans* alcohol $\overset{K_3}{\rightleftharpoons}$ olefin + H_2O	−2.40 ± 0.05	+8.6 ± 0.8	+32 ± 3

and this assumption has been borne out by recent detailed theoretical calculations.[7] A 1,3 arrangement of substituents has been found to yield a small but definite lack of additivity,[8] and calculations[7] show that this results from the small geometrical changes which accompany substitution.

Few studies of 1,1 disubstitution have been reported. It has been calculated[9] that the 1-chloro-1-methylcyclohexane system will favor the equatorial chlorine to a slightly greater extent than additivity (based on cyclohexyl chloride and methylcyclohexane) would predict. The experimental measurements[10] are in good agreement with the calculations, but also within experimental error of the values required for additivity.

The conformational energies of methyl and hydroxyl are known[11] to have values of 1.7 ± 0.2 and 0.9 ± 0.3 kcal/mol. This paper is concerned with a measurement of the difference between these values when the two groups have a 1,1 relationship.

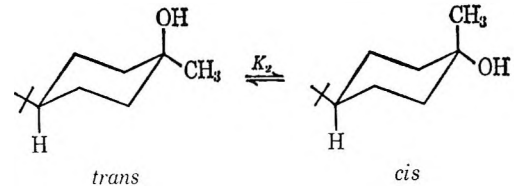
The equilibrium of interest is given in eq 1. The most straightforward way of finding the equilibrium



(1)

constant K_1 appeared to be to measure K_2, and assume $K_1 = K_2$. The usual assumption is made, *i.e.*, that the effect of the 4-*t*-butyl group is negligible.[6]

The required compounds are known (see Experimental Section) and their structures have been established. It was necessary only to equilibrate them, and this was done as a function of temperature so that the enthalpy and entropy of the equilibrium could be determined.[12] It was decided that, since the hydration of an olefin to a tertiary alcohol is a reversible reaction which takes place readily in the presence of acid, the equilibrium (eq 2) should be easily established with



(2)

perchloric acid in aqueous dioxane at elevated temperatures, and such was found to be the case. Equilibrium (eq 2) was approached from both starting alcohols and the product was analyzed by vpc. Some 1-methyl-4-*t*-butylcyclohexene was also formed in the equilibration, and the amount of this olefin was also measured. The thermodynamic parameters for the reaction *trans*-4-*t*-butyl-1-methylcyclohexanol ⇌ 4-*t*-butyl-1-methylcyclohexene (equilibrium 3) were also determined. The equilibration data are given in Tables I and II.

The thermodynamic quantities for the reactions were found to have the numerical values given in Table III.

The value of $\Delta G°$ for eq 2 shows that qualitatively the methyl group prefers to be equatorial and the hydroxyl is axial, as the $\Delta G°$ values of the groups indicate they should. The observed value for $\Delta G°_{343}$ is only 0.24 ± 0.01 kcal/mol, whereas the value calculated[11] from the group conformational energies[11] is larger, 0.8 ± 0.3 kcal/mol. Quantitatively, the experimental difference is significantly smaller than the strict additivity of the group energies would predict. It should be noted that the $\Delta H°$ is only 0.14 kcal/mol, but there is a small entropy term working in the same direction. Since these numbers are quite small, we do not wish to speculate as to the reasons for the observed values. We hope that detailed structural calculations will eventually provide an answer, but we are not able to carry out the calculations at this time. Meanwhile, it seems worthwhile to point out that a quantitative lack of additivity of conformational energies has now been observed in the 1,1-disubstituted case, and this observation may serve as a warning that even a qualitative lack of additivity may be possible in other cases, and examples of such a situation will probably be uncovered in due course. It would therefore seem prudent to avoid assumptions of group additivity in previously unstudied systems.

For equilibrium 3, the large entropy change characteristic of a reaction involving one molecule going to two is observed, the numerical value being

(7) N. L. Allinger, M. A. Miller, F. A. Van-Catledge, and J. A. Hirsch, *J. Amer. Chem. Soc.*, **89**, 4345 (1967).

(8) E. L. Eliel and T. J. Brett, *ibid.*, **87**, 5039 (1965).

(9) M. A. Miller and J. A. Hirsch, unpublished results.

(10) N. L. Allinger and C. D. Liang, *J. Org. Chem.*, **32**, 2391 (1967).

(11) Reference 3, pp 204, 208. The value for the latter is for hydroxylic solvents.

(12) Reference 4, p 141.

roughly the translational entropy of water. The enthalpy change is also large, but favors the reverse reaction, and hence the balance gives a relatively small free-energy change.

Experimental Section

cis- and *trans*-4-*t*-Butyl-1-methylcyclohexanol.—A mixture of the alcohols was prepared by the addition of methyl Grignard to 4-*t*-butyleyclohexanone.[13] A 3.0-g sample of the mixture was dissolved in hexane and chromatographed on 150 g of Merck chromatographic grade alumina. The column was developed with a hexane–benzene mixture (100 to 100%) and each fraction collected was 150 ml. Totally, 80 fractions were collected and the elution was effected with benzene. The first eluate (fractions 30 to 51) contained the *trans*-1-methyl-4-*t*-butylcyclohexanol: yield 1.2 g (40%); mp 69–70° from hexane (lit.[13] mp 71°). The second eluate (fractions 64 to 76) contained *cis*-1-methyl-4-*t*-butylcyclohexanol: yield 1.0 g (33%); mp 91–92° from petroleum ether (bp 30–60°) (lit.[13] mp 97.9°).

Equilibration of the *cis* and *trans* Isomers of 1-Methyl-4-*t*-butylcyclohexanol.—A 0.5-g sample of *trans*-enriehed (1.8:1) 1-methyl-4-*t*-butylcyclohexanol was dissolved in 6 ml of dioxane containing 4 ml of 1.75 *M* aqueous perchloric acid.[14] The equilibration was carried out at 75°. Aliquots of reaction mixture were removed after 18 and 36 hr and were worked up and analyzed immediately by vpc using a column of Dow polyglycol E-20,000 on base-washed firebrick at 130° and 11 psi of helium pressure. The equilibration reaction was quenched with a large amount of ice and water and the mixture was extracted with ether. The ether layer was thoroughly washed with water and then dried over magnesium sulfate. After removal of the solvent, the liquid remaining was analyzed. The retention times of *trans*- and *cis*-1-methyl-4-*t*-butylcyclohexanol were 17 min and 24 min, respectively. The retention time of 1-methyl-4-*t*-butylcyclohexane was 3 min. The ratio of the isomeric alcohols was taken as equal to the ratio of the peak areas, as determined by the product of the band height and the half-band width. Each sample was analyzed at least four times. The equilibrium mixture contained 59% *trans* and 41% *cis* alcohol at 75°.

The equilibration data at 58 and 93° were also obtained in a similar manner and the values of $\Delta H°$ and $\Delta S°$ for the reaction *cis*-4-*t*-butyl-1-methylcyclohexanol $\rightleftharpoons$ *trans*-4-*t*-butyl-1-methylcyclohexanol were determined from the slope and intercept of a line drawn by the method of least squares through points obtained from a plot of ln K against $1/T$. The values along with the probable errors (estimated by statistical methods) are $\Delta H° = -0.14 \pm 0.06$ kcal/mol and $\Delta S° = 0.3 \pm 0.18$ cal/deg mol.

The equilibrations were carried out in homogeneous solution, but in a few cases an oil suspension (olefin) appeared on the surface. In such a case, care was taken in the process of quenching so as not to get oil into the aliquot being removed.

The gas phase analysis indicated that during the prolonged heating of the reaction mixture, some undesired products were beginning to form which made the analysis inaccurate. The amount of decomposition product became significant if the period of heating was longer than twice that which was needed for equilibration. If the heating was continued beyond this time, the total percentge of alcohol decreased with respect to the increased amount of the side products, and, in addition, the ratio of the alcohols changed. The retention times for these side products were 20 and 29 min. No attempt was made to identify them, but they are believed to be ethers of *cis*- and *trans*-4-*t*-butyl-1-methylcyclohexanol with glycols which arose from decomposition of the dioxane. The results are summarized in Table I.

The temperature variation of the equilibrium between olefin (from dehydration) and *trans*-4-*t*-butyl-1-methylcyclohexanol was also measured. The vpc peak corresponding to 4-*t*-butyl-1-methylcyclohexene was collected, and the structure of the compound was assigned from the nmr (chloroform solvent) spectrum which showed a multiplet at τ 4.5 (1 H), a singlet at 8.35 (3 H) and 9.2 (9 H), and multiplets at 8.15 (4 H) and 9.0 (3 H).

In Tables I and II, the data for the calculation of entropy and enthalpy of isomerization of 4-*t*-butyl-1-methylcyclohexanol and the interconversion of *trans*-4-*t*-butyl-1-methylcyclohexanol $\rightleftharpoons$ 4-*t*-butyl-1-methylcyclohexene are tabulated.

(13) W. J. Houlihan, *J. Org. Chem.*, **27**, 3860 (1962).

(14) C. A. Bunton, K. Khaleeluddin, and D. W. Whittaker, *Tetrahedron Lett.*, 1825 (1963).

Registry No.—1-Methylcyclohexanol, 590-67-0; *trans*-4-*t*-butyl-1-methylcyclohexanol, 16980-55-5; *cis*-4-*t*-butyl-1-methylcyclohexanol, 16980-56-6; 4-*t*-butyl-1-methylcyclohexene, 3419-74-7.

Synthesis of (*R*)-3-Methylpentanoic Acid

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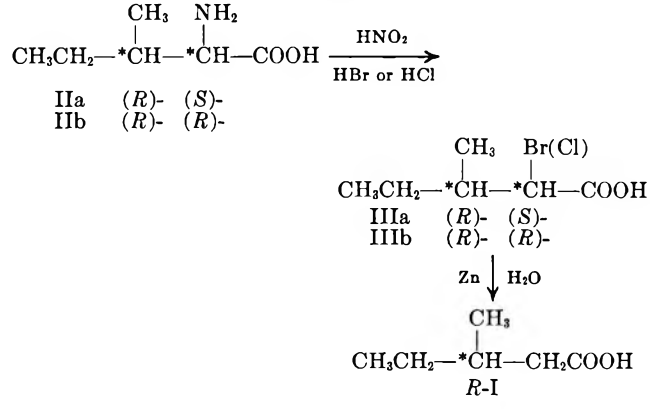
In the course of our study of optically active imidazole-containing polymers,[1] we found it necessary to obtain (*R*)-3-methylpentanoic acid (*R*-I) and (*S*)-3-methylpentanoic acid (*S*-I) in high optical purity in order to prepare the corresponding enantiomeric pair of substrate esters. While *S*-I could be readily prepared from the commercially available (*S*)-2-methylbutyl alcohol,[2] *R*-I was difficult to obtain because *R* isomers are not usually naturally occurring. All attempts to resolve racemic 3-methylpentanoic acid utilizing alkaloids failed. Moreover, there have been no reports in the literature describing the preparation of *R*-I or of (*R*)-2-methylbutyl alcohol in high optical purity or in workable quantity. (*R*)-2-Methylbutyric acid, prepared by Markwald[3] in 1896, can be reduced[4] to (*R*)-2-methylbutyl alcohol which can then be converted into *R*-I. However, the low optical purity (61%) of the acid ruled out the possibility of utilizing it in our work.

In the present investigation, however, we found that *R*-I could be obtained in good optical purity (92%) and in reasonable quantity from optically active isoleucines (IIa or IIb) *via* diazotization[5] in concentrated acids (HCl or HBr) at ~5° and subsequent reductive dehalogenation of the resulting α-halo acids (IIIa or IIIb) by zinc in neutral water (Scheme I).

SCHEME I



This synthesis would give the desired acid *R*-I from both D-isoleucine (IIb) and L-alloisoleucine (IIa),

(1) C. G. Overberger and I. Cho, *J. Polym. Sci., Part A-1*, in press.

(2) K. B. Wiberg and T. W. Hutton, *J. Amer. Chem. Soc.*, **78**, 1640 (1956).

(3) O. Schütz and W. Markwald, *Ber.*, **29**, 52 (1896).

(4) D. S. Noyce and D. B. Denney, *J. Amer. Chem. Soc.*, **72**, 5743 (1950).

(5) For a review of the diazotization of amino acids, see A. Neuberger, *Advan. Protein Chem.*, **4**, 333 (1948).

IIa and IIb being prepared by Greenstein's procedure.[6] However, this procedure affords IIa more easily than IIb. It is also interesting to note that under identical diazotization conditions, the yield of the resulting α-bromo acids was higher when prepared from alloisoleucine (50%) than isoleucine (35%). This effect may reflect the steric requirements[7] governing the diazotization of amino acids.

A zinc–acetic acid system has been used in many instances to dehalogenate reductively not only α-halo ketones[8] but also α-halo acids. In 1859, Ulrich[9] reduced α-chloropropionic acid to propionic acid with zinc in hydrochloric acid. Paal[10] reported a successful conversion of α-chlorobutyric acid into butyric acid by hydrogenation in the presence of Pd.

$$\mathrm{R{-}\underset{\displaystyle X}{\underset{|}{CH}}{-}COOH \xrightarrow{Zn\ (H_2O)} R{-}CH_2{-}COOH}$$

R = CH_3, Bz, *sec*-butyl
X = Cl, Br

Compound *R*-I obtained from IIa ($[\alpha]^{25}D$ +40.0°, 4.5 *N* HCl) exhibited rotation $\alpha^{25}D$ −7.5° (neat, 1 dm). This rotation corresponds to an optical purity of 92%, based on optically pure *S*-I.[11] It is not certain during which step 4% racemization occurred.

When an asymmetric, acyclic, alkylcarboxylic acid does not occur naturally in optically active form, the classical resolution of the asymmetric acid ultilizing alkaloids is often unsuccessful, or, if successful, an extensive purification of the diastereomers by many recrystallizations is usually required.[12] We report the present synthesis as an alternative route for the preparation of optically active, acyclic, alkyl carboxylic acids when the classical alkaloid resolution fails.

Experimental Section

α-Bromo Acids (IIIa and IV).—According to the procedure reported previously,[1] IIIa was prepared in 50% yield from IIa and IV in 35% yield from isoleucine. Nmr spectra showed the α proton as a doublet at 4.20 ppm (J = 6.0 cps) for IIIa and at 4.10 ppm (J = 8.0 cps) for IV.

General Procedure for the Reductive Dehalogenation of α-Halo Acids.—To a dispersion of 15 g (0.25 g-atom) of zinc dust in 500 ml of distilled water was added 0.05 mol of α-halo acid. The resulting mixture was stirred overnight, and, during this time, zinc hydroxide precipitated. When the acid was insoluble in water, the mixture was allowed to reflux for the same time period. The reaction mixture was then acidified with dilute hydrochloric acid and the product acid was extracted with ether. After the ether extract was dried over anhydrous sodium sulfate, distillation afforded dehalogenated acid in almost quantitative yield.

(*R*)-3-Methylpentanoic Acid (*R*-I).—Employing the above procedures, 13 g (0.1 mol) of L-alloisoleucine[6] ($[\alpha]^{25}D$ +40.0°, c 1.70 in 4.5 *N* HCl) gave *R*-I {$[\alpha]^{25}D$ −7.5° (neat, 1 dm)} in 50% over-all yield.

(6) J. P. Greenstein, S. M. Birnbaum, and L. Levintow, *Biochem. Prep.*, **3**, 84 (1951).

(7) Assuming that the α-propiolactone intermediate proposed by Neuberger[5] is correct, the attack of nucleophile Br^- would be more hindered in the case of isoleucine.

(8) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965, p 56.

(9) C. Ulrich, *Ann.*, **109**, 268 (1859).

(10) C. Paal and H. Schiedewitz, *Ber.*, **62**, 1935 (1929).

(11) L. Lardicci and L. Conti, *Ann. Chim.* (Rome), **51**, 823 (1961).

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Registry No.—*R*-I, 16958-25-1.

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A New Synthesis of 11H-Indeno[2,1-*a*]phenanthrenes

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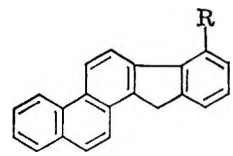
The incentive for the synthesis of 11H-indeno-[2,1-*a*]phenanthrene (**1**) and its alkyl derivatives stems from a desire to prepare materials of known structure for comparison with certain complex dehydrogenation products. Steroids in particular furnish an array of dehydrogenation products,[2] among which indenophenanthrenes have been recognized.[3-8] The structures of several of these pentacyclic dehydrogenation products are unknown;[2] the compounds presumably arise from unknown or unrecognized transformations.



1, R = H
2, R = CH_3

All previous syntheses[7-12] of substituted 11H-indeno[2,1-*a*]phenanthrenes have a common characteristic. A partially aliphatic precursor with the same skeletal features as the desired compound is first synthesized, and then this precursor is aromatized by dehydrogenation. Since the syntheses produce the comparison samples by dehydrogenation methods which may promote obscure transformations, the conclusions based on comparisons with these samples lack logical rigor. While the results and conclusions of earlier workers may not eventually prove to be invalid, they certainly warrant reinvestigation.

Obviously, a synthesis of 11H-indeno[2,1-*a*]phenanthrenes which does not include dehydrogenation would be highly desirable. This objective has been

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(2) L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," 3rd ed, Reinhold Publishing Corp., New York, N. Y., 1949, pp 147–156.

(3) W. O. Godtfredsen and S. Vangedal, *Tetrahedron*, **18**, 1029 (1962).

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(9) D. Nasipuri and D. N. Roy, *ibid.*, 3361 (1961).

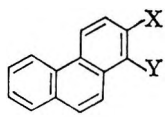
(10) E. Buchta and H. Krätzer, *Ber.*, **95**, 1820 (1962).

(11) B. B. Datta and J C. Bardhan, *J. Chem. Soc.*, 3974 (1962).

(12) S. Uyeo, T. Mizutani, A. Yoshitake, and A. Ito, *Yakugaku Zasshi*, **84**, 458 (1964); *Chem. Abstr.*, **61**, 4286 (1964).

achieved. A method[13] which proved to be successful in the synthesis of chrysofluorene derivatives has been modified and extended, and it serves as a synthesis of the pentacyclic ring system.

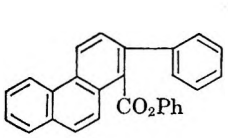
The key intermediate in this synthesis is phenyl 2-methoxy-1-phenanthrenecarboxylate (**3**). In a fashion that parallels the behavior of the hindered phenoxycarbonyl group of phenyl 2-methoxy-1-naphthoate,[13] the ester group of **3** is not extensively attacked by an aromatic Grignard reagent, even when the reagent is present in large excess. Rather, the organic portion of the Grignard reagent replaces the methoxyl group instead. Hence, this treatment joins two fully aromatic fragments at specific points, and no aromatization step is required. Moreover, an aryl group thus joined to the phenanthrene nucleus undergoes cyclization with the surviving ester group, which affords a second unambiguous point of attachment to the tricyclic nucleus.



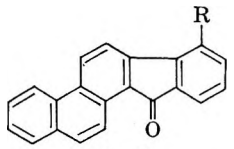
3, X = OCH_3; Y = CO_2Ph
4, X = OH; Y = H
5, X = OCH_3; Y = H
6, X = OCH_3; Y = CHO
7, X = OCH_3; Y = CO_2H

The key intermediate was prepared by the following sequence of reactions. Barium 2-phenanthrenesulfonate was isolated from the sulfonation products of phenanthrene.[14] Alkali fusion of the barium salt gave 2-phenanthrol (**4**)[15] which was methylated by the procedure of Mosettig and Stuart.[16] Formylation of the 2-methoxyphenanthrene (**5**) with dimethylformamide and phosphorus oxychloride gave 2-methoxy-1-phenanthrenecarboxaldehyde (**6**) in good yield. Permanganate oxidation of the aldehyde furnished the corresponding acid (**7**) which was converted into the phenyl ester (**3**) *via* the acid chloride.

The unusual and distinctive step in the synthesis is the reaction between the key intermediate and a Grignard reagent. Treatment of **3** with phenylmagnesium bromide furnishes phenyl 2-phenyl-1-phenanthrenecarboxylate (**8**) in 80% yield.



8



9, R = H
10, R = CH_3

The phenyl ester **8** can be used directly in a ring-closure step with sulfuric acid. When **8** is allowed to stand in the concentrated acid for a short time, 11H-indeno[2,1-*a*]phenanthren-11-one (**9**) is produced in 71% yield. Finally, the sequence was completed by the modified Wolff–Kishner reduction devised by Weisburger and Grantham[17] which served admirably to produce pure 11H-indeno[2,1-*a*]phenanthrene (**1**) in excellent yield from **9**.

Products of the methoxyl group replacement, such as **8**, are isolated and purified with difficulty; however, use of crude material in the ring closure was not detrimental to the purity of the ketone **9** which was isolated in an over-all yield of 61% for the combined operations of replacement and ring closure.

Attention was next directed toward the preparation of an alkylated derivative. For comparison purposes, the 7-methyl derivative was chosen as the objective, because it alone of the alkylated derivatives had been prepared by several independent methods.[8–10] The combined operations of replacement of the methoxyl group by the organic portion of *o*-tolylmagnesium bromide and the ring closure effected by sulfuric acid gave 7-methyl-11H-indeno[2,1-*a*]phenanthren-11-one (**10**) in 49% yield. The modified Wolff–Kishner reduction afforded 7-methyl-11H-indeno[2,1-*a*]phenanthrene (**2**) in high yield.

An important observation deserves comment. The melting points of the polycyclic ketones **9** and **10** are appreciably influenced by traces of acid. Care must be exercised in ensuring removal of residual traces of acid remaining from previous steps in its preparation and in the avoidance of acidic crystallization media. When these precautions are observed, a more brightly colored product of higher melting point results.

Experimental Section

Melting points were determined in capillaries inserted into a heated aluminum block provided with a thermometer calibrated to 300°. Analyses were performed by the Microanalytical Laboratory, Department of Chemistry, University of California.

Barium 2-Phenanthrenesulfonate.—This salt was isolated in pure form in 20% yield from the sulfonation products of phenanthrene.[14]

2-Phenanthrol (4).—Alkali fusion of barium 2-phenanthrenesulfonate yielded 2-phenanthrol, mp 166.5–167.5° (lit.[15] mp 168°) in 78% yield.

2-Methoxyphenanthrene (5).—Methylation of 2-phenanthrol by the procedure of Mosettig and Stuart[16] gave 2-methoxyphenanthrene, mp 98.5–99° (lit.[18] mp 100–101°), in 98% yield.

2-Methoxy-1-phenanthrenecarboxaldehyde (6).—A mixture of 10.4 g of 2-methoxyphenanthrene, 8.5 ml of dimethylformamide, and 10.5 ml of phosphorus oxychloride was heated for 6 hr on the steam bath and poured into a mixture of ice and 200 ml of saturated sodium acetate solution. The precipitate was collected, washed with copious amounts of water, dried in air, and crystallized from chlorofor–methanol to give 8.2 g (69%) of 2-methoxy-1-phenanthrenecarboxaldehyde (**6**) as bright yellow needles, mp 159.5–161.5°. A small sample after recrystallization from the same solvent pair exhibited mp 161–161.5°; this aldehyde had previously been obtained as light brown crystals, mp 160°.[19]

2-Methoxy-1-phenanthrenecarboxylic Acid (7).—To a suspension of 7.09 g of the aldehyde **6** in 150 ml of boiling acetone, 9.5 g of potassium permanganate in 200 ml of warm water was added with stirring over a period of 40 min. Stirring was continued for 1.5 hr while the temperature was maintained between 75 and 80°. A solution of 4 g of potassium hydroxide in 40 ml of water was added and the reaction mixture was filtered while warm. The filtrate and two washes of the precipitated manganese dioxide were cooled to 0° and acidified with hydrochloric acid. The yellowish precipitate was crystallized from ethanol–water to afford 4.98 g (66%) of the colorless methoxy acid, mp 247–248.5°, with gas evolution (lit.[19] mp 244–246° dec).

Phenyl 2-Methoxy-1-phenanthrenecarboxylate (3).—A mixture of 4.94 g of 2-methoxy-1-phenanthrenecarboxylic acid and 15 ml

(13) R. C. Fuson and F. W. Wassmundt, *J. Amer. Chem. Soc.*, **78**, 5409 (1956).
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(15) L. F. Fieser, *J. Amer. Chem. Soc.*, **51**, 2460 (1929).
(16) E. Mosettig and A. H. Stuart, *ibid.*, **61**, 1 (1939).
(17) J. H. Weisburger and P. H. Grantham, *J. Org. Chem.*, **21**, 1160 (1956).
(18) A. Werner and K. Rekner, *Ann.*, **321**, 305 (1902).
(19) E. Mosettig and A. Burger, *J. Amer. Chem. Soc.*, **55**, 2981 (1933).

of thionyl chloride was allowed to stand overnight and was then heated under reflux 1.5 hr before removal of the excess thionyl chloride under reduced pressure. To the residue was added 2.00 g of phenol in 25 ml of benzene, and the resulting mixture was boiled under reflux for 1 hr. Filtration and cooling of the solution after clarification with charcoal yielded 5.73 g (89%) of the phenyl ester, mp 147.5–149°. A crystallization from acetone–water gave needles, mp 150–150.5°.

Anal. Calcd for $C_{22}H_{16}O_3$: C, 80.47; H, 4.91. Found: C, 80.66; H, 4.79.

Phenyl 2-Phenyl-1-phenanthrenecarboxylate (8).—A suspension of 1.00 g of phenyl 2-methoxy-1-phenanthrenecarboxylate in 20 ml of benzene was added to the Grignard reagent prepared from 0.24 g of magnesium and 1.88 g of bromobenzene in 15 ml of ether. The reaction mixture was heated under reflux for 2.5 hr and hydrolyzed with ice and ammonium chloride. The organic layer and three benzene extracts of the aqueous portion were combined. Steam distillation removed the organic solvents and a small amount of biphenyl. The residue from the distillation was separated by filtration and dried in air. Crystallization from acetone afforded 0.91 g (80%) of white crystals, mp 185–186°. Sublimation in high vacuum gave an analytically pure sample mp 185.5–186°.

Anal. Calcd for $C_{27}H_{18}O_2$: C, 86.61; H, 4.85. Found: C, 86.28; H, 4.75.

11H-Indeno[2,1-*a*]phenanthren-11-one (9). From Pure 8.—A solution of 100 mg of the ester 8 in 5 ml of concentrated sulfuric acid was allowed to stand at room temperature for 1.5 hr. The permanganate-colored mixture was poured into ice water, and the resulting yellow precipitate was collected by filtration, washed with 5% aqueous sodium carbonate and water, and dried in air to give 53 mg (71%) of material, mp 207–212°. Crystallization from ethyl acetate gave golden yellow needles of the ketone 9, mp 213.5–214°; crystallization from acetic acid produced a darker product melting over a wider range at a lower temperature. The sample crystallized from acetic acid had properties more in keeping with those described in the literature[7] (reddish orange needles, mp 207–208°).

11H-Indeno[2,1-*a*]phenanthren-11-one (9). From 3 without Isolation of Pure 8.—A solution of 657 mg of phenyl 2-methoxy-1-phenanthrenecarboxylate (3) in 40 ml of benzene was added to the Grignard reagent prepared from 0.24 g of magnesium and 1.88 ml of bromobenzene in 15 ml of ether. The reaction mixture was heated under reflux for 2.5 hr and hydrolyzed with ice and ammonium chloride. The organic layer and three benzene extracts of the aqueous portion were combined and steam distilled. The solid in the cooled residue was separated by filtration and dried in air. The solid was next stirred into 15 ml of concentrated sulfuric acid and allowed to stand at room temperature for 1.5 hr. The permanganate-colored mixture was poured onto ice; the resulting precipitate was collected by filtration and washed with 5% aqueous sodium carbonate solution and water. Crystallization of the dried material from ethyl acetate furnished 341 mg (61%) of 9 as golden yellow needles, mp 214–214.5°.

11H-Indeno[2,1-*a*]phenanthrene (1).—The ketone 9 was reduced by the Wolff–Kishner reaction as modified by Weisburger and Grantham.[17] A suspension of 36 mg of ketone 9 in 20 ml of distilled diethylene glycol and 2 ml of 85% hydrazine hydrate was warmed at 100° for 5 min; 1 ml of 10% potassium hydroxide in the same solvent was added; and the solution was kept at 100° for 10 min longer. Water was driven off until the temperature rose to 200°; further heating for 2 hr was continued under reflux. The reaction mixture was cooled and poured into 100 ml of cold water and filtered. The solids were washed with water and dried in air to give 27.4 mg (80%) of the crude hydrocarbon, mp 330–331° (uncor). Crystallization from benzene gave blades, mp 331–332° (uncor) and 335–336° (uncor, in a sealed, evacuated capillary) (lit.[11] mp 335–336°).

7-Methyl-11H-indeno[2,1-*a*]phenanthren-11-one (10).—A solution of 200 mg of 3 in 6 ml of benzene was added to the Grignard reagent prepared from 82 mg of magnesium and 0.48 ml of *o*-bromotoluene in 8 ml of ether. Treatment of the reaction mixture was similar to that described for the direct preparation of 9 from 3. Crystallization of the crude, dry ketone from ethyl acetate gave 89 mg (49%) of 10 as yellow needles, mp 211–212°. After sublimation and recrystallization from ethyl acetate, the ketone melted at 213–214° (lit.[8] mp 209–210°).

7-Methyl-11H-indeno[2,1-*a*]phenanthrene (2).—Reduction of 20 mg of the ketone 10 by the procedure described for the preparation of 1 gave 16 mg (84%) of the crude, colorless hydrocarbon, mp 272.5–274°. Sublimation followed by crystallization from ethyl acetate gave colorless crystals, mp 274–275° (lit.[8] mp 275–276°).

Registry No.—1, 220-97-3; 2, 16793-26-3; 3, 16793-27-4; 8, 16793-28-5; 9, 4599-92-2; 10, 16793-30-9.

10-Hydroxy-10,9-boroxarophenanthrene. A Lewis Acid[1]

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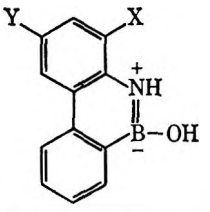
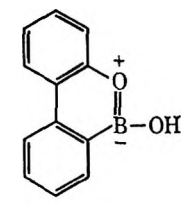
Received April 9, 1968

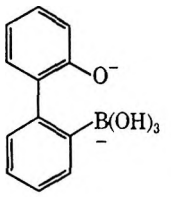
A large number of boron-containing heteroaromatic compounds, isoelectronic with "normal" aromatic systems and derived from them by replacing a pair of adjacent carbon atoms by boron and nitrogen or boron and oxygen, are now known.[3] At an early stage, it was shown that the ultraviolet spectra of 10-hydroxy-10,9-borazarophenanthrene (Ia),[4] and of 10-hydroxy-10,9-boroxarophenanthrene (II)[5] in neutral and alkaline so-



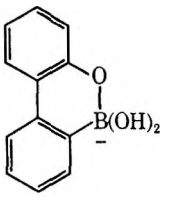
Ia, X = Y = H
b, X = H; Y = NO_2
c, X = NO_2; Y = H



II



III



IV

lution suggested that these compounds behaved as protic acids, unlike normal boronic or borinic acids that seem to form salts by addition to boron. This difference was attributed to aromatic stabilization of the boron-containing rings, and indeed was cited as evidence that such compounds are aromatic. Since that time it has usually been assumed that other analogous hydroxyborazaro and hydroxyboroxaro compounds show similar behavior to base by acting as protic acids, rather than Lewis acids.

Recently[6] it was shown that ^{11}B nmr spectroscopy provides a simple and unambiguous criterion of the mode of

(1) This work was supported by a grant from The Robert A. Welch Foundation.

(2) Robert A. Welch Postdoctoral Fellow, 1966–1968.

(3) See M. J. S. Dewar, *Prog. Boron Chem.*, **1**, 235 (1964); R. F. Gould, "Boron-Nitrogen Chemistry," Advances in Chemistry Series, No. 42, American Chemical Society, Washington, D. C., 1964, p 227.

(4) M. J. S. Dewar, V. P. Kubba, and R. Pettit, *J. Chem. Soc.*, 3076 (1958).

(5) M. J. S. Dewar and R. Dietz, *J. Chem. Soc.*, 1344 (1960).

(6) M. J. S. Dewar and R. Jones, *J. Amer. Chem. Soc.*, **89**, 2408 (1967).

reaction of boron acids with base. Salt formation by addition of base to boron leads to a very large upfield shift (~25 ppm) with narrowing of the ^{11}B resonance, while salt formation by loss of a proton leads to a downfield shift of *ca.* 5 ppm with extreme broadening, the half-width of the ^{11}B absorption increasing to 1–3 kHz. Application of this technique to several β-hydroxyborazaro compounds, including Ia, showed that they do indeed behave as protic acids, confirming the earlier conclusions based on uv spectroscopy. No measurements were made at that time on the oxygen analog II, since no sample was available and since the uv spectrum seemed to provide equally definitive evidence that it too functions as a protic acid.

We have now measured the ^{11}B nmr spectrum of II in alcohol and in alcoholic potash and have found, much to our surprise in view of the uv evidence, that it does in fact act as a Lewis acid, rather than as a protic acid. As the results in Table I show, salt formation leads to a large upfield shift and a narrowing of the ^{11}B resonance, in analogy to phenylboronic acid and in marked contrast to the protic acid (Ia) where salt formation leads to a large downfield shift with extreme broadening of the ^{11}B nmr line.

TABLE I

^{11}B NMR SPECTRA OF BORON ACIDS IN NEUTRAL AND ALKALINE SOLUTIONS

Compd	Solvent	Chemical shift[a]	Line width[b]
Ia	EtOH	−29.3[c]	221
	EtOH–5% KOH	−43.9[c]	2500
Ib	DMSO	−36.9[c]	1250
	DMSO–5% KOH	−12.5[c]	780
Ic	THF	−41.0[c]	380
	THF–5% KOH	−21.5[c]	310
II	EtOH	−28.8	233
	EtOH–5% KOH	−5.5	162
$PhB(OH)_2$	EtOH	−28.4	272
	EtOH–5% KOH	−3.2	80

[a] In parts per million relative to boron trifluoride–etherate. [b] At half-height, in hertz (Hz). [c] Reference 9.

Since the original spectroscopic evidence seemed to provide convincing evidence that II behaves as a protic acid, we reexamined the uv spectrum (Figure 1). Addition of alkali to a solution of II in ethanol did indeed lead to a bathochromic shift of *ca.* 20 mμ, and the long wave absorption maxima of the salt was at much longer wavelength than that of 2-hydroxybiphenyl (286 mμ); however, the long wave band of II in alkali (Figure 1) consisted of a single maximum only, whereas the long wave bands of I or II in ethanol, or of Ia in alcoholic potash, showed double maxima, and the bathochromic shift of II on addition of alkali was much greater than that observed in the case of I.

The spectrum of II in alkali was in fact almost identical with that of the 2-hydroxybiphenate ion (Figure 1), suggesting that base converts II into the dianion III, with opening of the central ring. However, two lines of evidence show that this cannot be the case. First, the ^{11}B nmr spectrum of II in alkali differed very markedly from that of phenylboronic acid, both in chemical shift and line width, although in ethanol both compounds show very similar spectra (Table I). Secondly, the proton nmr spectrum of II in ethanol was almost unchanged by addition of base, retaining a two-proton signal 48 Hz

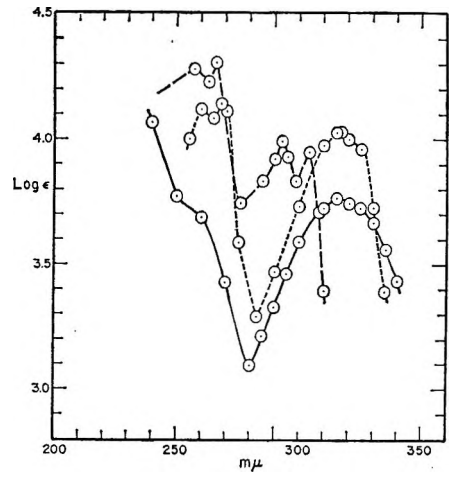


Figure 1.—Ultraviolet spectra of II in ethanol (— —) and 5% ethanolic potassium hydroxide (- - - -) and of 2-hydroxybiphenyl in 5% ethanolic potassium hydroxide (——).

downfield from the remaining aromatic protons; this behavior is characteristic of the hindered 4 and 5 protons in phenanthrene and compounds of related structure and is not observed in derivatives of biphenyl.[7] The anion formed from II by base must therefore have the structure IV.

A referee has suggested that hydrogen bonding in III might lead to a sufficient degree of coplanarity for the 4 and 5 protons to remain hindered; this, however, seems very unlikely, for two reasons.

First, the effect depends very critically on the degree of coplanarity of the rings, separation of the 4- and 5-proton signal from the main aromatic multiplet being much less (27 Hz) for 9,10-dihydrophenanthrene than for phenanthrene (55 Hz) or for II in ethanol (48 Hz). Even dibenzothiophene shows a reduced separation (39 Hz), due presumably to bending of the bond joining the phenyl groups with a consequent small increase in the distance between the 4 and 5 protons. As examination of models shows that the dihedral angle in III must be at least as great as that in 9,10-dihydrophenanthrene, the fact that the separation of the 4- and 5-proton signal of II is unchanged by alkali seems to show unambiguously that the resulting anion is not III.

Secondly, the sulfur analog of II *does* undergo ring opening on treatment with alkali; in the resulting solution, containing the sulfur analog of III, the nmr signal for the aromatic protons appear as a single multiplet.[8]

It is not of course surprising that II should, unlike I, behave as a Lewis acid; for II should be, and is, less aromatic that I. It is, however, very surprising that the spectrum of II in alkali should be so nearly identical with that of 2-hydroxybiphenyl for it implies that combination of the ion ArO^- (Ar = 2-biphenyl) with trivalent boron to form an ion of the type $ArOBR_3^-$ leads to no change in the absorption spectrum, whereas combination of ArO^- with a proton to form ArOH leads to a large hypsochromic shift. From the accepted theory of the spectra of phenols and phenolate ions, one would conclude that oxygen has the same effective electronegativity in $ArOBR_3^-$ as in ArO^-, clearly a very unexpected and theoretically interesting result.

(7) C. Reid, *J. Mol. Spectrosc.*, **1**, 18 (1957).
(8) F. A. Davis and M. J. S. Dewar, *J. Amer. Chem. Soc.*, **90**, 3511 (1968).

In conclusion, it should be added that, in the course of another investigation in these laboratories, it has been found that the 6-nitro II (Ib) and 8-nitro II (Ic) derivatives of I also function as Lewis acids and that their salt formation is also accompanied by large bathochromic shifts.[9] Here, however, one cannot make an analogous comparison of the groups $ArNH^-$ and $ArNHBR_3^-$ since the ion $ArNH^-$ cannot of course exist in ethanol.

Experimental Section

^{11}B nmr spectra were measured with a Varian DP-60 spectrometer using procedures described[6] previously. Ultraviolet spectra were measured using a Beckman DK-2 spectrometer. The nmr spectra were measured on a Varian A-60 instrument.

10-Hydroxy-10,9-boroxarophenanthrene[5] (II).—The proton nmr spectrum of II in chloroform-*d* consists of multiplets at δ 8.2 and 7.4 (ratio of integrated intensities 1:3). There was no change in the multiplets position on using ethanol or 5 or 10% potassium hydroxide in ethanol as the solvent.

Registry No.—Ia, 17012-25-8; Ib, 15813-11-3; Ic, 15889-55-1; II, 14205-96-0; $PhB(OH)_2$, 98-80-6.

(9) M. J. S. Dewar, R. Jones, and R. Logan, Jr., *J. Org. Chem.*, **33**, 1359 (1968).

cis- and *trans*-Bicyclo[6.1.0]nonan-2-one

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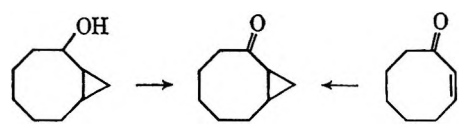
In connection with our continuing interest in cyclopropane chemistry, we have had occasion to synthesize both *cis*- and *trans*-bicyclo[6.1.0]nonan-2-one (I and II, respectively). We wish to report this synthesis and to describe the behavior of the strained *trans* isomer II.

Strained bicyclic compounds are ordinarily quite stable. However, in the case of II, a ready pathway is available for isomerization to the *cis* isomer I, *viz.*, enolization. We were interested in knowing how facile this epimerization process was. Furthermore, studies with molecular models indicated that there just might be little difference between the free energies of I and II. We therefore were interested in determining if substantial amounts of II existed when equilibrium was established between the two isomers.

The *cis* ketone I was synthesized by the Jones oxidation[1] of *cis*-bicyclo[6.1.0]nonan-2-ol[2] (III) and also by the Corey procedure[3] by allowing *cis*-cycloocten-3-one[4] (IV) to react with dimethyloxosulfonium methylide.

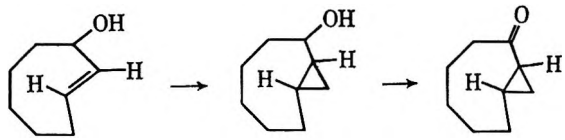


III I IV

(1) W. G. Dauben and G. H. Berezin, *J. Amer. Chem. Soc.*, **89**, 3449 (1967).
(2) A. C. Cope, *et al.*, *ibid.*, **79**, 3900 (1957).
(3) E. J. Corey and M. Chaykovsky, *ibid.*, **87**, 1353 (1965).
(4) A. C. Cope, M. R. Kinter, and R. T. Keller, *ibid.*, **76**, 2757 (1954).

The material obtained by either route was identical in all respects.

The *trans* ketone II was synthesized by the Jones oxidation[1] of *trans*-bicyclo[6.1.0]nonan-2-ol (VI), which was prepared by the Simmons–Smith reaction[5] of *trans*-cycloocten-3-ol[6] (V).



V VI II

Samples of I and II were shown to be different by comparison of their nmr and infrared spectra and vpc retention times and by comparison of the melting points of their 2,4-dinitrophenylhydrazone derivatives. The structure of the *trans* ketone was conclusively established when it was found that the ketone could be isomerized to the *cis* ketone I by treatment with base (*vide infra*).

It was first established that the *cis* ketone I was inert to the usual acid or base treatments. When treated with sodium methoxide in methyl alcohol, potassium *t*-butoxide in *t*-butyl alcohol, or 2 *N* sulfuric acid in ether, I was recovered unchanged.

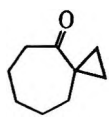
Next, the *trans* ketone II was subjected to a variety of basic and acidic reaction conditions. After being treated with 2 *N* sulfuric acid in ether for 15 hr at room temperature, or after being eluted through grade I neutral Woelm alumina, II was recovered unchanged. However, after being treated with 1.5 *M* sodium methoxide in methyl alcohol for 87 hr at room temperature, II was completely converted into the *cis* ketone I (>99%); the half-life for this conversion was found to be about 8 hr. When treated with 1.5 *M* sodium hydroxide in methyl alcohol, the rate of isomerization was about the same. The *trans* ketone II could also be isomerized with sodium carbonate in 50:50 water–methyl alcohol, but the reaction was slower; after 16 hr at room temperature, about 2% conversion into I had occurred, whereas after 15 hr at reflux (73°), complete conversion into I had occurred.

These isomerization studies thus establish that I and II are epimers and that the structure of II is that formulated above. These studies further prove that the *cis* ketone I is much more thermodynamically stable than the *trans* ketone II. Finally, it has been shown that II is stable under mild acidic treatment but is readily isomerized by base.

There is one reference in the literature to the *cis* ketone I. Gutsche[7] has claimed that I is one of the products obtained when N,N′-dicarbethoxy-N,N′-dinitroso-1,3-propane is treated with cyclohexanone in the presence of base. However, the infrared and nmr data of his ketone and the melting point (113–114°) and color (blood red) of its 2,4-dinitrophenylhydrazone derivative are clearly incompatible with those of the ketone and its 2,4-dinitrophenylhydrazone derivative studied by us. In view of the two unambiguous syntheses of I described in this communication, we feel that

(5) W. G. Dauben and G. H. Berezin, *ibid.*, **85**, 468 (1963).
(6) G. H. Whitham and M. Wright, *Chem. Commun.*, 294 (1967). We are indebted to Dr. Whitham for supplying us with the detailed procedure for synthesizing V.
(7) C. D. Gutsche and T. D. Smith, *J. Amer. Chem. Soc.*, **82**, 4067 (1960).

Gutsche has isolated a different compound. We further suggest that Gutsche's compound is actually spiro[2.5]nonan-4-one (VII). Published data on an au-



VII

thentic sample of VII and its 2,4-dinitrophenylhydrazone derivative[8] are completely in agreement with the data reported by Gutsche for his ketone.

Experimental Section

Melting points are uncorrected. Infrared spectra were obtained on a Beckman IR-10 infrared spectrophotometer. Vapor phase chromatographic work was performed with an F & M Model 700 gas chromatograph using 15% Apiezon L on Chromosorb W.

cis-**Bicyclo[6.1.0]nonan-2-one** (I).—*cis*-Bicyclo[6.1.0]nonan-2-ol[2] (3.00 g) was converted by the Jones oxidation[1] into 1.92 g (65%) of I, bp 72–74° (2.5 mm). *cis*-Cycloocten-3-one[4] (6.99 g) was converted by the Corey procedure[3] into 0.945 g (12%) of I, bp 99–100° (5 mm), ν_{max} 1695 cm^{-1} (C=O).

A 2,4-dinitrophenylhydrazone derivative was prepared,[9] yellow-orange prisms (eluted through grade I neutral Woelm alumina with benzene and recrystallized from 95% ethyl alcohol), mp 159–160.5°.

Anal. Calcd for $C_{15}H_{18}N_4O_4$: C, 56.60; H, 5.70; N, 17.60. Found: C, 56.77; H, 5.91; N, 17.73.

trans-**Bicyclo[6.1.0]nonan-2-one** (II).—A sample of *trans*-cycloocten-3-ol[6] (V) (8.87 g) was converted by the Simmons-Smith reaction[5] into 7.83 g (80%) of VI, a viscous clear oil, bp 63–65° (0.3 mm). A sample of VI (4.00 g) was converted by the Jones oxidation[1] to 2.74 g (70%) of II, bp 75–76° (2.5 mm), ν_{max} 1702 cm^{-1} (C=O).

A 2,4-dinitrophenylhydrazone derivative was prepared,[9] fine yellow needles (eluted through grade I neutral Woelm alumina with benzene and recrystallized from 95% ethyl alcohol), mp 177–179.5°. A mixture melting point with the 2,4-dinitrophenylhydrazone derivative of I was depressed, mp 141–149°.

Anal. Calcd for $C_{15}H_{18}N_4O_4$: C, 56.60; H, 5.70; N, 17.60. Found: C, 56.46; H, 5.88; N, 17.77.

Registry No.—I, 16793-31-0; I (2,4-dinitrophenylhydrazone), 16793-32-1; II, 16793-33-2; II (2,4-dinitrophenylhydrazone), 16793-34-3.

Acknowledgment.—This work was supported by a postdoctoral fellowship to J. L. M. from the National Institutes of Health, Public Health Service (GM-31, 823-01 and GM-31, 823-02).

(8) P. Leriverend and J. M. Conia, *Bull. Soc. Chim. Fr.*, 121 (1966).

(9) 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., 1964, p 219.

Benzocyclobutenes. I. Nitration of 1-Cyanobenzocyclobutene[1]

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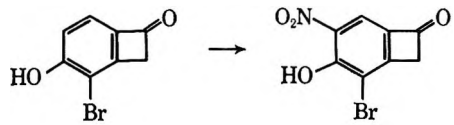
The electrophilic substitution of the now readily available benzocyclobutene has become well documented. The nitration of benzocyclobutene has been carried out by Horner[2] and by Lloyd and Ongley.[3]

Lloyd and Ongley have shown that, in benzocyclobutene, electrophilic substitution takes place preferentially at the 4 or 5 position. These positions are equivalent in benzocyclobutene but are nonequivalent in 1-substituted benzocyclobutenes.

There is only one report of an electrophilic reaction of a benzocyclobutene containing a functional group in the four-membered ring.[4] Birch nitrated 3-bromo-4-hydroxybenzocyclobuten-1-one (**1**) with nitric acid in aqueous acetic acid and obtained **2** in 46% yield. In



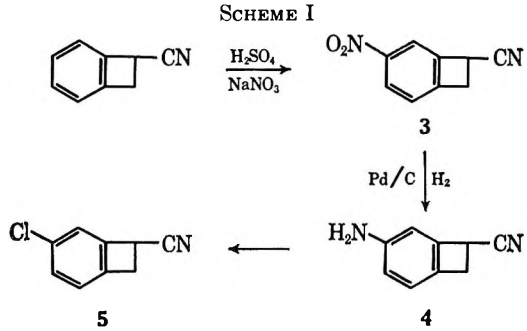
1 **2**

this molecule there is only one pertinent position for electrophilic substitution, *i.e.*, the 5 position.

We have now successfully nitrated 1-cyanobenzocyclobutene with sodium nitrate in concentrated sulfuric acid.[5] The product which is easily isolated by crystallization from ethanol is 1-cyano-5-nitrobenzocyclobutene (**3**).

The infrared spectrum of the crude product possessed bands corresponding to nitrile, nitro, and amide functional groups with the amide band being a minor peak. Tlc showed **3** to be the major component and also the presence of three minor components which ran faster than **3**. Crystallization of a portion of the crude nitration mixture followed by column chromatography of the mother liquors gave **3** in a total yield of 73%. 1-Cyano-5-nitrobenzocyclobutene (**3**) was the only nitronitrile that was isolated from the reaction. The minor components of the reaction mixture (9%) were shown *via* their infrared spectra to contain nitro and amide functional groups. These could be ring-opened products as well as the product resulting from the hydrolysis of **3**. Lloyd and Ongley[3] have shown that nitration of benzocyclobutene produces a mixture of ring-opened products in 31% yield.

SCHEME I



Catalytic reduction of **3** over 5% palladium on carbon (Scheme I) gave 5-amino-1-cyanobenzocyclobutene (**4**). Treatment of **4** with nitrous acid and

(1) The numbering of positions is according to M. P. Cava and D. R. Napier, *J. Amer. Chem. Soc.*, **79**, 1701 (1957).

(2) (a) L. Horner, H.-G. Schmelzer, and B. Thompson, *Chem. Ber.*, **93**, 1774 (1960); (b) L. Horner, K. Muth, and H.-G. Schmelzer, *ibid.*, **92**, 2953 (1959).

(3) J. B. F. Lloyd and P. A. Ongley, *Tetrahedron*, **20**, 2185 (1964).

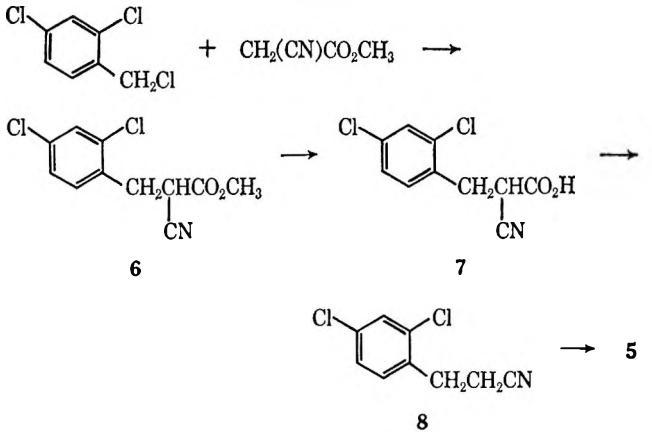
(4) A. J. Birch, J. M. Brown, and F. Stansfield, *J. Chem. Soc.*, 5343 (1964).

(5) H. H. Hodgson and H. G. Beard, *ibid.*, 147 (1926).

cuprous chloride gave 5-chloro-1-cyanobenzocyclobutene (**5**).

An alternate synthesis of **5** using the procedure of Bunnett[6] was carried out as shown in Scheme II.

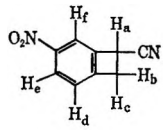
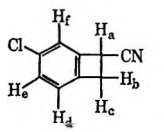
SCHEME II



The pmr spectra of **3** and **5** (Table I) agree with the assigned structure and reasonably well with those of similar compounds.[7] The samples of **5** prepared by both routes gave superimposable pmr and infrared spectra and showed no depression on mixture melting point.

TABLE I[a]

PMR SPECTRA OF BENZOCYCLOBUTENES

Compound	H_a	H_b, H_c	H_d	H_e	H_f
	4.36 (t) $J \approx 4.5$ Hz	3.72 (m)	7.33 (d)	8.25 (d) $J_{de} = 8$ Hz	8.08 (s)
	4.25 (t) $J \approx 4$ Hz	3.60 (m)	7.11 (d)	7.38 (d) $J_{de} = 9$ Hz	7.30 (s)

[a] Pmr spectra are determined in $CDCl_3$ solution on a Varian A-60A spectrometer and the absorption peaks are given in parts per million downfield from tetramethylsilane (TMS) used as an internal standard. Abbreviations used here include s = singlet; d = doublet; t = triplet; m = multiplet.

Experimental Section[8]

5-Nitro-1-cyanobenzocyclobutene (3).—In a 250-ml three-necked flask were placed 90 ml of concentrated sulfuric acid and 9.4 g (0.11 mol) of sodium nitrate. The mixture was cooled to −5° and 13 g (0.10 mol) of 1-cyanobenzocyclobutene[6] added dropwise at such a rate as to keep the temperature below 2°. The reaction mixture was then stirred at 0–5° for 30 min, poured onto 700 g of ice, and extracted with four 200-ml portions of methylene chloride. The methylene chloride solution was washed with four 100-ml portions of 10% sodium bicarbonate and once with 200 ml of water and dried over anhydrous magnesium sulfate. Removal of the solvent gave 17 g of residue which was recrystallized from 125 ml of absolute ethanol to give 8.6 g (49% yield) of product, mp 107–110°. Several recrystallizations from ethanol gave an analytical sample, mp 111.5–113°.

Anal. Calcd for $C_9H_6N_2O_2$: C, 62.06; H, 3.48; N, 16.08. Found: C, 62.16; H, 3.58; N, 16.17.

Chromatographic Examination of the Nitration Mixture.—A nitration on the same scale as that described above was repeated. Removal of the solvent gave 16.3 g of a light yellow solid. Tlc on silica gel with isopropyl ether as the solvent revealed one major spot, **3**, and three minor spots moving faster than **3** and one spot at the origin. A portion (5 g) of the crude product was recrystallized twice from ethanol to give 2.8 g of **3**, mp 111–112.5°. The mother liquors were concentrated and chromatographed over 200 g of neutral alumina (Ventron Corp., activity 1); 100-ml fractions were collected. Nothing was obtained from the column after elution with 500 ml of petroleum ether, 1500 ml of 5% benzene, and 1200 ml of 10% benzene. Elution with 1000 ml of 20% benzene gave 0.16 g of a mixture of products. The infrared spectrum showed the presence of amide and nitro functional groups and the absence of a nitrile group. Elution with 1500 ml of 30% benzene produced an additional 0.34 g of a mixture identical with the previous fraction. Elution with 1600 ml of 40% benzene gave 1.07 g of **3**. A dark band remained at the top of the column.

5-Amino-1-cyanobenzocyclobutene Hydrochloride (4).—A mixture of 1.75 g (0.01 mol) of 5-nitro-1-cyanobenzocyclobutene, 0.6 ml glacial acetic acid, 0.4 g of 5% palladium on carbon, and 100 ml of ethanol was hydrogenated at atmospheric pressure and ambient temperature. The catalyst was removed by filtration and the mixture was evaporated to dryness. The residue was treated with sodium hydroxide solution. The aqueous solution was extracted with three 25-ml portions of ether. The extracts were dried over potassium carbonate, filtered, and acidified with ether saturated with dry hydrogen chloride. The solid that formed was isolated by filtration and triturated in 50 ml of hot acetonitrile to give 1.3 g (72.3%) of a white solid, mp >300°.

Anal. Calcd for $C_9H_9ClN_2$: C, 59.83; H, 5.02; Cl, 19.63; N, 15.51. Found: C, 59.55; H, 5.20; Cl, 19.68; N, 15.16.

5-Chloro-1-cyanobenzocyclobutene (5) (*via* the Sandmeyer Reaction).—A mixture of 4.4 g (25.3 mmol) of 5-nitro-1-cyanobenzocyclobutene, 1 ml of glacial acetic acid, 1 g of 5% palladium on carbon, and 250 ml of ethanol was hydrogenated at 1 atm of pressure and room temperature. The catalyst was removed by filtration and the solution was evaporated to dryness. The residue was treated with 29 ml of 2 *N* hydrochloric acid and cooled to 0°. To the above suspension was added 1.94 g (28.2 mmol) of sodium nitrite and the reaction mixture was stirred for 5 min and then transferred under nitrogen to a solution of 3.35 g (33.8 mmol) of commercial cuprous chloride in 6 ml of concentrated hydrochloric acid cooled to 0°. After the evolution of nitrogen ceased (about 3 min), the reaction was heated to about 50° on a steam bath and then cooled. The green aqueous layer was decanted from an insoluble semisolid. The insoluble solid was triturated with three 100-ml portions of hot chloroform and filtered. The aqueous solution was extracted once with chloroform. The chloroform extracts were combined, washed with three 100-ml portions of 10% sodium bicarbonate, and dried over magnesium sulfate. The residue obtained after removal of the solvent was purified *via* "Kugelrohr" distillation to give 1.3 g (31%) of product: bp 40–80° (0.02 mm); mp 54–57.5°. This was recrystallized from pentane to give 1.2 g, mp 57–58.5°. Mixture melting point with an authentic sample of 5-chloro-1-cyanobenzocyclobutene was undepressed, mmp 57.5–58.5°.

Anal. Calcd for C_9H_6ClN: C, 66.07; H, 3.70; Cl, 21.68; N, 8.56. Found: C, 66.27; H, 3.64; Cl, 21.3; N, 8.43.

Methyl α-Cyano-2,4-dichlorohydrocinnamate (6).—A solution of 54 g (1 mol) of commercial sodium methoxide in 650 ml of absolute methanol was cooled to 15° and 296 g (4 mol) of methylcyanoacetate was added over a 15-min period with stirring. To the above solution was added 196 g (1 mol) of α-2,4-trichlorotoluene over a 1-hr period. The mixture was slowly heated to reflux and held there for 10 hr. The salt was filtered off and washed with methanol. The filtrate was concentrated to dryness, diluted with 600 ml of ether, washed with three 250-ml portions of water, dried over magnesium sulfate, and then fractionally distilled to give 134 g (52%) of a liquid which solidified on standing: bp 145–148° (0.4 mm); mp 53–58°.

Anal. Calcd for $C_{11}H_9Cl_2NO_2$: C, 51.19; H, 3.52; N, 5.43. Found: C, 51.43; H, 3.71; N, 5.48.

α-Cyano-2,4-dichlorohydrocinnamic Acid (7).—To a stirred solution of 61.4 g (1.54 mol) of sodium hydroxide in 555 ml of water at 25° was added 132 g (0.51 mol) of methyl α-cyano-2,4-dichlorohydrocinnamate as a melt. The reaction was stirred at 25° for 1 hr and then acidified at 25° (cooling required) with 450 ml of 4 *N* hydrochloric acid. The resulting mixture was stirred

(6) J. F. Bunnett and J. A. Skorcz, *J. Org. Chem.*, **27**, 3836 (1962).

(7) H. Hart, J. A. Hartlage, R. W. Fish, and R. R. Rafos, *ibid.*, **31**, 2244 (1966), and references therein.

(8) Melting points are taken on a Thomas–Hoover Unimelt and are uncorrected. Boiling points are uncorrected.

for 0.5 hr and then filtered. The solid was washed with water until the washings were neutral and dried in a vacuum oven at 50° to give 120 g (97.5% yield) of a white solid, mp 145–147°.

Anal. Calcd for $C_{10}H_7Cl_2NO$: C, 49.20; H, 2.89; Cl, 29.04; N, 5.74. Found: C, 49.21; H, 2.82; Cl, 29.03; N, 5.38.

2,4-Dichlorohydrocinnamonitrile (8).—A solution of 560 g (2.29 mol) of α-cyano-2,4-dichlorohydrocinnamic acid in 950 ml of dimethylacetamide was heated at 150° for 1.5 hr. The reaction mixture was cooled and poured into 1 l. of water with stirring. The dark organic layer was separated from the water and the water was extracted with three 500-ml portions of ether. The ether extracts were combined with the original organic layer and then washed with 300 ml of water, 300 ml of 5% hydrochloric acid, and again with 300 ml of water. The ether solution was dried over magnesium sulfate and evaporated to dryness, and was fractionally distilled to give 360 g (79%) of a colorless liquid, bp 121° (0.3 mm).

Anal. Calcd for $C_9H_7Cl_2N$: C, 54.00; H, 3.50; N, 7.00. Found: C, 53.90; H, 3.61; N, 6.83.

5-Chloro-1-cyanobenzocyclobutene (5).[9]—To a well-stirred suspension of 27.7 g (0.71 mol) of commercial sodium amide and 400 ml of liquid ammonia under nitrogen was added 36 g (0.18 mol) of 2,4-dichlorohydrocinnamonitrile over a 10-min period. The mixture was stirred at reflux for 3 hr, neutralized with 62.5 g (0.78 mol) of solid ammonium nitrate, and allowed to stand overnight. The residue was diluted with 350 ml of water and the organic material was extracted with four 150-ml portions of chloroform. The combined extracts were washed with three 150-ml portions of 5% hydrochloric acid and two 100-ml portions of water and dried over magnesium sulfate. The residue (19.2 g after removal of the solvent) was fractionally distilled to give 11.3 g (38.5% yield) of **5**: bp 76–78° (0.08 mm), mp 50–52.5°. An analytical sample was prepared by crystallization from pentane, mp 56.5–57.5°.

Anal. Calcd for C_9H_6ClN: C, 66.07; H, 3.70; N, 8.56. Found: C, 66.32; H, 3.77; N, 8.55.

Registry No.—1-Cyanobenzocyclobutene, 6809-91-2; **3**, 16994-04-0; **4** HCl, 16994-05-1; **5**, 16994-06-2; **6**, 16994-07-3; **7**, 16994-08-4; **8**, 16994-09-5.

(9) Caution: the addition of 2,4-dichlorohydrocinnamonitrile is exothermic.

Deoxygenation of Organic Nitrites[1]

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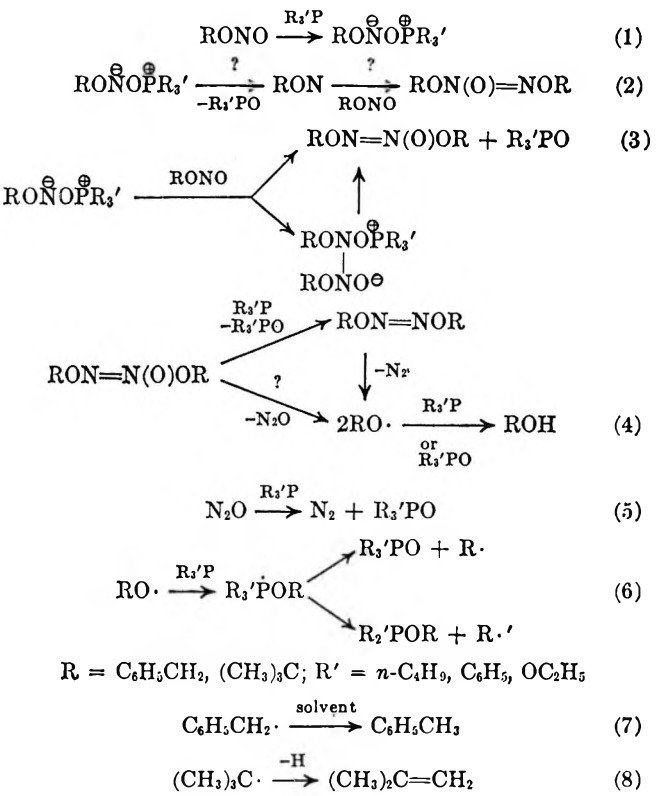
Received February 19, 1968

In an attempt to produce examples of the unknown alkoxy nitrenes, the deoxygenation of nitrite esters by tervalent phosphorus reagents was investigated.[3] Benzyl and *t*-butyl nitrite have been transformed into the corresponding alcohol by both tri-*n*-butyl- and triphenylphosphine and triethyl phosphite as a phosphine oxide or triethyl phosphate is formed.[4] The intermediacy of an alkoxy nitrene is not required; however, a hyponitrite ester, which may be recognized as the formal dimer of an alkoxy nitrene, is a probable intermediate.[5]

An initial nucleophilic attack by tervalent phosphorus upon the terminal nitrite oxygen is proposed (eq 1).[6] Since attempts to trap the monomeric nitrene, which might have been produced by dissociation of the zwitterionic adduct (eq 2), through addition to an



olefinic bond or by insertion with a C—H bond were unsuccessful, it is tentatively assumed that an alkoxynitrene is not generated. This evidence does not rigorously exclude capture of the nitrene on formation of a nitrite ester molecule in a reaction leading directly to a hyponitrite N-oxide (eq 2). It is assumed, however, that the initial adduct combines with another nitrite ester molecule to bring about the formation of the azoxy compound in a reaction requiring either concerted or stepwise elimination of a phosphine oxide (eq 3). Conceivably, alkoxy radicals could be produced directly by the fragmentation of the proposed, but unknown, hyponitrite N-oxide ester. In an alternate sequence a hyponitrite may result from deoxygenation of its N-oxide and subsequently undergo loss of nitrogen with the generation of alkoxy radicals (eq 4 and 5).[7] Abstraction of hydrogen from the organophosphorus solvent then accounts for the formation

(1) Financial support was received from NASA Grant No. NGR 14-012-004.

(2) Address inquiries to this author.

(3) Arylnitrenes have been assumed intermediates in the deoxygenation of aromatic C-nitroso compounds by tervalent phosphorus reagents [G. Smolinsky and B. I. Feuer, *J. Org. Chem.*, **31**, 3882 (1966); R. J. Sundberg, *J. Amer. Chem. Soc.*, **88**, 3781 (1966); J. I. G. Cadogan and M. J. Todd, *Chem. Commun.*, 178 (1967)]. Triphenylphosphine was found to be inert to nitrosamines [L. Horner and H. Hoffmann, *Angew. Chem.*, **68**, 473 (1956)].

(4) Isolation of ethyl nitrite from the reaction between *o*-dinitrobenzene and triethylphosphite [J. I. G. Cadogan, D. J. Sears, and D. M. Smith, *Chem. Commun.*, 491 (1966)] apparently requires the escape of the gaseous ester on formation.

(5) P. J. Bunyan and J. I. G. Cadogan [*J. Chem. Soc.*, 42 (1963)] reported the formation of azoxybenzene during the deoxygenation of nitrosobenzene by triphenylphosphine. Further deoxygenation by the same reagent gives azobenzene [L. Horner and H. Hoffmann, *Angew. Chem.* **68**, 473 (1956)].

(6) Deoxygenation of aromatic nitroso compounds has been accounted for by both nucleophilic [J. I. G. Cadogan, M. Cameron-Wood, R. K. Mackie, and J. G. Searle, *J. Chem. Soc.*, 4831 (1965)] and electrophilic [L. Horner and H. Hoffmann, *Angew. Chem.*, **68**, 473 (1956)] attack by tervalent phosphorus on nitroso oxygen.

(7) Tervalent phosphorus is known to deoxygenate nitrous oxide (eq 5): R. F. Hudson, "Structure and Mechanism in Organophosphorus Chemistry," Academic Press Inc., New York, N. Y., 1965, pp 191 and 192.

of the expected alcohol.[8] This last step had been independently established in the formation of *t*-butyl alcohol from the *t*-butoxy radical, in turn produced from di-*t*-butyl peroxide in triphenylphosphine[9] and has now been confirmed by the transformation of authentic benzyl and *t*-butyl hyponitrite in tri-*n*-butylphosphine into benzyl and *t*-butyl alcohol, respectively.

An alkoxy radical also combines with a phosphine to generate an alkyl radical[9] (eq 6). With this explanation for the presence of benzyl and *t*-butyl radicals, hydrogen abstraction by one and elimination by the other accounts for the minor yields of toluene and isobutylene respectively from benzyl and *t*-butyl nitrite (eq 7 and 8). Insofar as butene-1 was not detected by the formation of its dibromide, the formation of the *n*-butyl radical (eq 6) is doubtful.

Both the cleavage of the benzyloxy radical into the phenyl radical and formaldehyde and of the *t*-butoxy radical into the methyl radical and acetone as well as the apparent disproportionation of the benzyloxy radical into benzaldehyde and benzyl alcohol are established reactions.[10] Detection of low-boiling and gaseous products other than isobutylene and/or other olefins was not attempted here and evidence for the formation of either benzene or benzaldehyde was not found. The observation, from a separate experiment, that benzaldehyde does not react with tri-*n*-butylphosphine under comparable conditions renders the absence of benzaldehyde formation from both benzyl nitrite and hyponitrite in an organophosphorus solvent unresolved.[11] A solution to the problem may require an explanation for the formation and identification of high-boiling oils which contain phosphorus and oxygen but no nitrogen. A similar high-boiling fraction was obtained from *t*-butyl nitrite.[12]

With a molar excess of triphenylphosphine or triethyl phosphite a lower yield of *t*-butyl alcohol was obtained from di-*t*-butyl peroxide.[9] This was attributed to an increase in the production of *t*-butyl radicals (eq 6) required for an increase in hydrocarbon products. In contrast, a slight increase in the yield of benzyl alcohol from benzyl nitrite is realized when a molar excess of tri-*n*-butylphosphine is used. As determined by yields of alcohols produced, the latter reagent appears to be more effective than triphenylphosphine or triethyl phosphite but less effective than isooctane[13] in donating hydrogen to an alkoxy radical produced under comparable conditons.

(8) Assuming that a radical may attack at the phosphorus atom in a phosphine oxide (compare the formation of nitroxides from nitroso compounds and free radicals), an additional sequence of reactions leading to an alcohol can be visualized.

$$RO\cdot + R_3'PO \longrightarrow R_3'P(OR)O\cdot \xrightarrow{\text{solvent}} R_3'P(OR)OH \rightleftharpoons R_3'PO + ROH$$

Elimination of isobutylene from the adduct between a phosphine oxide and *t*-butyl alcohol would partially account for the lower yield of *t*-butyl alcohol in the deoxygenation of *t*-butyl nitrite and pyrolysis of the hyponitrite.

$$(CH_3)_3COP(OH)R_3' \longrightarrow (CH_3)_2C{=}CH_2 + R_3'P(OH)_2$$

Stable phosphine oxide hydrates are known (see ref 7, p 282).

(9) C. Walling, O. H. Basedow, and E. S. Savas [*J. Amer. Chem. Soc.*, **82**, 2181 (1960)] reported the formation of *t*-butyl alcohol (16% yield) from the *t*-butoxy radical and isobutane, isobutylene, neopentane, isopentane, isooctane, octenes, and tetramethylbutane from the *t*-butyl radical in the reaction between di-*t*-butyl peroxide and triphenylphosphine.

(10) P. Gray and A. Williams, *Chem. Rev.*, **59**, 239 (1959).

(11) The resistance of benzaldehyde to tervalent phosphorus has been reported: F. Ramirez, S. B. Bhatia, and C. P. Smith, *Tetrahedron*, **23**, 2067 (1967).

(12) S. A. Buckler [*J. Amer. Chem. Soc.*, **84**, 3093 (1962)] investigated the reaction between equimolar quantities of di-*t*-butyl peroxide and tri-*n*-butylphosphine. It was assumed that deoxygenation of the intermediate *t*-butoxy radical accounted for the formation of tri-*n*-butylphosphine oxide in unspecified yield. Another phosphorus-containing product was detected and characterized by unreported nmr and ir spectral data and vpc. It was assigned the structure of *t*-butyl di-*n*-butylphosphonite (eq 6). Other products were not reported.

Experimental Section

Deoxygenation of Nitrites.—With stirring, 17.39 g (0.127 mol) of freshly prepared and redistilled benzyl nitrite[14,15] was added dropwise over a period of 2 hr to 25.60 g (0.127 mol) of tri-*n*-butylphosphine which had been rigorously dried over calcium hydride. By external cooling the temperature of the exothermic reaction was kept below 15° during addition but was then allowed to rise to room temperature for continued stirring overnight. Distillation of the reaction mixture under ordinary pressure gave 0.35 g (3% yield) of toluene, bp 109–111°; ir and nmr absorption was identical with that of an authentic sample.

Continued distillation at 3 mm separated a low-boiling fraction, 60–155°, from which 8.15 g (65% yield) of benzyl alcohol, bp 202–204° (1 atm), was separated by redistillation; ir and nmr spectra were identical with those obtained from authentic material. From a higher boiling fraction, 155–165° (3 mm), 19.20 g (75% yield) of tri-*n*-butylphosphine oxide, mp 65–68°, was obtained after redistillation; ir and nmr spectra were identical with those obtained from authentic material. Finally 2.02 g of a high-boiling oil, 190–210° (0.25 mm), and a pot residue (0.35 g) were not identified.

When the reaction was repeated with a molar excess of tri-*n*-butylphosphine, the yield of benzyl alcohol in the reaction mixture was estimated to be 78% as determined from the nmr absorption at δ 4.55 (benzylic protons).

With the substitution of triethyl phosphite for tri-*n*-butylphosphine, about 30% benzyl nitrite remained unreacted after heating the reaction mixture under nitrogen at 100° for 2 days and a 55% yield of benzyl alcohol was obtained. The same yield of alcohol was obtained from a moderately exothermic reaction between benzyl nitrite and triphenylphosphine in benzene. Attempts to obtain products by insertion or abstraction with C—H bonds in hydrocarbon solvents or by addition to the C=C double bond in cyclohexene which might be characteristic of benzyloxynitrene were unsuccessful.

With stirring 29.60 g (0.287 mol) of freshly prepared and redistilled *t*-butyl nitrite[16] was added dropwise over a period of 2 hr to 61.00 g (0.302 mol) of tri-*n*-butylphosphine in a 250-ml, three-necked flask equipped to deliver evolved gas into a solution of 3 ml of bromine in 250 ml of carbon tetrachloride. The reaction temperature was carefully held between 65 and 70° (there does not appear to be a reaction at room temperature), and stirring was continued at this temperature overnight. By distilling at ordinary pressure 1.42 g of unreacted *t*-butyl nitrite was recovered and 8.18 g (43.5% yield based on recovered nitrite) of *t*-butyl alcohol, bp 80°, was collected; ir and nmr absorptions were identical with those obtained from an authentic sample. Continued distillation gave 57.74 g (91% yield) of tri-*n*-butylphosphine oxide, bp 182° (23 mm); ir and nmr absorptions were identical with those from authentic material. An unidentified oil (5.00 g), bp 220–230° (23 mm), was also obtained.

By distillation 1.95 g (5.5% yield) of isobutylene dibromide, bp 114–150°, was isolated from the reaction between the evolved

(13) H. Kiefer and T. G. Traylor [*Tetrahedron Lett.*, 6163 (1966); *J. Amer. Chem. Soc.*, **89**, 667 (1967)] reported an 89% yield of *t*-butyl alcohol during the pyrolysis of *t*-butyl hyponitrite in isooctane.

(14) N. Kornblum, R. A. Smiley, R. K. Blackwood, and D. C. Iffland, *J. Amer. Chem. Soc.*, **77**, 6269 (1955).

(15) Benzaldehyde, detected by nmr, appears in samples of benzyl nitrite after storage for a few days. This may be accounted for by a chain reaction with oxygen as the initiator.

$$C_6H_5CH_2ONO \xrightarrow[-\cdot OH]{O_2} C_6H_5\overset{ONO}{\underset{|}{C}}HO\cdot \xrightarrow{C_6H_5CH_2-ONO} C_6H_5\overset{ONO}{\underset{|}{C}}HOH + C_6H_5\dot{C}HONO$$

$$C_6H_5\dot{C}HONO \xrightarrow{-NO} C_6H_5CHO$$

$$C_6H_5CH_2ONO \xrightarrow[-NOH]{NO} C_6H_5\dot{C}HONO$$

(16) C. S. Coe and T. F. Doumani, *ibid.*, **70**, 1516 (1948).

gas, isobutylene, and bromine in carbon tetrachloride [δ 1.90 (six protons) and 3.88 (two protons)]. From the nmr the product was judged to be about 90% pure.

Pyrolysis of Hyponitrites.—In a 10-ml, round-bottom flask fitted with a reflux condenser, 0.66 g (3.79 mmol) of *t*-butyl hyponitrite[13] was slowly mixed with 3.86 g (19.1 mmol) of tri-*n*-butylphosphine while external control kept the temperature near 55° (below 50° the two liquids appear to be immiscible). After stirring for 20 hr at this temperature, *t*-butyl alcohol was detected in 35% yield by measuring peak areas by vpc from an SE-30 10-ft column operated at 60°. Standards for comparison in calculating yield consisted of prepared mixtures of tri-*n*-butylphosphine and *t*-butyl alcohol. *Caution.* In one experiment with inadequate external control of the reaction temperature, the mixture of *t*-butyl hyponitrite and tri-*n*-butylphosphine became explosive.

In a similar reaction, 0.1471 g (0.608 mmol) of benzyl hyponitrite, mp 44–46° dec,[17] and 0.5846 g (2.89 mmol) of tri-*n*-butylphosphine were stirred overnight at room temperature. The initially clear solution became dark brown after 24 hr and then yellow. Benzyl alcohol was detected in 38.2% yield by vpc. Standards for comparison in calculating yield consisted of prepared mixtures of tri-*n*-butylphosphine and benzyl alcohol.

Registry No.—Benzyl nitrite, 935-05-7; *t*-butyl nitrite, 540-80-7.

(17) J. R. Partington and C. C. Shah, *J. Chem. Soc.*, 2071 (1931).

The Timing of Covalency Changes in Nucleophilic Substitutions at Sulfenyl Sulfur. The Influence of *meta* and *para* Substituents on the Rate of Reaction of Aryl Bunte Salts with Cyanide Ion[1]

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Nucleophilic substitution at a sulfenyl sulfur, shown in a generalized representation in eq 1, is one of

$$Nu^- + R—S—Y \longrightarrow R—S—Nu + Y^- \quad (1)$$

the most important and fundamental reactions of organic sulfur chemistry.[2] As a consequence, detailed knowledge about all aspects of its mechanism is highly desirable.

In a classic study, Fava and Ilceto[3] have shown, through examination of the effect of changes in R on rate, that the steric requirements of the displacement reaction

$$*SO_3^{2-} + R—S—SO_3^- \longrightarrow R—S—*SO_3^- + SO_3^{2-} \quad (2)$$

are remarkably similar to those for bimolecular nucleophilic substitution at primary carbon (eq 3). They

$$Nu^- + RCH_2Y \longrightarrow RCH_2Nu + Y^- \quad (3)$$

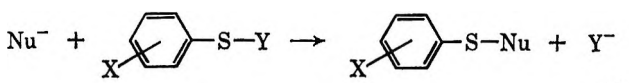
have suggested that this means that the preferred transition-state geometry for nucleophilic substitution at sp³ carbon and sulfenyl sulfur is the same, namely, a trigonal bipyramid with the entering and leaving groups occupying the apical positions.

This clarification of transition-state geometry does not, however, tell us anything about the relative progress of bond making *vs.* bond breaking in the transition states of eq 1 or 2. In SN2 displacements at sp³ carbon bond making and bond breaking are synchronous. The same could well be true for nucleophilic displacements at sulfenyl sulfur, but, at the same time, given the ability of sulfur to expand its valence shell, serious consideration must also be given to the possibility that bond making may well be ahead of bond breaking when the transition state is reached. In the most extreme representation one might even conceive of an actual intermediate (I) being formed during the reaction, *i.e.*

$$Nu^- + R—S—Y \longrightarrow Nu—\underset{\underset{R}{|}}{S}—Y \longrightarrow R—S—Nu + Y^- \quad (4)$$

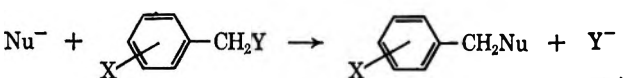
I

One way of probing this matter of the timing of the several covalency changes involved in eq 1 is through measurement of the effect of selected *meta* and *para* substituents on the rate of a substitution of the type



(5)

One can then compare the results with those for analogous displacements at sp³ carbon (eq 6) and silicon (eq 7). Those substitutions at silicon, where bond making



(6)

$$Nu^- + R_3Si—Y \longrightarrow R_3Si—Nu + Y^- \quad (7)$$

is well ahead of bond breaking in the transition state, owing to the use of silicon d orbitals, are characterized[4] by a very pronounced dependence of rate on substituents and large positive values of ρ.* In contrast, substitutions at a benzylic sp³ carbon (eq 6), where bond making and brond breaking are truly synchronous, show relatively little dependence of rate on X and no satisfactory correlation with the Hammett equation, rates frequently being faster for both electron-withdrawing and electron-releasing substituents than they are for the unsubstituted compound.[5] There is thus reason to feel that, if the substitution at sulfenyl sulfur (eq 5) involves the use of the d orbitals on that atom, as in eq 4, it will show a considerably different response to changes in the nature of X than if it involves essentially synchronous bond making and bond breaking.

The specific example of eq 5 examined in the present work was the reaction of cyanide ion with S-aryl thio-

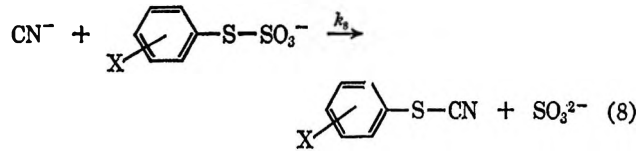
(1) This research supported by the National Institutes of Health under Grant GM-12104.

(2) (a) A. J. Parker and N. Kharasch, *Chem. Rev.*, **59**, 583 (1959); (b) O. Foss in "Organic Sulfur Compounds," Vol. 1, N. Kharasch, Ed., Pergammon Press, Oxford, Chapter 9, 1961.

(3) A. Fava and A. Ilceto, *J. Amer. Chem. Soc.*, **80**, 3478 (1958).

(4) (a) O. W. Steward and O. R. Pierce, *ibid.*, **83**, 1916 (1961); (b) for a summary of all studies of this type, see L. H. Sommer, "Stereochemistry, Mechanism and Silicon," McGraw-Hill Book Co., Inc., New York, N. Y., 1965, pp 127–146.

(5) (a) R. F. Hudson and G. Klopman, *J. Chem. Soc.*, 1062 (1962); (b) R. Fuchs and D. M. Carlton, *J. Amer. Chem. Soc.*, **85**, 104 (1963); (c) for a summary of various earlier data, see A. Streitwieser, *Chem. Rev.*, **56**, 591 (1956).



sulfates (eq 8).[6] Reaction rates can be followed spectrophotometrically (see Experimental Section). The reactions were studied in aqueous carbonate–bicarbonate buffers (pH 9.00–10.36). Other experiments showed that the rate of disappearance of the Bunte salt in the absence of cyanide ion at these pH's was negligible. The reactions were run using a large stoichiometric excess of cyanide over Bunte salt. The concentration of free cyanide ion was varied by using a fixed amount of sodium cyanide (0.016 M) for all runs and varying the pH at which runs were carried out. Since K_a for HCN is 7×10^{-10}, only 41% of the total cyanide is present as CN^- at pH 9, while at pH 10.36 94% is present as CN^-. The initial concentration of Bunte salt was varied over the range $1.0\text{–}8.0 \times 10^{-4}$ M. Because the final optical density of the solution shows significant drift (due, presumably, to subsequent reactions of ArSCN), rate constants were determined from the initial rate of change of the optical density of the solution, assuming the kinetics of eq 8 to be given by

$$\text{initial rate} = k_8(\text{ArSSO}_3^-)_0(\text{CN}^-) \quad (9)$$

The constancy of k_8 for a given Bunte salt as determined from

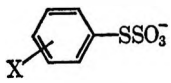
$$k_8 = \frac{\text{initial rate}}{(\text{ArSSO}_3^-)_0(\text{CN}^-)}$$

for a series of runs in which both the initial concentration of Bunte salt and the concentration of cyanide ion were varied (see Experimental Section for typical results) established that the kinetics of reaction 8 are indeed correctly given by eq 9.

Table I lists the rate constants for the reaction of six *meta*- and *para*-substituted S-aryl thiosulfates with cyanide ion at 25° in aqueous solution at an ionic strength

TABLE I

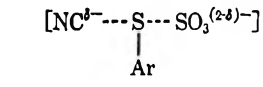
RATE CONSTANTS FOR REACTION OF CYANIDE ION WITH ARYL BUNTE SALTS[a]



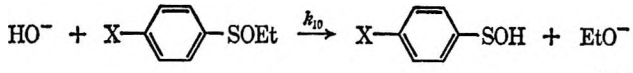
X[b]	$k_8 \times 10^2$, M^{-1} sec^{-1}	$(k_X/k_{p\text{-H}})$
p-CH_3	1.0	1.1
p-H	0.91	(1.0)
p-Cl	1.6	1.8
p-Br	1.2	1.3
m-NO_2	1.1	1.2
p-NO_2	1.2	1.3

[a] All runs were at 25° in water at pH 10.36 and an ionic strength of 2.0. [b] Registry numbers are given in consecutive order: 16727-96-1, 16723-24-3, 16723-25-4, 16723-26-5, 16723-27-6, 16723-28-7.

of 2.0. Examination of Table I reveals that the rate constant for eq 8 shows no obvious dependence on the electron-withdrawing or electron-releasing character of the substituent attached to the aromatic ring. Although one electron-withdrawing substituent, p-Cl (σ = +0.23), causes a fairly substantial increase in rate, others, much more strongly electron withdrawing, such as m-NO_2 (σ = +0.71) and p-NO_2 (σ = +0.78), lead to only small increases in rate. These are, in fact, not much larger than that caused by p-CH_3 (σ = −0.17), an electron-releasing substituent. Because of the necessity of evaluating k_8 from initial rate measurements the values given in Table I are probably accurate to no better than ±15%. This could perhaps be responsible for the apparent anomalously high rate for the p-Cl compound. However, even if the k_8 values were subject to even greater uncertainty (±50%) this would not change the basic conclusion from these results, which is that the electron density at the sulfenyl sulfur must be essentially the same in the transition state for eq 8 as it is in the Bunte salt itself. This is hardly in accord with what would be expected if the mechanism were as shown in eq 4, or in any variant of it in which bond making is significantly ahead of bond breaking at the transition state. We conclude that in the transition state for eq 8 the making of the new bond has progressed no further than the breaking of the old one. Its structure should therefore be represented as



Despite the availability of the d orbitals on sulfur the timing of the various covalency changes in this nucleophilic substitution seems to be closely comparable with the timing for an S_N2 reaction at sp^3 carbon and quite different from the timing for substitutions at silicon. This conclusion is also in accord with the results of another recent study[7] dealing with the effect of substituents on the rate of a nucleophilic substitution involving aryl sulfenyl compounds. Equation 10 represents the rate-determining step in the alkaline hydrolysis of a series of p-substituted ethyl benzenesulfenates.



(10)

The observed[7] variation of k_{10} with X was as follows: X, $(k_X/k_{p\text{-H}})$; CH_3, 1.21; Cl, 3.0; CF_3, 1.47. Although substituents exert generally a somewhat larger effect than in the Bunte salt–cyanide reaction, one still finds that a strong electron-withdrawing group, p-CF_3 (σ = +0.54), accelerates the rate considerably less than p-Cl and not much more than p-CH_3.

Acceleration of the rate by both electron-withdrawing and electron-releasing *para* substituents has, as noted earlier, also been observed in a number of nucleophilic displacements involving substituted benzyl halides (eq 6).[5] Unlike the two substitutions at sulfenyl sulfur, however, in most of the benzyl halide reactions the acceleration produced by a strong electron-withdrawing substituent like p-NO_2 clearly exceeds that produced by either a weaker electron-withdrawing one like p-Cl or an electron-releasing one like p-CH_3. One case (Y = Cl, Nu = $S_2O_3^{2-}$) is known,[5b] however, where $k_{m\text{-}NO_2}/k_{p\text{-H}}$ is slightly less than $k_{p\text{-Cl}}/k_{p\text{-H}}$.

(6) H. B. Footner and S. Smiles, *J. Chem. Soc.*, **121**, 2887 (1925).

(7) C. Brown and D. R. Hogg, *Chem. Commun.*, 38 (1967).

(8) A. Fava, private communication.

In conclusion one should also note some unpublished work by Fava,[8] in which he studied the effect of *para*

$$*SO_3^{2-} + ArSSO_3^- \xrightarrow{k_{11}} ArS—\overset{*}{S}O_3^- + SO_3^{2-} \qquad (11)$$

substituents on the rate of the exchange reaction in eq 11 involving aryl Bunte salts. The variation of k_{11} with *para* substituent X was as follows: X, $(k_{p\text{-}X}/k_{p\text{-}H})$; CH_3, 0.76; Cl, 1.70; NO_2, 5.22. Even though in this instance the rate for the *p*-NO_2 compound is considerably faster than the rate for the *p*-chloro compound, substituent effects are still rather small ($\rho = +0.85$), and Fava[8] has concluded, like ourselves and Brown and Hogg,[7] that little if any d orbital participation involving sulfur occurs in such substitutions at sulfenyl sulfur.

Experimental Section

Preparation of Bunte Salts.—Except for the *m*-nitrophenyl compound[9] all of the Bunte salts were first prepared as pyridinium S-aryl thiosulfates.[9] They were then converted into the sodium S-aryl thiosulfates using the ion-exchange procedure previously described.[9] Analytical data were obtained on those salts which had not been previously prepared. All were isolated as the monohydrate: sodium S-*p*-tolyl thiosulfate (Calcd for $C_7H_7NaO_3S_2 \cdot H_2O$: C, 34.42; H, 3.71. Found: C, 34.41; H, 3.88), sodium S-*p*-chlorophenyl thiosulfate (Calcd for $C_6H_4ClNaO_3S_2 \cdot H_2O$: C, 27.23; H, 2.29. Found: C, 27.28; H, 2.43), sodium S-*p*-bromophenyl thiosulfate (Calcd for $C_6H_4BrNaO_3S_2 \cdot H_2O$: C, 23.34; H, 1.96. Found: C, 23.26; H, 2.03), sodium S-*p*-nitrophenyl thiosulfate. (Calcd for $C_6H_4NNaO_5S_2 \cdot H_2O$: C, 26.18; H, 2.20. Found: C, 26.00; H, 2.29).

Procedure for Kinetic Runs.—Bicarbonate–carbonate buffer solutions of the proper pH and containing the desired amount of sodium cyanide were made up volumetrically. A solution of the appropriate Bunte salt in water was made up separately. The reaction vessel used for the kinetic runs was the type described in another paper.[10] For a run measured aliquots of the buffer–cyanide and the Bunte salt solutions were placed separately in chambers A and B of the reaction vessel and brought to temperature. They were then mixed rapidly, and the resulting solution was poured into the 1-cm cell which was attached to the side of chamber B. The apparatus was placed in the cell compartment of Cary Model 15 spectrophotometer, which was equipped to permit thermostatting of the 1-cm cell. The decrease in the absorbance of the reaction solution was then followed at a wavelength between 260 and 268 mμ. Because the final optical density of the solution tended to drift significantly, rates were evaluated from the initial rate of change of the optical density. This was determined by drawing a line tangent to the initial portion of the absorbance *vs.* the time curve. At least three separate runs were made for each set of reaction conditions. Some typical results obtained upon variation of the initial concentrations of Bunte salt and cyanide ion are shown in Table II.

TABLE II

$(ArSSO_3^-)_0$, *M*	(CN^-), *M*	$-d(ArSSO_3^-)_0/dt$, *M* sec^{-1}	$k_0 = \frac{-d(ArSSO_3^-)_0/dt}{(ArSSO_3^-)_0(CN^-)}$
8×10^{-4}	1.5×10^{-2}	1.1×10^{-7}	0.0092
4×10^{-4}	1.5×10^{-2}	0.55×10^{-7}	0.0091
4×10^{-4}	0.66×10^{-2}	0.26×10^{-7}	0.0098

(The data in question are for the S-phenyl Bunte salt.) Similar sorts of results were found with the other Bunte salts. It therefore seems clear that the Bunte salt–cyanide reaction is first order in each reactant, and also that the procedure of determining its rate constant from initial rates does not lead to any significant error.

Registry No.—Cyanide ion, 57-12-5.

(9) J. L. Kice, J. M. Anderson, and N. E. Pawlowski, *J. Amer. Chem. Soc.*, **88**, 5245 (1966).

(10) J. L. Kice, G. Guaraldi, and C. G. Venier, *J. Org. Chem.*, **31**, 3561 (1966).

Chemistry of Trialkylthiomethyl Ions. II. A Convenient Synthesis of Tetrathioorthocarbonate Esters

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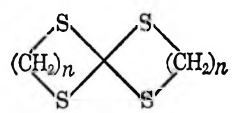
Received March 26, 1968

Our investigation into the chemistry of trimethylthiomethyl cation (1) has utilized the corresponding tetrathioorthocarbonate esters (2) as precursors for 1 and its homologs.[1] Orthocarbonates of this type have been known for many years but their synthesis has been indirect and laborious. Arndt[2,3] and, later, Backer and Stedehouder[4] prepared several aromatic tetrathioorthocarbonates in unspecified yields by nitrosation of isothiouronium salts followed by the decomposition of the nitrosated adduct in aqueous or methanolic ammonia (eq 1). This method was extended to a series of alkyl tetrathioorthocarbonates in yields averaging about 20%.[4-6]

$$\left[RSC(NH_2)_2\right]^+ \cdot X^- \xrightarrow[2.\ NH_3,\ RSH]{1.\ HONO} (RS)_4C \qquad (1)$$
$$\mathbf{2}$$

More recently the preparation of 2 has been achieved by a sequence of reactions involving removal of the proton from an orthothioformate and thioalkylation of the resulting anion with the appropriate disulfide (eq 2).[7-9] The synthesis of the spiran derivative 3, a special case of 2, by methods whose general applicability has not been tested, was reported by Johnson[10] and by D'Amico and Campbell.[11]

$$(RS)_3CH \xrightarrow[\text{or } n\text{-}C_4H_9Li]{\overline{NH_2},\ NH_3} (RS)_3C^- \xrightarrow{(RS)_2} \mathbf{2} \qquad (2)$$



3, $n = 2$ or 3

We have found that trimethylthiomethyl fluoroborate (1), which is an easily prepared and stable material,[1] serves as a convenient intermediate in the preparation

(1) W. P. Tucker and G. L. Roof, *Tetrahedron Lett.*, 2747 (1967).

(2) F. Arndt, *Ann.* **384**, 322 (1911).

(3) F. Arndt, *ibid.*, **396**, 1 (1913).

(4) H. J. Backer and P. L. Stedehouder, *Rec. Trav. Chim. Pays-Bas*, **52**, 1039 (1933).

(5) H. J. Backer and P. L. Stedehouder, *ibid.*, **52**, 923 (1933).

(6) We have prepared most of the compounds listed in Table I by this method but always in low and unsatisfactory yields.

(7) A. Fröling and J. F. Arens, *Rec. Trav. Chim. Pays Bas*, **81**, 1009 (1962).

(8) D. Seebach, *Angew. Chem. Intern. Ed.*, **6**, 442 (1967).

(9) Yields in this reaction are on the order of 50% but we have encountered difficulty in separation of the desired product from the tetrakisalkylthioethylene which is produced in a side reaction.[7]

(10) T. P. Johnson, C. R. Stringfellow, and A. Gallagher, *J. Org. Chem.*, **27**, 4068 (1962).

(11) J. J. D'Amico and R. H. Campbell, *ibid.*, **32**, 2567 (1967).

of a variety of tetrathioorthocarbonates in good yields. Although the reaction between 1 and thiols represents an equilibrium (eq 3), the removal of the very volatile

$$\underset{1}{(CH_3S)_3C^+BF_4^-} + 4RSH \rightleftharpoons \underset{2}{(RS)_4C} + 3CH_3SH + HBF_4 \quad (3)$$

methanethiol displaces the reaction in favor of 2. A second equilibrium is thereby established (eq 4),

$$2 + H^+ \rightleftharpoons (RS)_3C^+ + RSH \quad (4)$$

but the formation of 2 can be favored by using excess thiol (method A) or by using sodium bicarbonate to remove the acid which promotes the equilibrium (method B). Method A was employed for the synthesis of alkyl tetrathioorthocarbonates and method B was used for the preparation of aryl derivatives.

The properties and yields of the tetrathioorthocarbonates prepared from 1 are given in Table I.

TABLE I

TETRATHIOORTHOCARBONATE ESTERS (2a–h)

R	Method of preparation[a]	% yield[b]	Recrystn solvent	Mp, °C[c]	Lit. mp, °C
CH_3 (a)	A	97	95% EtOH	65	65[d]
C_2H_5 (b)	A	88	95% EtOH	31–32	33–33.5[d]
n-C_3H_7 (c)	A	86[e]		[f]	
i-C_3H_7 (d)	A	92	95% EtOH	60–61.5	61.5[d]
C_6H_5 (e)	B	85	C_6H_6	159–160	159[g,h]
p-$CH_3C_6H_4$ (f)	B	85	C_6H_6-heptane	145–146	147[i]
p-ClC_6H_4 (g)	B	90[j]	C_6H_6	210–211 dec	212–213[g]
β-$C_{10}H_7$ (h)	B	86[k]	$CHCl_3$	189–192 dec	134–136[h]

[a] See Experimental Section. [b] Yields are based on unrecrystallized products. [c] Melting points were taken on a Thomas–Hoover melting point apparatus and are uncorrected. [d] Reference 5. [e] *Anal.* Calcd for $C_{13}H_{28}S_4$: C, 49.94; H, 9.03. Found: C, 50.10; H, 8.90. [f] Bp 123° (0.16 mm). [g] Reference 3. [h] Reference 4. [i] Reference 2. [j] *Anal.* Calcd for $C_{25}H_{16}Cl_4S_4$: C, 51.20; H, 2.75. Found: C, 51.43; H, 2.83. [k] The melting point of our product differed markedly from that reported in ref 4. A good elemental analysis was obtained. *Anal.* Calcd for $C_{41}H_{28}S_4$: C, 75.88; H, 4.35. Found: C, 75.63; H, 4.40.

Experimental Section

Tetrathioorthocarbonate Esters (2). Method A.—A stirred mixture of 1.15 mol of alkanethiol and 0.1 mol of trimethylthiomethyl fluoroborate (1) was refluxed for 48 hr.[12] After cooling, 75 ml of 10% sodium hydroxide was added, and the organic layer was separated and washed three times with 10% sodium hydroxide and three times with water. Volatile materials were removed *in vacuo* and the crude product was purified by recrystallization or by distillation under reduced pressure.

Method B.—A stirred mixture of 0.06 mol of arylthiol, 0.01 mol of 1, and 0.01 mol of solid sodium bicarbonate in 50 ml of dry benzene was refluxed for 12 hr. After removal of the solvent *in vacuo* the residue was washed with 10% sodium hydroxide and then three times with water. The crude product was dried before recrystallization from an appropriate solvent.

Registry No.—**2a**, 6156-25-8; **2b**, 16876-57-6; **2c**, 16876-58-7; **2d**, 16876-59-8; **2e**, 14758-47-5; **2f**, 16915-94-9; **2g**, 16876-61-2; **2h**, 16876-62-3.

Acknowledgment.—We are grateful to the National Science Foundation for support of this work under Grant GP-7460.

(12) Dry 1,2-dichloroethane was used as a solvent with both methane and ethanethiol. In the first case, methanethiol was bubbled into a suspension of 1 at room temperature until homogeneity was achieved. In the ethyl case, the solvent was used to obtain a higher reaction temperature.

A Convenient Gas Chromatographic Method for Determining Activation Energies of First-Order Reactions

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Received March 6, 1968

In the study of the vapor phase thermal isomerization of stilbene it was necessary to determine the activation energy for this first-order reaction rapidly and reasonably accurately. The gas chromatographic method developed to do this should provide a generally useful technique for the rapid determination of activation energies using exceedingly small amounts of compounds and very simple equipment. We envisage this technique as being particularly valuable for the rapid examination of reactions of a series of structurally related organic compounds.

In its simplest form, the technique uses a gas chromatographic injection chamber as a constant time and temperature flow reactor. The reaction is rapidly quenched by the gas chromatographic column which is at a temperature sufficiently low to preclude reaction in this region, yet at a temperature high enough to produce an adequate separation of the reactant and products in a reasonable period of time. The extent of conversion is then determined as a function of the injection block equilibrium temperature while maintaining the same flow rate at each temperature and assuring reproducible injection technique. The conversion can be related to the activation energy in the following way.

$$\ln \ln \left(\frac{C_0}{C}\right) = -\frac{E_a}{RT} + \ln (At)$$

This equation was obtained by taking the logarithims of the integrated first-order rate expression, $\ln (C_0/C) = kt$, and the Arrhenius equation, $k = A \exp(-E_a/RT)$, and eliminating $\ln k$. With a constant preexponential factor A over the range of injector block temperatures studied, as well as a constant time t in the block, it is evident that the slope of a plot of $\ln \ln (C_0/C)$ *vs.* $1/T$ yields the Arrhenius activation energy as $-E_a/R$.

Three unrelated reactions were chosen to test the method; first, the isomerization of *cis*-stilbene; second, the Diels–Alder retrogression of norbornene; and third, the Claisen rearrangement of allyl phenyl ether. All of the measurements described were made on a Wilkins Aerograph Model 600-D gas chromatograph, which was modified only by embedding a thermocouple into a cavity of the injection block, surrounding the block with extra insulation, and adding a Matheson precision gas flow meter. A second thermocouple, placed in the flow section of the block and centered for maximum temperature response, indicated that the block temperature was at the most 2–3° higher at thermal equilibrium than that of the carrier gas. Typical sample sizes were 0.2 to 0.4 μl of neat liquid, permitting the determination of an activation energy with less than 50 μl of sample which need not be pure so long as the impurities do not interfere analytically, and in a period on the order of

(1) National Science Foundation Graduate Trainee, 1965–1968.
(2) National Institutes of Health Predoctoral Fellow 1965–1966.

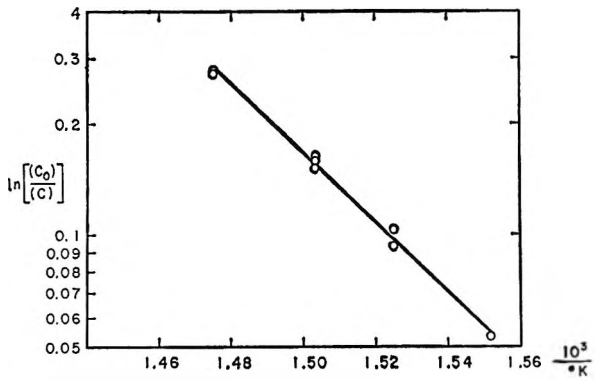

Figure 1.—Semilogarithmic plot of ln (C_0/C) *vs.* reciprocal of injection block absolute temperature for *cis*-stilbene isomerization.

several hours after devising a suitable product analysis. For the analytical separations 0.125 in. × 5 ft packed columns were used: for the stilbenes, 5% SE-30, on 60/80 Chromosorb W; for the allyl phenyl ether system, 2% xylenyl phosphate, on 80/100 Chromosorb G; for the norbornene system, 15% Apiezon L, on 60/80 Chromosorb W.

Figure 1 is a semilogarithmic plot of ln (C_0/C) *vs.* the reciprocal of the absolute temperature of the injection block for the isomerization of *cis*-stilbene. The activation energy obtained from the slope of this plot is 42.6 ∓ 1.0 kcal mol^{-1} (lit.[3] 42.8 kcal mol^{-1}). Similarly the activation energy for the Diels–Alder retrogression of norbornene was found to be 41.3 ∓ 1.5 kcal mol^{-1} (lit.[4] 42.8 ∓ 0.6 kcal mol^{-1}), and that for the Claisen rearrangement of allyl phenyl ether was found to be 33.2 ∓ 1.5 kcal mol^{-1} (lit.[5] 32.2 kcal mol^{-1} in Carbitol).

Several notes of caution should be given. Owing to the nature of the logarithmic function the spread of experimental points is expected to be greater at low rather than at high conversions under conditions of equal precision in temperature measurement, flow rate regulation, sample introduction, and analysis. Nonlinearity, however, is also observed at very high temperatures, where appreciable back reaction becomes evident for *cis*-stilbene or, in the case of the Claisen rearrangement of allyl phenyl ether, where a concurrent reaction with a greater temperature coefficient becomes important. In the allyl phenyl ether reaction at high temperatures cleavage to phenol competes favorably with *ortho* rearrangement and is the preferred reaction above 380° at a helium flow rate of 6 cc min^{-1} with the particular block geometry of our instrument. The activation energy given in the case of allyl phenyl ether is that for its disappearance, determined from the linear, lower temperature portion of the plot analogous to Figure 1.

An increase in flow rate from 10 to 14 cc min^{-1} did not afford an experimentally significant difference (>1.0 kcal mol^{-1}) in activation energy for the *cis*-stilbene isomerization, although it decreased the extent of reaction.

Acknowledgment.—This investigation was supported in part by Research Grant GM 12988 from the Division of General Medical Sciences, Public Health Services, National Institutes of Health.

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On a Supposed Preparation of α-Chloroanisole

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Received March 26, 1968

Because of a need for α-chloroanisole (chloromethyl phenyl ether) in connection with some synthetic work in progress, we had a chance to repeat the most recent preparation for this compound given in the literature.[1] Following the instructions given in ref 1, anisole in methylene chloride solution was brought to reflux temperature, and sulfuryl chloride was added dropwise, exactly as specified. The product was distilled and exhibited the physical constants quoted, namely, bp 74–77° (13 mm) and n^{25}D 1.5342.

To our surprise, however, the product was insensitive to silver nitrate solution and did not react with benzyldimethylamine.[2] The nmr spectrum in $CDCl_3$ solution clearly showed two doublets centered at δ 6.78 and 7.31 (J = 10 cps), characteristic of an aromatic AB system. It therefore appeared probable that our product was *p*-chloroanisole rather than the expected α-chloroanisole. The preparation was repeated four times with identical results, so that aromatic chlorination always occurred. Spectral (nmr and ir) comparison of the synthetic material with an authentic sample (Eastman Distillation Products) of *p*-chloroanisole indicated the two compounds to be essentially identical, but gas chromatography showed our product to be only 90% pure, as specifically stated in the preparation given.[1]

Aromatic chlorination by means of sulfuryl chloride is not unusual, and has been amply recorded in the literature.[3] It is claimed that the procedure utilized in ref 1 is that of Bordwell and Pitt. These authors prepared a number of α-chloromethyl sulfides by this procedure, but it was never suggested that the method could be extended to prepare α-chloromethyl ethers.[4]

It is easy to see in retrospect how *p*-chloroanisole could be mistaken for α-chloroanisole. Besides having identical elemental analyses, the two compounds possess very close boiling points and refractive indices as indicated in Table I.

TABLE I

	Bp, °C (mm)	n_D
p-Chloroanisole	90–92 (18)	1.5351 at 20°
α-Chloroanisole	88–90 (15)	1.5362 at 20°

In conclusion, therefore, the best method for preparing α-chloroanisole is still that used by Schollkopf and coworkers.[5] The supposed preparation of α-chloroanisole given in ref 1 is at best a procedure for obtaining slightly impure *p*-chloroanisole.

Registry No.—α-Chloroanisole, 6707-01-3; *p*-chloroanisole, 623-12-1.

Acknowledgment.—The authors wish to thank the National Institutes of Health for Grant GM-10608.

(1) C. S. Davis and G. S. Lougheed, *Org. Syn.*, **47**, 23 (1967).
(2) H. J. Barber and M. B. Green, *J. Appl. Chem.*, 115 (1954).
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A ^{15}N Isotope Tracer Study on 3-Anilino-1-phenyl-2-pyrazolin-5-one

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Certain pyrazolin-5-ones have found use in medicine as analgesics and antipyretics and in color photography as magenta dye formers.[2] An important addition to this last class of compounds has been the 3-anilino-1-aryl-2-pyrazolin-5-ones. The simplest example of this group, 3-anilino-1-phenyl-2-pyrazolin-5-one, was first synthesized by Weissberger[3] in the manner shown by eq 1. The purpose of the present work was to determine the tautomeric forms of **1** in solvents of different polarities and to show some relationships between the tautomers of **1** and those of other 2-pyrazolin-5-ones.

We have synthesized **1a** by an improved method (eq 2) from aniline containing more than 90% ^{15}N isotope. In this preparation, equivalent amounts of reactants were refluxed in acetic acid containing 10% aqueous hydrochloric acid. This method gave a clean anilinopyrazolinone in 30% yield; the ammonia formed as a by-product was isolated as ammonium chloride. Compound **1a** had the same melting point and infrared spectrum as the unlabeled material.

Mass spectrometric analysis of labeled and unlabeled compounds showed that **1a** contained more than 95% labeled material of mol wt 252, *i.e.*, 1 mass unit (mu) higher than the unlabeled sample. Moreover, a similar analysis of the recovered ammonium chloride showed no nitrogen-15 beyond its natural abundance. These results indicate that the 3-amino group in the starting pyrazolinone was displaced by the labeled aniline (eq 2). Further analysis of the fragmentation pattern of **1a** showed that the nitrogen-15 was located only at the 3-anilino position. The mass spectra of **1** and **1a** contained metastable ion peaks which indicated that the pyrazolinone ring opened in a one-step cleavage to give the fragments $C_6H_5NHC_2H_2$, 118.0655 mu (calcd, 118.0657 mu) and $C_6H_5{}^{15}NHC_2H_2$, 119.0628 mu (calcd, 119.0627 mu), respectively.[4] In the absence of any ion rearrangements these fragments probably originated from the anilino moiety and carbon atoms 3 and 4 of the pyrazolinone ring.

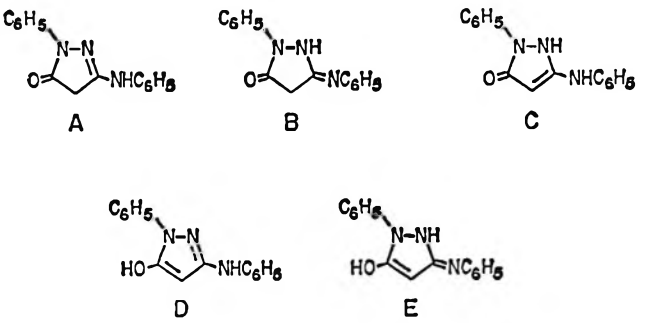

Figure 1.—Possible tautomeric forms of 3-anilino-1-phenyl-2-pyrazolin-5-one.

The relative abundance of the various tautomeric forms of pyrazolin-5-ones has been the subject of much work[5] since Knorr's synthesis[6] of the first example of this class. Some of the possible tautomeric forms (A–E) of **1** are shown in Figure 1. With the knowledge that **1a** was enriched with more than 95% nitrogen-15 at the 3-anilino site, we analyzed the nmr spectra of **1** and **1a** in the hope of determining the preferred tautomeric form(s) in solvents of different polarities, namely, deuterated chloroform, pyridine, and DMSO.

Typical nmr spectra of **1** and **1a** are shown for their DMSO-d_6 solutions in Figure 2. For the unlabeled compound, **1**, the methylene proton peak at 3.85 ppm and the aromatic proton peaks at 7–8 ppm are easily distinguishable. An olefinic proton, if present, would absorb upfield from the aromatic grouping. The single peak at 9.45 ppm is assigned to an N–H resonance.

Integration gave a good 1:10:2 ratio for one nitrogen-bonded proton to ten aromatic protons to two methylene protons. The methylene proton ratio plus the absence of an olefinic resonance peak shows that there is very little carbonyl enolization, even though the methylene protons rapidly exchange with deuterium oxide. Since the spectra in both chloroform and pyridine showed similar results, we must conclude that C, D, and E do not exist in detectable concentrations.

The choice between forms A and B was determined by the splitting of the ^{15}N–H resonance into a doublet[7] in the nmr spectrum of **1a** (Figure 2). Since there is no evidence of a ^{14}N–H resonance in this spectrum, all of the nitrogen-bonded protons must be attached to the 3-anilino nitrogen exclusively. This evidence, coupled with the lack of an olefinic resonance peak, means that form A correctly represents the only detectable species of **1** and **1a** in solution in the three solvents used.

A summary of the pertinent nmr data is given in Table I. The data for compound **1** show that the methylene peak position has remained fairly constant over the range of experimental conditions, but the position of the ^{14}N–H peak has varied from 6.4 ppm in

(1) To whom inquiries should be sent.

(2) R. H. Wiley and P. Wiley, "Pyrazolones, Pyrazolidones, and Derivatives," A. Weissberger, Ed., John Wiley and Sons, Inc., New York, N. Y., 1964, Part 2, Chapters 1 and 2.

(3) A. Weissberger and D. Porter, *J. Amer. Chem. Soc.*, **64**, 2133 (1942).

(4) One referee commented that the $C_6H_5NHC_2H_2$ fragment could be the protonated ketenimine $C_6H_5NH{=}C{=}CH_2{}^+$.

(5) (a) A. R. Katritzky and F. W. Maine, *Tetrahedron*, **20**, 299 (1964); (b) J. Elguero, R. Jacquier, and G. Tarrago, *Bull. Soc. Chim. Fr.*, 3780 (1967).

(6) L. Knorr, *Ber.*, **16**, 2597 (1883).

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chloroform to 9.45 ppm in DMSO and 10.3 ppm in pyridine. These shifts in the N–H resonance probably reflect the differences in hydrogen bonding of **1** with these solvents.

The large ^{15}N–H coupling constant (91–92 Hz) in pyridine remained relatively unchanged when the solution was heated to 100°, although at this temperature the resonance peaks had broadened considerably. However, when this heated solution was cooled to 38°, the nmr spectrum was identical with that of a freshly prepared solution.

The lack of detectable tautomerization in DMSO-d_6 for compound **1** and **1a** is contrary to what we have observed for some other pyrazolinones in this solvent. As shown in Table II, some other pyrazolin-5-ones, which differ from **1** in the nature of the 3-substituent, exist substantially in another tautomeric form(s).

In summary, we have synthesized **1a** with a labeled nitrogen exclusively at the 3-anilino site and shown by mass spectrometry a decomposition path for this compound under electron impact. By means of nmr spectroscopy we have shown that **1** and **1a** exist in only one detectable tautomeric form in chloroform, pyridine, and DMSO solutions.

TABLE I

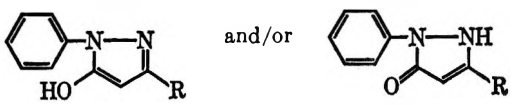
THE NMR SPECTRA[a] OF 3-ANILINO-1-PHENYL-2-PYRAZOLIN-5-ONE

Solvent	Temp, °C	δ,[b] ppm CH₂	δ,[b] ppm NH	Relative area[c] of NH peak	J ^{15}NH
Unlabeled Compound (1)					
$CDCl_3$[d]	50	3.63	6.40	...	
Pyridine-d_5	38	3.7	10.3	0.854	
Pyridine-d_5	100[e]	3.7 ± 0.05	9.5 ± 0.1	...	
DMSO-d_6	38	3.85	9.45	1.0	
Labeled Compound (1a)					
$CDCl_3$[d]	30	3.61	6.35[f]	1.0	92 ± 1
$CDCl_3$[d]	50	3.63	6.45	...	91.5 ± 0.5
Pyridine-d_5	38	3.74	10.3	0.88	91.5 ± 0.5
Pyridine-d_5	100[e]	3.70 ± 0.03	9.6 ± 0.1	...	91 ± 1
DMSO-d_6	38	3.87	9.43	0.96	92 ± 0.5

[a] Recorded on the Varian A-60 nmr spectrometer. [b] δ is parts per million downfield from internal TMS. [c] The CH_2 area is assigned the value 2.0. [d] Spectra in $CDCl_3$ were recorded at 100 MHz on the Varian HA-100. [e] At 100° the peaks had broadened considerably and are less exact. [f] Center of gravity positions.

TABLE II

THE PER CENT TAUTOMER CONTENT[a] OF SOME 3-SUBSTITUTED PYRAZOLIN-5-ONES IN DMSO-d_6



R	Tautomer, %	δ, ppm =CH-	δ, ppm -CH₂-
CH_2	74[b]	5.43	3.55
NHCCH₃ (O)	70	6.03	4.08
NHCC₆H₅ (O)	67	6.32	4.30
NHC₆H₅	0	...	3.85

[a] These values were obtained by integration of the respective olefinic proton peaks. [b] An accuracy within ±5% is expected.

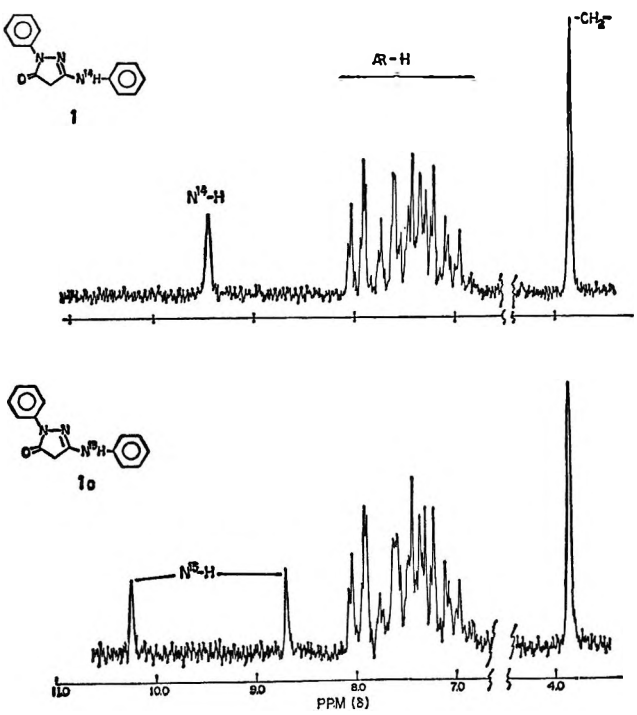


Figure 2.—Nmr spectra of **1** and **1a** in *ca.* 10% (w/v) DMSO-d_6 solution.

Experimental Section

All melting points are uncorrected. Infrared spectra were obtained with a Beckman IR-12 grating spectrophotometer. Samples were examined as potassium bromide pressings. The solutions of **1** and **1a** were *ca.* 10% (w/v) in DMSO and pyridine and about 5% in chloroform. A 60° sector type of mass spectrometer fitted with an all-glass inlet system was operated at 230°. The exact masses were measured on a Consolidated Electrodynamics 21-110-B high-resolution mass spectrometer.

3-^{15}N-Anilino-1-phenyl-2-pyrazolin-5-one (1a).—A solution of 0.94 g (5.4 mmol) of 3-amino-1-phenyl-2-pyrazolin-5-one (EK 3841) in 10 ml of acetic acid containing 1 ml of concentrated hydrochloric acid and 0.5 g (5.3 mmol) of ^{15}N-aniline[8] was refluxed for 1 hr. On standing, the solution deposited a white solid which, after it had been washed with water and recrystallized from acetonitrile, gave 0.4 g (30%) of **1a** as a white solid, mp 218–219°. Unlabeled **1** melted at 218–219° (lit.[3] mp 219–221°). The infrared spectrum of **1a** was identical with that of **1**.

Isolation of Ammonium Chloride.—The filtrate from the reaction mixture was drowned in 100 ml of water. After the resulting solids were removed, 3 ml of concentrated hydrochloric acid was added, and the solution was evaporated under reduced pressure to a gummy solid. Trituration of this material with ethanol gave 0.05 g (0.9 mmol) of a white solid, mp >320°. The infrared and mass spectrograms of the residual material were identical with those of an authentic unlabeled sample of ammonium chloride.

Registry No.—**1**, 7186-66-5; **1a**, 16774-23-5.

(8) Obtained from Merck Sharpe and Dohme of Canada, Ltd.

The Synthesis of o-Di-*t*-butyl Heteroaromatics

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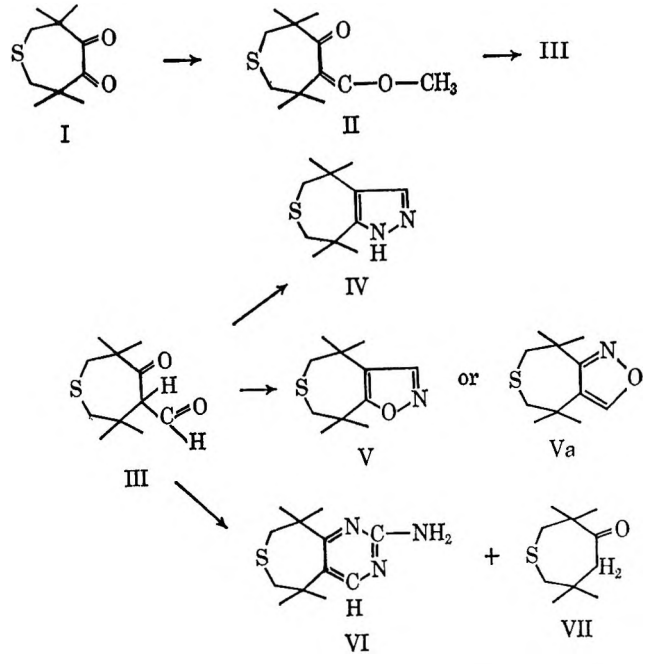
Received February 7, 1968

The use of 3,3,6,6-tetramethyl-1-thiacycloheptane-4,5-dione (I) as the starting compound in the synthesis of several *o*-di-*t*-butyl heteroaromatics has been reported.[1,2] A Wittig reaction with diketone I gave 5-methoxymethylene-3,3,6,6-tetramethyl-1-thiacyclo-

(1) Ae. de Groot and Hans Wynberg, *J. Org. Chem.*, **31**, 3954 (1966).
(2) Ae. de Groot, Ph.D. Thesis, Groningen, 1967.



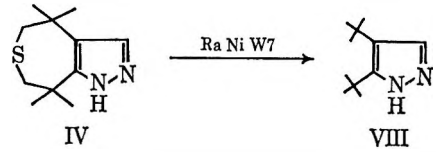
heptan-4-one (II) which upon hydrolysis yielded 5-formyl-3,3,6,6-tetramethyl-1-thiacycloheptan-4-one (III). This keto aldehyde III is also a suitable starting material for several ring-closure reactions to aromatic compounds.

Methoxymethylene ketone II was prepared in 75% yield by reaction of diketone I with (methoxymethylene)triphenylphosphorane in dimethyl sulfoxide as solvent and with the corresponding anion as base.[3] The ultraviolet spectrum of II showed a maximum at λ 242 mμ (ϵ 720) and a shoulder at λ 308 mμ (ϵ 87). This suggests that there is little resonance between the double bond and the carbonyl function in II. The same feature can be noticed in diketone I (λ_{max} 333 mμ) and in 4,5-dimethylene-3,3,6,6-tetramethyl-1-thiacycloheptane (λ_{max} < 185 mμ). The abnormally low absorption maxima in the ultraviolet spectra of these compounds indicate that here too normal conjugation is lacking.[4]

Methoxymethylene ketone II was hydrolyzed with perchloric acid[5] to keto aldehyde III in 93% yield. The infrared spectrum of III showed no enol absorption at 1600 cm^{-1}; a strong carbonyl absorption was present at 1720 cm^{-1}. The ultraviolet spectrum of III, taken in cyclohexane and in ethanol, showed maxima at λ 240 mμ (ϵ 850), 302 (60), and 312 (70), and at 243 (760), 301 (84), and 310 (82), respectively. Keto aldehyde III gave no color with ferric chloride solution. These facts indicate that enolization of this 1,3-dicarbonyl compound is prevented by steric inhibition of resonance.

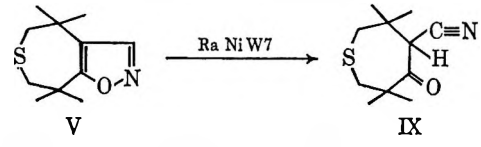
A reaction of keto aldehyde III with hydrazine in boiling acetic acid gave 4,4,8,8-tetramethyl-4,5,7,8-tetrahydro-6-thiacyclohepta[*c*]pyrazole (IV) in 90% yield. The reaction of keto aldehyde III with hydroxylamine gave 4,4,8,8-tetramethyl-4,5,7,8-tetrahydro-6-thiacyclohepta[*d*]isoxazole (V) in 75% yield. The formation of two isomeric isoxazole derivatives V and Va is possible in this reaction. However, the hydroxylamine will probably react with the aldehyde function first. In addition, the greater steric hindrance around the keto function will be important in preventing initial reaction at this point. It is very likely, therefore, that the isoxazole V is the only product in this reaction. The 2-amino-5,5,9,9-tetramethyl-5,6,-8,9-tetramethyl-5,6,8,9-tetrahydro-7-thiacyclohepta[*e*]-pyrimidine (VI) is formed in only 35–40% yield when keto aldehyde III and guanidine carbonate are heated to 160–170° in absolute ethanol in a sealed tube. This low yield is due to the competing ketone cleavage reaction, which occurs under the basic reaction conditions. The 3,3,6,6-tetramethyl-1-thiacycloheptan-4-one (VII) is formed in ~50% yield in this reaction.

Desulfurization of the pyrazole derivative IV with Raney nickel W7 in boiling dioxane as solvent gave 3,4-



di-*t*-butylpyrazole (VIII) in 45% yield. 3,4-Di-*t*-butylpyrazole is a stable white crystalline solid, mp 129–130°.

Isoxazole and derivatives normally give ring opening when treated with Raney nickel[6] or with base.[7] Thus, desulfurization of V with retention of the isoxazole ring cannot be expected. Indeed, one experiment in which isoxazole V was treated with Raney nickel W7 in boiling acetone gave at least three reaction products. The only product which was isolated and identified was keto nitrile IX.[7] The other two products still contained sulfur and showed strong carbonyl absorption in the infrared spectrum, indicating that again no desulfurization but ring opening had occurred.



Attempts to desulfurize pyrimidine derivative VI were unsuccessful. The reason for the failure of this desulfurization is not clear. In seven experiments, carried out with variation in solvent, reaction temperature, and pH, only small amounts of starting material VI were recovered. No desulfurized products were isolated.

Experimental Section

Infrared spectra were determined in CCl_4, in KBr disks, or neat on a Perkin-Elmer Infracord Model 137 or on a Unicam SP 200. Ultraviolet spectra were recorded on a Zeiss spectrophotometer, Model PMQ II; the solvents are indicated. Nuclear magnetic resonance (nmr) spectra were taken on a Varian A-60 spectrometer with tetramethylsilane as internal standard and are reported in τ values (parts per million); the solvents are indicated. Melting points and boiling points are uncorrected. Microanalysis were performed by the Analytical Department of this laboratory under the supervision of Mr. W. M. Hazenberg.

5-Methoxymethylene-3,3,6,6-tetramethyl-1-thiacycloheptan-4-one (II).—A dispersion of sodium hydride in mineral oil, containing 2.9 g (0.06 mol) of sodium hydride, was washed three times with dry pentane. Then 50 ml of dimethyl sulfoxide was added with a syringe and the mixture was heated for 45 min at 75–80°. At that time the solution was clear and no gas evolution was observed. After cooling to room temperature a solution of 20.5 g (0.06 mol) of (methoxmethyl)triphenylphosphonium chloride in 100 ml of dimethyl sulfoxide was injected and the deep

(3) R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, **28**, 1128 (1963).
(4) Ae. de Groot, B. Evenhuis, and Hans Wynberg, *ibid.*, in press.
(5) S. G. Levine, *J. Amer. Chem. Soc.*, **80**, 6150 (1958).
(6) G. Stagno D'Alcontres, *Gazz. Chim. Ital.*, **80**, 441 (1950).
(7) L. Claisen and R. Stock, *Chem. Ber.*, **24**, 130 (1891).

dark red solution was stirred for 15 min. Then a solution of 8.0 g (0.04 mol) of diketone I in 30 ml of dimethyl sulfoxide was injected and the reaction mixture was stirred for 16 hr at room temperture and for 2 hr at 50–60°. The reaction mixture was poured on 200 g of crushed ice and the water–dimethyl sulfoxide mixture was extracted with pentane. The pentane solution was washed with aqueous dimethyl sulfoxide (1:1) and with a saturated salt solution and dried ($MgSO_4$). The dried pentane solution was chromatographed on neutral alumina to remove all of the triphenylphosphine oxide and the pentane was evaporated. The solid residue was recrystallized from petroleum ether (bp 40–60°). The yield of methoxymethylene ketone II, mp 109–110°, was 60–77%: ir (CCl_4) 1690, 1640, and 1100 cm^{-1}; uv max (95% ethanol) 242 mμ (ε 720), 308 (87); nmr (CCl_4), τ 8.87 and 8.84 s (ring methyl protons), 7.60 and 7.48 s (ring methylene protons), 6.47 s (ether methyl protons), 4.21 s (vinyl proton).

Anal. Calcd for $C_{12}H_{20}O_2S$ (228.35): C, 63.11; H, 8.82; S, 14.04. Found: C, 62.7, 63.0; H, 8.8, 8.8; S, 13.9, 14.0.

5-Formyl-3,3,6,6,6-tetramethyl-1-thiacycloheptan-4-one (III).—A solution of 4.0 g (0.017 mol) of methoxymethylene ketone II and 10 ml of perchloric acid in 50 ml of ether was refluxed for 30 min. The reaction mixture was poured into water and the ether layer was separated and washed with water and with sodium bicarbonate solution. The ethereal extract was dried (Na_2SO_4) and concentrated. The residue was recrystallized from petroleum ether (bp 40–60°). The yield of keto aldehyde III was 3.4 g (93%): mp 97–99°; ir (CCl_4) 1705 and 1735 cm^{-1}; uv (see discussion); nmr (CCl_4), τ 8.96, 8.84, and 8.78 s (methyl protons), 7.40 7.82, 7.58, 7.40, and 7.17 q (methylene protons), 6.58 and 6.50d (proton at C_4), 0.30 and 0.22 d (aldehyde proton).

Anal. Calcd for $C_{11}H_{18}O_2S$ (214.32): C, 61.64; H, 8.47; S, 14.96. Found: C, 61.6, 61.5; H, 8.5, 8.3; S, 15.0, 15.0.

4,4,8,8-Tetramethyl-4,5,7,8-tetrahydro-6-thiacyclohepta[*c*]pyrazole (IV).—A solution of 1.0 g (0.0047 mol) of keto aldehyde III, 3 ml of hydrazine hydrate, and 1 drop of hydrochloric acid in 15 ml of acetic acid was refluxed for 1 hr. The reaction mixture was poured on ice and the precipitated compound was separated and washed with water. After recrystallization from aqueous methanol (1:1), 0.86 g (90%) of pyrazole IV was obtained: mp 186–188°; ir (KBr) 3200, 1570, and 1505 cm^{-1}; nmr (CCl_4), τ 8.63 s (methyl protons), 7.54 s (methylene protons), 2.80 s (C–H aromatic proton), 2.42 s (N–H proton).

Anal. Calcd for $C_{11}H_{18}N_2S$ (210.32): C, 62.81; H, 8.63; N, 13.32; S, 15.24. Found: C, 62.5, 62.6; H, 8.6, 8.7; N, 13.4, 13.4; S, 14.8, 14.8.

4,4,8,8-Tetramethyl-4,5,7,8-tetrahydro-6-thiacyclohepta[*d*]isoxazole (V).—A solution of 1.5 g (0.007 mol) of keto aldehyde III and 1.5 g (0.022 mol) of hydroxylamine hydrochloride in 25 ml of acetic acid was refluxed for 1 hr. The reaction mixture was poured on ice and the precipitated compound was separated and washed with water. Recrystallization from aqueous methanol (1:1) yielded 1.1 g (75%) of isoxazole V: mp 111–112°; ir (KBr) 1590 cm^{-1}; nmr (CCl_4), τ 8.65 and 8.55 s (methyl protons), 7.37 and 7.35 s (methylene protons), 2.12 s (aromatic proton).

Anal. Calcd for $C_{11}H_{17}NOS$: C, 62.51; H, 8.11; N, 6.63; S, 15.18. Found: C, 62.7, 62.6; H, 8.3, 8.2; N, 6.7, 6.5; S, 14.7, 15.0.

2-Amino-5,5,9,9-tetramethyl-5,6,8,9-tetrahydro-7-thiacyclohepta[*e*]pyrimidine (VI).—A mixture of 2.0 g (0.009 mol) of keto aldehyde III, 2.0 g (0.017 mol) of guanidine carbonate, and 25 ml of absolute ethanol was heated in a sealed tube at 160–170° for 8 hr. The tube was opened and the contents were washed with water and ether. The water layer was separated and extracted with ether. The combined ether layers were extracted with dilute hydrochloric acid. The ethereal extract was dried ($CaCl_2$) and concentrated. The organic residue proved to be 3,3,6,6-tetramethyl-1-thiacycloheptan-4-one (VII). The yield of VII was 900 mg (52%). The hydrochloric acid extracts were neutralized with sodium hydroxide solution and extracted with ether. The ether solution was washed with water, dried ($CaCl_2$), and concentrated. The residue was recrystallized from petroleum ether (bp 60–80°). The yield of pyrimidine VI was 900 mg (42%): mp 109–110.5°; ir (KBr) 3400, 3230, 1645, 1580, and 1530 cm^{-1}; nmr ($CDCl_3$), τ 8.54 s (methyl protons), broad 7.25 s (methylene protons), broad 4.73 s (NH_2 protons), 1.72 s (aromatic proton).

Anal. Calcd for $C_{12}H_{19}N_3S$ (237.35): C, 60.72; H, 8.04; N, 17.70. Found: C, 61.0, 60.9; H, 8.2, 8.1; N, 17.8, 17.8.

3,4-Di-*t*-butylpyrazole (VIII).—A suspension of 20 g of Raney nickel W7 and 1.6 g (0.008 mol) of pyrazole IV in 150 ml of dioxane was stirred and refluxed for 5 hr. The reaction mixture was cooled to room temperature and filtered. The Raney nickel was refluxed twice with 200 ml of dioxane to remove the absorbed pyrazole. The dioxane was evaporated and 800 mg of residue was obtained. Recrystallization from aqueous methanol (1:1) yielded 500 mg (45%) of white crystalline 3,4-di-*t*-butylpyrazole: mp 129–130°; ir (KBr) 3200 and 1550 cm^{-1}; nmr (CCl_4), τ 8.63 and 8.58 s (*t*-butyl protons), 2.75 s (C–H aromatic proton), 2.03 s (N–H proton).

Anal. Calcd for $C_{11}H_{20}N_2$ (180.28): C, 73.28; H, 11.18; N, 15.54. Found: C, 73.4, 73.3; H, 11.1, 11.1; N, 15.6, 15.7.

5-Cyano-3,3,6,6-tetramethyl-1-thiacycloheptan-4-one (IX).—A suspension of 10 g of Raney nickel W7 and 1.1 g (0.005 mol) of isoxazole V in 200 ml of acetone was stirred and refluxed for 5 hr. After cooling to room temperature the mixture was filtered and the Raney nickel was refluxed twice with 200 ml of acetone to remove all of the absorbed materials. The combined acetone solutions were concentrated and the residue was dissoved in petroleum ether (bp 40–60°). The warm petroleum ether solution was filtered and upon cooling 300 mg of cyanide IX crystallized: mp 114–116°; ir (KBr) 2280 and 1720 cm^{-1}; nmr ($CDCl_3$), τ 8.83 and 8.75 s (methyl protons), 7.38 s and 7.61, 7.38, 7.28, and 7.00 q (methylene protons), 6.15 s (proton at C_5).

Anal. Calcd for $C_{11}H_{17}NOS$ (211.32): C, 62.51; H, 8.11; N, 6.63; S, 15.18. Found: C, 62.6, 62.7; H, 8.3, 8.2; N, 6.6, 6.6; S, 15.3, 15.3.

Concentration of the petroleum ether solution gave 200 mg of a solid. It was shown by tlc that at least three products were present. The infrared spectrum of this mixture showed a strong absorption at 1690 cm^{-1}.

Registry No.—II, 16867-90-6; III, 16867-91-7; IV, 16867-92-8; V, 16867-93-9; VI, 16867-94-0; VIII, 16867-95-1; IX, 16867-96-2.

Pteridines. XIII.[1] Aromatization during the Attempted Synthesis of a 6,6-Disubstituted 5,6-Dihydropteridine

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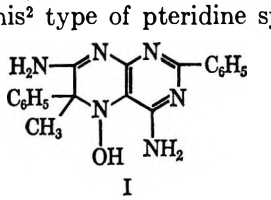
In the course of our work on the diuretic pteridines we wished to prepare 4,7-diamino-5-hydroxy-6-methyl-2,6-diphenyl-5,6-dihydropteridine (I) as an example of a pteridine in which a 5,6-dihydro form has been fixed by the presence of two stable substituents at position 6. In an approach to this, 2-phenylpropionitrile was condensed with 4,6-diamino-5-nitroso-2-phenylpyrimidine (III) in ethanol in the presence of alkali in a Timmis[2] type of pteridine synthesis. The



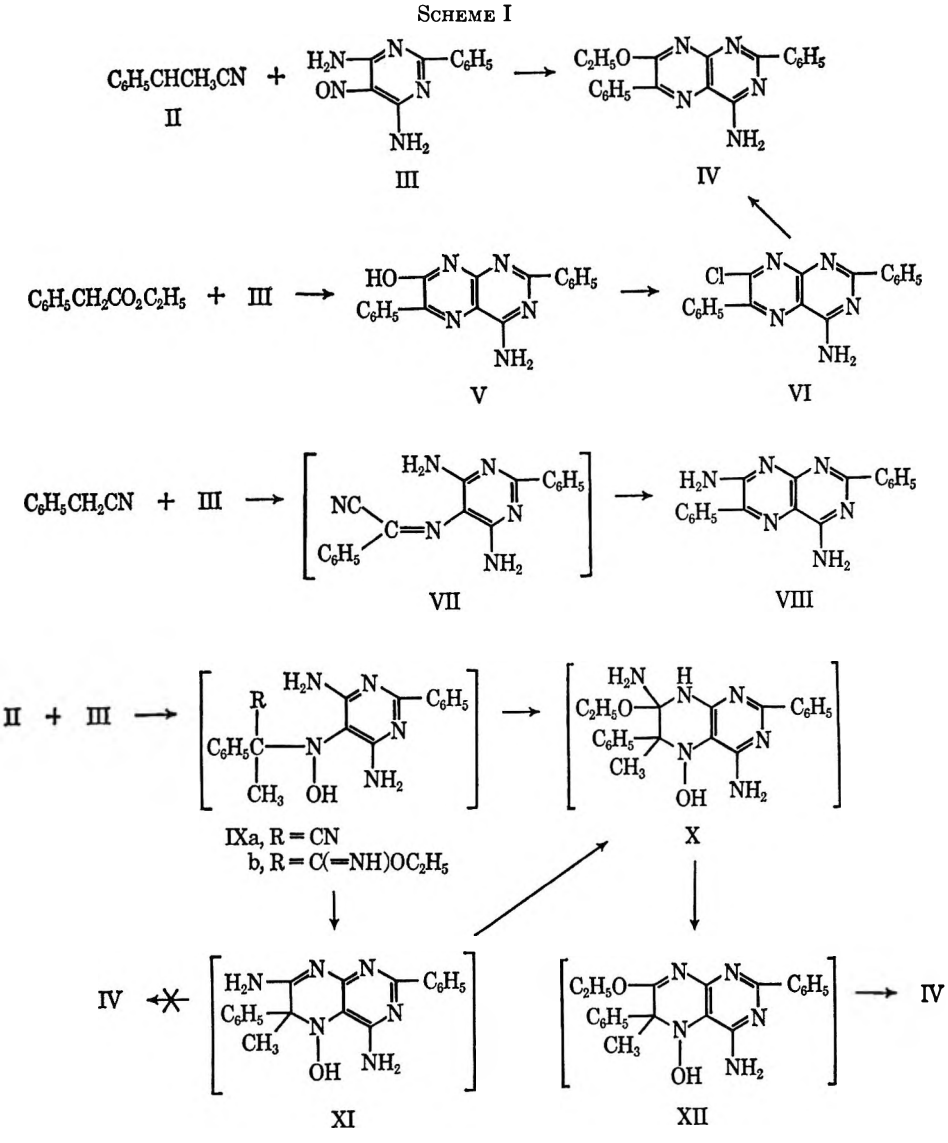
I

only product isolated (in 16% yield) was 4-amino-7-ethoxy-2,6-diphenylpteridine (IV). The structure of

(1) Previous paper in this series: J. Weinstock, J. W. Wilson, V. D. Wiebelhaus, A. R. Maass, F. T. Brennan, and G. Sosnowski, *J. Med. Chem.*, **11**, 573 (1968).

(2) G. M. Timmis, *Nature*, **164**, 139 (1949).

SCHEME I



IV was first indicated by elemental analysis and the presence of the typical ethoxy proton pattern in the nmr spectrum. The structure was established by an unequivocal synthesis as shown in Scheme I. Condensation of ethyl phenylacetate with III in a Timmis reaction gave 4-amino-7-hydroxy-2,6-diphenylpteridine (V), which on reaction with phosphorus pentachloride in phosphorus oxychloride gave VI. Reaction of this with sodium ethoxide in ethanol gave IV, whose infrared spectrum and melting point were in agreement with those of the sample isolated from the 2-phenylpropionitrile condensation.

A possible mechanism for the formation of IV from II and III is indicated in Scheme I. A postulated initial adduct IXa could not have lost the elements of methanol to form VII because this would have given VIII, the 7-amino analog of IV. The condensation of phenylacetonitrile with III under similar conditions gave an excellent yield of VIII. A ring-closed intermediate X could form from the imino ether IXb or by addition of ethanol to XI (or its 8-H tautomer). The 8-H tautomer of XI could be formed by the usual addition of the pyrimidine 4-NH_2 in IXa to the nitrile. The elements of methanol could not be lost from XI because this would also lead to VIII. However, XII, formed by loss of the elements of ammonia from X, could have given rise to the observed product IV by loss of the elements of methanol. We have no evidence to indicate the exact nature of these transformations, but this reaction illustrates the ease with which a 5,6-dihydropteridine will become aromatic, even if a carbon–carbon bond must be broken in the process. Similar driving forces play a role when hydropteridines are involved as cofactors in biological systems.[3]

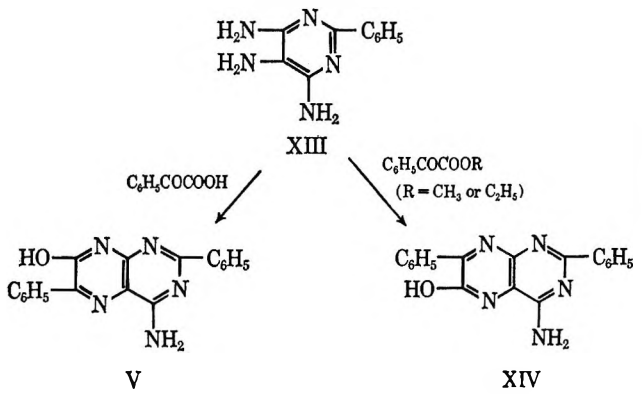
In our first attempt to prepare IV, methyl phenylglyoxylate was treated with 4,5,6-triamino-2-phenylpyrimidine (XIII) in ethanol. We had anticipated the formation of V because the reaction of tetraaminopyrimidine with ethyl phenylglyoxylate in 1 *N* acetic acid[4] and with phenylglyoxylic acid at pH 5[5] gave 2,4-diamino-7-hydroxy-6-phenylpteridine. However, the product obtained after purification was different from authentic V prepared *via* the Timmis reaction, and thus must be 4-amino-6-hydroxy-2,7-diphenylpteridine (XIV). This was converted into the corresponding 6-chloro- and 6-ethoxypteridines, each of which was different from the authentic 7 isomers described above.

(3) A. Ehrenberg, P. Hemmerick, F. Müller, T. Okada, and M. Viscontini, *Helv. Chim. Acta*, **50**, 411 (1967).

(4) A. G. Renfrew, P. C. Piatt, and L. H. Cretcher, *J. Org. Chem.*, **17**, 467 (1952).

(5) R. G. W. Spickett and G. M. Timmis, *J. Chem. Soc.*, 2887 (1954).

SCHEME II



The course of the condensation to form the 6-hydroxypteridine can be rationalized by assuming that in methyl phenylglyoxylate the ester carbonyl is more reactive than the ketone carbonyl, and that the former condenses with the 5-amino group of XIII which is the most reactive amino group.[6,7] The previously reported condensations can be rationalized by assuming that in aqueous media ester hydrolysis precedes amine condensation, and that in an α-keto acid the ketone carbonyl is more reactive than the acid carbonyl. This rationalization is supported by the synthesis of V in excellent yield by the reaction of phenylglyoxylic acid with XIII in ethanol. Since many 7-hydroxypteridines have been prepared by the reaction of methyl pyruvate with 4,5-diaminopyrimidines in alcohols, the order of reactivity in α-keto acids and esters appears to be $-COOH < -COC_6H_5 < -CO_2CH_3 < -COCH_3$.

Experimental Section[8]

Infrared spectra were obtained on a Perkin-Elmer Infracord, ultraviolet spectra on a Cary Model 14 spectrometer, and nmr spectra on a Varian A-60 spectrometer. Paper chromatography was done by the circular system using a cotton wick to bring the solvent to the paper. The following systems were used: (1) EtOH–H_2O (2:1) on mineral oil pretreated paper; (2) 5.6 *N* NH_4OH–BuOH (4:5); (3) EtOH–H_2O (2:1) on mineral oil–castor oil (1:1) pretreated paper.

4-Amino-2,6-diphenyl-7-ethoxypteridine (IV). A.—To a solution of 4.6 g (0.20 mol) of sodium in 200 ml of absolute ethanol was added 6.66 g (0.02 mol) of 4-amino-7-chloro-2,6-diphenylpteridine and the mixture refluxed for 3 hr. Chilling gave a yellow-orange solid whose infrared spectrum was identical with that of the sample obtained in B. Recrystallization from ethanol gave 1.75 g (25%) of yellow crystals, mp 239–241°.

B.—A solution of 2.15 g (0.010 mol) of 4,6-diamino-5-nitroso-2-phenylpyrimidine, 2.00 g (0.015 mol) of 2-phenylpropionitrile,[9] and 1.35 g (0.012 mol) of potassium *t*-butoxide in 300 ml of absolute ethanol was refluxed for 20 hr. Addition of 250 ml of water and chilling gave 0.54 g (16%) of a light tan solid. Recrystallization of this from 125 ml of ethanol gave 0.40 g of pink crystals: mp 241.5–242° (a second recrystallization from the same solvent did not change the melting point); R_f 0.65 (system 1); $\lambda_{max}^{4.5\%\ HCOOH}$ 273, 359 mμ (log ϵ 4.45, 4.40).

Anal. Calcd for $C_{20}H_{17}N_5O$: C, 69.95; H, 4.99; N, 20.40. Found: C, 70.00; H, 5.00; N, 20.22.

4-Amino-7-hydroxy-2,6-diphenylpteridine (V). A.—A solution of 21.5 g (0.10 mol) of 4,6-diamino-2-phenyl-5-nitrosopyrimidine in 500 ml of absolute ethanol was treated with 20 g (0.122 mol) of ethyl phenylacetate and 6.6 g (0.122 mol) of sodium methoxide. After refluxing for 80 min, acetic acid was added to bring the pH to 6. The solid formed was collected by filtration, washed with hot ethanol, and dried to give 22.8 g (72%) of yellow crystals. Recrystallization from dimethylformamide–water gave 16.6 g (53%) of yellow crystals: mp >300°; R_f 0.53 (system 2), blue fluorescence under ultraviolet light; $\lambda_{max}^{0.1\ N\ HCl\text{-}C_2H_5OH}$ 227.5, 256, 378.5 mμ (log ϵ 4.38, 4.29, 4.41); $\lambda_{max}^{C_2H_5OH,\ pH\ 11.5}$ 250, 377.5 mμ (log ϵ 4.75, 4.69).

B.—A solution of 1.0 g (0.005 mol) of 4,5,6-triamino-2-phenylpyrimidine and 1.0 g (0.0067 mol) of phenylglyoxylic acid in 35 ml of absolute ethanol was refluxed for 1.5 hr. Filtration of the chilled reaction mixture gave 1.45 g (92%) of a yellow solid whose infrared spectrum and paper chromatographic behavior were identical with those of the sample obtained above.

4-Amino-6-hydroxy-2,7-diphenylpteridine (XIV).—A mixture of 10.0 g (0.05 mol) of 4,5,6-triamino-2-phenylpyrimidine and 9.85 g (0.06 mol) of methyl phenylglyoxylate in 350 ml of absolute ethanol was refluxed for 16 hr. Cooling and filtration gave a yellow solid. Recrystallization from dimethylformamide–water gave 11.2 g (71%) of yellow crystals: mp > 300°; R_f (system 2), 0.85, major, yellow fluorescence under uv light; 0.95, minor, blue fluorescence under uv light. This was dissolved in dilute ammonium hydroxide and an insoluble portion removed by filtration. Adjustment of the pH to 8 with acetic acid gave a product which was recrystallized once from dimethylformamide–water to give yellow crystals: mp >310°; R_f 0.66 (system 3), R_f 0.85 (system 2), yellow-green fluorescence under ultraviolet light; $\lambda_{max}^{4.5\%\ HCOOH}$ 284, 382 mμ (log ϵ 4.37, 4.29); $\lambda_{max}^{1N\ NaOH}$ 281, 401 mμ (log ϵ 4.36, 4.15).

Anal. Calcd for $C_{18}H_{13}N_5O$: C, 68.56; H, 4.16; N, 22.21. Found: C, 68.56; H, 4.41; N, 22.34.

The reaction of XIII with ethyl phenylglyoxylate was carried out as described above. Cooling the reaction mixture to room temperature and filtering gave an 85% yield of yellow crystals of XIV in which ir and chromatography (system 2) showed the presence of a small quantity of V. Interruption of the reaction after 7 hr of reflux gave only a 51% yield of product. Thus this reaction is much slower than that of the corresponding acid.

4-Amino-7-chloro-2,6-diphenylpteridine (VI).—A mixture of 16.55 g (0.053 mol) of 4-amino-7-hydroxy-2,6-diphenylpteridine, 83.4 g (0.40 mol) of phosphorus pentachloride, and 600 ml of phosphorus oxychloride was heated for 2 hr on a steam bath. The excess phosphorus oxychloride was evaporated under vacuum and the residue poured onto ice. A yellow solid formed which was collected and washed with ether. Recrystallization from dimethylformamide–water gave 13.25 g (75%) of a yellow solid: mp 274–276°; R_f 0.35 (system 3).

Anal. Calcd for $C_{18}H_{12}N_5Cl$: C, 64.77; H, 3.62; N, 20.98. Found: C, 65.74; H, 3.99; N, 21.22.

4-Amino-6-chloro-2,7-diphenylpteridine.—A mixture of 10.0 g (0.0317 mol) of 4-amino-6-hydroxy-2,7-diphenylpteridine, 50 g (0.24 mol) of phosphorus pentachloride, and 500 ml of phosphorus oxychloride was refluxed for 2 hr. The phosphorus oxychloride was removed under vacuum and the residue treated with an ice–water mixture. The aqueous suspension was warmed briefly on a steam bath and then chilled and filtered. Neutralization of the filtrate gave an additional quantity of product. Recrystallization from a dimethylformamide–water mixture gave 7.0 g (63%) of a yellow solid: mp 257–258°; R_f 0.49 (system 3); $\lambda_{max}^{4.5\%\ HCOOH}$ 281, 367 mμ (log ϵ 4.30, 4.32).

Anal. Calcd for $C_{18}H_{12}ClN_5$: C, 64.77; H, 3.62; N, 20.98. Found: C, 64.95; H, 3.52; N, 21.06.

4-Amino-2,7-diphenyl-6-ethoxypteridine.—A suspension of 1.0 g (0.003 mol) of 4-amino-6-chloro-2,7-diphenylpteridine in a solution of 0.69 g (0.03 mol) of sodium in 30 ml of absolute ethanol was refluxed for 3 hr. Addition of water gave a yellow-orange solid, mp 241–244°. Three recrystallizations from methanol gave a bright yellow solid, mp 248–249.5°.

Anal. Calcd for $C_{20}H_{17}N_5O$: C, 69.95; H, 4.99; N, 20.40. Found: C, 69.92; H, 4.81; N, 20.64.

(6) With methylglyoxal, XIII forms 2-phenyl-4-amino-7-methylpteridine: J. Weinstock, R. Y. Dunoff, J. E. Carevic, J. G. Williams, and A. J. Villani, *J. Med. Chem.*, **11**, 618 (1968).

(7) A referee suggested that the formation of XIV might be favored by the use of the methyl ester which would be expected to react at the ester carbonyl more rapidly than the corresponding ethyl ester. To check this point, ethyl phenylglyoxylate was treated with XIII in absolute ethanol. This also gave XIV as the predominant product. However, the ir spectrum and chromatography of the crude reaction product did show the presence of a small amount of V. It is noteworthy that XIII undergoes reaction more slowly with these esters than with phenylglyoxylic acid.

(8) We wish to thank Mr. Richard J. Warren for spectral data, Miss Margaret Carroll and her staff for microanalytical data, and Mr. Alex Post for chromatographic data.

(9) M. S. Newman and R. D. Closson, *J. Amer. Chem. Soc.*, **66**, 1553 (1944).

Registry No.—IV, 16878-41-4; V, 16878-42-5; VI, 16878-43-6; XIV, 16878-44-7; 4-amino-6-chloro-2,7-diphenylpteridine, 16878-45-8; 4-amino-2,7-diphenyl-6-ethoxypteridine, 16878-46-9.

Synthesis of a 10,10a-Dihydro-1H-imidazo-[3,4-*b*][1,2]benzothiazine 5,5-Dioxide

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Received March 6, 1968

Chlorosulfonation of an aromatic, followed by treatment of the resulting sulfonyl chloride with ammonia, is a generally useful method for the preparation of aryl sulfonamides.[1] We applied this sequence to 5-(4-chlorophenyl)-5-methylhydantoin (**1**) and its 3-chloro isomer (**4**), with different results in each instance. As anticipated from steric considerations, **1** gave 5-(4-chloro-3-sulfamylbenzyl)-5-methylhydantoin (**2**)[2] in 83% yield, and this was hydrolyzed with barium hydroxide to give 4-chloro-α-methyl-3-sulfamylphenylalanine. However, when **4** was treated with chlorosulfonic acid followed by ammonia, it gave a product in 72% yield; the composition differed from that of **4** by two less hydrogens and an additional SO_2. Barium hydroxide hydrolysis gave a product which displayed a peak at 5.92 μ in its infrared spectrum, characteristic of a carboxylic acid, and which lacked peaks at 6.3 and 6.55 μ, characteristic of amino acids.

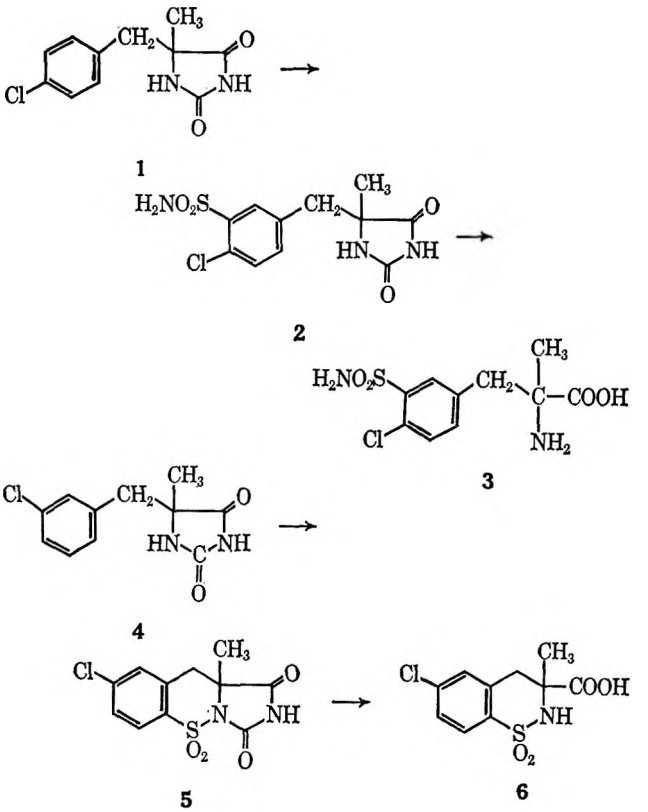
These data are best explained by assuming that the chlorosulfonation of **4** proceeded *para* to the chlorine, and that the sulfonyl chloride cyclized to structure **5** when treated with base. Basic hydrolysis of **5** then opened the hydantoin portion of **5** and the elements of NCO^- were lost, to give 6-chlorobenzo-1,2-thiazine 1,1-dioxide (**6**). The orientation of the chlorosulfonation is confirmed by the nmr spectrum of **5**, which shows a doublet at δ 7.93 (J = 8 Hz). This is expected for an aromatic proton *ortho* to a sulfonyl group which is one of an AB pair.

This orientation is in accord with the generalization that the *para* directive influence of a halogen in sulfonation is greater than that of a methyl group.[3a] However, the results with the 4-chloro isomer are not in agreement with the generalization[3] that a methyl is more strongly *ortho* directing than halogen.[3b]

Experimental Section[4]

The chromatographic R_f values were determined in the following systems: (1) tlc, silica gel G, chloroform–acetone (1:1); (2) 3 MM Whatman paper, 5.6 N ammonium hydroxide–butanol (125:80); (3) tlc, silica gel G, ethyl acetate–acetic acid (99:1); and (4) tlc, Avicel, 5.6 N ammonium hydroxide–butanol (125:80).

SCHEME I



5-(4-Chlorobenzyl)-5-methylhydantoin (1).—A mixture of 1-(4-chlorophenyl)-2-propanone[5] (8.4 g, 0.05 mol), ammonium carbonate (45 g), potassium cyanide (5.0 g), water (75 ml), and ethanol (75 ml) was heated at 55–60° for 8 hr. After cooling, 50 ml of water was added and the mixture was chilled and filtered to give 10.1 g (84%) of white crystals, mp 215–217°. Recrystallization from ethanol–water gave white crystals: mp 214–215°; R_f 0.43 (system 1).

Anal. Calcd for $C_{11}H_{11}ClN_2O_2$: C, 55.35; H, 4.64; N, 11.74. Found: C, 55.57; H, 4.77; N, 11.97.

5-(3-Chlorobenzyl)-5-methylhydantoin (4).—Using 1-(3-chlorophenyl)-2-propanone,[6] the above procedure gave 82.4% of product: mp 240–242°; R_f 0.43 (system 1); nmr (D_2O/KOH), δ 1.42 (S, 3, CH_3), 2.89 (S, 2, CH_2), and 7.23 (m, 4).

Anal. Calcd for $C_{11}H_{11}ClN_2O_2$: C, 55.35; H, 4.64; N, 11.74. Found: C, 55.29; H, 4.69; N, 11.87.

5-(4-Chloro-3-sulfamybenzyl)-5-methylhydantoin (2).—A 32.9-g sample of **1** (0.14 mol) was added in portions to 200 ml of $ClSO_3H$ at 0°. The reaction mixture was then stirred at 100–110° for 3 hr, cooled, and added dropwise to 1500 g of ice. This gave a tan solid, mp 208–210°, which was immediately added to 250 ml of 14 N NH_4OH. After being stirred for 1 hr on a steam bath, the cooled reaction mixture was brought to pH 1 with concentrated HCl, and a tan solid, mp 143–148°, was collected. When this solid was purified by dissolving in dilute NaOH and reprecipitating with HCl, it gave 32.5 g (73%) of white crystals: mp 144–147°; R_f 0.30 (system 1); nmr (D_2O/KOD), δ 1.42 (s, 3, CH_3), 2.98 (d, 2, J = 0.5 Hz, CH_2), 7.34 (q, 1, $J_{5,6}$ = 8 Hz, $J_{2,6}$ = 3 Hz, 6 H of phenyl), 7.57 (d, 1, J = 8 Hz, 5 H of phenyl), and 7.89 (d, 1, J = 3 Hz, 2 H of phenyl).

Anal. Calcd for $C_{11}H_{12}ClN_3O_4S \cdot {}^1/_4H_2O$: C, 41.00; H, 3.91; N, 13.04. Found: C, 40.95; H, 4.06; N, 12.84.

4-Chloro-3-sulfamylphenyl-α-methylalanine (3).—A stirred mixture of 3.2 g (0.01 mol) of **2**, 15.8 g (0.05 mol) of $Ba(OH)_2 \cdot 8H_2O$, and 60 ml of H_2O was refluxed for 48 hr. The cooled

(1) C. M. Suter, "The Organic Chemistry of Sulfur," John Wiley and Sons, Inc., New York, N. Y., 1944, p 573.

(2) This structural assignment is supported by the difference of δ 0.09 observed for the $-CH_2-$ in the nmr spectra of **2** and **4**. In comparison, the difference of δ between the CH_3 of toluene and the 2-CH_3 and the 5-CH_3 of 2,5-dimethylbenzenesulfonamide is δ 0.37 and 0.085.

(3) (a) See ref 1, p 217. (b) At least 86% of the sulfonation product of 4-chlorotoluene is 3-chloro-6-methylbenzenesulfonic acid: W. P. Wynne and J. Bruce, *J. Chem. Soc.*, 731 (1898).

(4) We wish to thank Mr. R. Warren for nmr spectral data, Miss M. Carroll and staff for microanalytical data, and Mr. A. Post for thin layer and paper chromatographic data.

(5) C. G. Overberger and H. Biletch, *J. Amer. Chem. Soc.*, **73**, 4880 (1957).

(6) J. H. Biel, A. E. Drukker, T. F. Mitchell, E. P. Sprengeler, P. A. Nuhfer, A. C. Conway, and A. Horita, *ibid.*, **81**, 2805 (1959).

mixture was brought to pH 1 with 2 *N* H_2SO_4 and the insoluble product was collected by filtration. The filtrate was concentrated *in vacuo* and the residue was dissolved in 40 ml of H_2O and neutralized with 40% NaOH. Chilling gave 2.4 g (82%) of crystals, mp 305–308°. These crystals were purified by dissolving them in 25 ml of H_2O made basic with diethylamine; the solution was treated with charcoal and then neutralized with acetic acid. Chilling gave 1.6 g of a white solid: mp 299–301°; R_f 0.28 (system 2).

Anal. Calcd for $C_{10}H_{13}ClN_2O_4S$: C, 41.03; H, 4.48; N, 9.57. Found: C, 41.10; H, 4.56; N, 9.33.

8-Chloro-10a-methyl-10,10a-dihydro-1H-imidazo[3,4-*b*][1,2]-benzothiazine-1,3(2H)-dione 5,5-Dioxide (5).—A mixture of 11.9 g (0.05 mol) of **4** in 75 ml of $ClSO_3H$ was stirred at 25° for 3 hr. The mixture was added dropwise with stirring to 500 g of ice, and a white solid, mp 143–154°, was collected by filtration. This was immediately added to 150 ml of concentrated NH_4OH, and the mixture was heated on a steam bath for 1 hr. After standing for 18 hr at 25° the pH was brought to 1 with concentrated HCl, and the resulting solid was collected by filtration. This was dissolved in dilute NH_4OH, treated with charcoal, and reprecipitated at pH 1 to give 10.8 g (72%) of product, mp 265–268°. Another base–acid purification gave white crystals: mp 267–269°; R_f 0.71 (system 3); nmr (CF_3COOH), δ 1.92 (S, 3, CH_3), 3.58 (S, 2, $-CH_2-$), 7.56 (m, 2) and 7.93 (d, 1, J = 8 Hz).

Anal. Calcd for $C_{11}H_9ClN_2SO_4$: C, 43.93; H, 3.02; N, 9.32. Found: C, 43.87; H, 3.16; N, 9.15.

6-Chloro-3-methyl-3,4-dihydro-2H-benzothiazine-3-carboxylic Acid 1,1-Dioxide (6).—A stirred mixture of 7.5 g (0.025 mol) of **5** and 39.4 g (0.25 mol) of $Ba(OH)_2 \cdot 8H_2O$ in 150 ml of H_2O was refluxed for 48 hr. After cooling, the pH was adjusted to 1 with concentrated H_2SO_4. The solid was collected and stirred for 30 min with ethanol. Concentration of the ethanol gave an oil which crystallized when triturated with dilute HCl to give 4.4 g of product, mp 127–152°. This was purified by dissolving in dilute NaOH and reprecipitating at pH 1 with dilute HCl. Two such treatments gave 3.7 g (53%) of product: mp 158–160°; R_f 0.72 (system 4).

Anal. Calcd for $C_{10}H_{10}ClNO_4S$: C, 43.56; H, 3.66; N, 5.08. Found: C, 43.80; H, 3.77; N, 4.86.

The nmr peaks (CF_3COOH) for **2,5-dimethylbenzenesulfonamide** were at δ 2.38 (S, 3, 5-CH_3), 2.67 (S, 3,2-CH_3), 7.45 (broad S, 2), and 8.02 (S, 1). The nmr peak for the CH_3 of toluene (CF_3COOH) is at δ 2.30.

Registry No.—**1**, 16793-24-1; **2**, 16793-21-8; **3**, 16793-22-9; **4**, 16793-23-0; **5**, 16793-19-4; **6**, 16793-20-7.

Fluoroalkylpyridines. A Novel Rearrangement

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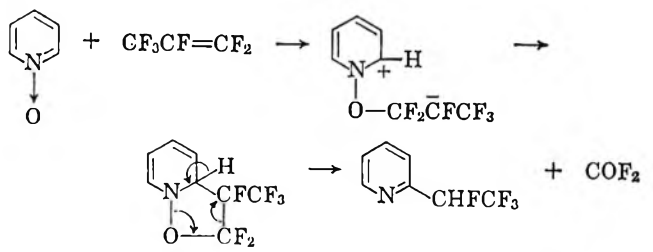
Received March 7, 1968

Rearrangements have been shown to occur in pyridine N-oxide chemistry.[1] For instance, pyridine N-oxide and acetic anhydride produced 2-pyridyl acetate, while 2-picoline N-oxide and acetic anhydride yielded 2-pyridylmethyl acetate and 6-methyl-2-pyridinol. Although the reaction of pyridine N-oxide and 2-bromopyridine to give 1-(2-pyridyl)-2-(1H)-pyridone is not a rearrangement, it does show the cyclization that occurs in pyridine N-oxide reactions. Other rearrangements in pyridine N-oxide reactions are also known.[1]

The similarity of pyridine N-oxides to nitrones should also be mentioned because it further supports the intermediates postulated below. For example, nitrones of the 1-pyrroline N-oxide type have been treated with olefinic compounds to form isoxazolidines.[2,3]

The novel rearrangement described below furnishes another preparative method for certain alkylpyridines. Alkylpyridines have been obtained previously in a variety of ways: from natural sources, by cyclizations of N-containing compounds; and by alkylation of the pyridine nucleus. These have been reviewed and have been reported by many investigators.[4–7] Our new method of alkylation produces 2-polyfluoroalkylpyridines. Treatment of pyridine N-oxides with terminally unsaturated perfluoroalkenes has yielded 2-polyfluoroalkylpyridines, probably through rearrangement of a postulated isooxazolidine intermediate. For example, pyridine N-oxide and hexafluoropropylene have yielded 2-(1,2,2,2-tetrafluoroethyl)pyridine. One possible mechanism that can account for the product is represented in Scheme I.

SCHEME I



Carbonyl fluoride was found in the off-gases but not in stoichiometric or large amounts, however. Whether some carbonyl fluoride had reacted to give other products was not investigated. Furthermore, solids were always obtained in the short-path distillation of the crude reaction mixture. These air-sensitive solids, when added to water and worked up, provided additional product. No attempt was made to identify these solids. It was later found that the crude reaction mixture could be added directly to water and the resulting mixture then either steam distilled or extracted with an organic solvent. No other reaction variables were investigated.

Mass spectral and nuclear magnetic resonance (F and H) data are consistent with the structures of the 2-polyfluoroalkylpyridines derived from the N-oxides of pyridine and the three picolines. In the case of the 3-picoline product, nmr data indicate it to be an 80:20 mixture of 2- and 6-substituted 3-picoline, respectively.

Experimental Section

Gases were analyzed on a vapor phase fractometer containing a column of DC 200 on Chromosorb P; liquids were analyzed, identified, and isolated on a column containing SE-30 on Chromosorb W. Only medium and strong absorbance bands are re-

(1) E. N. Shaw, "The Chemistry of Heterocyclic Compounds, Pyridine and Its Derivatives," Part II, E. Klingsberg, Ed., Interscience Publishers, Inc., New York, N. Y., 1961, Chapter 4.

(2) G. R. Delpierre and M. Lamchen, *J. Chem. Soc.*, 4693 (1963).

(3) B. G. Murray and A. F. Turner, *ibid., C.*, 1338 (1966).

(4) L. E. Tenenbaum, "The Chemistry of Heterocyclic Compounds, Pyridine and Its Derivatives," Part II, E. Klingsberg, Ed., Interscience Publishers, Inc., New York, N. Y., 1961, Chapter 5.

(5) D. Bryce-Smith, *et al.*, *Chem. Ind.* (London), 495 (1964).

(6) R. C. Myerly and K. G. Weinberg, *J. Org. Chem.*, **31**, 2008 (1966).

(7) G. J. Janz and A. R. Monahan, *ibid.*, **29**, 569 (1964).

ported from the infrared spectra obtained on an Infracord 337. Nmr spectra were run on chromatographically isolated fractions to which were then added trifluoroacetic acid as external standard for F^{19} spectra and tetramethylsilane in carbon tetrachloride as external reference standard for H^1 spectra.

2-(1,2,2,2-Tetrafluoroethyl)pyridine.—To a 500-ml stainless steel pressure vessel were added 99.7 g (1.05 mol) of pyridine N-oxide and 80 g (0.53 mol) of hexafluoropropylene, and the resulting mixture was heated at 62° for 16.5 hr. Then the gases (5.1 g) were bled off at ambient temperatures to a residual pressure of one atmosphere. The off-gas contained CO_2, COF_2, CF_3CFHCF_3, and a small amount of $CF_3CF{=}CF_2$. The residue (174 g of brown liquid) from the pressure vessel was transferred to a suitable flask and was distilled by short-path distillation at a pot temperature of 25–90° (0.1 mm) to yield 92 g of slightly colored oil. This oil was added to 300 ml of water with stirring. After all the carbon dioxide had evolved, the water layer was made basic (pH 8) with 50% aqueous KOH. The bottom (oil) phase was then separated, the water phase was washed twice with 20-ml portions of methylene chloride, and the organic phases were combined and dried ($MgSO_4$). After the salt was removed by filtration and the solvent removed by flash evaporation under reduced pressure, the remaining liquid was distilled at 142° (ambient pressures) on a spinning-band column to yield 42 g (44% yield based on hexafluoropropylene) of a colorless oil: $n^{28}D$ 1.4109; mol wt (*m/e* found by mass spectroscopy) 179 (calcd 179); infrared spectrum, 1600 (m, doublet), 1270 (s), 1190 (s), 1140 (s); F^{19} nmr spectrum (ppm), 0.75 (doubled doublet, CF_3), 121.6 (doubled quartet, CFH); H^1 spectrum (ppm), 5.41 (doubled quartet, CFH), 6.49–7.27 (complex bands, H_3, H_4, H_5), 8.04 (doublet, H_6).

Anal. Calcd for $C_7H_5F_4N$: C, 46.95; H, 2.81; F, 42.43; N, 7.82. Found: C, 47.08; H, 3.06; F, 42.15; N, 7.56.

6-(1,2,2,2-Tetrafluoroethyl)-2-picoline.—To a 100-ml stainless steel pressure vessel were added 14.5 g (0.14 mol) of 2-picoline N-oxide and 10 g (0.067 mol) of hexafluoropropylene. After the mixture was heated at 68° for 67 hr and then cooled, the gases (4.3 g) were removed and were found to consist mainly of CO_2 and CF_3CFHCF_3. The remaining contents of the pressure vessel were distilled by short-path distillation at a pot temperature of 25–63° (0.01 mm) to give 9.1 g of yellow liquid. Isolation and purification of the product was made by vpc to give a colorless liquid (19% yield based on hexafluoropropylene). Physical properties of the product are as follows: bp (micro) 154°; $n^{25}D$ 1.4189; mol wt (*m/e* found by mass spectroscopy) 193 (calcd 193); infrared spectrum, 1600 (m doublet), 1275 (s), 1190 (s), 1400 (s); F^{19} nmr spectrum (ppm), 0.68 (doubled doublet, CF_3), 121.1 (doubled quartet, CHF); H^1 spectrum (ppm), 1.88 (singlet, CH_3), 6.41–7.13 (broad lines, H_3, H_4, H_5), 5.32 (doubled doublet, CFH).

Anal. Calcd for $C_8H_7F_4N$: C, 49.75; H, 3.65; F, 39.34; N, 7.25. Found: C, 50.39; H, 4.14; F, 40.00; N, 7.39.

2- and 6-(1,2,2,2-Tetrafluoroethyl)-3-picoline.—To a 100-ml stainless steel vessel were added 21.8 g (0.2 mol) of 3-picoline N-oxide and 15.0 g (0.1 mol) of hexafluoropropylene, and the resulting mixture was heated at 60° for 16.5 hr. The work-up procedure, similar to that used for the 2-picoline N-oxide reaction, gave a colorless oil (36% yield based on hexafluoropropylene). Physical properties of the product are as follows: bp (micro) 166°; $n^{26}D$ 1.4248; mol wt (*m/e* found by mass spectroscopy) 193 (calcd 193); infrared spectrum, 1610 (s), 1270 (s), 1190 (s), 1140 (s); F^{19} nmr spectrum (ppm), 0.59 (doubled doublet, CF_3), 119.6 (doubled quartet, CFH); H^1 spectrum (ppm), 2-substituted 3-picoline, 1.82 (str doublet, CH_3), 5.56 (doubled quartet, CFH), 6.96, 6.60, 7.91 (H_4, H_5, H_6, respectively) 6-substituted 3-picoline, 1.68 (wk singlet, CH_3), 5.56 (doubled quartet, CFH), 7.87, 6.91, 6.78 (H_2, H_4, H_5, respectively).

Anal. Calcd for $C_8H_7F_4N$: C, 49.75; H, 3.65; F, 39.34; N, 7.25. Found: C, 49.95; H, 4.17; F, 39.94; N, 7.25.

2-(1,2,2,2-Tetrafluoroethyl)-4-picoline.—To a 60-ml stainless steel pressure vessel were added 21.8 g (0.20 mol) of 4-picoline N-oxide and 15.0 g (0.10 mol) of hexafluoropropylene, and the resulting mixture was heated at 47–74° for 17.5 hr. The work-up procedure, similar to that used for the 2-picoline N-oxide reaction, gave a colorless oil (36% yield based on hexafluoropropylene). Physical properties of the product are as follows: bp (micro) 166°; $n^{26}D$ 1.4248; mol wt (*m/e* found by mass spectroscopy) 193 (calcd 193); infrared spectrum, 1610 (s), 1270 (s), 1190 (s), 1140 (s); F^{19} nmr spectrum (ppm), 0.53 (doubled doublet, CF_3), 121.7 (doubled quartet, CHF); H^1 spectrum (ppm), 1.71 (singlet, CH_3), 6.88, 6.50, 7.88 (H_3, H_5, H_6, respectively, 5.41 (doubled quartet, CHF).

Anal. Calcd for $C_8H_7F_4N$: C, 49.45; H, 3.65; F, 39.34; N, 7.25. Found: C, 50.46; H, 3.86; F, 39.23; N, 7.26.

Miscellaneous.—Short-path distillation of the crude reaction mixture to yield the crude product can be eliminated if the mixture is added directly to water. The procedure can be continued as in the preparation of 2-(1,2,2,2-tetrafluoroethyl)pyridine, or it can be modified to include steam distillation.

Registry No.—2-(1,2,2,2-Tetrafluoroethyl)pyridine, 16876-47-4; 6-(1,2,2,2-tetrafluoroethyl)-2-picoline, 16876-48-5; 6-(1,2,2,2-tetrafluoroethyl)-3-picoline, 16876-49-6; 2-(1,2,2,2-tetrafluoroethyl)-3-picoline, 16876-50-9; 2-(1,2,2,2-tetrafluoroethyl)-4-picoline, 16876-51-0.

Acknowledgment.—We gratefully acknowledge Dr. Gordon Leader for his nmr data, Dr. James Smith for his mass spectral information, Mr. Howard Francis for the elemental analyses, and Mr. Richard Fayter, Jr., and Mr. William Staas for their experimental work.

Reaction of Aziridines with Benzoic Anhydride

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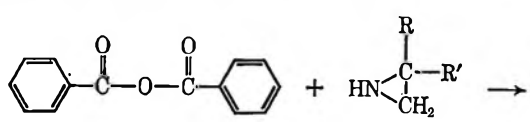
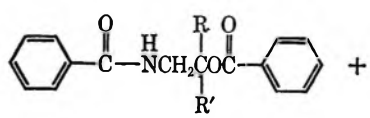
At least two examples of the reaction of anhydrides with aziridines are reported in the patent literature. Ester amides were prepared from N-alkylethylenimines and anhydrides of saturated monocarboxylic acid,[1] while poly(ester amides) were obtained from the reaction of N-alkylethylenimines and phthalic anhydride.[2] In both of these cases, only one isomer is possible through ring opening of the aziridine moiety.

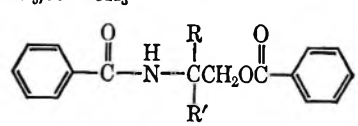
We wish to report on the reactions of 2-methylethylenimine (Ia) and 2,2-dimethylethylenimine (Ib) with benzoic anhydride in acetone or tetrahydrofuran. The quantitative identification of the reaction products from these reactions was accomplished with the aid of



Ia, R = H; R′ = CH_3
b, R = CH_3; R′ = CH_3



IIa, R = H; R′ = CH_3
b, R = CH_3; R′ = CH_3



IIIa, R = H; R′ = CH_3
b, R = CH_3; R′ = CH_3

(1) Bradische Anilin and Soda-Fabrik Aktiengesellschaft of Germany, British Patent, 784,058 (1957).

(2) Bradische Anilin and Soda-Fabrik Aktiengesellschaft of Germany, British Patent, 784,059 (1957).

TABLE I
NMR SPECTRAL DATA

Ester amide	Chemical shifts, δ, ppm[a] Methyl	J, cps	Methylene	J, cps	Methinyl
N,O-Dibenzoyl(1-amino-2-propanol) (IIa)	1.45 (d)	6	3.7 (t)	5.5	5.39 (m)
N,O-Dibenzoyl(2-amino-1-propanol) (IIIa)	1.33 (d)	6	4.47 (d)		4.5 (m)
N,O-Dibenzoyl(1-amino-2-methyl-2-propanol) (IIb)	1.63 (s)		3.88 (d)	4.5	
N,O-Dibenzoyl(2-amino-2-methyl-1-propanol) (IIIb)	1.55 (s)		4.56 (s)		

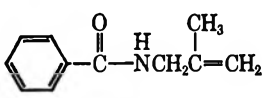
[a] Spectra were determined in $CDCl_3$ using TMS as a standard. Abbreviations used are s = singlet, d = doublet, t = triplet, m = multiplet.

proton nmr spectroscopy. This technique was especially suitable for differentiating the resulting ester amide isomers, since the chemical shifts were significantly different and distinguishable. For example, the assignments presented in Table I were based on authentic model compounds of the four possible ester amide isomers which could result from the reaction of benzoic anhydride with Ia or Ib.

The isomer ratios in the reaction mixtures could be conveniently determined by integrating the areas of the methylene and methinyl protons of IIa and IIIa, or simply the methylene protons in the case of IIb and IIIb, if all the isomers were indeed formed. Product identification *via* gas–liquid partition chromatography (glpc) was used to supplement the nmr spectra of the mixtures. Finally, the products of the reaction were isolated and their structures were confirmed by comparison with the corresponding authentic model compounds.

It was found that the reaction of Ia with benzoic anhydride in either THF or acetone resulted in the formation of the two isomeric ester amides IIa and IIIa. Integration of the nmr spectrum of the reaction mixture indicated that the mole ratio of IIa and IIIa was 3:1. Furthermore, since the amount of unreacted benzoic acid in the mixture is indicative of the moles of by-product in the reaction, the ratio of the benzoic acid nmr signal at δ 9.9 to the total ester amide integration was used as the criterion for estimation of yield. A yield of 80% was generally obtained utilizing this procedure.

In the case of the reaction of benzoic anhydride with Ib, the only ester amide produced was IIb, along with a considerable amount of N-(β-methylallyl)benzamide (IV) and benzoic acid. The important chemical shifts of IV appeared as a broad signal at δ 4.88 due to the



IV

terminal vinylic protons, at 1.77 due to the methyl group, and 3.98 due to the methylene protons. Since overlapping of the methylene protons of IIb and IV occurred in the nmr spectrum of the reaction mixture, it was necessary to subtract a quantity equal to the signal produced by the terminal vinyl protons of IV from the area integration produced by the overlapping methylene protons of both IIb and IV. This could be done since the signal produced by the vinylic protons of IV is exactly equal in area to the signal of its methylene protons. This procedure afforded a product ratio of 1.7:1 of IIb to IV, respectively. The total yield of IIb in the reaction mixture was 63%.

Experimental Section[3]

Preparation of Authentic Compounds.—1-Amino-2-propanol, 2-amino-1-propanol, and 2-amino-2-methyl-1-propanol were allowed to react with benzoyl chloride at a 1:2 mole ratio in a CH_2Cl_2–H_2O solvent mixture utilizing NaOH as the acid acceptor. The resulting dibenzoyl ester amides were isolated from the dried organic phase *via* vacuum stripping followed by recrystallization from acetone: **N,O-dibenzoyl(1-amino-2-propanol) (IIa)**, mp 106° (lit.[4] 102–104°); **N,O-dibenzoyl(2-amino-1-propanol) (IIIa)**, mp 102–103° (lit.[5] 104–105°); **N,O-dibenzoyl(2-amino-2-methyl-1-propanol) (IIIb)**, mp 112–114° (lit.[6] 111–112°). **1-Amino-2-methyl-2-propanol** was prepared by a literature method:[7] bp 146–148°, $n^{25}D$ 1.4440 (lit.[7] 147.8–148°, $n^{25}D$ 1.4435).

N,O-Dibenzoyl(1-amino-2-methyl-2-propanol) (IIb) was prepared by treating 2 g of 1-amino-2-methyl-2-propanol (0.02 mol) with 6.5 g of benzoyl chloride (0.05 mol) in 40 ml of $CHCl_3$ and utilizing 5 g of pyridine as the acid acceptor. On completion of the addition of benzoyl chloride to the amino alcohol, the mixture was refluxed for 4 hr. Then 30 ml of a 6 *N* HCl solution was added to the cooled mixture, This mixture was extracted three times with 100-ml portions of diethyl ether, and the ether extract was washed with a dilute HCl solution, followed by two washings with water. The ether extract was evaporated to dryness. Recrystallization of the crude solid from acetone yielded IIb, mp 136–138°.

Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.73; H, 6.40; N, 4.71. Found: C, 72.51; H, 6.58; N, 4.87.

N-(β-Methallyl)benzamide (IV) was prepared from benzoyl chloride and β-methallylamine,[8] mp 69.5–70.5°. The reported melting point of IV is 67.5–69°.[8]

Reactions of Benzoic Anhydride with 2-Methylethylenimine (Ia) or 2,2-Dimethylenimine (Ib).—To a solution of 11.3 g (0.05 mol) of benzoic anhydride in 71.3 g of THF or acetone was added either 2.85 g (0.05 mol) of Ia or 3.60 g (0.05 mol) of Ib, maintaining the reaction temperature of 25° during the addition with an ice bath. When the addition was completed, the reaction was stirred at 25° for 4 hr, followed by heating at reflux for 20 hr. The solution was then cooled to room temperature, and an aliquot sample was removed for glpc analysis. The rest of the reaction mixture was vacuum stripped at room temperature to remove the solvent. An nmr spectrum was obtained on the solvent-free product. In the case of the benzoic anhydride–Ia reaction, both analyses confirmed that the product was composed mainly of a mixture of IIa and IIIa (3:1 mole ratio) along with benzoic acid and a small amount of an undetermined impurity. Glpc and nmr analysis of the benzoic anhydride–Ib reaction mixture indicated that it was composed of IIb and IV (at a 1.7:1 mole ratio) along with some benzoic acid. The solvent-stripped reaction syrup was next extracted with a large volume of ether.

(3) The nmr analysis was carried out on a Varian A-60A spectrometer in $CDCl_3$ solutions at room temperature, with tetramethylsilane (TMS) as an internal standard. Gas chromatography was conducted with an F & M 810 gas chromatograph utilizing a 6 ft × 0.125 in. o.d. column of 10% SE 30 on Diatoport S (60–80 mesh). The column temperatures were programmed from 100 to 250°, at a rate of 20°/min. Melting points were determined on a "Mel-Temp" melting point apparatus, and all temperature measurements are uncorrected. Molecular weights were determined by vapor pressure osmometry in acetone (Mechrolab osmometer, Model 301A). Elemental analyses were performed by the Analytical Department of the Interchemical Central Research Laboratories.

(4) G. Bach and M. Zahn, *J. Prakt. Chem.*, **8**, 68 (1959).

(5) D. E. Wolf, W. H. Jones, J. Valiant, and K. Folkers, *J. Amer. Chem. Soc.*, **72**, 2820 (1950).

(6) R. N. Boyd and R. H. Hansen, *ibid.*, **75**, 5896 (1953).

(7) R. A. Bafford, Ph.D. Thesis, University of Maryland, College Park, Md., p 27, 1960.

(8) P. E. Fanta and A. Deutch, *J. Org. Chem.*, **23**, 72 (1958).

In the case of the benzoic anhydride–Ia reaction mixture, the extraction left 10.5 g of a mixture of IIa and IIIa (74.2% yield). Fractional recrystallization of this mixture with acetone afforded 8.7 g of IIa, mp 104–106°, and 1.1 g of IIIa, mp 101–103°. The ether extract was washed several times with a 5% NaOH solution, and the aqueous layer was acidified by the addition of Dry Ice. Extraction of the aqueous solution with fresh ether, drying with anhydrous $MgSO_4$ and evaporation of the ether yielded 0.5 g of benzoic acid, mp 121–122°. The benzoic anhydride–Ib reaction mixture was treated in a similar manner, resulting in the isolation of 8.8 g of the ether-insoluble IIb (59% yield), mp 136–138°, and 1.8 g of benzoic acid. Finally, the original water-washed ether layer was dried with anhydrous $MgSO_4$ and evaporated to dryness. Recrystallization of the crude semisolid from petroleum ether resulted in the recovery of 2.3 g of IV, mp 67–69°. Mixture melting points of isolated IIa, IIb, IIIa, IV, and benzoic acid with the corresponding authentic samples were not depressed.

Registry No.—Benzoic anhydride, 93-97-0; IIa, 16888-96-3; IIb, 16888-97-4; IIIa, 16888-98-5; IIIb, 16888-99-6.

The Condensation of Enamines with Substituted *p*-Benzoquinones

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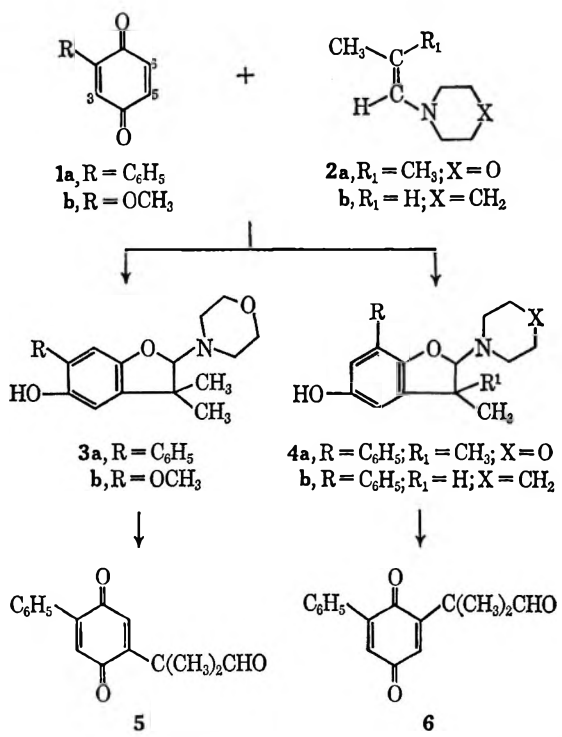
The introduction of a formylalkyl group into quinones by oxidation of 2-amino-2,3-dihydrobenzofurans **3**, which are available from the interaction of quinones **1** and enamines **2**,[1-3] was recently reported[1] (see Scheme I). The purported preparation of the 5-phenyl-2-formylalkylquinone **5**, mp 142–143°, by oxidation of the dihydrobenzofuran **3a** is illustrative of this procedure. Our experience[4] with the condensation of benzoquinones and enamines led us to believe that the quinone of mp 142–143° is, in fact, the 6-phenyl isomer **6**. Thus, inasmuch as the formation of the dihydrobenzofurans **3** and **4** probably proceeds by nucleophilic addition of the enamine to the benzoquinone and subsequent cyclization,[3] the position assumed by the quinone substituent in the product will reflect its electronic and steric character. Electron-withdrawing groups direct reaction toward C-3 in **1** or, alternatively, in the presence of strong steric effects, *e.g.*, phenyl, toward C-6, whereas electron-donating groups favor condensation at C-5.[5]

Indeed, as predicted by these considerations, condensation of 2-phenyl-1,4-benzoquinone (**1a**) with isobutenylmorpholine (**2a**)[6] gave 70% 7-phenyldihydrobenzofuran **4a** (δ 6.45 and 6.75, J = 3.0 cps), accompanied by 7% 6 isomer **3a** (δ 6.67). The reaction of **1a** with 1-propenylpiperidine (**2b**)[7] to give

SCHEME I



62% dihydrobenzofuran **4b** (δ 6.46 and 6.78, J = 3.0 cps) as the sole product further illustrates the directive influence of the phenyl substituent. In the instance of 2-methoxy-1,4-benzoquinone (**1b**), reaction with **2a** affords the expected 6-methoxydihydrobenzofuran **3b** (87%) (δ 6.45 and 6.51, unsplit). The position of the aryl substituent in the dihydrobenzofurans **3** and **4** follow from the cited proton resonances and their splitting patterns.

Oxidation of the 6-phenyldihydrobenzofuran **3a** with ferric chloride[1] afforded the 5-phenylquinone **5**, mp 127–128° (δ 6.60 and 6.78, unsplit), whereas a similar oxidation of the 7-phenyl isomer **4a** gave the 6-phenylquinone **6**, mp 141–142° (δ 6.76 and 6.84, J = 2.4 cps). These data clearly indicate that the quinone of mp 142–143°, to which structure **5** was previously assigned,[1] must possess the isomeric structure **6**. Moreover, the reaction of quinones and enamines in this and related examples proceeds in a predictable manner, the verification of which is readily furnished by nmr spectroscopy.[8]

Experimental Section[9]

Reaction of 1,4-Benzoquinones with Enamines.—The following experiment illustrates the general procedure. A solution of 1.49 g (10 mmol) of isobutenylmorpholine (2a) in 3 ml of methanol was added dropwise over 30 min to an ice-cooled, stirred mixture of 1.84 g (10 mmol) of 2-phenyl-1,4-benzoquinone (1a) in 7 ml of methanol. The solid dissolved to give a red solution that was stirred at ambient temperature for 1 hr. The solvent was removed, and the residue was dissolved in ether. This solution was passed through a magnesia–silica gel column, using ether as the eluting solvent. The yellow eluate was

(1) K. Ley and R. Nast, *Angew. Chem. Intern. Ed. Engl.*, **6**, 174 (1967).
(2) K. C. Brannock, R. D. Burpitt, H. E. Davis, H. S. Pridgen, and J. G. Thweatt, *J. Org. Chem.*, **29**, 2579 (1964).
(3) G. Domschke, *J. Prakt. Chem.*, **32**, 144 (1966).
(4) (a) G. R. Allen, Jr., C. Pidacks, and M. J. Weiss, *J. Amer. Chem. Soc.*, **88**, 2536 (1966); (b) G. R. Allen, Jr., and M. J. Weiss, *J. Org. Chem.*, **33**, 198 (1968); (c) R. Littell and G. R. Allen, Jr., *ibid.*, **33**, 2064 (1968).
(5) H. S. Wilgus, III, E. Frauenglass, E. T. Jones, R. F. Porter, and J. W. Gates, Jr., *ibid.*, **29**, 594 (1964).
(6) E. Benzing, *Angew. Chem.*, **71**, 521 (1959).
(7) C. Mannich and H. Davidsen, *Ber.*, **69**, 2106 (1936).
(8) These results indicate that the Bunte salt derived from 2-phenyl-1,4-benzoquinone is most likely sodium 2,5-dihydroxy-3-biphenylylthiosulfate rather than sodium 2,5-dihydroxy-4-biphenylylthiosulfate: W. Alcalay, *Helv. Chim. Acta*, **30**, 578 (1947). If true, the derived 2-methylmercapto-1,4-benzoquinone is the 6-phenyl isomer, rather than the previously assigned 5-phenyl isomer.
(9) Melting points are uncorrected. Evaporations were carried out under reduced pressure. Nmr spectra were determined in deuteriochloroform using tetramethylsilane as an internal standard on a Varian A-60 spectrometer.

evaporated to give 3.47 g of an oil that was purified by partition chromatography[10] on diatomaceous silica using a heptane–methanol (1:1) solvent system. The fraction with peak hold-back volume 4.0 (v_m/v_s = 2.7) was evaporated; recrystallization of the residue from acetone–hexane gave 238 mg (7%) of **2,3-dihydro-5-hydroxy-3,3-dimethyl-2-(4-morpholinyl)-6-phenylbenzofuran (3a)** as white crystals, mp 215–217°.

Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.80; H, 6.97; N, 4.29.

The fraction with peak hold-back volume 6.0 was evaporated; the residue was recrystallized from acetone–hexane to furnish 2.033 g (70%) of **2,3-dihydro-5-hydroxy-3,3-dimethyl-2-(4-morpholinyl)-7-phenylbenzofuran (4a)** as white crystals, mp 164–165°.

Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.53; H, 7.10; N, 4.26.

Reaction of 4.70 g (37.5 mmol) of 1-piperidyl-1-propene (**2b**) and 4.60 g (25 mmol) of 2-phenyl-1,4-benzoquinone (**1a**) in benzene gave 3.65 g of **2,3-dihydro-5-hydroxy-3-methyl-7-phenyl-2-(1-piperidyl)benzofuran (4b)** as crystals, mp 130–133°, by direct crystallization. Partition chromatography of the material in the filtrate using a heptane–methanol (1:1) system afforded an additional 1.13 g (62%) of crystals, mp 135–137°, in that fraction with peak hold-back volume 3.4 (V_m/V_s = 2.5). A sample was recrystallized from ether–hexane to give white crystals, mp 135–137°.

Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.91; H, 7.51; N, 4.52.

Treatment of 1.38 g (10 mmol) of 2-methoxy-1,4-benzoquinone (**1b**) with 1.49 g (10 mmol) of isobutenylmorpholine (**2a**) in methylene chloride, solvent removal, and trituration of the residue with ether gave 2.44 g (87%) of **2,3-dihydro-5-hydroxy-6-methoxy-3,3-dimethyl-2-(4-morpholinyl)benzofuran (3b)** as crystals, mp 157–161°. A sample recrystallized from methanol had mp 168–169°.

Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.49; H, 7.58; N, 5.01. Found: C, 64.23; H, 7.29; N, 4.71.

Oxidation of the 2-Amino-2,3-dihydrobenzofurans.—The following experiment illustrates the general procedure. A solution of 1.080 g (2.0 mmol) of ferric chloride hexahydrate in 7.5 ml of water was added dropwise with stirring to a suspension of 650 mg (1.0 mmol) of 2,3-dihydro-5-hydroxy-3,3-dimethyl-2-(4-morpholinyl)-7-phenylbenzofuran (**4a**) in 75% methanol. The mixture was stirred for 3 hr after completion of the addition, at which time it was bright yellow. The solid was collected by filtration and dissolved in methylene chloride. This solution was passed through a magnesia–silica gel column using methylene chloride as the eluting solvent. The yellow eluate was evaporated to give a residue that was recrystallized twice from ether to give 340 mg (67%) of **α-(6-phenyl-2-*p*-quinoyl)isobutyraldehyde (6)** as orange crystals: mp 141–142°; λ_{max} 291 mμ (ε 4840), 314 (5340).

Anal. Calcd for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.30; H, 5.63; N, 0.0.

In the manner described above, treatment of 120 mg (0.36 mmol) of 2,3-dihydo-5-hydroxy-3,3-dimethyl-2-(4-morpholinyl)-6-phenylbenzofuran (**3a**) with 270 mg (1.0 mmol) of ferric chloride hexahydrate furnished 43 mg (43%) of **α-(5-phenyl-2-*p*-quinoyl)isobutyraldehyde (5)** as needles, mp 127–128°, after recrystallization from ether–hexane: λ_{max} 300 mμ (ε 5970), 312 (6480).

Anal. Calcd for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.65; H, 5.42; N, 0.0.

Registry No.—**3a**, 16793-13-8; **3b**, 16793-14-9; **4a**, 16793-15-0; **4b**, 16793-16-1; **5**, 14348-69-7; **6**, 16793-18-3.

Acknowledgment.—The author is indebted to Mr. C. Pidacks and his staff for the partition chromatography, to Mr. W. Fulmor and his associates for the spectral data, and to Mr. L. Brancone and his group for the microanalyses.

(10) For a complete description of this technique, as developed by Mr. C. Pidacks of these laboratories, see M. J. Weiss, R. E. Schaub, G. R. Allen, Jr., J. F. Poletto, C. Pidacks, R. B. Conrow, and C. J. Coscia, *Tetrahedron*, **20**, 357 (1964).

Preparation of A-Ring Conjugated Enones and the Corresponding α,β-Epoxy Ketones of 17β-Acetoxy-5α-androstane

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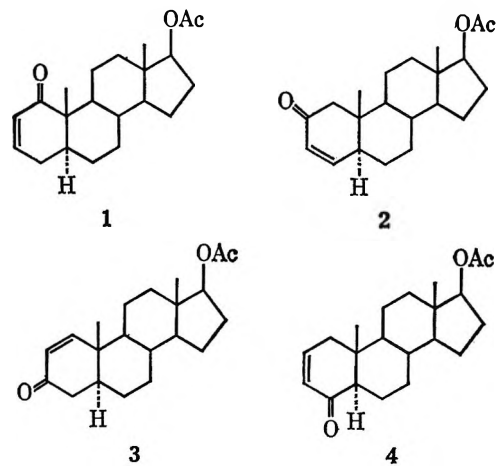
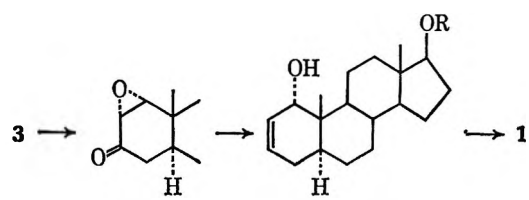
Received March 6, 1968

In connection with other studies, the title compounds were needed. While the A-ring conjugated enones (**1**–**4**) are already known, there were some different observations between those reported by earlier authors[1] and ours during the course of preparing the enones (**1**, **2**, and **4**). The epoxy ketones (*e.g.* **5**, **14**, **24**, and **26**) are believed to be interesting compounds for CD[2a] and biological[2b] studies. These compounds, except for **5**, have not been reported to date.



Reductive elimination of the 1α,2α-epoxy-3-one **5**[3] with 60% $NH_2NH_2 \cdot H_2O$ gave the enol **6** in 57% yield, which upon oxidation afforded the 2-en-1-one **1**. In our hands, the reaction of the epoxy ketone **5** with 100% $NH_2NH_2 \cdot H_2O$ according to Djerassi, *et al.*,[1a] who obtained only the enol **6** (40%), yielded a mixture of the enol **6** (12%) and the 2-ene-1α,17β-diol **7** (37%). Furthermore, the use of 95% $NH_2NH_2 \cdot H_2O$[1b] could not prevent cleavage of the C_{17} acetoxyl group.



Dehydrobromination of the 3α-bromo-2-one **9**, derived from the bromohydrin **8**,[4] with Li_2CO_3 alone af-

(1) (a) C. Djerassi, D. H. Williams, and B. Berkoz, *J. Org. Chem.*, **27**, 2205 (1962); (b) P. D. Klimstra and R. E. Counsell, *J. Med. Chem.*, **8**, 48 (1965); (c) P. D. Klimstra, U. S. Patent 3,166,578 (1965); *Chem. Abstr.*, **62**, 9207*a* (1965).

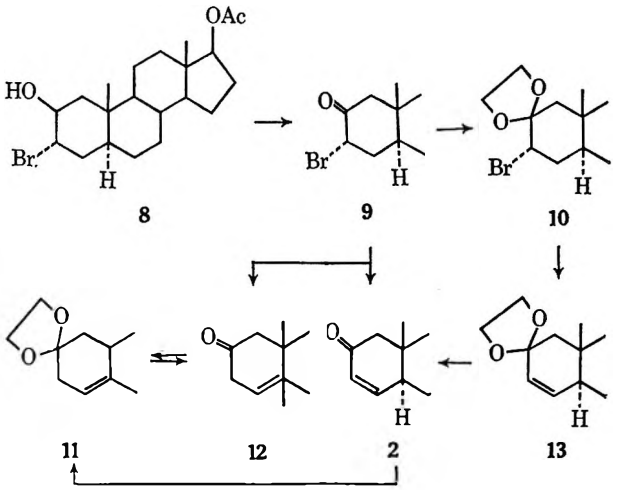
(2) (a) K. Kuriyama, H. Tada, Y. K. Sawa, S. Itô, and I. Itoh, *Tetrahedron Lett.*, 2539 (1968); (b) Dr. Miyake of our laboratory, unpublished results.

(3) W. M. Hoehn, *J. Org. Chem.*, **23**, 929 (1958).

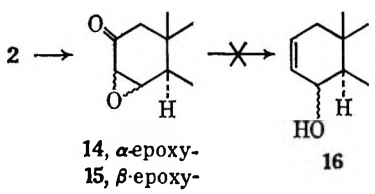
(4) Kindly supplied by Dr. Komeno of our laboratory.

forded a mixture of the 3-en-2-one **2** and the isomeric 4-en-2-one **12**, whose separation either by column chromatography or by preparative tlc was unsuccessful, but recrystallization from a large amount of ether gave the pure enone **2** (mp 134–136°; $[\alpha]_D$ +105.0°). Although the physical values are considerably different from those reported (mp 87–90°; $[\alpha]_D$ +8°),[1b] the structure of our compound **2** is undoubtedly correct judging from its typical spectral properties and from the chemical transformations shown in Scheme I.

SCHEME I

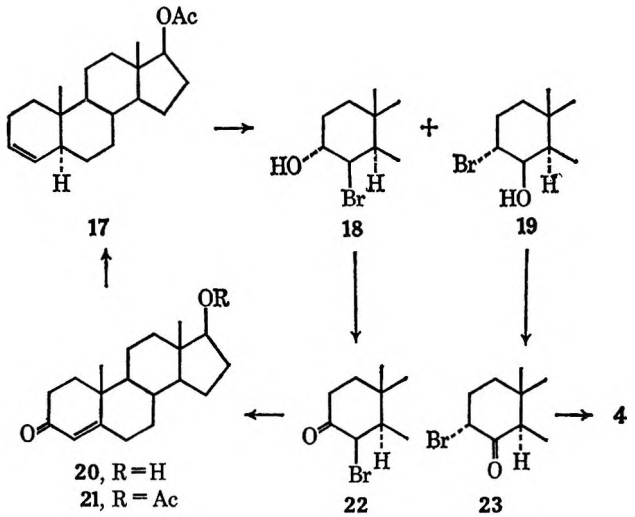


Ketalization of the dehydrobromination product (a mixture of **2** and **12**) gave only the Δ^4-2-ketal **11**, which on hydrolysis afforded the 4-en-2-one **12** (mp 146–148°; $[\alpha]_D$ +128.3°). Dehydrobromination of the bromo ketal **10** with *t*-BuOK in DMSO and subsequent acetylation led to the Δ^3-2-ketal **13**, which on a brief treatment with diluted hydrochloric acid gave the enone **2**.

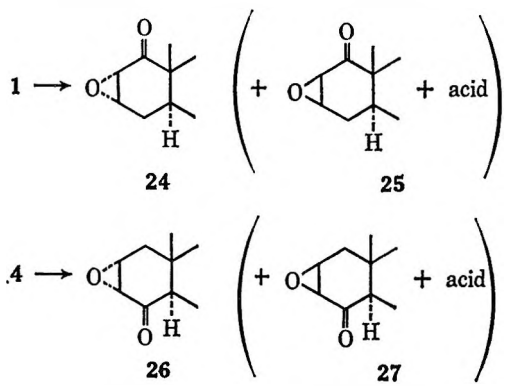


Epoxidation of the enone **2** with alkaline hydrogen peroxide according to Hoehn[3] afforded the 3α,4α-epoxy-2-one **14** (mp 184–185°; $[\alpha]_D$ +58.9°) together with the 3β,4β-epoxy-2-one **15** (mp 163–165°; $[\alpha]_D$ +114.9°). Configuration of the epoxy ring was confirmed by the chemical shift of the 19-methyl group in the nmr spectrum. Reductive elimination of the epoxy ketone **14**, however, gave only an intractable material.

An alternative route to the 2-en-4-one **4** *via* the olefin **17**, prepared by hydroboration of testosterone **20** followed by treatment with Ac_2O,[5] was then examined. Reaction of the olefin **17** with hypobromous acid either in dioxane[6] or in DMSO gave a mixture of bromohydrins, which was chromatographed to give the 3α-bromo-4β-ol **19** (mp 212–213°; $[\alpha]_D$ −7.1°) and the 4β-bromo-3α-ol **18** (mp 195–196°; $[\alpha]_D$ +2.8°). Both isomeric bromohydrins were characterized as the corresponding bromo ketones **23**[7] (mp 152–154°; $[\alpha]_D$ −131.4°) and **22** (mp 171–172°; $[\alpha]_D$ −98.8°). Treatment of both bromo ketones **22** and **23** with Li_2CO_3 afforded respective enones **21** and **4**. The former enone **21** was proved to be testosterone acetate.



Epoxidation of the 2-en-1-one **1** with alkaline hydrogen peroxide according to Julian, *et al.*,[8] afforded the 2α,3α-epoxy-1-one **24** (mp 174–175°; $[\alpha]_D$ +20.6°) as a major product. The epimeric 2β,3β-epoxy-1-one **25** was only detected in the nmr spectrum of the residue



after separation of the α isomer. Unexpectedly, an acidic component was isolated as a minor product, whose structure is now under study.

An analogous result was obtained for epoxidation of the 2-en-4-one **4**. The 2α,3α-epoxy-4-one **26** (mp 122–124°; $[\alpha]_D$ +9.0°) was a major product and the epimeric 2β,3β-epoxy-4-one **27** was only detected in the nmr spectrum of the residue after separation of the α isomer. In this case, an acidic component after esterification showed many spots on tlc.

Experimental Section[9]

17β-Acetoxy-5α-androst-2-en-1α-ol (6).—Reductive cleavage of the epoxy ketone **5**[3] with 60% $NH_2NH_2 \cdot H_2O$ alone, in place of

(5) *Cf.* L. Caglioti, G. Cainelli, G. Maina, and A. Selva, *Gazz. Chim. Ital.*, **92**, 309 (1962); *Tetrahedron*, **20**, 957 (1964).

(6) Klimstra and Counsell reported isolation of only one bromohydrin, **19** (mp 166–168°; $[\alpha]_D$ −4.5°), without description of the yield.[1c]

(7) In the literature,[1b,c] mp 130–132° (hemihydrate) and $[\alpha]_D$ −79.5° are reported.

(8) P. L. Julian, W. Cole, E. W. Meyer, and B. M. Regan, *J. Amer. Chem. Soc.*, **77**, 4601 (1955).

(9) Melting points were observed in capillaries and are corrected. Specific rotations were measured in $CHCl_3$ (*c* 1) with Perkin-Elmer polarimeter, Type 141. The infrared spectra were recorded in $CHCl_3$ with JASCO DS-201 B spectrometer. The nmr spectra were obtained on a Varian A-60A spectrometer using $CDCl_3$ solutions. The chemical shifts are expressed in parts per million downfield from a standard (TMS). The ORD and CD curves were measured in MeOH on a JASCO Model ORD/UV-5 equipped with CD attachment. Data are presented as follows: ORD λ_{max} ($[\Phi]$); CD λ_{max} ($[\theta]$).

100% $NH_2NH_2 \cdot H_2O$ in *i*-PrOH containing AcOH,[1a] yielded the enol **6** (57%; mp 144–153°). After recrystallization it melted at 154–156°, $[\alpha]D$ +122.1°.

17β-Acetoxy-5α-androst-2-en-1-one (**1**).—Oxidation of the enol **6** with Jones reagent[10] gave the enone **1**: mp 193–194° (from *i*-PrOH); $[\alpha]D$ +124.5°; nmr, δ 6.67 (C_3-H, doublet of triplets, J = 10.0 and 3.5 cps), 5.79 (C_2-H, doublet of triplets, J = 10.0 and 1.5 cps), 1.06 (19-Me), and 0.18 ppm (18-Me); ORD 360 (−1810) and 305 mμ (+8290); CD 335 mμ (−5990).

Dehydrobromination of 17β-Acetoxy-3α-bromo-5α-androstan-2-one (**9**).—A solution of the bromo ketone **9** (2.0 g) in DMF (20 ml) was refluxed with Li_2CO_3 (1.2 g) for 4 hr under nitrogen. Dilution with water and extraction with benzene afforded a halogen-free solid, which was triturated with ether to give a crystalline product (1.3 g; tlc, two spots). Recrystallization from a large amount of ether gave **17β-acetoxy-5α-androst-3-en-2-one** (**2**): mp 134–136°; $[\alpha]D$ +105.0°; ir, 1725 and 1670 cm^{-1}; nmr δ 6.55 (C_4-H, doublet of doublets, J = 10.0 and 2.0 cps), 5.97 (C_3-H, octet, J = 10.0, 3.0, and 1.0 cps), 0.89 (19-Me, d, J = 1.0 cps), 0.81 ppm (18-Me); uv max (95% EtOH), 233 mμ (ε 8500) and 312 (56); CD 347 (−760) and 294 mμ (+470).

Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.21; H, 9.11.

17β-Acetoxy-2,2-ethylenedioxy-5α-androst-4-ene (**11**).—A mixture of the above mentioned dehydrobromination product (2.0 g), ethylene glycol (4 ml), and benzene (100 ml) containing *p*-TsOH·H_2O (120 mg) was refluxed for 3 hr using a water separator. The usual treatment and crystallization of a crude product from EtOH gave 1.48 g (65%) of the Δ⁴-2-ketal **11**: mp 159–160°; $[\alpha]D$ +0.5°; nmr, δ 5.25 (C_4-H, m), 1.15 (19-Me), and 0.82 ppm (18-Me).

Anal. Calcd for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.84; H, 9.00.

17β-Acetoxy-5α-androst-4-en-2-one (**12**).—The Δ⁴-2-ketal **11** (1.0 g) was heated with 80% aqueous AcOH (20 ml) on a boiling-water bath for 8 min and poured into water. A precipitate was filtered (0.9 g; mp 141–144°) and recrystallized from EtOH to give 415 mg of the enone **12**: mp 146–148°; $[\alpha]D$ +128.3°; ir, 1720 cm^{-1}; nmr, δ 5.29 (C_4-H, m), 1.01 (19-Me), and 0.82 ppm (18-Me); ORD 307 (+6790) and 271 mμ (−5040); CD 290 mμ (+8900).

Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.16; H, 9.12.

17β-Acetoxy-3α-bromo-2,2-ethylenedioxy-5α-androstane (**10**).—A mixture of the bromo ketone **9** (2.0 g), ethylene glycol (3 ml), *p*-TsOH·H_2O (970 mg), and benzene (100 ml) was refluxed for 6 hr using a water separator. The usual treatment and subsequent acetylation gave a solid, which on recrystallization from acetone yielded 1.8 g of the bromo ketal **10**: mp 197–199°; $[\alpha]D$ +64.6°; nmr, δ 4.18 ppm ($C_{3\beta}$-H, m, $W_{1/2}$ = 5 cps).

Anal. Calcd for $C_{23}H_{35}BrO_4$: C, 60.65; H, 7.75; Br, 17.55. Found: C, 61.06; H, 7.84; Br, 17.73.

17β-Acetoxy-2,2-ethylenedioxy-5α-androst-3-ene (**13**).—A solution of the bromo ketal **10** (1.5 g) and *t*-BuOK (2.2 g) in DMSO (60 ml) was left at room temperature for 24 hr. Dilution with water and extraction with benzene gave a solid (1.16 g; tlc, one spot), which on acetylation yielded the amorphous Δ³-2-ketal **13** (1.16 g; tlc, one spot): nmr, δ 5.53 (C_3-H and C_4-H, s, two protons), 0.90 (19-Me), and 0.78 ppm (18-Me).

Hydrolysis of the Δ³-2-Ketal 13.—Treatment of the Δ³-2-ketal **13** (563 mg) in acetone (5 ml) with 1 *N* HCl (0.5 ml) at room temperature for 20 min gave the enone **2** (485 mg; tlc, one spot). After recrystallization from ether, it melted at 134–135°: $[\alpha]D$ +104.1°.

Epoxidation of the Enone 2.—To a solution of the enone **2** (4.6 g) in MeOH (120 ml) was added 30% H_2O_2 (5 ml) and 10% NaOH (1 ml) in MeOH (25 ml) at 0°. After 30 min at room temperature, a crystalline solid was filtered (2.2 g, mp 171–175°). The filtrate was concentrated *in vacuo* and a precipitate was separated (0.9 g, mp 155–163°). Dilution of the second filtrate and extraction with ether gave a solid, which on trituration with ether yielded the third crop (252 mg). The first two crops were chromatographed on silica gel (300 g). Elution with EtOAc–benzene (3:97) and recrystallization from EtOH gave **17β-acetoxy-3α,4α-epoxy-5α-androstan-2-one** (**14**): mp 184–185°; $[\alpha]D$ + 58.9°; nmr, δ 3.20 and 3.08 (C_3-H and C_4-H, AB quartet, J = 3.5 cps), 0.83 (19-Me), and 0.78 ppm (18-Me); ORD 322 (+2450) and 282 mμ (−1350); CD 303 mμ (+3120).

Anal. Calcd for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.97; H, 8.84.

The third crop was purified by preparative tlc and crystallized from EtOH to yield **17β-acetoxy-3β,4β-epoxy-5α-androstan-2-one** (**15**): mp 163–165°; $[\alpha]D$ +114.9°; nmr, δ 3.30 and 3.20 (C_3-H and C_4-H, AB quartet, J = 4.0 cps), 1.09 (19-Me), and 0.78 ppm (18-Me); ORD 329 (+6580) and 286 mμ (−4850); CD 308 mμ (+9490).

Anal. Calcd for $C_{21}H_{30}O_4$: C, C, 72.80; H, 8.73. Found: C, 72.81; H, 8.77.

17β-Acetoxy-5α-androst-3-ene (**17**).—A solution of **testosterone** (**20**, 5.0 g) in diglyme (150 ml) was treated with a large excess of diborane for 1 hr at room temperature. Acetic anhydride (80 ml) was added and the mixture was refluxed for 1.5 hr (all operations were carried out under nitrogen). The reaction mixture was concentrated *in vacuo*, poured into water, and extracted with benzene. The product (6.2 g) was chromatographed on Al_2O_3 (250 g), and elution with benzene gave a solid (2.9 g; mp 93–102°; tlc, one spot), which was recrystallized twice to afford 1.35 g (25%) of the olefin **17**: mp 117–118°; $[\alpha]D$ +28.2° (lit.[11] mp 117–118°; $[\alpha]D$ +42.0°); nmr, δ 5.56 (C_3-H, d, J = 10 cps), 5.25 (C_4-H, d, J = 10 cps), and 0.79 ppm (19- and 18-Me).

Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.59; H, 10.28.

Reaction of the Olefin 17 with Hypobromous Acid.—To a solution of the olefin **17** (632 mg) in dry DMSO (18 ml) was added water (0.1 ml) and N-bromosuccinimide (NBS) (712 mg) with cooling under nitrogen. After stirring for 40 min at room temperature, the reaction mixture was diluted with water (120 ml) and extracted with ether to give a product (812 mg; tlc, two spots), which was chromatographed on silica gel (40 g). Elution with EtOAc–benzene (2:98) gave a bromohydrin (263 mg; 32%; mp 205–208°), which on recrystallization from acetone afforded **17β-acetoxy-3α-bromo-5α-androstan-4β-ol** (**19**): mp 212–213° dec; $[\alpha]D$ −7.1°; nmr, δ 4.35 ($C_{3\beta}$-H, q, J = 2.3 cps), 3.87 ($C_{4\alpha}$-H, m, $W_{1/2}$ = 5.5 cps), 1.03 (19-Me), and 0.78 ppm (18-Me).

Anal. Calcd for $C_{21}H_{33}BrO_3$: C, 61.01; H, 8.04; Br, 19.32. Found: C, 61.11; H, 8.09; Br, 19.56.

Further elution with EtOAc–benzene (5:95) gave another bromohydrin (426 mg; 52%; mp 192–194°), which on recrystallization from acetone afforded **17β-acetoxy-4β-bromo-5α-androstan-3α-ol** (**18**): mp 195–196° dec; $[\alpha]D$ +2.8°; nmr, δ 4.24 ($C_{3\beta}$-H, m), 4.06 ($C_{4\alpha}$-H, m), 1.08 (19-Me), and 0.78 ppm (18-Me).

Anal. Calcd for $C_{21}H_{33}BrO_3$: C, 61.01; H, 8.04; Br, 19.32. Found: C, 61.28; H, 8.10; Br, 19.53.

17β-Acetoxy-3α-bromo-5α-androst-4-one (**23**).—The bromohydrin **19** (1.0 g) in acetone (40 ml) was oxidized with chromic acid to give 987 mg of the bromo ketone **23**: mp 154–156°; $[\alpha]D$ −131.4°; nmr, δ 4.28 ($C_{3\beta}$-H, t, J = 3 cps), 3.10 ($C_{5\alpha}$-H, doublet of doublets, J = 10.8 and 4.2 cps), 0.78 (18-Me), and 0.75 ppm (19-Me); ORD 334 (−1460) and 288 mμ (+1830); CD 309 mμ (−27700).

Anal. Calcd for $C_{21}H_{31}BrO_3$: C, 61.31; H, 7.60; Br, 19.42. Found: C, 61.15; H, 7.58; Br, 19.39.

17β-Acetoxy-4β-bromo-5α-androstan-3-one (**22**).—Oxidation of the bromohydrin **18** (1.0 g) in acetone (40 ml) with Jones reagent yielded 968 mg of the bromo ketone **22**: mp 174–175°; $[\alpha]D$ −98.8°; nmr, δ 4.13 ($C_{4\alpha}$-H, m, $W_{1/2}$ = 6.5 cps), 3.10 ($C_{2\beta}$-H, triplet of doublets, J = 15.0 and 6.0 cps), 1.28 (19-Me), and 0.80 ppm (18-Me); ORD 334 (−7480) and 285 mμ (+7600); CD 309 mμ (−14100).

Anal. Calcd for $C_{21}H_{31}BrO_3$: C, 61.31; H, 7.60; Br, 19.42. Found: C, 61.52; H, 7.71; Br, 19.79.

17β-Acetoxy-5α-androst-2-en-4-one (**4**).—A solution of the bromo ketone **23** (1.56 g) in DMF (18 ml) was refluxed with Li_2CO_3 (940 mg) for 1.5 hr under nitrogen. Dilution with water and extraction with ether gave a product (1.29 g; mp 181–185°), which on recrystallization from EtOH yielded 1.05 g (84%) of the enone **4**: mp 187–188°; $[\alpha]D$ +9.0° (lit.[1b] mp 182–184°; $[\alpha]D$ +7.5°); ir, 1726 and 1676 cm^{-1}; nmr, δ 6.80 (C_2-H, octet, J = 10.0, 5.0, and 3.0 cps), 6.03 (C_2-H, octet, J = 10.0,

(10) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(11) J. McKenna, J. K. Norymberski, and R. D. Stubbs, *ibid.*, 2502 (1959).

2.3, and 1.0 cps), 0.87 (19-Me), and 0.80 ppm (18-Me); ORD 352 (−3250) and 297 mμ (+6700); CD 331 mμ (−7760).

Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.06; H, 9.15.

Testosterone Acetate (21). A.—Acetylation of **testosterone 20** in the usual way gave **21**: mp 141–142°; $[\alpha]D$ +96.2°.

B.—The bromo ketone **22** (300 mg) was dehydrobrominated with Li_2CO_3 (180 mg) in DMF (4 ml) to give the enone **21** (221 mg; mp 136–138°, mmp 138–140°; $[\alpha]D$ +93.1°), whose tlc showed a faint spot of the enone **3**, besides a main spot of **21**.

Epoxidation of the Enone 1.—To a solution of the enone **1** (600 mg) in MeOH (20 ml) and CH_2Cl_2 (6 ml) was added 30% H_2O_2 (1.8 ml) and 4 *N* NaOH (0.9 ml) at 0°, and the reaction mixture was kept in an ice chest at 3° for 48 hr. Dilution with water and extraction with CH_2Cl_2 gave a product (423 mg; mp 167–174°), which on recrystallization from EtOH afforded 297 mg (47%) of **17β-acetoxy-2α,3α-epoxy-5α-androstan-1-one (24)**: mp 177–178°; $[\alpha]D$ +20.6°; nmr, δ 3.43 ($C_{3\beta}$-H, m), 3.13 ($C_{2\beta}$-H, d, J = 3.5 cps), 1.01 (19-Me), and 0.78 ppm (18-Me); ORD 342 (−2110) and 298 mμ (+3670); CD 321 mμ (−4080).

Anal. Calcd for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.41; H, 8.74.

The residue after separation of the α isomer **24** showed, in addition to the signals which are due to the α isomer, a doublet at 3.21 ppm (J = 5 cps) and a singlet at 1.22 ppm, ascribable to the presence of the β isomer **25**. The aqueous solution, after extraction of the neutral component, was acidified with dilute HCl, extracted with CH_2Cl_2, esterified with CH_2N_2, and separated by preparative tlc to afford an ester (145 mg, 20%).

Epoxidation of the Enone 4.—A solution of the enone **4** (507 mg) in CH_2Cl_2 (5 ml) and MeOH (10 ml) was treated with 30% H_2O_2 (1.5 ml) and 4 *N* NaOH (0.75 ml) at 0°. Working up as mentioned above gave 494 mg of a neutral product, which on recrystallization from ether afforded 319 mg (60%) of **17β-acetoxy-2α,3α-epoxy-5α-androstan-4-one (26)**: mp 123–125°; $[\alpha]D$ +9.0°; nmr, δ 3.50 ($C_{2\beta}$-H, m), 3.23 ($C_{3\beta}$-H, d, J = 3.8 cps), 0.76 (19-Me), and 0.79 ppm (18-Me); ORD 324 (−1850), 314 (−1620), and 280 mμ (+3060); CD 307 (−2850) and 300 mμ (−3020).

Anal. Calcd for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 73.02; H, 8.71.

The 2β,3β-epoxy-4-one **27** was detected by the additional signals (multiplet at 3.05 and singlet at 1.10 ppm) in the nmr spectrum of the residue after separation of the α isomer. An acidic component (30 mg) was isolated but resisted purification, even as a methyl ester as shown by a multiplicity of spots on tlc.

Registry No.—**1**, 6199-40-2; **2**, 68-61-1; **4**, 65-01-0; **6**, 5846-70-8; **10**, 16801-95-9; **11**, 16801-96-0; **12**, 16801-97-1; **13**, 16801-98-2; **14**, 16801-85-7; **15**, 16801-86-8; **17**, 1236-50-6; **18**, 16801-88-0; **19**, 2311-73-1; **21**, 1045-69-8; **22**, 16801-91-5; **23**, 1242-08-6; **24**, 16801-93-7; **26**, 16801-94-8.

The Alkaloids of *Tabernaemontana crassa*. Crassanine, a New Oxindole Alkaloid

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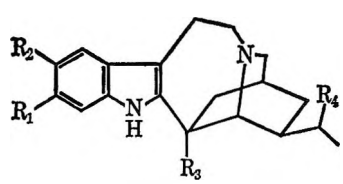
As part of an extended chemotaxonomic study of the genus *Tabernaemontana* (Apocynaceae),[1] we now describe the results of a study of the alkaloids of the African species, *Tabernaemontana crassa* Benth.

The major alkaloid of *T. crassa* proved to be the known ibogamine-type base, conopharyngine (**1**);[2] an amorphous base, which we were unable to completely purify by chromatography, was the second most abundant alkaloid. This latter base, which was assigned the structure of 20-hydroxyconopharyngine (**2**), was purified instead by a new procedure which should be widely applicable for the isolation of related bases.[3] Thus, the reaction of impure **2** with benzyl chloroformate in pyridine afforded the crystalline carbobenzoxy ester **3**, from which pure **2** was readily regenerated by hydrogenolysis in the presence of palladium.

The assigned structure of **2** fully agreed with its spectral properties. Its ultraviolet absorption spectrum was that of a typical 5,6-dimethoxyindole; indeed, it was essentially identical with that of conopharyngine (**1**). In addition, the nmr spectrum of **2** was similar to that of its unmethoxylated analog, heyneanine (**4**),[4] except that the spectrum of **2** clearly showed the presence of the 5,6-dimethoxyindole system in the form of methoxyls at δ 3.78 and 3.86 and a pair of unsplit aromatic protons at 6.71 and 6.83. Furthermore, the mass spectrum of **2** was exactly analogous to the published spectrum of heyneanine (**4**),[4] except that the fragments from **2** containing the indole nucleus were 60 mass units heavier than those from **4** because of two methoxy substituents on the aromatic ring.



1, $R_1 = R_2 = OCH_3$; $R_3 = COOCH_3$; $R_4 = H$
2, $R_1 = R_2 = OCH_3$; $R_3 = COOCH_3$; $R_4 = OH$
3, $R_1 = R_2 = OCH_3$; $R_3 = COOCH_3$; $R_4 = OCO_2CH_2C_6H_5$
4, $R_1 = R_2 = H$; $R_3 = COOCH_3$; $R_4 = OH$
5, $R_1 = R_2 = OCH_3$; $R_3 = R_4 = H$
6, $R_1 = R_2 = OCH_3$; $R_3 = H$; $R_4 = OH$

The structure of **2** was confirmed by its chemical conversion into ibogaline (**5**), using the general degradative scheme which has been employed previously with other 20-hydroxyibogamine-type bases.[5-8] Thus, hydrolysis of the ester function of **2**, followed by decarboxylation, yielded the amorphous 20-hydroxyibogaline (**6**). Reaction of **6** with tosyl chloride in pyridine gave the corresponding quaternary tosylate (**7**) which was reduced directly by lithium aluminum hydride to give ibogaline (**5**). After this work was completed, a preliminary report appeared on the isolation of 20-hydroxyconopharyngine (**2**) from *Conopharyngia jol-*

(1) For the previous report in this series, see M. P. Cava, S. S. Tjoa, Q. A. Ahmed, and A. I. daRocha, *J. Org. Chem.*, **33**, 1055 (1968).

(2) U. Renner, D. A. Prins, and W. G. Stoll, *Helv. Chim. Acta*, **42**, 1572 (1959).

(3) The conversion of the amorphous isovoacristine into its crystalline carbobenzoxy ester has been described by S. K. Mowdood [Ph.D. Dissertation, The Ohio State University, Columbus, Ohio, 1966].

(4) T. R. Govindachari, B. S. Joshi, A. K. Saksena, S. S. Sathe, and N. Viswanathan, *Tetrahedron Lett.*, 3873 (1965).

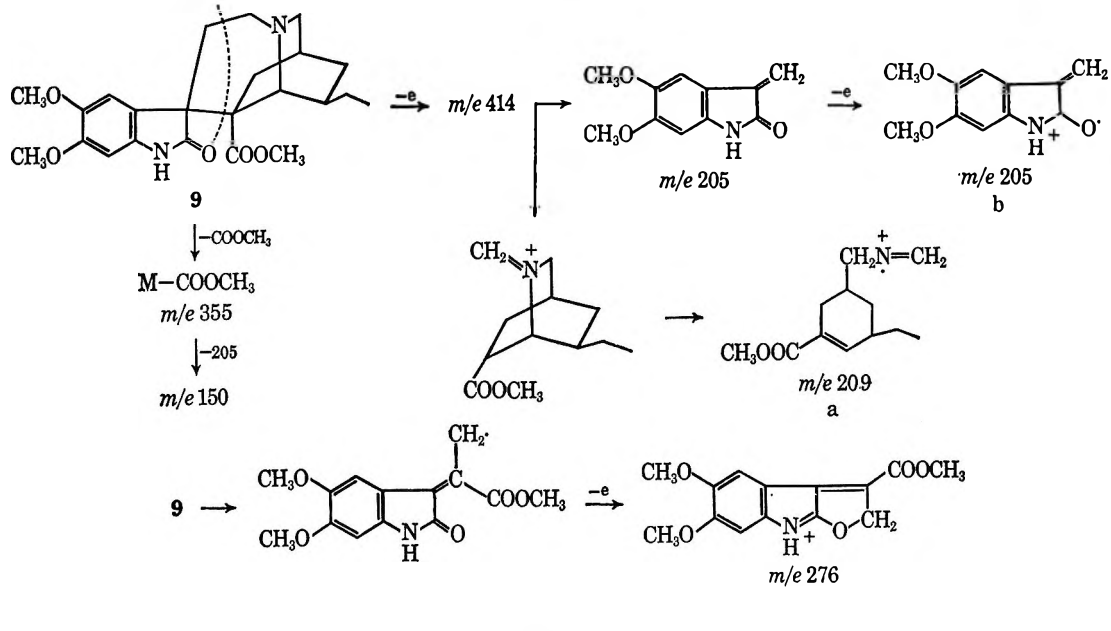
(5) U. Renner and D. A. Prins, *Experientia*, **15**, 456 (1959).

(6) M. P. Cava, S. K. Mowdood, and J. L. Beal, *Chem. Ind.* (London), 2064 (1965).

(7) T. R. Govindachari, B. S. Joshi, A. K. Saksena, S. S. Sathe, and N. Viswanathan, *Chem. Commun.*, 97 (1966).

(8) S. M. Kupchan, J. M. Cassady, and S. A. Telang, *Tetrahedron Lett.*, 1251 (1966).

SCHEME I



CRASSANINE

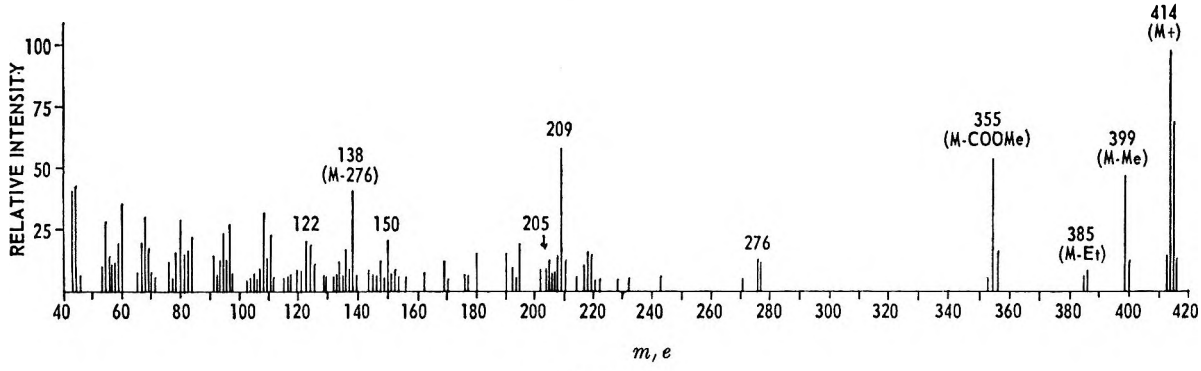
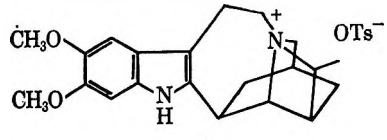


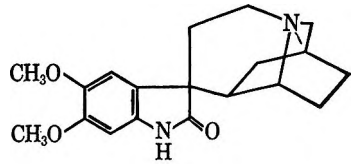
Figure 1.

lyana and *C. durissima*, and on its structure proof, using methods similar to those just described.[9]

The least abundant base isolated from *T. crassa* was a new crystalline alkaloid, crassanine, mp 190–191°, which was isomeric (M^+ 414) with 20-hydroxyconopharyngine (2). The infrared spectrum of crassanine indicated the presence of two carbonyl groups (1739 and 1709 cm^{-1}). Its ultraviolet absorption spectrum (see Experimental Section) was different from that of a 5,6-dimethoxyindole, but was very similar to that of known 5,6-dimethoxyoxindole alkaloids such as kisantine (8).[10] In addition to a carbomethoxy methyl at δ 3.47, the nmr spectrum of crassanine reveals two aromatic methoxyls at δ 3.83, single unsplit aromatic protons at 6.50 and 7.01, and the low-field oxindole NH at 9.30. The latter values are to be compared with the similar corresponding values (δ 3.9, 6.56, 7.1, and 9.1) recorded for kisantine (8).[10] On this basis, crassanine has been assigned structure **9**, which is that of an oxindole corresponding to the indole conopharyngine. At this time, no evidence is available on the configuration at the C-3 spiro carbon. It is interesting to note that a Dreiding model of either of the C-3 epimers of **9** suggests that the carbomethoxy methyl will be somewhat shielded by the aromatic ring, and the carbomethoxy methyl of crassanine does appear, in fact, at the rather shielded position of δ 3.47.



7



8

The mass spectrum of crassanine (Figure 1) is in good accord with structure **9**. In common with the corresponding spectrum of kisantine,[10] peaks are observed at $M - CH_3$ and $M - C_2H_5$, and the fragments derived from the isoquinuclidine system are observed at *m/e* 122 and 138. Loss of the carbomethoxy function of **9** leads to the strong peak at *m/e* 355. The most significant pair of peaks in the spectrum of **9** are those at *m/e* 209 and 205; these correspond to fragments a and b, the formation of which can be easily rationalized, as shown in Scheme I; the origin of the peaks at *m/e* 150 and 276 is also suggested in this scheme.

(9) C. Hootele, J. Pecher, U. Renner, and R. H. Martin, *Chimia*, **21**, 133 (1967).

(10) W. I. Taylor, *J. Org. Chem.*, **30**, 309 (1965).

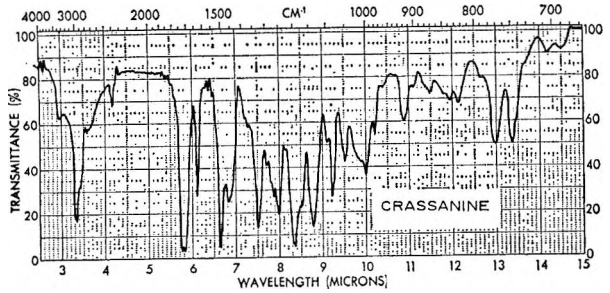


Figure 2.

A number of indole alkaloids have been converted into their oxindole analogs.[11,12] Preliminary attempts to adapt the procedures described in the literature to the transformation of conopharyngine into crassanine have not been successful to date. We plan to continue this investigation when additional supplies of conopharyngine can be obtained.

Experimental Section

Plant Material and Crude Tertiary Bases.—Although *T. crassa* is native to Africa rather than to the South Pacific, the material used in this investigation was collected near the botanical garden in Tahiti in December 1964, by Mr. George Uhe of the Department of Botany, University of Auckland, New Zealand. A voucher specimen (no. 718) has been preserved in Mr. Uhe's personal herbarium. We gratefully acknowledge Mr. Uhe's assistance in collecting and identifying this plant.

The dried and ground plant material (23.75 lb of bark, leaves, twigs, and fruit) was extracted with alcohol in the usual manner. The concentrated extract was refluxed for about 1 hr with ethyl acetate containing 5% concentrated aqueous ammonia. After it had cooled, the ethyl acetate was decanted, and the residue was reextracted until it was free of alkaloids (Mayer's test). The tertiary bases were removed from the combined ethyl acetate extracts by extraction with 5% aqueous H_2SO_4. The acid extract was washed with benzene and made basic with ammonia, and the alkaloids were extracted with chloroform to give 26.5 g of crude tertiary bases after solvent evaporation.

Separation and Characterization of the Tertiary Bases.—A major aliquot (21.4 g) of the crude tertiary bases was dissolved in chloroform (50 ml) and benzene (200 ml) was added. The resulting precipitate (8.0 g) was removed by filtration; it was not further investigated. The filtrate was shaken successively with the following aqueous phases to give, after the usual work-up, the weights of alkaloidal material recorded: (a) 1% NaOH, 0.1 g; (b) pH 5 McIlvain buffer, 0.8 g; (c) pH 4 McIlvain buffer, 2.2 g; and (d) 3.5% HCl, 9.2 g. Additional work described in this paper was carried out with the major 3.5% HCl fraction; thin layer chromatography of the only other major fraction (pH 4) indicated the absence of additional major constituents.

The pH 3.5 fraction (9.2 g) appeared by tlc ($CHCl_3$–CH_3OH on silica gel H) to consist of two major constituents of similar R_f, and one minor constituent. The less polar compound was partially separated by repeated chromatography on alumina (neutral, grade II), the columns being eluted with benzene, followed by benzene–chloroform mixtures. When the pure benzene fractions were evaporated and crystallized from ether, they afforded conopharyngine (**1**, 4.48 g), mp 133–136° (lit.[1] mp 141–143°). This material was identical (ir and uv spectra) with an authentic sample kindly supplied by Dr. U. Renner (Geigy, A. G., Basel).

On concentration, some of the benzene–chloroform fractions deposited crystals (0.070 g) of the minor base, crassanine (**9**). Crassanine crystallized from chloroform as colorless plates, mp 190–191°. The physical data for crassanine were as follows: $[\alpha]^{26}D$ +21.4 (*c* 0.013, EtOH); λ_{max}, mμ (log ε), 210 (4.37), 275 (3.68), and 302 (3.55); $\nu_{max}^{CHCl_3}$ 1739 and 1701 cm^{-1}; nmr, δ 9.30 (NH, singlet), 6.50 and 7.01 (aromatic singlets, 1 H each), 3.83 (aromatic OCH_3, singlet, 6 H), and 3.47 (ester OCH_3, singlet, 3 H). See Figure 1 for the mass spectrum of **9**. Infrared spectral data is given in Figure 2.

The more polar major, alkaloid was the principal constituent of the benzene–chloroform fractions. This material, 20-hydroxyconopharyngine (**2**), was obtained in pure form as follows: a sample of crude **2** (0.0988 g) was dissolved in dry pyridine (1.6 ml) and treated with an excess of benzyl chloroformate, work-up in the usual manner, followed by crystallization from methanol, afforded 20-carbobenzoxyconopharyngine (**3**, 0.0396 g), mp 193°.

Anal. Calcd for $C_{31}H_{36}N_2O_7$: C, 67.87; H, 6.61. Found: C, 68.14, 67.98; H, 6.92, 6.79.

Hydrogenolysis of ester **3** in methanol in the presence of 5% palladium–charcoal gave pure 20-hydroxyconopharyngine (**2**) as an amorphous glass, tlc of which showed only one clear spot.

The physical data for 20-hydroxyconopharyngine were as follows: $[\alpha]^{26}D$ −36.4 (*c* 1.62, $CHCl_3$); λ_{max}, mμ (log ε), 226 (4.42) and 304 (3.93); $\nu_{max}^{CHCl_3}$, 3521, 1730, and 1639 cm^{-1}; nmr, δ 6.71 and 6.83 (aromatic singlets, 1 H each), 3.86 (aromatic OCH_3, 3 H), 3.78 (aromatic OCH_3, 3 H) 3.70 (ester OCH_3, 3 H) 1.12 δ (CH_3-CH(OH)-, doublet, J = 6). The mass spectrum showed significant peaks at 414 (M^+), 396, 370, 369, 312, 274, 268, 255, 254, 214, 190, 152, 140, 122, 108, and 94.

Degradation of 20-Hydroxyconopharyngine (2) to Ibogaline (5).—Purified base **2** (0.227 g) was hydrolyzed by heating with 20% KOH in methanol. After methanol was removed, the resulting salt was made strongly acid with aqueous HCl and heated on the steam bath for 1 hr to effect decarboxylation. Basification of the solution afforded the amorphous 20-hydroxyibogaline (**6**, 0.164 g), which was treated with tosyl chloride in pyridine. A portion (0.025 g) of the resulting crude quaternary tosylate (**7**, 0.063 g) was reduced with $LiAlH_4$ in refluxing tetrahydrofuran to give, after work-up and crystallization, ibogaline (**5**, 0.003 g), mp 138–142°. This material was identical (mixture melting point and ir spectra) with material prepared from conopharyngine by hydrolysis and decarboxylation.[2]

Registry No.—**2**, 16790-93-5; **3**, 16790-91-3; **9**, 16790-92-4.

(11) N. Finch and W. I. Taylor, *J. Amer. Chem. Soc.*, **84**, 3871 (1962).
(12) J. Shavel and H. Zinnes, *ibid.*, **84**, 1320 (1962).

3-Hydroxy- and Alkoxyaryl Derivatives of 1,2-Dithiolium Salts

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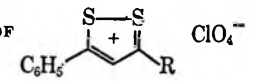
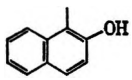
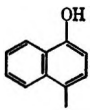
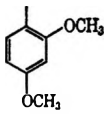
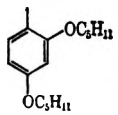
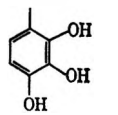
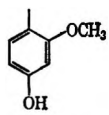
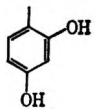
Certain 1,2-dithiolium salts have been shown to undergo substitution reactions at the 3 position of the dithiolium ring with nucleophiles such as amines, hydrazines, and the anions of active methylene compounds.[1]

It has now been found that 3-chloro-5-phenyl-1,2-dithiolium perchlorate (**1**) reacts with relatively unreactive nucleophiles such as hydroxy- and alkoxy-substituted aromatic compounds to give 3-aryl-1,2-dithiolium salts. Benzene derivatives which contain one hydroxy, alkoxy, or thioalkyl group fail to yield aryldithiolium salts when allowed to react with **1**. However, the corresponding *meta*-disubstituted benzene derivatives readily react with **1**, and naphthalene derivatives containing only one hydroxy group give aryldithiolium salts. These results are similar to many other substitution reactions of strong electrophiles with benzene and naphthalene derivatives of this type.[2]

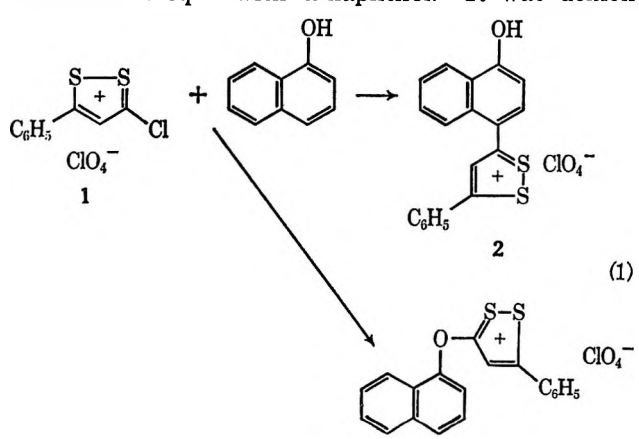
(1) P. S. Landis, *Chem. Rev.*, **65**, 237 (1965).
(2) *Cf.* M. R. DeMaheas, *Bull. Soc. Chim. Fr.*, 1989 (1962).

TABLE I

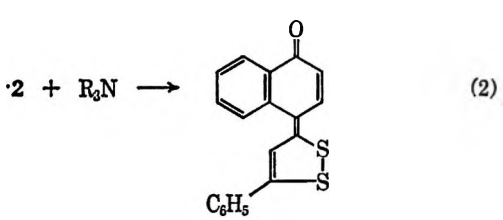
3-ARYL DERIVATIVES OF 

R	Mp, °C	Yield, %	Empirical formula (registry no.)	Anal, % Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
	180–181	60	$C_{19}H_{13}ClO_5S_2$ (16915-98-3)	54.2	3.1	15.2	53.9	3.1	14.8
	279–280	63	$C_{19}H_{13}ClO_5S_2$	54.2	3.1	15.2	54.0	3.2	14.9
	230	72	$C_{17}H_{15}ClO_6S_2$ (16915-99-4)	49.4	3.6	15.5	49.6	3.6	15.3
	162	38	$C_{25}H_{31}ClO_6S_2$ (16957-25-8)	57.0	5.9	12.2	56.7	6.0	12.1
	239–240	64	$C_{15}H_{11}ClO_7S_2$ (16916-00-0)	44.8	2.7	15.8	44.7	3.0	15.7
	231–232	61	$C_{16}H_{13}ClO_6S_2$ (16916-01-1)	46.9	3.2	15.6	47.2	3.6	15.9
	250–251	58	$C_{15}H_{11}ClO_6S_2$ (16916-02-2)	46.7	2.9	16.6	46.4	3.2	16.4

In the cases in which hydroxy derivatives of benzene and naphthalene were employed, there is a possibility that **1** has reacted at either an oxygen or a carbon atom, as shown in eq 1 with α-naphthol. It was demonstrated that substitution occurs at the carbon atom to yield **2**, since the product shows a strong absorption in the hydroxy region of the infrared spectrum, and treatment of **2** with base results in the formation of the dye **3** (eq 2).



(1)



(2)

Experimental Section

3-Chloro-5-phenyl-1,2-dithiolium Perchlorate (1).—A mixture of 15 g (0.077 mol) of 5-phenyl-1,2-dithiol-3-one[3] and 40 ml of phosphorous oxychloride was heated on the steam bath for 1 hr. After cooling, the mixture was diluted with two volumes of ether and the solid collected and washed with ether. The hygroscopic solid was dissolved in acetone and 5 ml of 70% perchloric acid was added to the solution; after chilling the solid which separated was collected and recrystallized from acetone to yield 18 g of product, mp 177–178°.

Anal. Calcd for $C_9H_6Cl_2O_4S$: C, 34.6; H, 1.9; Cl, 22.4. Found: C, 34.9; H, 2.1; Cl, 22.7.

The 3-aryl-1,2-dithiolium salts listed in Table I were prepared by the following general procedure.

A mixture of 3.1 g (0.01 mol) of **1**, 0.015 mol of the hydroxy- or alkoxyaryl derivative, and 25 ml of acetic acid was refluxed for 3 hr and cooled to room temperature, and the solid was collected and recrystallized. Acetonitrile was a satisfactory recrystallization solvent for all of the compounds listed in Table I.

Treatment of 2 with Base.—A solution of 1 g of **2**, 1 ml of triethylamine, and 75 ml of acetonitrile was stirred for 1 hr and chilled, and the dark solid was collected and recrystallized from acetonitrile to yield 0.6 g of **3**, mp 145–146°.

Anal. Calcd for $C_{19}H_{12}OS_2$: C, 71.2; H, 3.7; S, 20.0. Found: C, 71.1; H, 3.5; S, 20.2.

The absorption spectrum of **3** (in acetonitrile) showed the following absorption maxima recorded as $m\mu$ ($\epsilon \times 10^3$): 243 (19.9); 305 (15.0); 380 (3.2); 517 (26.6). The maxima recorded for **2** were 228 (30.4); ~245 (11.4); 355 (13.5); 490 (15.0).

Registry No.—**1**, 5541-12-8; **2**, 16960-02-4; **3**, 16915-97-2.

(3) E. Klingsberg, *J. Amer. Chem. Soc.*, **83**, 2937 (1961).

The Reactions of Alkyl Acrylates and Acrylonitrile with Guanidine in Dimethylformamide[1,2]

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The reaction of acrylic esters or acrylonitrile with guanidine has not previously been reported. We have found that, on addition of different alkyl acrylates to a DMF solution of free guanidine, a basic compound (I′) separated in almost quantitative yield. No C=C double bond was detected by infrared analysis or by the reaction of potassium permanganate or bromine with I′. Hydrolysis of the compound with water gave the guanidinium salt II′, and further alkaline hydrolysis led to 3,3′-iminodipropionic acid.

A different compound (III) was obtained in a yield as high as 75% by adding acrylonitrile to a DMF solution of free guanidine. This product was a strongly basic, hygroscopic crystalline substance which absorbed carbon dioxide when allowed to stand in air; the ir spectrum showed neither CN group nor C=C double-bond absorption. These properties suggested the cyclic structure III. Treatment of III with 12 *N* hydrochloric acid gave the hydrochloride IV′. The base IV was hydrolyzed in water to the amino acid I which, when treated with barium hydroxide, gave the monobarium salt of iminodipropionic acid. The structures are consistent with the interconversion shown in Chart I.

For example, I′ could be converted into IV′ by treating it with 6 *N* hydrochloric acid and, by adding IV′ to a methanolic solution of guanidine, the reaction could be reversed, converting IV′ into I′. When the hydrochloride of I′ was refluxed in ethanol, IV was obtained with the liberation of 1 mol of guanidine hydrochloride; IV could also be reversely converted into I′ in the same manner as described above. Also when I′ was boiled with an equimolar amount of hydrochloric acid, it was converted into I; I was converted into II′ by boiling it with an aqueous solution of guanidine. Also II was converted into I with dehydration by boiling its aqueous solution.

Experimental Section

2-Amino-3-(3-propionic acid guanidine)-6-oxy-3,4,5,6-tetrahydropyrimidine (I′).—To a solution of 29.5 g (0.5 mol) of free guanidine in 250 ml of dimethylformamide was added 45 ml (0.5 mol) of methyl acrylate dropwise with agitation at 25–30° over 1 hr period. After 2 hr the precipitate was collected, washed successively with methanol and ether, and dried, yielding 52.0 g (92%) of I′: mp 247° dec (recrystallization from methanol gave white crystals, mp 251° dec); ultraviolet, $\lambda_{max}^{H_2O}$ 226 mμ (ε 15500), 262 (7160).

Anal. Calcd for $C_8H_{14}N_6O_2$: C, 42.47; H, 6.24; N, 37.14. Found: C, 42.51; H, 6.20; N, 37.70.

N,N-(3,3′-Dipropionic acid)guanidine (II) and Its Guanidonium Salt (II′).—A solution of 10 g of I′ in 200 ml of water was boiled for 2 hr and the resulting solution was evaporated to dryness at reduced pressure. The syrup formed was crystallized by the addition of 50 ml of isopropanol. The crystals were collected, washed with ether, and dried, yielding 10.7 g of II′ (93%), mp 167–170° (recrystallization from methanol–2-propanol mixture raised the melting point to 176°).

Anal. Calcd for $C_8H_{18}N_6O_4$: C, 36.64; H, 6.92; N, 32.05. Found: C, 36.93; H, 6.95; N, 32.30.

Removal of guanidine from II′ with an equimolar amount of 6 *N* hydrochloric acid gave II in a yield of 89%, mp 175–176° (picrate, mp 178–180°). No ultraviolet absorption appeared.

Anal. Calcd for $C_7H_{12}N_3O_4$: C, 41.38; H, 6.45; N, 20.68. Found: C, 41.90; H, 6.70; N, 20.50.

3,4,6,7,8,9-Hexahydro-2H-pyrimido[1,2-*a*]pyrimidine-2,8-diimine (III).—To a solution of 5.9 g (0.1 mol) of free guanidine in 20 ml of dimethylformamide was added 14 ml (0.2 mol) of acrylonitrile dropwise with agitation at 5–10° over a 0.5 hr period. After 3 hr the precipitate was collected, washed with 2-propanol, and dried in a vacuum desiccater provided with sodium hydroxide, yielding 12.7 g (76%) of III, mp 140–143°. It was easily converted into carbonate by absorption of carbon dioxide from air. The carbonate decomposed at 209–210°.

Anal. Calcd for $C_7H_{11}N_5 \cdot {}^1/_2H_2CO_3$: C, 45.69; H, 6.13; N, 35.49. Found: C, 45.58; H, 6.53; N, 35.47.

3,4,6,7,8,9-Hexahydro-2H-pyrimido[1,2-*a*]pyrimidine-2,8-dione (IV) and Its Hydrochloride (IV′).—III (1.7 g, 0.01 mol) was dissolved in 5 ml of 12 *N* hydrochloric acid and allowed to stand overnight. The solution was diluted with ethanol to obtain white crystals of IV′, yielding 1.1 g (54%), mp 290–292° dec (recrystallization from aqueous ethanol raised the decomposition point to 299–303°).

Anal. Calcd for $C_7H_9N_3O_2HCl$: C, 41.29; H, 4.95; N, 20.64; Cl, 17.41. Found: 41.30; H, 5.14; N, 20.47; Cl, 17.42.

Removal of hydrochloric acid from IV′ with an equimolar amount of sodium methoxide in methanol gave IV in a yield of 95%: mp 229° after recrystallization; ultraviolet, $\lambda_{max}^{H_2O}$ 226 mμ (ε 26100), 262 (6210); picrate, dp 234–238°.

Anal. Calcd for $C_7H_9N_3O_2$: C, 50.29; H, 5.43; N, 25.14. Found: C, 50.12; H, 5.46; N, 24.96.

2-Amino-3-(3-prioponic acid)-6-oxy-3,4,5,6-tetrahydropyrimidine Monohydrate (I).—A solution of 1.7 g of IV in 30 ml of water was boiled for 3 hr and then evaporated to dryness, yielding 1.8 g (90%) of I: mp 18–3186° (recrystallization from water raised the melting point to 190°); ultraviolet, $\lambda_{max}^{H_2O}$ 220 mμ (ε 6770); picrate, dp 204–205°.

Anal. Calcd for $C_7H_{11}N_3O_3 \cdot H_2O$: C, 41.38; H, 6.45; N, 20.68. Found: C, 41.47; H, 6.74; N, 20.64.

Hydrolyses of II and I with Barium Hydroxide Formation of Monoammonium Salt of 3,3′-Iminodipropionic Acid. A.—To a solution of 4.0 g (0.02 mol) of II in 200 ml of water was added 19.0 g (0.06 mol) of barium hydroxide octahydrate and the solution was boiled for 24 hr. During the reaction, the ammonia evolved was caught by a trap containing hydrochloric acid and determined by titration to be 95% of the theoretical. After the precipitate ($BaCO_3$) was filtered off and washed with hot water, the combined filtrate was saturated with carbon dioxide and the resulting barium carbonate precipitate was again filtered off and washed with hot water. The second combined filtrate was then evaporated at reduced pressure to obtain a syrup which could be crystallized by treating it with ethanol, yielding 4.3 g (91%) of monobarium salt of 3,3′-iminodipropionic acid. An aqueous solution of the crude monobarium salt was treated with an equivalent amount of ammonium sulfate, the precipitate ($BaSO_4$) was filtered off, and the filtrate was again evaporated at reduced pressure to a 50% concentration and diluted with methanol to obtain 2.5 g (70%) of monoammonium salt of 3,3′-iminodipropionic acid which melted at 172–176° after recrystallization from aqueous methanol.

Anal. Calcd for $C_6H_{14}N_2O_4$: C, 40.44; H, 7.92; N, 15.72. Found: C, 40.19; H, 7.85; N, 15.64.

A mixture melting point with an authentic sample[3] showed no depression.

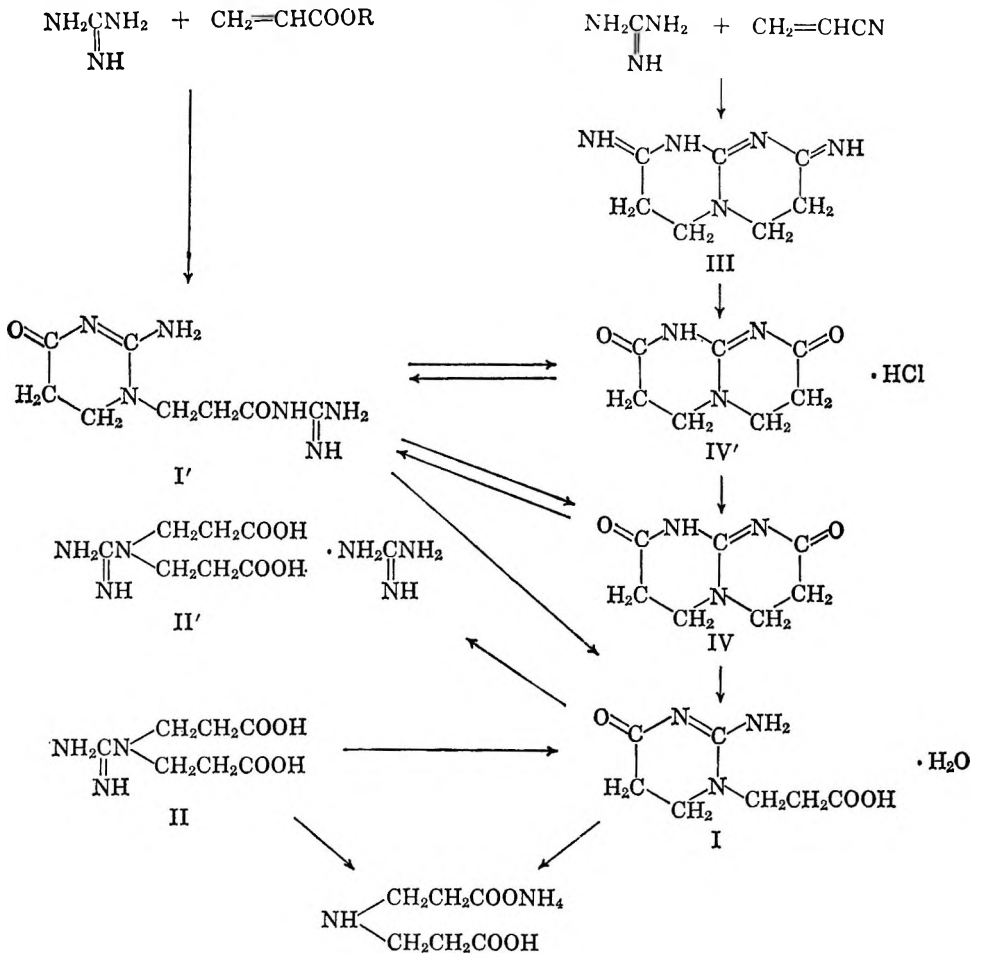
B.—To a solution of 3.5 g of I in 200 ml of water was added 19.0 g of barium hydroxide octahydrate and the mixture was boiled for 27 hr. After the reaction, the resulting mixture was

(1) Cyanamide Derivatives. LXXV. Previous paper of this series: LXXIV, K. Odo, *et al.*, *Yuki Gosei Kegaku Kyokai Shi*, **25**, 1048 (1967).

(2) Presented at the 20th Annual Meeting of the Chemical Society of Japan, Tokyo, March 31–April 4, 1967.

(3) Prepared by the procedure of J. H. Ford, *J. Amer. Chem. Soc.*, **67**, 876 (1945).

CHART I



worked up the same as in the above experiment to obtain 2.2 g (71%) of monoammonium salt of 3,3′-iminodipropionic acid.

Conversion of I′ into IV′.—A solution of 11.3 g (0.05 mol) of I′ dissolved in 17 ml of 6 *N* hydrochloric acid (0.1 mol) was allowed to stand for 3 hr to obtain 8.3 g (82%) of IV′ which melted at 299–303° dec after purification.

Conversion of the Hydrochloride of I′ into IV.—A solution of 4.0 g of the hydrochloride of I′ (prepared in ethanol) in 200 ml of ethanol was refluxed for 3 hr and concentrated at reduced pressure to obtain 1.6 g (63%) of IV which melted at 229° after recrystallization.

Conversion of IV and IV′ into I′.—To a solution of 0.6 g (0.01 mol) of free guanidine in 50 ml of methanol was added 1.7 g (0.01 mol) of IV [or 1.0 g (0.005 mol) of IV′] dissolved in 200 ml of methanol and the solution was allowed to stand for 3 hr at room temperature to obtain 2.1 g (93%) [or 0.9 g (80%)] of I′ which melted at 250° dec after purification.

Conversion of I′ into I.—A solution of 11.3 g (0.05 mol) of I′ dissolved in 100 ml of water containing 8.5 ml of 6 *N* hydrochloric acid (0.05 mol) was boiled for 3 hr and concentrated at reduced pressure to obtain 6.9 g (68%) of I which melted at 190° after recrystallization.

Conversion of I into II′.—To a solution of 0.6 g (0.01 mol) of free guanidine in 10 ml of water was added 2.0 g (0.01 mol) of I and the solution was boiled for 1 hr. The resulting solution was worked up the same as in the preparation of II′ from I′: yield 2.4 g (92%); mp 176° after recrystallization.

Conversion of II into I.—A solution of 2.0 g of II in 50 ml of water was boiled for 3 hr and evaporated to dryness to obtain 1.8 g (90%) of I which melted at 190° after recrystallization.

Registry No.—I, 16675-75-5; I picrate, 16675-76-6; I′, 16675-77-7; II, 16675-32-4; II picrate, 16675-78-8; II′, 16675-79-9; III, 16675-80-2; IV, 16675-81-3; IV picrate, 16675-82-4; IV′, 16675-31-3; monoammonium salt of 3,3′-iminodipropionic acid, 16675-33-5; acrylonitrile, 107-13-1; guanidine, 113-00-8; dimethylformamide, 68-12-2.

Acknowledgment.—This investigation was promoted by a grant from Nippon (Japan) Carbide Industries, Inc., for which the authors wish to express their deep appreciation. The authors also wish to thank Professor Masaki Ohta of the same institute for his helpful discussions. Our thanks are also extended to the staff of the microanalytical services in the Laboratory of Organic Chemistry of this institute for the microanalyses.

Cyclizations of Substituted N-(Purin-6-yl)-2-aminoethanol System[1]

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Received February 15, 1968

The current interest [2–6] in the internal cyclization of suitably substituted 6-aminopurine derivatives (Ia, Ib,

(1) Presented in part at the 2nd Annual Great Lakes Regional Meeting of the American Chemical Society, Milwaukee, Wis., June 1968.

(2) N. J. Leonard, S. Achmatowicz, R. N. Loeppky, K. L. Carraway, W. A. H. Grimm, A. Szweykowska, H. Q. Hamzi, and F. Skoog, *Proc. Natl. Acad. Sci. U. S.*, **56**, 709 (1966).

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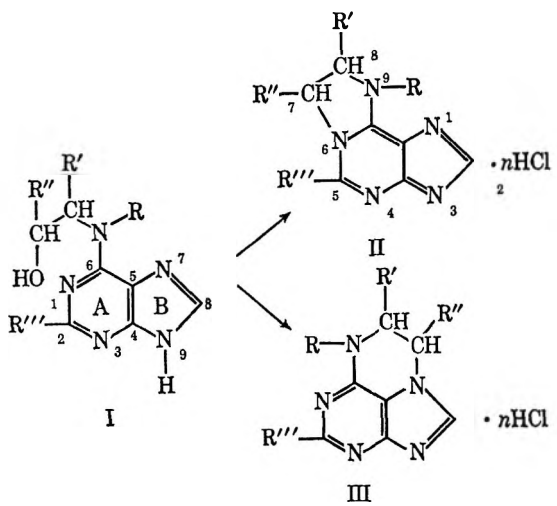
Ic) encouraged us to report our findings in this area. Compounds Id–h were used to determine if the direction of cyclization of I could be modified by changing the electrophilic center and the electron density at the nucleophilic center (Scheme I). The pendent alcohol function was varied from primary, Id, to secondary, If, to benzylic secondary, Ig, with the expectation of changing the relative rate of reaction[7] and the nature of the attacking electrophile.[7] The purine ring system, especially ring A, was made less electronegative by the introduction of a chlorine atom at the 2 position.[8] This can be seen from the pK_a values of alcohols Id (3.80) and Ie (1.82).

SCHEME I



a, R = R′ = R″ = R‴ = H; n = 1
b, R = $HOCH_2CH_2$; R′ = R″ = R‴ = H; n = 1
c, R = CH_3CH_2; R′ = R″ = R‴ = H; n = 1
d, R = R″ = R‴ = H; R′ = CH_3CH_2; n = 2
e, R = R″ = H; R′ = CH_3CH_2; R‴ = Cl; n = 1
f, R = R′ = R‴ = H; R″ = CH_3; n = 2
g, R = R′ = R‴ = H; R″ = C_6H_5; n = 2
h, R = R′ = H; R″ = C_6H_5; R‴ = Cl; n = 1

Alcohols Id–h were prepared from 6-chloropurine (IV) and 2,6-dichloropurine (V) in fair to good yields according to standard techniques available in the literature.[9–12] The displacement of the 6-chloro group in V in preference to the 2-chloro group was anticipated on the basis of their known relative reactivities.[8,13]

When primary alcohols Id and Ie and secondary benzylic alcohols Ig and Ih were treated with thionyl chloride under the described conditions (see Experimental Section), the only products isolated were 8-ethyl-7,8-dihydro-9H-imidazo[2,1-*i*]purine dihydrochloride (IId), 5-chloro-8-ethyl-7,8-dihydro-9H-imidazo[2,1-*i*]-purine hydrochloride (IIe), 7-phenyl-7,8-dihydro-9H-imidazo[2,1-*i*]purine dihydrochloride (IIg), and 5-chloro-7-phenyl-7,8-dihydro-9H-imidazo[2,1-*i*]purine hydrochloride (IIh). The conversion of IIh into IIg *via* hydrogenolysis proved that the direction of cyclization was the same and substantiated the displacement of the 6-chloro group. Although the conversion of IIe into IId was not attempted, the similarities in physical properties indicated that they had cyclized in the same direction. The ultraviolet absorption correlation of Leonard, *et al.*,[14] and the dissociation constants[3,5,15,16] of all the products are consistent with cyclization occurring at N-1.

The reaction of N-(purin-6-yl)-1-amino-2-propanol (If) with thionyl chloride was studied at 79, 50, 25, and −70°. The only product isolated from the high-temperature reaction was 7-methyl-7,8-dihydro-9H-imidazo[2,1-*i*]purine dihydrochloride (IIf). The spectral and paper chromatographic data of the isolated crude solids from the other reactions indicated that IIf was the major product.

Our results indicate that the direction of cyclization is not dependent upon temperature, nature of the electrophile, or the basicity of the nucleophile. These results can be rationalized on the basis of (1) the much greater nucleophilicity of N-1 compared with N-7, (2) the greater probability of forming a five-membered heterocyclic ring,[17,18] or (3) a combination of these effects.

Experimental Section[19]

N-(Purin-6-yl)-2-aminobutanol (Id).—To a 500-ml, one-necked, round-bottom flask equipped with a condenser were added 6-chloropurine (30 g, 0.195 mol), 2-amino-1-butanol (34.5 g, 0.39 mol, 36.8 ml), and water (200 ml). The mixture was heated at reflux temperature for 3 hr and then reduced under vacuum to a dark, viscous liquid. The oily liquid was triturated with water (170 ml) to yield crude Id (22.2 g, 55%), mp 198–201°. Crystallization from water after decolorization with charcoal gave pure Id (17.9 g, 45%), mp 165–167°. The trituration filtrate was decolorized with charcoal and reduced in volume to give solids which were crystallized from water to yield pure Id (2.2 g, 5.5%), mp 200.5–204°. Mixture melting points of the low- and high-melting forms (50:50 and 90:10 ratios) were 199–204.5 and 200–203°, respectively. The infrared spectra were identical.

An analytical sample, mp 203–206°, was prepared from water from a mixture of the two forms and had the following properties: pK_a 3.80, 10.0; ir (KBr), 3.0, 3.2, 9.2, and 9.7 μ; uv max (H_2O, pH 1.0) 273.5 mμ (ϵ 17,050), (pH 10) 273.0 (15,850).

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(19) The melting points were determined with a Fisher-Johns melting point apparatus or a Thomas–Hoover capillary melting point apparatus and are corrected. The microanalyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill., or by our analytical department. The infrared spectra were determined on either a Perkin-Elmer Infracord or a Perkin-Elmer Model 521 spectrophotometer. The ultraviolet spectra were determined in aqueous solutions using a Beckman DK-2A ratio recording spectrophotometer. The nuclear magnetic resonance spectra were determined in deuterium oxide with tetramethylsilane as an external standard at 60 Mc/sec on a Varian Associates A-60 spectrometer at Simon Research Laboratory, Elgin, Ill., by Dr. W. Simon. pK_a values were obtained spectroscopically by our analytical department. Chromatograms were developed by the ascending technique with Whatman No. 1 paper. The solvent systems employed were A, *n*-butyl alcohol–acetic acid–water (4:1:1); B, isopropyl alcohol–acetic acid–water (69:1:30); C, dimethylacetamide-concentrated ammonium hydroxide–isopropyl alcohol (25:10:65); and D, 5% aqueous ammonium sulfate–isopropyl alcohol (95:5).

Anal. Calcd for $C_9H_{13}N_5O$: C, 51.8; H, 6.31; N, 33.6. Found: C, 51.8; H, 6.31; N, 33.4.

N-(2-Chloropurin-6-yl)-2-aminobutanol (Ie).—The general procedure followed in preparation of Id was used. Crude Ie (25.8 g, 100%), mp 194.5–196.5°, prepared from 2,6-dichloropurine (19.5 g, 0.104 mol), was dissolved in hot aqueous sodium hydroxide, decolorized with charcoal, and acidified to pH 6, and the precipitated solids, after cooling, were isolated to yield pure Ie (22 g, 85%), mp 210–212°. An analytical sample, mp 217–218.5°, was prepared by this same base–acid cycle and had the following properties: pK_a 1.82, 9.35; ir (KBr), 2.9 (OH), 3.0 (N–H), 7.3 (CH_3), and 9.6 μ; uv max (H_2O, pH 1) 277.5 mμ (ϵ 15,750), (pH 10) 277.5 (16,200).

Anal. Calcd for $C_9H_{12}ClN_5O$: C, 44.75; H, 5.01; N, 29.00; Cl, 14.7. Found: C, 44.70; H, 5.31; N, 29.00; Cl, 14.5.

N-(Purin-6-yl)-2-amino-1-phenylethanol (Ig).—To a 500-ml, one-necked, round-bottom flask equipped with condenser was added 6-chloropurine (10.3 g, 0.066 mol), 2-amino-1-phenylethanol (9.0 g, 0.066 mol), sodium carbonate (3.5 g, 0.033 mol), sodium hydroxide (1 pellet), and water (120 ml). The mixture was heated at reflux for 3 hr and then cooled overnight. The precipitated white solids were isolated, washed with water, and dried to yield Ig (12.1 g, 72%), mp 254–255°. The filtrate was heated for an additional 2 hr to yield impure Ig (1.8 g, 10.7%), mp 255.5–260°. An analytical sample, mp 256–257°, was prepared by crystallization from isopropyl alcohol and had the following spectral properties: ir (KBr), 2.95 (OH), 9.1, 9.4, 9.7, 13.1, and 14.3 μ; uv max (H_2O, pH 1.0) 275.0 mμ (ϵ 17,600), (pH 10) 271.0 (17,300).

Anal. Calcd for $C_{13}H_{13}N_5O$: C, 61.16; H, 5.13; N, 27.4. Found: C, 61.30; H, 5.36; N, 27.2.

N-(2-Chloropurin-6-yl)-2-amino-1-phenylethanol (Ih).—The general procedure followed in preparation of Ig was used. Crude Ih (20.1 g, 88%), mp 240–247°, prepared from 2,6-dichloropurine (15.0 g, 0.079 mol), on crystallization from a concentrated isopropyl alcohol solution afforded a higher melting form, mp 249–252°, while crystallization from a dilute isopropyl alcohol solution gave a lower melting form, mp 235–238°. Paper chromatography of the two forms in solvent systems A, B, and C and their infrared spectra showed them to be identical. The analytical sample, mp 235–238°, had the following spectral properties: ir (KBr), 3.1, 3.3, 9.2, 9.4, 9.7, 13.2, and 14.2 μ; uv max (H_2O, pH 1) 276.5 mμ (ϵ 16,250), (pH 10) 271.0 (17,520).

Anal. Calcd for $C_{13}H_{12}ClN_5O$: C, 53.89; H, 4.18; N, 24.2; Cl, 12.2. Found: C, 53.78; H, 3.97; N, 24.0; Cl, 12.2.

N-(Purin-6-yl)-1-amino-2-propanol (If).—The general procedure followed in preparation of alcohol Ig was used. Crude If (18.2 g, 41.5%), mp 214.5–219.5°, prepared from 6-chloropurine (35 g, 0.228 mol) and 1-amino-2-propanol (17.2 g, 0.23 mol), on crystallization from water gave pure If (16.6 g, 38%), mp 232.5–235.5°. Further fractionation of the filtrates afforded additional If (18.1 g, 41.0%), mp 232.5–235.5°, which had the following spectral properties: ir (KBr), 3.2, 7.25 (CH_3), and 9.3 μ; uv max (H_2O, pH 1) 272.5 mμ (ϵ 15,950), (pH 10) 273.5 (17,000). Nuclear magnetic resonance spectrum of If dissolved in deuterium oxide and treated with anhydrous hydrogen chloride showed the following peaks: δ 8.50 (s, 1, aromatic C**H**), 8.44 (s, 1, aromatic C**H**), 4.19 (m, 1, CH_2C**H**), 3.77 (m, 2, N-CH_2), and 1.30 ppm (d, 3, J = 6 Hz, CH-CH_3).

Anal. Calcd for $C_8H_{11}N_5O$: C, 49.73; H, 5.75; N, 36.2. Found: C, 49.70; H, 5.79; N, 36.2.

The alcohols were thoroughly dried at 90° under vacuum before use. The apparatus was flame dried, and all reactions were conducted under an atmosphere of dry nitrogen.

8-Ethyl-7,8-dihydro-9H-imidazo[2,1-*i*]purine Dihydrochloride (IId).—To a 1-l., three-necked, round-bottom flask equipped with stirrer, reflux condenser with drying tube, gas inlet tube, and thermometer was added thionyl chloride (250 ml). Then alcohol Id (10.3 g, 0.05 mol) was added slowly to the rapidly agitated liquid, and a slight evolution of gas was noticed. The resulting mixture was heated at reflux for 18 hr, cooled in an ice bath, and then diluted with sodium-dried benzene (400 ml). The solids were isolated by filtration, washed with benzene, and dried to yield crude IId (12.3 g, 95%), mp 258–262°. A portion (6 g) of the crude product was slurried in absolute ethanol (100 ml) and treated with anhydrous hydrogen chloride to yield pure IId: mp 259–262°; pK_a 7.2; ir (KBr), 3.2–4.8 (HCl salt), 6.2, 6.7, 7.1, 7.35 (CH_3), 10.7, 12.8 μ; uv max (H_2O pH 1) 262 mμ (ϵ 13,980), (pH 7) 265 (13,050), (pH 10) 273 (15,620) and 281 (14,200); nmr (D_2O), δ 8.58 (s, 1, aromatic ring C**H**), 8.50 (s, 1, aromatic ring CH), 4.90–4.30 (m, 3, ring C**H** and CH_2), 1.80 (m, 2, J = 7 Hz, CH_2CH_3), and 0.98 ppm (t, 3, J = 7 Hz, CH_2CH_3). Paper chromatography in solvent system A showed only one product.

Anal. Calcd for $C_9H_{11}N_5 \cdot 2HCl$: C, 41.2; H, 5.00; N, 26.7. Found: C, 41.4; H, 5.08; N, 26.8.

5-Chloro-8-ethyl-7,8-dihydro-9H-imidazo[2,1-*i*]purine Hydrochloride (IIe).—The general procedure followed in preparation of IId was used. Crude IIe (9.8 g, 91%), mp >360°, prepared from chloro alcohol Ie (10 g, 0.042 mol) at 40°, was homogeneous as indicated by paper chromatography in solvent system A. An analytical sample was prepared by recrystallization from methanol: pK_a 6.7; ir (KBr), 6.3, 6.7, 6.8, 7.0, 10.5, and 13.0 μ; uv max (H_2O, pH 1) 265 mμ (ϵ 13,670), (pH 7) 272 (11,400), (pH 10) 272.5 (15,370) and 281.5 (14,370); nmr (D_2O), δ 8.63 (s, 1, aromatic C**H**), 5.28–4.70 (m, 3, ring C**H** and CH_2), 2.16 (m, 2, J = 7 Hz, CH_2CH_3), and 1.33 (t, 3, J = 7 Hz, CH_2CH_3).

Anal. Calcd for $C_9H_{10}ClN_5 \cdot HCl$: C, 41.55; H, 4.26; N, 26.9; Cl^-, 13.6. Found: C, 41.84; H, 4.28; N, 26.5; Cl^-, 13.5.

7-Phenyl-7,8-dihydro-9H-imidazo[2,1-*i*]purine Dihydrochloride (IIg).—The general procedure followed in preparation of IId was used. Crude IIg (4.4 g, 85%), prepared from alcohol Ig (4.0 g, 0.016 mol) at 40°, was slurried in ethanol and treated with anhydrous hydrogen chloride to yield pure IIg, mp 175° dec. Paper chromatography in solvent systems A, B, C, and D indicated one component: pK_a 6.7; ir (KBr), 3.3–4.6 (HCl salt), 6.3, 6.7, 7.1, 10.7, 11.7, 13.0, and 14.3 μ; uv max (H_2O pH 1) 262 mμ (ϵ 13,650), (pH 7) 267.5 (12,100), (pH 10) 272.5 (12,800) and (1 *N* NaOH) 281.0; nmr (D_2O), δ 8.44 (s, 1, aromatic C**H**), 8.13 (s, 1, aromatic C**H**), 7.41 (s, 5, phenyl C**H**), 6.19 (quadruplet, 1, J_{ab} = 8 Hz, J_{ac} = 11 Hz, C_6H_5CH-CH_2), 4.61 [d, 1, J_{ca} = 11 Hz, J_{cb} = 11 Hz, C_6H_5CH-C(**H**)], and 4.15 ppm [quadruplet, 1, J_{ba} = 8 Hz, J_{bc} = 11 Hz, C_6H_5CH-(**H**)CH].

Anal. Calcd for $C_{13}H_{11}N_5 \cdot 2HCl$: C, 50.33; H, 4.23; N, 22.6; Cl, 22.9. Found: C, 50.44; H, 4.51; N, 22.6; Cl, 22.8.

5-Chloro-7-phenyl-7,8-dihydro-9H-imidazo[2,1-*i*]purine hydrochloride (IIh).—The general procedure followed in preparation of IId was used. Pure IIh (4.8 g, 100%), mp >310°, prepared from chloro alcohol Ih (4.6 g, 0.016 mol) at 40°, was homogeneous as indicated by paper chromatography in solvent systems B and C: ir (KBr), 6.7, 7.5, 10.5, 13.1, and 14.3 μ; uv max (H_2O pH 1) 266 mμ (ϵ 12,540), (pH 7) 271.5 (10,900), (pH 10) 273.5 (12,780) and 281.5 (12,380); nmr (D_2O), δ 8.34 (s, 1, aromatic C**H**), 7.36 (s, 5, phenyl C**H**), 6.22 (quadruplet, 1, J_{ab} = 5 Hz, J_{ac} = 11 Hz, C_6H_5CH-CH_2), 4.65–5.20 (m), and 4.08 [quadruplet, J_{ba} = 5 Hz, J_{bc} = 11 Hz, C_6H_5CH-(**H**)CH].

Anal. Calcd for $C_{13}H_{10}ClN_5 \cdot HCl$: C, 50.66; H, 3.61; N, 22.7. Found: C, 50.45; H, 3.84; N, 22.5.

Hydrogenolysis of IIh.—A solution of IIh (1 g, 3.25 mmol) in water (150 ml) was prepared; then 10% Pd–C (0.35 g) was added; and the mixture was treated with hydrogen (20 psi) at room temperature with shaking. Theoretical hydrogen uptake was completed in 2 hr. The catalyst was removed and paper chromatography of the filtrate, IIg and IIh, in solvent systems B and D showed the major product to be IIg with small quantity of IIh. The filtrate was reduced to dryness and the dry solid contained IIg (80%) and IIh (20%) as indicated by nuclear magnetic resonance hydrogen integral analysis. The ultraviolet spectrum had the following absorptions: (pH 1) 263.5 mμ, (pH 7) 269.0, (pH 10) 273.0 and 282.

Effect of Temperature on the Reaction of Alcohol If and Thionyl Chlorides. A. At 79°.—The general procedure followed in preparation of IId was used. Pure IIf, mp 225–226° dec (251 mg, 1.01 mmol, 89%), prepared from alcohol If (220 mg, 1.14 mmol) had, after crystallization from methanol–benzene–ethyl acetate, the following spectral properties: uv max (H_2O pH 1) 262.0 mμ (ϵ 12,300), (pH 7) 266.5 (11,030), (pH 10) 272.0 (11,900); nmr spectrum (D_2O), δ 8.64 (s, 1 aromatic C**H**), 8.50 (s, 1, aromatic C**H**), 5.32 (m, 1, CH_3C**H**), 4.48 (t, 1, J = 11 Hz, $CHCH_2$), 3.92 (quadruplet, 1, J = 7 and 11 Hz, $CHCH_2$), and 1.78 (d, 3, J = 7 Hz, $CHCH_3$).

Anal. Calcd for $C_9H_9N_5 \cdot 2HCl$: C, 38.72; H, 4.47; N, 28.23. Found: C, 38.56; H, 4.52; N, 28.08.

B. At 50°.—The above sequence was repeated on alcohol If (2.0 g, 0.01 mol). Paper chromatography in solvent systems A and D of the crude product (2.5 g, mp 220–223°dec, softening from 212°) showed the presence of two ultraviolet absorbing spots; the minor one could be related to the R_f value of the starting alcohol. The nmr hydrogen integral analysis of the pendent

methyl groups showed the mixture to be composed of alcohol If (≅10%) and IIf (≅90%). The spectral properties of this mixture (pK_a 7.2) were as follows: uv max (H_2O, pH 1) 263.5 mμ (ε 12,700), (pH 7) 266.0, (pH 10) 270.5 (13,200) and 280.0.

C. At 25°.—The above sequence was repeated on alcohol If (1.0 g). The nmr hydrogen integral analysis of the pendent methyl groups of the crude product (0.9 g) showed it to contain alcohol If (≅10%), IIf (≅55–60%), and a third unidentified material XI (≅30–35%). The mixture had the following element analysis: C, 38.56; H, 4.52; Cl, 25.7; Cl^-, 18.6. These results suggest that the third component (XI) contains covalently bonded chlorine.

D. At −70°.—The above sequence was repeated on alcohol If (1.0 g). The nmr analysis of the isolated crude product (0.95 g) indicated it to be composed of If (60%) and IIf (40%).

Registry No.—Id, 16958-58-0; Ie, 16958-59-1; If, 16958-60-4; Ig, 16958-61-5; Ih, 16969-36-1; IId, 16958-64-8; IIe, 16958-65-9; IIf, 16958-62-6; IIg, 16958-63-7; IIh, 16958-66-0.

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Self-Condensation of Anthranilic Acid

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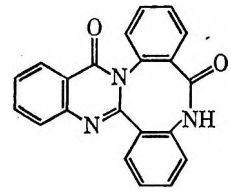
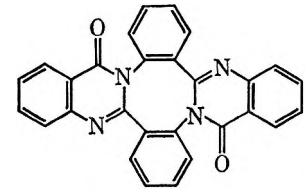
Anthranilic acid undergoes condensation with a wide variety of compounds[1,2] but its self-condensation reaction has not been reported as yet. The present communication concerns studies on the self-condensation products of anthranilic acid.

Heating anthranilic acid with phosphorous pentoxide in refluxing xylene furnished[3] a compound with mp 285° as the major product together with a minor compound (yield, 2%) with mp >360°.

On the basis of its molecular formula, $C_{21}H_{13}N_3O_2$ (M^+339), spectral data [uv λ_{max}^{EtOH} 280 and 306 mμ (log ε 4.53 and 4.30) and ir λ_{max}^{Nujol} 5.9, 6.05, and 6.3 μ], and, most importantly, its mode of formation, the major compound was assigned the structure I, a trimer of anthranilic acid. This is further supported by the nmr spectrum[4] of the compound which shows all of the 13 protons in its molecule appearing as a broad multiplet between δ 7.2 and 8.0.



I



II

The minor component, mp >360°, shows spectral properties (uv, ir, and nmr) very much similar to those of I. These observations conjointly with its molecular formula, $C_{28}H_{16}N_4O_2$ (M^+440), led us to propose structure II for the compound, a tetramer of anthranilic acid. The fact that II could also be obtained by heating I with additional anthranilic acid provided final confirmation for the assigned structure of the minor component.

Experimental Section[5]

Anthranilic acid (0.5 g) in dry xylene (8 ml) was refluxed for 3 hr over phosphorous pentoxide (1.5 g). The reaction mixture after cooling was poured over crushed ice and diluted with benzene. The benzene layer was then separated and extracted with three 40-ml portions of 6 *N* hydrochloric acid. The total acidic extract was subsequently basified with ammonia and treated with three 60-ml portions of chloroform. The chloroform extract was then washed and dried. The residue upon concentration of the chloroform extract was chromatographed over alumina. Benzene–chloroform (9:1) eluate gave II (yield, 0.01 g) which crystallized from methanol as granules: mp >360°; λ_{max}^{EtOH} 280 and 306 mμ (log ε 4.26 and 4.05); λ_{max}^{Nujol} 5.95, 6.25, 6.30, and 6.40 μ; nmr 16 H (broad multiplet) between δ 7.4 and 8.05.

Anal. Calcd for $C_{28}H_{16}N_4O_2$: C, 76.36; H, 3.64; N, 12.72; O, 7.27. Found: C, 76.20; H, 3.83; N, 12.66; O, 7.50.

The chloroform eluate on removal of solvent gave I (yield, 0.30 g) crystallized from a chloroform–acetone mixture, mp 285°.

Anal. Calcd for $C_{21}H_{13}N_3O_2$: C, 74.33; H, 3.83; N, 14.15; O, 9.43. Found: C, 74.20; H, 3.51; N, 14.20; O, 9.70.

Compound I (0.65 g) mixed with anthranilic acid (0.30 g) was refluxed in dry xylene (10 ml) for 3 hr. The reaction mixture was treated as above. The basic portion in chloroform extract after concentration was chromatographed and gave II (0.09 g) together with I (0.50 g).

Registry No.—I, 17-223-74-4; II, 17-223-75-5; anthranilic acid, 118-92-3.

Acknowledgments.—The authors wish to express their sincere thanks to Dr. B. C. Das, Institut de Chimie des Substances Naturelles, Gif-sur-Yvette, France, for determining the mass numbers, and to the Council of Scientific & Industrial Research, New Delhi, for financial assistance to one of them (M. G.).

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(2) Br. Pawlewski, *ibid.*, **38**, 136 (1905).

(3) These compounds were also obtained for the first time during the synthesis of deoxyvasicinone from anthranilic acid and γ-aminobutyric acid. The major compound, designated as DVQ, was also assigned a tentative structure mainly on the basis of spectral evidence which in the present communication is being revised: A. Chatterjee and M. Ganguly, *Phytochemistry*, **7**, 307 (1968).

(4) The nmr spectra were taken in DMSO in a 60-Mc instrument with tetramethylsilane as the internal standard.

(5) Melting points were determined on a Kofler block and are uncorrected.