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THE JOURNAL OF Organic Chemistry

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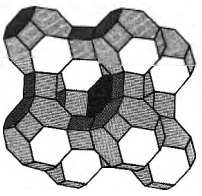

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THE JOURNAL OF Organic Chemistry®

VOLUME 38, NUMBER 21

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The Total Synthesis of *dl*-Oplopanone[1a-c]

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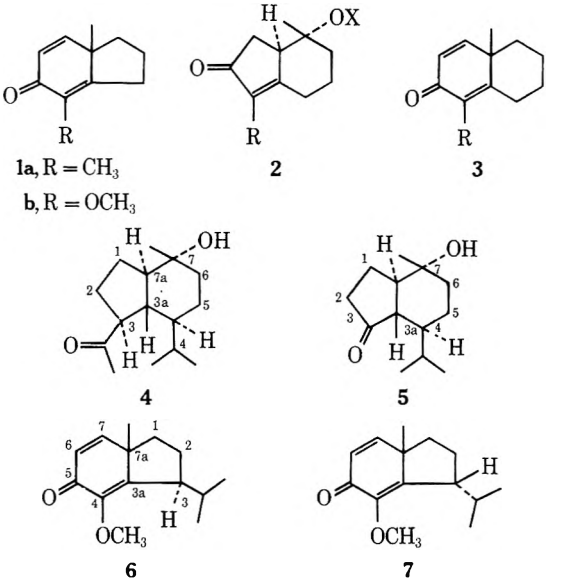
Received April 19, 1973

The total synthesis of *dl*-oplopanone (**4**) is described. The acetoxy ketone **12**, having the ring skeleton and three of the asymmetric centers of the natural product intact, was produced by photochemical rearrangement of the 6/5-fused, cross-conjugated cyclohexadienone **6** in glacial acetic acid. The transformation of **12** into *dl*-**4** was accomplished in a straightforward manner.

A number of successful syntheses of hydroazulene sesquiterpenoids have involved photochemical rearrangement of various 6/6-fused cross-conjugated cyclohexadienone derivatives as a means of establishing the 5/7-fused ring system.[2] In studies on the photochemistry of 6/5-fused cross-conjugated cyclohexadienone systems we have found that the 4-methyl dienone **1a** yields exclusively the 5/6-fused hydroxy ketone **2a** (X = H) on irradiation in aqueous acetic acid.[3] This behavior, which is analogous to that of the related 6/6-fused system **3a**,[4,5] suggested that photolysis of 6/5-fused dienones might provide useful intermediates for the synthesis of sesquiterpenes having a six-membered B ring. The sesquiterpene oplopanone (**4**), isolated from *Oplopanax japonicus* by Minato and coworkers,[6] has the same carbon skeleton and stereochemistry at positions 7 and 7a as does the photoproduct **2**. Thus a total synthesis of **4** by a route involving the photochemical rearrangement of an appropriately substituted 6/5-fused dienone appeared easily possible. As a key intermediate we hoped to prepare the hydroxy ketone **5**, which was obtained from oplopanone by Baeyer–Villiger oxidation followed by hydrolysis and oxidation.[6] Compound **5** has four of the five asymmetric centers of oplopanone intact and the addition of an appropriate two-carbon unit to the carbonyl group would provide a means of elaborating the acetyl group of the natural product. It was felt that the 4-methoxy dienone **6** would serve as a useful precursor to **5**. Provided that photochemical rearrangement of this compound occurred in the desired manner, the α-methoxy-α,β-unsaturated ketone system of the photoproduct could be converted into an enol ether which would then serve as a source of the carbonyl group. However, of major concern was the readiness with which the cis relationship of the methyl and isopropyl groups in **6** could be established. Examination of models of **6** and its 3α-isopropyl epimer **7** revealed that $A^{1,3}$ strain[7] involving the methoxyl and isopropyl



(1) (a) This investigation was supported by Public Health Service Research Grants No. GM 15044 from the National Institute of General Medicine and No. CA 12193 from the National Cancer Institute. (b) Abstracted from the Ph.D. Dissertation of F. Norman Tuller, Georgia Institute of Technology, 1971. (c) For a preliminary publication of this work see D. Caine and F. N. Tuller, *J. Amer. Chem. Soc.*, **93**, 6311 (1971). (d) NDEA Title IV Fellow, 1966–1968; Union Camp Fellow, 1969–1970.

(2) (a) D. H. R. Barton, J. T. Pinhey, and R. J. Wells, *J. Chem. Soc.*, 2518 (1964); (b) G. Buchi, S. M. Kauffman, and H. J. E. Loewenthal, *J. Amer. Chem. Soc.*, **88**, 3403 (1966); (c) E. H. White, S. Eguchi, and J. N. Marx, *Tetrahedron*, **25**, 2099 (1969); (d) J. N. Marx and E. H. White, *ibid.*, **25**, 2117 (1969); (e) E. Piers and K. F. Cheng, *Can. J. Chem.*, **48**, 2234 (1970); (f) D. Caine and P. F. Ingwalson, *J. Org. Chem.*, **37**, 3751 (1972).

(3) D. Caine, W. J. Powers, III, and J. T. Gupton, III, Abstracts of Papers, 159th National Meeting of the American Chemical Society, Houston, Texas, Feb 23–27, 1970, No. ORGN 97.

(4) (a) D. Caine and J. B. Dawson, *J. Org. Chem.*, **29**, 3108 (1964); (b) P. J. Kropp, *ibid.*, **29**, 3110 (1964).

(5) For comprehensive reviews on the photochemistry of 6/6-fused dienones see (a) P. J. Kropp, *Org. Photo. Chem.*, **1**, 1 (1967); (b) K. Schaffner, *Advan. Photo. Chem.*, **4**, 81 (1966).

(6) K. Takeda, H. Minato, and M. Ishikawa, *Tetrahedron, Suppl.*, **No. 7**, 219 (1965); *Chem. Commun.*, 79 (1965).

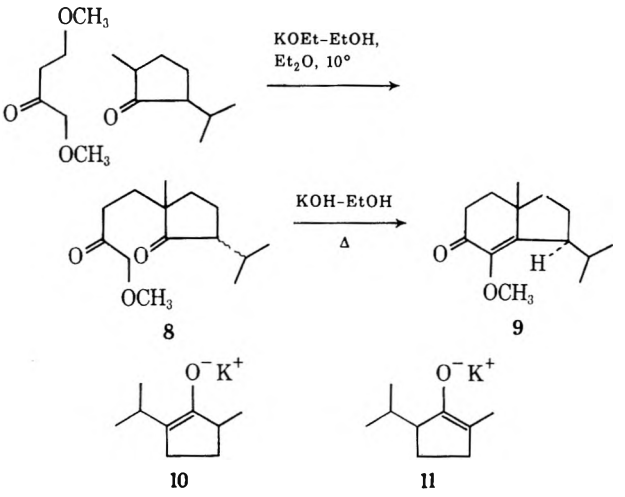
(7) F. Johnson, *Chem. Rev.*, **68**, 375 (1968).

groups was more severe when the latter was in the α configuration. It seemed possible that such an interaction in **7** might be sufficiently strong to outweigh the cis methyl–isopropyl interaction which exists in **6** so that the latter isomer might be the more thermodynamically stable of the two. Thus a method of synthesis of **6** which involved equilibration at C-3 appeared to have reasonable likelihood of success.

Before the synthesis of **6** was attempted the photochemical behavior of the model 4-methoxy dienone **1b** was investigated. This dienone was prepared by condensation of 1,4-dimethoxy-2-butanone with 2-methylcyclopentanone using the procedure of Wenkert and Berges[8] followed by oxidation of the resulting 6/5-fused enone with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in dioxane.[9] Previous work had shown that the 6/6-fused methoxy ketone **3b** was hydrolyzed to a diosphenol without rearrangement of the skeleton when irradiated in aqueous acetic acid; however, it was smoothly converted into a 5/7-fused acetoxy ketone when glacial acetic acid was employed as the solvent.[10] Thus methoxyl and methyl substituents at the 4 position exert a similar influence on the course of photochemical rearrangements of dienones such as **3** in nucleophilic solvents. This also proved to be the case for the 6/5-fused system. When a *ca.* 2% solution of **1b** in glacial acetic acid was irradiated for 4 hr using a 450-W Hanovia lamp fitted with a Pyrex sleeve, the 5/6-fused acetoxy ketone **2b** (X = Ac) was obtained in 85% yield. The structure and stereochemistry of this compound were assigned on the basis of the similarity of its nmr spectrum to that of **2a** (X = H) and the related 5/7-fused hydroxy and acetoxy ketones derived from **3a**[4] and **3b**,[10] respectively.

The behavior of **1b** clearly indicated that the photochemical rearrangement of **6** would be expected to take place in the desired manner. Dienone **6** was prepared by way of the diketone **8** and the enone **9**. Condensation of 1,4-dimethoxy-2-butanone[8] with 2-methyl-5-isopropylcyclopentanone[11] gave the diketone **8** in 25% yield as a mixture of cis and trans isomers.[12] It is of interest that none of the alternative diketone derived from alkylation at the α position bearing the isopropyl group was observed. The reaction was carried out under conditions which should allow equilibration between the two potassium enolates **10** and **11** which may be derived from 2-methyl-5-isopropylcyclopentanone. The enolate **11**, having the smaller methyl substituent on the double bond, might be expected to be both more stable thermodynamically and more reactive in the Michael reaction than the isomeric species **10**. Perhaps the combination of these factors accounts for the fact that **8** is formed exclusively.

On heating **8** with alcoholic potassium hydroxide for 1 hr a single aldol product, which was unaffected by prolonged base treatment, was obtained in 68% yield. The spectral properties of this product were consistent



with the enone structure **9** or the corresponding 3α-isopropyl isomer. As in the case of the dienones **6** and **7** discussed earlier, examination of models indicated that the strong $A^{1,3}$ interaction involving the methoxyl group and the 3α-isopropyl group might cause the 3β-isopropyl enone to be the more thermodynamically stable isomer. Although it was surprising that only a single isomer was obtained under thermodynamic conditions, the subsequent work provided support for the assignment of the 3β-isopropyl structure **9** to this material.

Oxidation of **9** with selenium dioxide in *tert*-butyl alcohol using a modification of the procedure of Bloom[13] yielded a 5:1 mixture of cross-conjugated dienones.[14] Treatment of this mixture with potassium *tert*-butoxide in *tert*-butyl alcohol left its composition unchanged, indicating that equilibrium was established under the conditions of the oxidation reaction. The subsequent conversion of the major component of this mixture into **5** (and its unstable 3α epimer) indicated that it was the desired 3β-isopropyl dienone **6**. Thus the minor component of the mixture was the 3α-isopropyl compound **7**. Examination of models in the α and β series revealed that the distances between the isopropyl groups and the angular methyl and the methoxyl groups change very little in going from the enones to the corresponding dienones. Therefore, it seemed likely that the 3β-isopropyl isomer would be the more thermodynamically stable one in both cases. However, since two isomeric dienones were isolated, it appears that the difference in energy between the α and β isomers is smaller in the dienone than in the enone systems. It is possible that the increased stability of the α-isopropyl dienone relative to the corresponding enone results from a decrease in the interaction between the isopropyl group and C-7 owing to the change in hybridization from sp^3 to sp^2 at the latter position.

Dienones **6** and **7** were separated by careful chromatography on silica gel. Irradiation of **6** under the same conditions as described for **1b** gave the crystalline acetoxy ketone **12** in 91% yield. The nmr spectrum (CCl_4) of **12** showed a singlet at δ 1.22 for the 7-methyl group, a singlet at δ 1.91 for the acetate group, a singlet

(8) (a) E. Wenkert and D. A. Berges, *J. Amer. Chem. Soc.*, **89**, 2507 (1967). (b) We are grateful to Professor Wenkert for making the details of this procedure available to us prior to publication.

(9) D. Burn, R. Kirk, and V. Petrow, *Proc. Chem. Soc.*, 14 (1960).

(10) D. Caine and P. F. Ingwalson, unpublished work.

(11) K. Sisido, S. Kurozumi, K. Utimoto, and T. Ishida, *J. Org. Chem.*, **31**, 2795 (1966).

(12) Although this condensation was attempted under a variety of conditions and 1-methoxy-3-buten-2-one was substituted for 1,4-dimethoxy-2-butanone, the yield of **8** could not be significantly improved.

(13) S. M. Bloom, *J. Amer. Chem. Soc.*, **81**, 4728 (1959).

(14) Treatment of **9** with DDQ in dioxane under the same conditions as were employed for the synthesis of **1b** from the corresponding enone gave a mixture of dienones composed mainly of the linearly conjugated system. The reasons for the difference in behavior of these two enones toward DDQ are not clear.

at δ 3.84 for the methoxyl group, and pairs of doublets (J = 6 Hz) at δ 0.88 and 0.97 for the nonequivalent methyls of the isopropyl group. An apparent triplet (J = 4.5 Hz) at δ 3.01 and an apparent doublet (J = 4.5 Hz) at δ 2.18 were assigned to the 7a proton and the 1-methylene protons. This apparent AB_2 pattern for the 7aα and 1 protons as well as the location of the absorption for the 7β-methyl group (which because of shielding by the 3,3a double bond is at higher field than is normally observed for a methyl group attached to a carbon bearing an acetoxy group) is characteristic of enones such as **2** and the related 5/7-fused systems. Thus the spectral properties of **12** were indicative of the cis relationship of the angular hydrogen and the adjacent oxygen function.

For comparison purposes the acetoxy ketone **13** having the isopropyl group α was prepared by irradiation of the 5:1 mixture of **6** and **7** followed by fractional crystallization of the photoproducts from ether–hexane. Compound **13** exhibited a similar nmr spectrum (CCl_4) to that of **12** except that the doublets for the methyl absorptions of the isopropyl group were somewhat more separated.

The transformation of **12** into the hydroxy ketone **5** was accomplished *via* a procedure similar to that employed for the conversion of other α-methoxy-α,β-unsaturated ketones into saturated ketones with the carbonyl group at this α position.[15,16] Treatment of **12** with sodium borohydride in ethanol followed by acetic anhydride in pyridine gave a 2:1 mixture of allylic acetates (**14**) in 94% yield. Addition of lithium to a solution of **14** in ethylamine containing 1 equiv of *tert*-butyl alcohol at −78° followed by quenching with ammonium chloride caused cleavage of the allylic acetate group[17] and reduction of the tertiary acetate group to produce the hydroxy enol ether **15**. Hydrolysis of **15** using 0.20 equiv of oxalic acid in aqueous methanol gave a 70% yield of the racemic trans-fused hydroxy ketone **5** which showed identical nmr and ir spectral properties with those reported by Minato and coworkers[6] for the product obtained from degradation of oplopanone. As reported,[6] compound **5** was stable to sodium methoxide in methanol. Alternatively, brief treatment of **15** with a trace of oxalic acid in aqueous methanol produced another hydroxy ketone which was converted into **5** on extended acid treatment or on reflux with sodium methoxide in methanol. Kinetic hydrolysis of **15** should yield the cis-fused hydroxy ketone **16**, since kinetic protonation of the enol ether function should occur from the side of the molecule opposite the axial 7β-methyl group. Structures A and B represent the most favorable conformation of the trans- and cis-fused ketones **5** and **16**. Clearly the cis isomer is the less stable of the two because of the unfavorable 1,3 interaction between the carbonyl group and the 7β-methyl group which is absent in the trans compound. Thus acid- or base-catalyzed epimerization of **16** at C-3a should occur readily to give **5**.

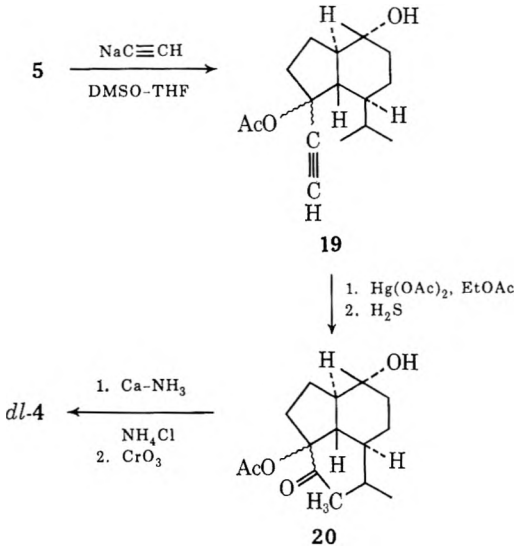
The photoproduct **13** was converted into the enol ether **17** by a route similar to that described above. Hydrolysis of **17** with oxalic acid under mild conditions produced a hydroxy ketone which was unchanged after being refluxed with sodium methoxide in methanol. We believe that this compound has the cis-fused ring structure **18**. Structure C represents the most stable

(15) D. Caine and J. B. Dawson, *Chem. Commun.*, 1232 (1970).
(16) R. E. Ireland, D. R. Marshall, and J. W. Tilley, *J. Amer. Chem. Soc.*, **92**, 4754 (1970).
(17) A. S. Hallsworth, H. B. Henbest, and T. I. Wrigley, *J. Chem. Soc.*, 1969 (1957).

conformation of **18** while the trans isomer in this series would be represented by D. The cis isomer should be the much more stable of the two because in the trans compound both the isopropyl group and the methyl group must be axial to the B ring unless it adopts a boat conformation. Kinetic β protonation of **17** at the 3a position to give a trans ring system would be hindered by the 7-methyl group. Thus it is not surprising that hydrolysis of **17** yielded the thermodynamically more stable cis product.

The nmr absorptions for the 7-methyl groups of hydroxy ketones **16**, **5**, and **18** occurred at δ 0.96, 1.14, and 1.17, respectively. The observed downfield shift in going from **16** to **5** is consistent with the structural assignments, because shielding of the methyl group by the carbonyl group would be removed in going from the cis to the trans ring fusion. It should be noted that, if the configuration of the isopropyl group were α as in **18** or its unstable 3a epimer, no such change in the chemical shift of the 7-methyl group would be expected. The formation of two hydroxy ketones from hydrolysis of **15** and only one from hydrolysis of **17** provides direct chemical evidence for the assignment of the β and α configurations, respectively, for the isopropyl groups in these compounds and in their dienone precusors.

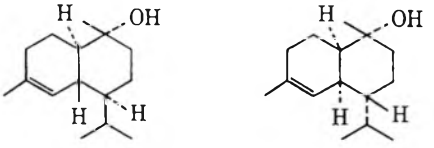
Completion of the synthesis of *dl*-oplopanone from **5** required introduction of the acetyl side chain at the 3 position. This was accomplished *via* intermediates **19** and **20**, which, although not fully characterized, exhibited the expected spectral properties. Treatment of **5** with sodium acetylide in dimethyl sulfoxide (DMSO)–tetrahydrofuran (THF)[18] gave the ethynyl carbinol **19**, which showed a one-proton absorption at δ 2.43 for the ethynyl proton. The crude product was then converted into the α-acetoxy ketone **20** by treatment



with mercuric acetate followed by hydrogen sulfide.[19] The nmr spectrum of **20** exhibited two three-proton singlets at δ 2.09 and 2.16 for the acetyl and acetoxyl groups, respectively. Reductive removal of the α-acetoxyl group with calcium in liquid ammonia[20] followed by oxidation with Jones reagent[21] and chromatography on silica gel afforded *dl*-oplopanone, mp 101.5–102.0°, which exhibited nmr, ir, and glc properties which were identical with those of an authentic sample of the natural product.[22]

The synthetic work provides no new evidence for the stereochemistry of oplopanone at C-3. Steric factors would favor α protonation of the enolate intermediate formed in the reductive removal of the acetoxyl group leading to a β acetyl side chain, but it is probable that equilibration at C-3 would have occurred prior to reduction of the carbonyl group or during the Jones oxidation and subsequent chromatography. Examination of models having the 3-acetyl group α and β does not allow one to say unambiguously which isomer is the more thermodynamically stable. The conditions employed by Minato and coworkers for the isolation of the natural product would very likely have allowed equilibration at C-3.[6] The evidence provided by these authors indicated that the C-3 side chain is β as shown in **4**.[6] Although this assignment is probably correct, further confirmation of this point would be desirable.

The stereochemistry of photoproducts **12** and **13** is the same as is found in α-cadinol (**21**)[23] and T-murrolol (**22**),[24] respectively, at three of the four asymmetric



centers. Approaches to these 6/6-fused natural products by ring expansion of the corresponding 5/6-fused systems are under investigation.

Experimental Section[25]

7,7a-Dihydro-4-methoxy-7a-methyl-5(6*H*)-indanone.—In a 500-ml round-bottom flask equipped with a mechanical stirrer and a dropping funnel was placed 1.47 g (0.9376 g-atom) of potassium, and 11 ml of absolute ethanol was added dropwise with stirring under nitrogen. After the reaction was complete and the flask had cooled to room temperature, 900 ml of anhydrous ether was added, and the mixture was cooled with an ice bath to 10°. To this was added 19.6 g (0.200 mol) of 2-methylcyclopentanone in 20 ml of anhydrous ether. A solution of 13.2 g (0.100 mol) of

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(25) Melting points and boiling points are uncorrected. Infrared spectra were taken on Perkin-Elmer Model 457 or 137 infrared spectrophotometers. Ultraviolet spectra were taken on a Cary Model 14 or a Beckman DBGT recording spectrophotometer using 1-cm matched quartz cells. Nmr spectra were determined at 60 MHz with a Varian A-60 spectrometer and at 100 MHz with a Jeolco 4H-100 spectrometer. Signals are reported in parts per million (δ) downfield from internal tetramethylsilane. The abbreviations s, d, d of d, t, and m refer to singlet, doublet, doublet of doublets, triplet, and multiplet, respectively. Mass spectra were obtained using a Varian M-66 spectrometer. Gas–liquid chromatography was carried out with a Perkin-Elmer Model 881 or Aerograph A-90-P3 gas chromatograph. The following columns were used: A (6 ft × 0.125 in. stainless steel, 10% Carbowax K-20M on 60/80 Chromosorb W HMDS); B (10 ft × 0.25 in. stainless steel, 12% tris(2-cyanoethoxy)propane on 80/100 Diataport silanized with dichlrodimethylsilane). Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn., or by Atlantic Microlab, Inc., Atlanta, Ga.

1,4-dimethoxy-2-butanone[26] in 120 ml of anhydrous ether was added dropwise with rapid stirring over about 2 hr, while the temperature was maintained at 8–10° with an ice bath. After the addition was complete, the reaction mixture was stirred for 3 hr longer while being warmed to room temperature. An ethereal solution of glacial acetic acid (10% by volume) was added dropwise until the red color of the reaction mixture changed to yellow. The ether layer was decanted from the solid, washed with 50 ml each of water and saturated brine, dried (Na_2SO_4), concentrated, and distilled, giving 11.13 g (62%) of 7,7a-dihydro-4-methoxy-7a-methyl-5(6*H*)-indanone as a colorless liquid, bp 85–88° (0.51 mm). Redistillation of a small portion afforded an analytical sample: bp 73° (0.04 mm); uv max (95% EtOH) 254 nm (ϵ 8260); ir (film) 1673 (α,β-unsaturated C=O), 1647 (conjugated C=C), 1210, 1110, and 1089 cm^{-1}; nmr (CCl_4) δ 1.18 (s, 3 H, 7a-CH_3), 1.62–2.02 (m, 6 H, 1, 2, and 7-CH_2), 2.24–2.78 (m, 4 H, 3- and 6-CH_2), and 3.54 ppm (s, 3 H, 4-OCH_3); mass spectrum (70 eV) *m/e* 180.11490 (M^+) (calcd, 180.11494) and 165 ($M^+ - CH_3$).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.34; H, 9.05.

4-Methoxy-7a-methyl-5(7a*H*)-indanone (1b).—A 1000-ml round-bottom flask equipped with a magnetic stirrer and reflux condenser and having a nitrogen atmosphere was charged with 400 ml of dioxane (freshly distilled over sodium), 5.4 g (0.03 mol) of 7,7a-dihydro-4-methoxy-7a-methyl-5(6*H*)-indanone, and 7.02 g (0.31 mol) of 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ). The mixture was stirred until homogeneous and then stirred at reflux for 36 hr. After it cooled to room temperature, the dioxane was removed *in vacuo* and the residue was dissolved in 100 ml of benzene and filtered to remove 2,3-dichloro-5,6-dicyano-*p*-hydroquinone (DDHQ). The filter cake was washed with 50 ml of benzene and the combined filtrates were concentrated. The residue was placed on a column of 50 g of neutral alumina and rapidly eluted with 500 ml of benzene. Evaporation of the benzene gave 3.86 g of a pale yellow oil which by glc analysis (column A) was shown to contain about equal amounts of **1b** and the starting material. Chromatography on 100 g of silica gel using hexane–ether as eluent afforded 1.85 g of the starting enone (20% ether in hexane) and 1.80 g (51%) of the dienone **1b** (40% ether in hexane). Distillation of a small portion of the latter afforded an analytical sample: bp 75° (0.03 mm); uv max (95% EtOH) 242 nm (ϵ 5430) and 276 (1371);[27] ir (film) 1649 (α,β-unsaturated C=O), 1608 (conjugated C=C), 1452, 1208, 1152, 1081, and 840 cm^{-1}; nmr (CCl_4) δ 1.22 (s, 3 H, 7a-CH_3), 3.68 (s, 3 H, 4-OCH_3), and 6.01 and 6.99) ppm (AB quartet, J_{AB} = 10 Hz, 2 H, 5,7-H); mass spectrum (70 eV) *m/e* 178.09907 (M^+) (calcd, 178.09930) and 163 ($M^+ - CH_3$).

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.12; H, 8.01.

Irradiation of 4-Methoxy-7a-methyl-5(7a*H*)-indanone (1b).—A solution of 2.0 g of **1b** in 250 ml of gacial acetic acid (dried over 5A molecular sieves and distilled) was irradiated with a 450-W high-pressure mercury lamp for 4 hr using a Pyrex probe. A slow stream of dry nitrogen was bubbled through the solution for 10 min prior to and during the entire irradiation period. The solution was washed into a 500-ml round-bottom flask with benzene and frozen quickly in a Dry Ice–acetone bath, and the solvents were removed by lyophilization to afford a yellow oil which on distillation gave 2.27 g (85%) of **2b**: bp 102–105° (0.05 mm); mp 54.5–55°; uv max (95% EtOH) 252 nm (ϵ 11,300); ir (film) 1732 (ester C=O), 1710 (α,β-unsaturated C=O), 1650 (conjugated C=C), 1450, 1370, 1257, 1237, and 1098 cm^{-1}; nmr (CCl_4) δ 1.28 (s, 3 H, 7-CH_3), 1.97 (s, 3 H, 7-OAc), 2.27 (d, J = 4 Hz, 2 H, 1-CH_2), 3.08 (t, J = 4 Hz, 1 H, 7a-CH), and 3.90 ppm (s, 3 H, 3-OCH_3); mass spectrum (70 eV) *m/e* 178 ($M^+ - HOAc$).

Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.26; H, 7.75.

2-Methyl-5-isopropylcyclopentanone.—A 3000-ml three-neck flask, equipped with a variable takeoff distilling head, a mechanical stirrer, and an addition funnel, was flame dried and established with a dry nitrogen atmosphere. Potassium (30.1 g, 0.771 g-atom) was introduced and 340 ml of anhydrous ethanol was added dropwise at a rate that allowed gentle reflux. After the reaction was complete, 136.4 g (0.675 mol) of diethyl adipate was added slowly with stirring, and the mixture was stirred at reflux for 7 hr. The ethanol (200 ml) was removed by distillation and 1000 ml of dry toluene was added. Distillation was continued until the temperature of the vapor was 110°. Often the addition of about 200–500 ml more of dry toluene was necessary during the distillation to sufficiently reduce the viscosity of the enolate sludge to allow efficient agitation. The mixture was allowed to cool slightly, and 131 g (0.77 mol) of 2-iodopropane was added. Stirring at reflux was continued for 12 hr, 30 g more of 2-iodopropane was added, and stirring at reflux was continued for 12 hr. After the reaction mixture had been cooled to room temperature, 200 ml of water was added with stirring, the layers were separated, and the aqueous layer was extracted with 100 ml of benzene. The combined organic layers were washed with saturated brine, concentrated, and distilled to give 110 g (82%) of 2-carbethoxy-2-isopropylcyclopentanone, bp 90° (1.5 mm) [lit.[28] bp 112° (11 mm)].

A 3000-ml three-neck flask, equipped with a variable takeoff distilling head, a mechanical stirrer, and an addition funnel, was flame dried and charged with 750 ml of anhydrous ethanol under nitrogen. Sodium, 50 g (2.3 g-atoms), was added in small pieces at a sufficient rate to maintain slow reflux. After the sodium had reacted, 396 g (2.00 mol) of 2-carbethoxy-2-isopropylcyclopentanone was added slowly and the mixture was refluxed with rapid stirring for 7 hr. The ethanol (500 ml) was distilled, 1500 ml of dry toluene was added, and distillation was continued until the temperature of the vapor was 110°. The mixture was cooled to room temperature, 142 g (2.0 mol) of methyl iodide was added, and stirring was continued for 8 hr at room temperature; additional methyl iodide (40 g) was added and the mixture was stirred at reflux for 6 hr. After the reaction mixture cooled to room temperature, 200 ml of water was added, the layers were separated, and the aqueous layer was extracted with 100 ml of benzene. The combined organic layers were washed with brine, concentrated, and returned to the 3000-ml three-neck flask along with 1200 ml of water and 600 ml of concentrated sulfuric acid. The mixture was refluxed with vigorous stirring for 24 hr and cooled to room temperature, and the layers were separated. The aqueous layer was extracted with 3 × 100 ml of benzene, and the combined organic extracts were washed with 100 ml of water, 150 ml saturated sodium bicarbonate solution, and 50 ml of water, dried (Na_2SO_4), concentrated, and distilled to give 186 g (67%) of 2-methyl-5-isopropylcyclopentanone, bp 185° (760 mm) [lit.[11] bp 181–186° (740 mm)].

2-(1-Methoxy-2-butanon-4-yl)-2-methyl-5-isopropylcyclopentanone (8).—In a 5000-ml round-bottom flask equipped with a mechanical stirrer, dropping funnel, a thermometer, and a condenser was placed potassium (13.2 g, 0.1128 g-atom), and 100 ml of anhydrous ethanol was added slowly. After the potassium had reacted and the solution was cooled to room temperature, 900 ml of anhydrous ether was added. The mixture was cooled to 10° and 252 g (1.8 mol) of 2-methyl-5-isopropylcyclopentanone in 120 ml of anhydrous ether was added. Then a solution of 132.0 g (1.0 mol) of 1,4-dimethoxy-2-butanone[26] in 1000 ml of anhydrous ether was added dropwise with rapid stirring over about 4 hr, while the temperature was maintained at 10–13° with an ice bath. After the addition was complete, the reaction mixture was stirred for 3 hr longer while being allowed to warm to room temperature. An ethereal solution of glacial acetic acid (10% by volume) was added dropwise until the red color of the reaction mixture changed to yellow. Saturated sodium bicarbonate solution (200 ml) was added with stirring, the layers were separated, and the aqueous layer was extracted with 100 ml of ether. The combined ethereal extracts were washed with water and dried (Na_2SO_4). The ether was removed *in vacuo* at room temperature and the unreacted 2-methyl-5-isopropylcyclopentanone (170 g) was removed by distillation at reduced pressure, bp 30–40° (20 mm), while the pot temperature was maintained at 75° or below. The residue was further distilled to yield 35 g (25%) of **8**, bp 140–150° (0.75 mm). A small portion was redistilled to afford an analytical sample: bp 113° (0.25 mm); ir (film) 1729 (C=O), 1460, 1370, 1200, and 1108 cm^{-1}; nmr (CCl_4) δ 0.90 and 0.98 (2 s, 3 H, 2-CH_3), 0.71–1.08 (m, 6 H, 5-*i*-Pr), 3.35 (s, 3 H, OCH_3),

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(27) The short and the less intense long wavelength uv absorption bands exhibited by dienones **1b**, **6**, and **7** are apparently characteristic of α-methoxy cross-conjugated dienone systems. For example, the 6/6-fused dienone related to **1b** exhibits similar bands. Also, for a somewhat related case, hydroxyeremophilone methyl ether, see L. H. Zalkow, F. X. Markley, and C. Djerassi, *J. Amer. Chem. Soc.*, **82**, 6354 (1960).

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and 3.86 ppm (s, 2 H, $COCH_2O$); mass spectrum (70 eV) m/e 240.17243 (M^+) (calcd, 240.17241) and 195 ($M^+ - CH_2OCH_3$).

Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07. Found: C, 70.09; H, 10.16.

7,7a-Dihydro-4-methoxy-7a-methyl-3-isopropyl-5(6*H*)-indanone (9).—To a 500-ml round-bottom flask fitted with a reflux condenser and a magnetic stirrer containing 20.0 g of potassium hydroxide in 200 ml of absolute ethanol was added 20.0 g (0.083 mol) of **8**. After stirring at reflux for 1 hr under nitrogen, the reaction mixture was cooled and glacial acetic acid was added dropwise with stirring until the red color of the solution had turned yellow (usually about 20 ml). The ethanol was removed *in vacuo* and the residue was mixed with ether and water. The layers were separated, the aqueous layer was extracted with ether, and the combined ethereal solutions were washed with 50 ml each of saturated sodium bicarbonate and water, dried (Na_2SO_4), concentrated, and distilled to yield 12.5 g (68%) of **9**, bp 100–105° (0.45 mm). Redistillation of a small portion afforded an analytical sample: bp 89–90° (0.04 mm); uv max (95% EtOH) 259 nm (ϵ 7969); ir (film) 1675 (α,β-unsaturated C=O), 1631 (C=C), 1461, 1295, 1209, 1112, and 1085 cm^{-1}; nmr (CCl_4) δ 0.83 and 0.95 (pair of d's, J = 7 Hz, 6 H, 3-CH_3CHCH_3), 1.19 (s, 3 H, 7a-CH_3), and 3.61 ppm (s, 3 H, 4-OCH_3); mass spectrum (70 eV) m/e 222.16196 (M^+) (calcd, 222.16186), 207 ($M^+ - CH_3$), and 179 ($M^+ - CH_3CHCH_3$).

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.44; H, 9.71.

Oxidation of 9 with Selenium Dioxide.—A 5000-ml three-neck flask fitted with a mechanical stirrer and variable takeoff distilling head was flame dried and charged with 22.2 g (0.200 mol) of freshly sublimed selenium dioxide, 3000 ml of *tert*-butyl alcohol (freshly distilled over sodium *tert*-butoxide), and 10 ml of glacial acetic acid. The mixture was stirred under nitrogen with warming until the selenium dioxide had dissolved and a solution of 11.1 g (0.05 mol) of **9** in 500 ml of *tert*-butyl alcohol was added. After the reaction mixture had been stirred at reflux for 4 days, 3000 ml of *tert*-butyl alcohol was removed by distillation. The remaining suspension was cooled and filtered through a fritted glass funnel to remove metallic selenium. The filtrate was concentrated *in vacuo* and the residue was dissolved in 500 ml of ether and filtered again to remove unreacted selenium dioxide. The ethereal filtrate was stirred with 200 ml of saturated sodium carbonate solution, and solid sodium carbonate was added slowly until the evolution of carbon dioxide ceased. The ether–water mixture was filtered with suction and the filter cake was washed with ether. The layers were separated, and the aqueous layer was extracted with ether. The combined ethereal extracts were washed with water, dried (Na_2SO_4), and concentrated. The residue was triturated with 3 × 75 ml of hot hexane, and the hexane extracts were concentrated and distilled to give 8 g of a yellow oil, bp 90–100° (0.3 mm), which by glc analysis (column A) was shown to be a 3:1 mixture of dienone products and the enone **9**. Chromatography on 200 g of neutal alumina using hexane–ether as the eluent afforded 1.95 g of **9** (10% ether in hexane) and 5.92 g (65%) of a mixture of dienones (25% ether in hexane). Analysis by glc (column B) and nmr showed that this mixture was composed of dienones **6** and **7** in a 5:1 ratio. Careful chromatography on silica gel permitted the isolation of the pure components of this mixture. The physical properties of the 3β-isopropyl compound **6** were bp 94–97° (0.07 mm); uv max (95% EtOH) 243 nm (ϵ 4145) and 283 (1113);[27] ir (film) 1659 (α,β-unsaturated C=O), 1608 (C=C), 1462, 1370, 1330, 1213, 1148, 1077, and 840 cm^{-1}; nmr (CCl_4) δ 0.92 and 0.97 (pair of d's J = 7 Hz, 6 H, 3β-CH_3CHCH_3), 1.21 (s, 3 H, 7a-CH_3), 3.79 (s, 3 H, 4-OCH_3), and 5.99 and 6.88 ppm (AB quartet, J_{AB} = 10 Hz, 2 H, 6,7-H); mass spectrum (70 eV) m/e 220.14607 (M^+) (calcd, 220.14622), 205 ($M^+ - CH_3$), and 177 ($M^+ - CH_3CHCH_3$).

Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.06; H, 9.26.

The physical properties of the 3α-isopropyl isomer **7** were bp 94–97° (0.07 mm); uv max (95% EtOH) 243 nm (ϵ 6700) and 283 (3600);[27] ir (film) 1661 (α,β-unsaturated C=O), 1609 (C=C), 1460, 1370, 1211, 1150, 1073 and 840 cm^{-1}; nmr (CCl_4) δ 0.68 and 0.97 (pair of d's, J = 7 Hz, 6 H, 3α-CH_3CHCH_3), 1.22 (s, 3 H, 7a-CH_3), 3.69 (s, 3 H, 4-OCH_3), and 5.99 and 6.94 ppm (AB quartet, J_{AB} = 10 Hz, 2 H, 6,7-H); mass spectrum (70 eV) m/e 220.14632 (M^+) (calcd, 220.14622), 205 ($M^+ - CH_3$), and 177 ($M^+ - CH_3CHCH_3$).

Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.51; H, 9.34.

Attempted Equilibration of a 5:1 Mixture of 6 and 7.—In a 25-ml three-neck flask fitted with a reflux condenser, a mechanical stirrer, and an addition funnel and maintained under a nitrogen atmosphere was placed 0.012 g (0.00033 g-atom) of potassium and 10 ml of dry *tert*-butyl alcohol. After the potassium had reacted, 0.67 g (0.0033 mol) of the 5:1 mixture of **6** and **7** in 10 ml of dry *tert*-butyl alcohol was added and the mixture was stirred at reflux overnight. After cooling and addition of 0.018 g (0.0003 mol) of glacial acetic acid in 10 ml of *tert*-butyl alcohol, the mixture was concentrated by lyophilization and the residue was dissolved in ether. The ethereal solution was washed with water, dried (Na_2SO_4), and concentrated to give a brown oil, which by glc (column B) and nmr analysis could not be distinguished from the starting material.

Irradiation of 4-Methoxy-7a-methyl-3β-isopropyl-5(7a*H*)-indanone (6).—A solution of 0.90 g of **6** in 250 ml of glacial acetic acid (dried over 5A molecular sieves and freshly distilled) was irradiated for 4 hr using a 450-W high-pressure mercury lamp fitted with a Pyrex probe. A slow stream of dry nitrogen was bubbled through the solution for 10 min prior to and during the entire irradiation period. Removal of the solvent by lyophilization and recrystallization of the residue from ether–hexane gave 1.04 g (91%) of 3-methoxy-4β-isopropyl-7α-acetoxy-7β-methyl-5,6,7,7aα-tetrahydro-2(4*H*)-indanone (**12**): mp 73–74.5°; uv max (95% EtOH) 252 nm (ϵ 9800); ir (CCl_4) 1738 (OAc), 1714 (α,β-unsaturated C=O), 1630 (C=C), 1444, 1383, 1370, 1250, 1237, and 1102 cm^{-1}; nmr (CCl_4) δ 0.88 and 0.97 (pair of d's, J = 6 Hz, 6 H, 4β-CH_3CHCH_3), 1.22 (s, 3 H, 7-CH_3), 1.91 (s, 3 H, 7-OAc), 2.18 (d, J = 4.5 Hz, 2 H, 1-CH_2), 3.01 (t, J = 4.5 Hz, 1 H, 7a-CH), and 3.84 ppm (s, 3 H, 3-OCH_3); mass spectrum (70 eV) m/e 220 ($M^+ - HOAc$).

Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.54; H, 8.63. Found: C, 68.33; H, 8.79.

Irradiation of a 5:1 Mixture of 6 and 7.—A solution of 2.0 g of a 5:1 mixture of **6** and **7** in 250 ml of glacial acetic acid was irradiated as described above. Removal of the solvent by lyophilization afforded 2.20 g (86%) of a yellow solid. This material was fractionally crystalized from ether–hexane to yield 1.80 g of **12**, mp 73–75°, and 0.36 g of 3-methoxy-4α-isopropyl-7α-acetoxy-7β-methyl-5,6,7,7aα-tetrahydro-2(4*H*)-indenone (**13**): mp 98–99°; uv max (95% EtOH) 254 nm (ϵ 10,900); ir (CCl_4) 1733 (OAc), 1709 (α,β-unsaturated C=O), 1643 (C=C), 1448, 1371, 1249, 1232, and 1098 cm^{-1}; nmr (CCl_4) δ 0.84 and 1.02 (pair of d's, J = 6 Hz, 6 H, 4α-CH_3CHCH_3), 1.28 (s, 3 H, 7-CH_3), 1.97 (s, 3 H, 7-OAc), 2.30 (d, J = 4 Hz, 2 H, 1-CH_2), 3.21 (t, J = 4 Hz, 1 H, 7a-CH), and 3.90 ppm (s, 3 H, 3-OCH_3); mass spectrum (70 eV) m/e 220 ($M^+ - HOAc$).

Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.54; H, 8.63. Found: C, 68.76; H, 8.47.

2,7α-Diacetoxy-3-methoxy-7β-methyl-4β-isopropyl-2,4,5,6,7,-7aα-hexahydroindene (14).—In a 10-ml round-bottom flask a mixture of 0.526 g (0.0188 mol) of **12**, 0.0720 g (0.00188 mol) of sodium borohydride, and 8 ml of absolute ethanol was stirred at room temperature under nitrogen for 48 hr. Acetone (1 ml) was added, and, after the mixture was stirred for 2 hr, the volatile material was removed *in vacuo* with warming. The residue was dissolved in a mixture of 10 ml of ether and 10 ml of water; the layers were separated; and the aqueous layer was extracted with ether. The combined ethereal extracts were washed with water, dried (Na_2SO_4), and concentrated to give 0.635 g of a pale yellow oil, which exhibited the nmr and ir spectral properties expected for a 2:1 mixture of the 2 epimers of 7α-acetoxy-2-hydroxy-3-methoxy-7β-methyl-4β-isopropyl-2,4,5,6,7,7aα-hexahydroindene. The crude reaction product was placed in a 25-ml round-bottom flask along with 1.5 g of acetic anhydride and 8 ml of dry pyridine and the mixture was stirred under nitrogen for 20 hr at room temperature. After the reaction mixture was cooled to 0° with an ice bath, 2 g of ice was added and the mixture was stirred for 2 hr while being allowed to warm to room temperature. The mixture was poured into 50 ml of ether and washed with water. The aqueous layer was extracted with 20 ml of ether and the combined ether extracts were washed with 5-ml portions of 10% aqueous sulfuric acid until the washing remained acidic. The ether layer was washed with saturated sodium bicarbonate, dried (Na_2SO_4), and concentrated to give 0.572 g (94%) of **14** as a viscous oil. Crystallization from hexane at −78° afforded a solid which melted upon warming to room temperature: ir (film) 1720 (ester C=O), 1668 (C=C), 1448, 1369, 1243, 1090, and 1018 cm^{-1}; nmr (CCl_4) δ 0.89 and 0.93 (pair of d's, J = 6 Hz, 6 H, 4β-CH_3CHCH_3), 1.27 and 1.33 (s, 3 H, 7-CH_3 of two

isomers), 1.89 (s, 3 H, 7-OAc), 2.01 (s, 3 H, 2-OAc), 3.51 (s, 3 H, 3-OCH_3) and 5.63–5.92 ppm (m, 1 H, 2-H); mass spectrum (70 eV) *m/e* 264 (M^+ − HOAc).

Anal. Calcd for $C_{18}H_{28}O_5$: C, 68.06; H, 9.28. Found: C, 68.32; H, 9.37.

2,7α-Diacetoxy-3-methoxy-7β-methyl-4α-isopropyl-2,4,5,6,7,-7aα-hexahydroindene.—Following the same procedure described above, a 10-ml round-bottom flask was charged with 0.526 g (0.0019 mol) of **13**, 0.072 g (0.0019 mol) of sodium borohydride, and 8 ml of absolute ethanol; the reaction mixture was stirred for 48 hr. The work-up gave 0.547 g of the expected alcohol as a pale yellow oil which was acetylated using 1.5 g of acetic anhydride and 8 ml of dry pyridine as described above to yield 0.521 g (86%) of a mixture of the 2 epimers of 2,7α-diacetoxy-3-methoxy-7β-methyl-4α-isopropyl-2,4,5,6,7,7aα-hexahydroindene. Crystallization from ether–hexane at −20° afforded an analytical sample: ir (film) 1728 (ester C=O), 1688 (C=C), 1458, 1368, 1238, 1072, and 1020 cm^{-1}; nmr (CCl_4) δ 0.78 and 0.94 (pair of d's, J = 6 Hz, 6 H, 4αCH_3CHCH_3), 1.35 (s, 3 H, 7-CH_3), 1.88 (s, 3 H, 7-OAc), 1.98 (s, 3 H, 2-OAc), 2.79 and 2.92 (d of d, J = 3 Hz, 1 H, 7a-H), 3.53 (s, 3 H, 3-OCH_3), and 5.70 and 5.83 ppm (d of d, J = 2 Hz, 1 H, 2 H); mass spectrum (70 eV) *m/e* 264 (M^+ − HOAc).

Anal. Calcd for $C_{18}H_{28}O_5$: C, 68.06; H, 9.28. Found: C, 67.85; H, 9.14.

3aα-Hydro-4α-hydroxy-4β-methyl-7β-isopropyl-*trans*-perhydroindan-1-one (5).—Ethylamine (30 ml, distilled from lithium wire) was introduced under nitrogen into a 50-ml three-neck flask equipped with a glass stirrer, a Dewar condenser, and a dropping funnel. The liquid was cooled to −78° in a Dry Ice–isopropyl alcohol bath. A solution of 0.696 g (0.00215 mol) of **14** and 0.159 g (0.00215 mol) of dry *tert*-butyl alcohol in 15 ml of anhydrous ether was added, followed by about 0.05 g of freshly cut pieces of lithium wire. The reaction mixture was stirred vigorously at −78° until the blue color persisted throughout the solution and then for 1 hr longer. The reaction mixture was rapidly filtered through glass wool into a flask containing about 0.1 g of solid ammonium chloride and swirled to destroy the excess lithium. The supernate was decanted and concentrated *in vacuo*, and the residue was dissolved in a mixture of ether and water. The layers were separated and the aqueous layer was extracted with ether. The combined ethereal extracts were washed with brine, dried (Na_2SO_4), and concentrated to give 0.415 g of a yellow oil which upon distillation in a Hickman microstill yielded 0.321 g (67%) of the enol ether **15**: bp 100–105° (0.05 mm); nmr (CCl_4) δ 0.82 and 0.92 (pair of d's, J = 6 Hz, 6 H, 7β-CH_3CHCH_3), 0.99 (s, 3 H, 4-CH_3), and 3.48 ppm (s, 3 H, OCH_3).

A solution of 0.309 g (0.00140 mol) of **15**, 6 ml of methanol, and 2 ml of water containing 0.027 g (0.00030 mol) of oxalic acid was stirred at room temperature for 2 hr, and 0.5 ml of saturated sodium bicarbonate solution was added. The solvents were removed *in vacuo*, and the residue was dissolved in ether and water. The layers were separated, and the aqueous layer was extracted with ether. The combined ethereal layers were washed with brine, dried (Na_2SO_4), and concentrated to give a yellow oil which yielded 0.2108 g (73%) of **5**: bp 102–108° (bath temperature, 0.07 mm); mp 79–80°; ir (CCl_4) 3520 (OH), 1730 (C=O), 1466, 1381, 1158, 1120, and 1056 cm^{-1}; nmr (CCl_4) δ 0.77 and 0.92 (pair of d's, J = 6 Hz, 6 H, 7β-CH_3CHCH_3) and 1.14 ppm (s, 3 H, CH_3); mass spectrum (70 eV) *m/e* 210.16201 (M^+) (calcd, 210.16186).

Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.29; H, 10.47. Found: C, 74.00; H, 10.36.

3aα-Hydro-4α-hydroxy-4β-methyl-7β-isopropyl-*cis*-perhydroindan-1-one (16).—A 5-ml round-bottom flask fitted with a magnetic stirrer and containing a nitrogen atmosphere was charged with a solution of 0.045 g (0.00020 mol) of **15**, 2 ml of methanol, and 0.5 ml of water with 0.002 g of oxalic acid. The mixture was stirred for 0.5 hr at room temperature and 5 drops of saturated sodium bicarbonate solution were added. The solvents were removed *in vacuo*, and the residue was dissolved in ether and water (10 ml each). The layers were separated, and the aqueous layer was extracted with ether. The combined ethereal layers were washed with brine, dried (Na_2SO_4), and concentrated to give a yellow oil which on distillation yielded 0.0320 g (76%) of **16**: bp 100–105° (bath temperature, 0.05 mm); ir (film) 3490 (OH), 1734 (C=O), 1470, 1390, 1160, and 1120 cm^{-1}; nmr (CCl_4) δ 0.88 and 0.90 (pair of d's, J = 7 Hz, 6 H, 7β-CH_3CHCH_3) and 0.96 ppm (s, 3 H, CH_3); mass spectrum (70 eV) *m/e* 210.16192 (M^+) (calcd, 210.16186).

Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.29; H, 10.47. Found: C, 74.36; H, 10.60.

In a 5-ml round-bottom flask fitted with a reflux condenser and a magnetic stirrer a solution of 0.050 g of **16** in 3 ml of 0.5% methanolic sodium methoxide was refluxed under nitrogen with stirring for 1 hr and was then cooled to room temperature. One drop of acetic acid was added, and the solvent was removed *in vacuo*. The residue was dissolved in ether and water, and the ether layer was isolated, dried (Na_2SO_4), and concentrated to yield 0.048 g (96%) of **5**.

3aα-Hydro-4α-hydroxy-4β-methyl-7α-isopropyl-*cis*-perhydroindan-1-one (18).—In a procedure similar to that described for the preparation of **15**, 30 ml of ethylamine was cooled to −78° with a Dry Ice–isopropyl alcohol bath and a solution of 0.389 g (0.00120 mol) of 2,7α-diacetoxy-3-methoxy-7β-methyl-4α-isopropyl-2,4,5,6,7,7aα-hexahydroindene and 0.0889 g (0.00120 mol) of dry *tert*-butyl alcohol in 15 ml of anhydrous ether was added. About 0.05 g of freshly cut lithium wire was added and the reaction mixture was stirred vigorously at −78° until the blue color persisted throughout the solution and then for 1 hr longer. The work-up procedure described earlier gave 0.2318 g (86%) of **17**: bp 100–105° (bath temperature, 0.05 mm); nmr (CCl_4) δ 0.79 and 0.92 (pair of d's, J = 6 Hz, 6 H, 7α-CH_3CHCH_3), 1.01 (s, 3 H, CH_3), and 3.51 ppm (s, 3 H, OCH_3).

In a 5-ml round-bottom flask a solution prepared from 0.141 g (0.00063 mol) of **17**, 3 ml of methanol, 1 ml of water, and 0.01 g of oxalic acid was stirred at room temperature under nitrogen for 2 hr and 0.25 ml of a saturated sodium bicarbonate solution was added. After the solvents were removed *in vacuo* and the residue was dissolved in ether and water (10 ml each), the organic and aqueous layers were separated, and the aqueous layer was extracted with 3 × 10 ml of ether. The combined ethereal extracts were washed with brine, dried (Na_2SO_4), and concentrated to give an oil which upon distillation yielded 0.1163 g (88%) of **18**: bp 103–105° (bath temperature, 0.08 mm); ir (film) 3420 (OH), 1733 (C=O), 1458, 1363, 1158, and 1073 cm^{-1}; nmr (CCl_4) δ 0.83 and 0.88 (pair of d's, J = 7 Hz, 6 H, 7α-CH_3CHCH_3) and 1.17 ppm (s, 3 H, CH_3); mass spectrum (70 eV) *m/e* 210.16188 (M^+) (calcd, 210.16186).

Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.29; H, 10.47. Found: C, 74.01; H, 10.65.

When **18** was treated with sodium methoxide in methanol under the same conditions as described for the isomerization of **16** into **5**, the starting material was recovered unchanged. Similarly, treatment of **18** with potassium *tert*-butoxide in *tert*-butyl alcohol–THF left it unchanged.

***dl*-Oplopanone (4).**—A 25-ml three-neck flask equipped with a mechanical stirrer, a gas dispersion tube, and an addition funnel was charged with 0.095 g of a 53% sodium hydride–oil dispersion under nitrogen. The dispersion was washed with 2 × 10 ml of anhydrous hexane to remove the oil, leaving 0.0540 g (0.00225 mol) of sodium hydride. Anhydrous DMSO (5 ml) was added and the suspension was warmed with vigorous stirring to 70° for 30 min, during which time a clear solution containing sodium methylsulfinylmethide was formed. The reaction mixture was cooled to room temperature and a steady stream of acetylene was bubbled through it for 30 min to form a clear, black solution of sodium acetylide in DMSO.[18] While a slow stream of acetylene was maintained through the reaction mixture, a solution of 0.158 g (0.00075 mol) of **5** in 5 ml of anhydrous THF was added dropwise over 30 min, and the mixture was stirred at room temperature overnight. The acetylene flow was discontinued and about 0.1 g of solid ammonium chloride was added. The reaction mixture was filtered and the solvents were removed by lyophilization. The residue was dissolved in a mixture of ether and water, and the aqueous layer was isolated and extracted with fresh ether. The combined ethereal extracts were washed with brine, dried (Na_2SO_4), and concentrated to give 0.1512 g of a viscous yellow oil whose nmr spectrum (CCl_4) displayed a one-proton absorption at δ 2.43 ppm, characteristic of an ethynyl proton, and a two-proton absorption at δ 3.83 ppm, for the OH protons, which was consistent with the expected ethynyl carbinol structure **19**.

The oil (0.1512 g) obtained above was dissolved in 15 ml of ethyl acetate containing 0.30 g of mercuric acetate and stirred at room temperature for 24 hr under nitrogen. With vigorous stirring, hydrogen sulfide was bubbled through the reaction mixture for about 10 min until a black precipitate had completely formed. After filtration through Celite, the solvent was removed *in vacuo* to leave 0.090 g of a yellow oil whose nmr spectrum (CCl_4) displayed two three-proton absorptions at δ 2.09 and 2.16 ppm,

characteritic of acetyl groups, and a one-proton absorption at δ 3.28 ppm for the OH proton, which was consistent with the expected α-acetoxy methyl ketone **20**.

In a 25-ml three-neck flask equipped with a Dewar condenser and mechanical stirrer was collected 10 ml of liquid ammonia (freshly distilled from dissolved sodium), and a solution of 0.090 g of **20** in 5 ml of anhydrous dioxane was added. To this solution was added 0.065 g of freshly cut calcium. After stirring for 1 hr, the blue solution was filtered into a flask containing about 0.1 g of solid ammonium chloride and swirled until the blue color disappeared. The solvent was removed *in vacuo*, and the residue was dissolved in ether and water. The ether layer was separated, dried (Na_2SO_4), and concentrated to give 0.0561 g of a light yellow oil which was dissolved in 5 ml of acetone and titrated with Jones reagent[21] until the color of the reagent persisted. One drop of isopropyl alcohol was added, and the reaction mixture was filtered. Removal of the solvent *in vacuo* left a yellow oil (0.050 g) which was chromatographed on 5 g of silica gel. Elution with 40% ether in hexane gave 0.015 g of *dl*-oplopanone (**4**): mp 101.5–102°; nmr ($CDCl_3$) δ 0.69 and 0.89 (pair of d's, J = 6 Hz, 6 H, CH_3CHCH_3), 1.19 (s, 3 H, CH_3), and 2.18 ppm (s, 3 H, Ac); ir (CCl_4) 3583 (OH), 1711 (C=O), 1466, 1385, 1370, and 1359 cm^{-1}.

The synthetic material exhibited nmr, ir, and glc properties identical with those of authentic oplopanone.[6,22]

Registry No.—**1b**, 35049-20-8; **2b** (X = Ac), 35049-21-9; **4**, 35049-27-5; **5**, 35049-26-4; **6**, 35049-23-1; **7**, 35106-10-6; **8**, 41263-23-4; **9**, 35049-22-0; **12**, 35049-25-3; **13**, 41263-25-6; 2α-**14**, 35049-37-7; 2β-**14**, 35049-36-6; **15**, 41263-27-8; **16**, 41263-28-9; **17**, 41263-29-0; **18**, 41263-30-3; **19**, 35049-28-6; **20**, 35049-29-7; 7,7a-dihydro-4-methoxy-7a-methyl-5(6*H*)-indanone, 41263-33-6; 2-methylcyclopentanone, 1120-72-5; 1,4-dimethoxy-2-butanone, 25680-86-8; 2-methyl-5-isopropylcyclopentanone, 6784-18-5; 7α-acetoxy-2α-hydroxy-3-methoxy-7β-methyl-4β-isopropyl-2,4,5,6,7,7aα-hexahydroindene, 41263-36-9; 7α-acetoxy-2β-hydroxy-3-methoxy-7β-methyl-4β-isopropyl-2,4,5,6,7,7aα-hexahydroindene, 41263-37-0; 2α,7α-diacetoxy-3-methoxy-7β-methyl-4α-isopropyl-2,4,5,6,7,7aα-hexahydroindene, 41312-35-0; 2β,7α-diacetoxy-3-methoxy-7β-methyl-4α-isopropyl-2,4,5,6,7,7aα-hexahydroindene, 41263-38-1.

The Synthesis of 7α-Trifluoromethyltestosterone Acetate[1]

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Attempted hydrolysis of 7α-cyanotestosterone acetate *via* an imino ether has given the novel bicyclic ring system of 5α-amino-7α-carboxy-17β-hydroxyandrostan-3-one lactam. Decomposition of the *N*-nitroso derivative of the lactam with hydroxide, ethoxide, and *tert*-butoxide has given 7-carboxyandrostanes with a varying amount of substitution at the 5 position. Reaction of 7α-carboxytestosterone acetate with sulfur tetrafluoride under mild conditions has given 7α-trifluoromethyltestosterone acetate.

The increased anabolic and androgenic activity associated with incorporation of certain 7α substituents into steroidal androgens, particularly the high activity of the 7α-methyl derivatives,[2] has led us to attempt the synthesis of 7α-trifluoromethyltestosterone acetate (**2e**). The trifluoromethyl group is about the same size as a methyl group[3] and would be expected to be compatible with biological activity. The metabolic stability as well as the high electron-withdrawing feature of this group gave us reason to anticipate that some unique change in biological activity might result with its incorporation into androgenic steroids.[4]

The most direct method of introduction of substituents into the 7α position of steroids is the conjugate addition of appropriate nucleophiles to the 3-keto-$\Delta^{4,6}$ system.[2d,5] Since the trifluoromethyl anion, because of its instability and difficulty of preparation,[6] would not be suitable for the direct preparation of the 7α-trifluoromethyl group, we sought to derive the desired compound from a 7α-cyano steroid obtained by conjugate addition of cyanide to the dienone system. The hydrolysis of the nitrile to a carboxyl function followed by its reaction with sulfur tetrafluoride appeared to be a suitable means of obtaining our objective.

Reaction of the dienone **1** with a mixture of excess anhydrous hydrogen cyanide and triethylaluminum[7] in tetrahydrofuran afforded a good yield of 7α-cyanotestosterone acetate (**2a**). This method of preparation of **2a** is vastly superior to that reported[8] in that it gives a much higher yield of cleaner product. No products of diaddition were encountered as is found when excess aqueous cyanide is condensed with dienones.[8] There was also no indication of the presence of the epimeric 7β-cyano compound showing that the reaction was also highly stereospecific.

It was hoped that the cyano group of **2a** could be converted to a carbomethoxy function by hydrolysis of its corresponding imino ether hydrochloride. However, when a solution of **2a** in methanol was treated with hydrogen chloride, a product hydrochloride having only weak absorption in the carbonyl region of its ir spectrum was obtained. Aqueous hydrolysis of this material afforded, in addition to traces of the ester **2b**, a material containing ir absorption at 5.88 and 5.94 μm and no uv absorption characteristic of an α,β-unsaturated ketone. The product, $C_{20}H_{29}NO_3$, is the steroidal

(1) Presented in part at the 163rd National Meeting of the American Chemical Society, Boston, Mass., April 1972, ORGN 125.

(2) (a) J. A. Vida, "Androgens and Anabolic Agents," Academic Press, New York, N. Y., 1970, p 61; (b) A. Segaloff, *Steroids*, **1**, 299 (1963); (c) J. A. Campbell, S. C. Lyster, G. W. Buncan, and J. C. Babcock, *ibid.*, **1**, 317 (1963); (d) G. C. Buzby, Jr., C. R. Walk, and H. Smith, *J. Med. Chem.*, **9**, 782 (1966).

(3) W. A. Sheppard and C. L. Sharts, "Organic Fluorine Chemistry," W. A. Benjamin, Inc., New York, N. Y., 1969, p 433.

(4) The introduction of a trifluoromethyl group into hormonal steroids at the 3, 4, 6, 9, 16, and 20 positions has been reported, respectively: (a) A. F. Pascual and M. Wolff, *J. Med. Chem.*, **14**, 164 (1971); (b) ref 1; (c) W. Godfredsen and S. Vangedal, *Acta Chem. Scand.*, **15**, 1786 (1961); (d) J. H. Fried, U. S. Patent 3,409,610 (1968) [*Chem. Abstr.*, **70**, 58144 (1968)]; (e) A. Bowers and J. Edwards, U. S. Patent 3,151,132 (1964) [*Chem. Abstr.*, **62**, 618 (1964)]; (f) S. Nakaniski, K. Morita, and E. V. Jensen, *J. Amer. Chem. Soc.*, **81**, 5260 (1959).

(5) J. A. Campbell and J. C. Babcock, *J. Amer. Chem. Soc.*, **81**, 4069 (1959); H. Kaneko, K. Nakamura, Y. Yamato and M. Kurokawa, *Chem. Pharm. Bull.*, **17**, 11 (1969).

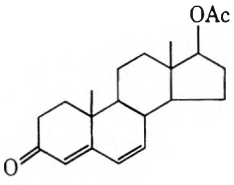
(6) J. Villiéras, *Bull. Soc. Chim. Fr.*, 1520 (1967).

(7) (a) H. Minato and T. Nagasaki, *J. Chem. Soc. C*, 1866 (1966); (b) W. Nagata, M. Yoshioka and M. Murakami, *J. Amer. Chem. Soc.*, **94**, 4654 (1972). The latter reference reports the successful preparation of 7α-cyanotestosterone utilizing Et_2AlCN. Contrary to their results we have found that the combination reagent ($AlEt_3$–HCN) works equally well in introducing a 7α-cyano group into these compounds.

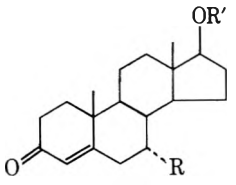
(8) R. G. Christiansen and W. S. Johnson, *Steroids*, **1**, 620 (1963).

lactam **4a** and the intermediate hydrochloride is probably that of the imino ether **3**. While somewhat frustrating in the attainment of our synthetic objective, the ease of formation of this material serves to verify the assignment of the 7α configuration to the original cyano group. A 7β-cyano group being equatorial would be expected to form such a lactam across the face of the steroid only with considerable distortion.

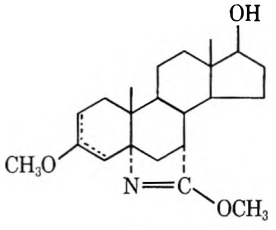
After several unsuccessful attempts at strong base or acid hydrolysis of **4a** the base-catalyzed decomposition of the *N*-nitroso derivative **4b** was attempted. This material was prepared by reaction of **4a** with nitrosyl chloride in acetic anhydride. Because the carbon atom at position 5 is fully substituted, decomposition of **4b** cannot be expected to form a diazo function at that position. Thus, a carbonium-ion-like transition state would be expected to form which could be neutralized by loss of a 4 proton to give the desired Δ^4-3-keto steroid. Treatment of **4b** with ethanolic potassium hydroxide gave an acidic steroid, $C_{22}H_{34}O_5$, containing a saturated carbonyl group. This material is most likely the 5-ethoxy compound **5a**. When the decomposition was



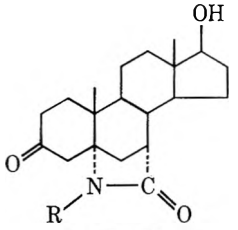
1



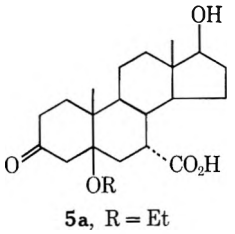
2a, R = CN R′ = Ac
b, R = CO_2CH_3 R′ = H
c, R = CO_2H R′ = H
d, R = CO_2H R′ = Ac
e, R = CF_3 R′ = Ac
f, R = COF R′ = Ac



3



4a, R = H
b, R = NO



5a, R = Et
b, R = H

carried out in the less nucleophilic system of potassium hydroxide in aqueous glyme, two acidic products were obtained in approximately equal amounts. One of these was the desired product **2c** as evidenced by its ir, uv, and mass spectra. The other product, which contained a saturated carbonyl group and had a M^+ of 350 in its mass spectrum, is presumably the 5-hydroxy compound **5b**. Both **5a** and **5b** resisted conversion to **2c** on treatment with aqueous base. The ethoxy group in **5a** and of the hydroxyl group in **5b** are probably β oriented as a result of back-side displacement of the diazonium-like intermediate. The resistance of these groups to elimination also affords an argument for the assignment of β sterochemistry as removal of the 4α proton, necessary for trans elimination, would be difficult both sterically and by charge repulsion with the diaxially oriented 7α-carboxylate group. Finally, when **4b** was treated with the poorly nucleophilic but highly basic potassium *tert*-butoxide in *tert*-butyl alcohol, the desired acid **2c** was the major product isolated.

Although other workers have shown that carboxylates and the intermediate acyl fluorides are more reactive toward sulfur tetrafluoride than unsaturated ketones and esters,[9] we were concerned that the hindered nature of the 7α-carboxyl function in **2d** might render it less reactive and thus upset the desired selectivity of the reaction. It was pleasing to find that reaction of **2d** with an excess of sulfur tetrafluoride–hydrogen fluoride in methylene chloride solution at room temperature for 40 hr resulted in the desired conversion to **2e**, albeit in low yield. If the reaction were interrupted after a shorter period of time the presence of the intermediate acyl fluoride **2f** could be detected by its ir absorption at 5.43 μm.

When tested subcutaneously in a standard assay in rats,[10] the trifluoromethyl testosterone acetate **2e** exhibited ~0.1 the androgenicity and 0.3 the anabolic activity of testosterone acetate.

Experimental Section[11]

7α-Cyanotestosterone Acetate (2a).—A solution of 0.355 g of hydrogen cyanide (freshly distilled) in 4 ml of anhydrous tetrahydrofuran was added under nitrogen with stirring to a cold (0°) solution of 2.00 g of triethylaluminum in 4 ml of tetrahydrofuran. After stirring at 0° for 10 min this solution was added dropwise at 0° to a solution of 880 mg of Δ^6-testosterone acetate in 6 ml of tetrahydrofuran. After 2 hr at 0° the reaction mixture was poured on a mixture of 100 g of ice and 100 ml of 10% sodium hydroxide solution. After brief mixing the product was isolated by chloroform extraction. The organic layer was washed with water until the washings were neutral and then dried and concentrated to a noncrystalline residue. This material was eluted through 100 g of a 6:5 mixture of Stahl silica gel G[12]–diatomaceous earth with 5–10% ether in benzene. Early fractions contained 278 mg of starting dienone **1**. The crystalline product **2a** eluted separately and amounted to 515 mg. Recrystallization from aqueous methanol gave 306 mg of needles: mp 204–207°; $[\alpha]_D$ (dioxane) +73°; uv max (CH_3OH) 237 nm (ε 1.6 × 10^4); nmr τ 4.14 (wide s, 4-CH), 7.96 (s, CH_3CO), 8.78 (s, 19-CH_3), 9.13 (s, 18-CH_3).

Anal. Calcd for $C_{22}H_{29}NO_3$: C, 74.33; H, 8.22; N, 3.94. Found: C, 74.03; H, 8.16; N, 3.79.

5α-Amino-7α-carboxy-17β-hydroxyandrostan-3-one Lactam (4a).—A solution of 500 mg of the cyano compound **2a** in 10 ml of anhydrous methanol was saturated with hydrogen chloride at 0° and was allowed to stand at 0–5° for 24 hr. The solution was then purged with dry nitrogen until the effluent gas indicated

(9) D. G. Martin and F. Kagan, *J. Org. Chem.*, **27**, 3164 (1962).

(10) Hershberger test [L. G. Hershberger, E. G. Shipley, and R. K. Meyer, *Proc. Soc. Exptl. Biol. Med.*, **83**, 175 (1953)] performed in these laboratories by Dr. D. J. Patanelli.

(11) Melting points were determined on a Kofler hot stage and are uncorrected. Ir spectra are in accord with the assigned structures and were taken either as Nujol mulls or as chloroform solutions. Nmr spectra were determined in deuteriochloroform solutions with a Varian Associates Model A-60A spectrometer unless otherwise noted. Rotational data were obtained on 1% solutions. Mass spectra were run on either a CEC Model 21-110 or an LKB Type 9000 spectrometer by the direct probe technique. The purity of isolated material was checked by thin layer chromatography (tlc) on silica gel coated glass plates.

(12) E. Merck, A. G. Darmstad, Germany. Distributed by Brinkmann Instrument Co., Catiague Road, Westbury, N. Y. 11590.

only traces of hydrogen chloride vapors. The remaining solution was concentrated under reduced pressure to a crystalline, hygroscopic solid which had weak, but sharp ir absorption at 5.91, 6.02 and 6.20 μm. This solid, after dissolving in 50 ml of water, gave a precipitate (369 mg) which was removed by filtration and was rinsed with water. After washing with ether material, **4a** of mp 310–315° was obtained: ir 5.89, and 5.94 μm; *m/e* 331 (M^+), 316, 313, 303, 288, 274, 96 (base).

Anal. Calcd for $C_{20}H_{29}NO_3$: C, 72.47; H, 8.82; N, 4.23. Found: C, 72.60; H, 8.66; N, 4.27.

This material (**4a**) was acetylated with 1:1 pyridine–acetic anhydride at room temperature for 16 hr. The product acetate was isolated by quenching with water, filtering, and recrystallization from ethyl acetate. This material had mp 310–314°; $[\alpha]_D$ ($CHCl_3$) −43°; no uv max; nmr τ (T-60) 3.44 (br, NH), 5.40 (m, CHO), 7.96 (s, CH_3CO), 8.76 (s, 19-CH_3), and 9.15 (s, 18-CH_3).

Anal. Calcd for $C_{22}H_{31}NO_4$: C, 70.75; H, 8.37; N, 3.75. Found: C, 70.52; H, 8.47; N, 3.73.

7α-Carbomethoxytestosterone (2b).—When the cyano compound **2a** (1.0 g) was allowed to react in methanolic hydrogen chloride as described above, but with the methanol being only partially removed in the work-up and quenching being carried out with aqueous sodium bicarbonate, the resulting crude product (613 mg) contained two components in roughly equal amounts. The more polar component, lactam **4a**, separated selectively from ethyl acetate. Concentration of the mother liquor gave crystalline material (**2b**) which after recrystallization from methanol amounted to 249 mg and had mp 221–223°; $[\alpha]_D$ ($CHCl_3$) +43.7° (lit.[8] mp 222–224°, $[\alpha]_D$ +46.8° for **2b**).

Anal. Calcd for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.71; H, 8.63.

Preparation of the *N*-Nitroso Derivative 4b.—A solution of 0.8 *N* nitrosyl chloride in acetic anhydride was added dropwise at 0° to a solution of 100 mg of the lactam **4a** in a mixture of 3 ml acetic acid, 0.6 ml acetic anhydride, and 2 ml of pyridine. Addition was stopped when the combined solution gave a persistent positive starch iodide test. The solution stood at 0° for 3 hr. It was poured into water and the product *N*-nitroso compound **4b** was worked up in chloroform. The material was usually used immediately in this form but crystalline **4b** could be obtained after treatment with ether: mp 235–255° with decomposition; ir 5.65 and 5.82 μm.

Decomposition of the *N*-Nitroso Derivative 4b with Ethanolic Potassium Hydroxide. 7α-Carboxy-5β-ethoxy-17β-hydroxyandrostan-3-one (5a).—A solution of the nitroso compound **4b** (prepared from 100 mg of lactam **4a**) in 10% ethanolic potassium hydroxide stood at 0° for 18 hr. The solution was concentrated at room temperature. The residue was treated with water and washed with ethyl acetate. The aqueous layer was acidified with 10% hydrochloric acid and the product was worked up in ethyl acetate to give 103 mg of crude product. Two crystallizations from aqueous methanol gave 54 mg of **5a**: mp 166–168°; ir (mull) 5.79 and 5.89 μm; nmr (DMSO-d_6) 5.98 (q, J = 7 Hz), 8.87 (t, J = 7 Hz), 9.02 (s, 19-CH_3), 9.36 (s, 18-CH_3); CD (dioxane) $[\theta]_{345}$ +594, $[\theta]_{319}$ 0, $[\theta]_{306}$ −171, $[\theta]_{280}$ +125, and $[\theta]_{253}$ 0; *m/e* 378 (M^+), 360, 333, 332, 305, 287 (base), and 231.

Anal. Calcd for $C_{22}H_{34}O_5$: C, 69.81; H, 9.05. Found: C, 69.52; H, 9.19.

Decomposition of the *N*-Nitroso Derivative 4b with Aqueous Potassium Hydroxide.—A solution of the nitroso compound **4b** (from 100 mg of the lactam **4a**) in 5 ml of dimethoxyethane was treated with excess 10% aqueous potassium hydroxide. After 60 min the reaction was diluted with water and extracted with ethyl acetate to remove any nonacidic impurities. The aqueous layer was acidified and the product extracted into ethyl acetate. Work-up afforded a mixture consisting of two components (tlc eluted with 3% formic acid in ether). These components were separated by preparative tlc in the same system to give about an equal quantity of each. The more mobile component had mp 225–230° and *m/e* 332 (M^+) and was identified as 7-carboxytestosterone **2c** described below. The less mobile component assigned the 5β-hydroxy-7-carboxyandrostanone structure (**5b**) had mp 222–224°, *m/e* 350 (M^+) and no α,β-unsaturated carbonyl chromophore in its ir spectrum.

7α-Carboxytestosterone (2c).—To a solution of the *N*-nitroso compound **4b** (from 350 mg of lactam **4a**) in 5 ml of anhydrous *tert*-butyl alcohol was added 5 ml of a 10% solution of potassium *tert*-butylate in *tert*-butyl alcohol under nitrogen. After 10 min the mixture was added to excess dilute hydrochloric acid solution. The crude product was extracted with ethyl acetate. After washing with water the organic layer was extracted with dilute potassium hydroxide. The alkaline layer was washed with ethyl acetate and then was acidified. The product was extracted and worked up in ethyl acetate to give 309 mg of product, **2c**, mp 226–230°, with decomposition. Material recrystallized from ethyl acetate had mp 230° with decomposition; *m/e* 332 (M^+, base), 317, 314, 304, 289, 124.

This material was acetylated by heating a 5% solution in 1:1 pyridine:acetic anhydride for 15 min on a steam bath. The solution was concentrated at room temperature under reduced pressure and the residue was triturated with water. The separated solid was crystallized from ethyl acetate to give **2d**: mp 304° dec; $[\alpha]_D$ (DMSO) +25°; uv max (MeOH) 243 nm (ε 1.55 × 10^4); nmr (DMSO-d_6) 4.43 (br s, 4-CH), 5.48 (m, CHOAc), 8.02 (s, CH_3CO), 8.82 (s, 19-CH_3), 9.20 (s, 18-CH_3).

Anal. Calcd for $C_{22}H_{30}O_5$: C, 70.56; H, 8.08. Found: C, 70.27; H, 7.94.

7α-Trifluoromethyltestosterone Acetate (2e).—A solution of 420 mg of the carboxy steroid **2d** in 8 ml of methylene chloride was treated successively with 18.4 g of sulfur tetrafluoride and 0.3 ml of water to form endogenous hydrogen fluoride. The reaction was kept in a sealed vessel at 20° for 40 hr. After the reaction was vented the resulting solution–suspension was poured onto 5% sodium bicarbonate solution. The product mixture was diluted with methylene chloride. After washing with water and drying ($CaSO_4$) the solution was concentrated. The residue was eluted through a mixture of 80 g of Stahl silica gel H[12] and 80 g of diatomaceous earth with 2% ether in benzene using a fraction collector. The crystalline product (143 mg) was separated twice from heptane to give 60 mg of **2e**: mp 153.5–155°; $[\alpha]_D$ ($CHCl_3$) +13°; uv max (MeOH) 238 nm (ε 1.6 × 10^4); nmr (HR-100) τ 4.26 (br s, 4-CH), 5.40 (m, CHOAc), 7.99 (s, CH_3CO), 8.77 (s, 19-CH_3), 9.17 (s, 18-CH_3); *m/e* 398 (M^+, base), 356, 296 and 124.

Anal. Calcd for $C_{22}H_{29}F_3O_3$: C, 66.33; H, 7.28; F, 14.32. Found: C, 65.95; H, 7.29; F, 14.52.

Registry No.—**1**, 2352-19-4; **2a**, 41498-96-8; **2b**, 3461-03-8; **2c**, 41498-98-0; **2d**, 41498-99-1; **2e**, 41499-00-7; **4a**, 41499-01-8; **4a** acetate, 41499-02-9; **4b**, 41499-03-0; **5a**, 41499-04-1; **5b**, 41499-05-2; hydrogen cyanide, 74-90-8.

Synthesis of Some Novel Trifluoromethanesulfonates and Their Reactions with Alcohols[1]

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Allyl triflate, propargyl triflate, pentyl triflate, 2-(2-fluoro-2,2-dinitroethoxy)ethyl triflate, 2-fluoro-2,2-dinitroethyl triflate, and 1,2,3-propanetritriflate were prepared from the alcohols using triflic anhydride and pyridine. 1,4-Butaneditriflate was formed from tetrahydrofuran and triflic anhydride. In the presence of potassium carbonate, pentyl triflate, allyl triflate, propargyl triflate, 1,4-butaneditriflate, and 2-(2-fluoro-2-2-dinitroethyoxy)ethyl triflate reacted in chlorinated hydrocarbon solvents at ambient temperature with 2-fluoro-2,2-dinitroethanol to give the corresponding ethers, without skeletal rearrangement. 1,2,3-Propanetritriflate underwent monosubstitution and elimination to yield 3-(2-fluoro-2,2-dinitroethoxy)-2-propenyl triflate. Pentyl triflate and 2,2,2-trifluoroethanol gave pentyl 2,2,2-trifluoroethyl ether. When sodium sulfate was used instead of potassium carbonate to scavenge liberated triflic acid, pentyl triflate and 2,2-dinitropropanol gave a mixture of the 1-, 2-, and 3-pentyl ethers. Under these conditions, 2-fluoro-2,2-dinitroethanol, 2,2-dinitropropanol, and 2,2,2-trinitroethanol, as well as pentanol, reacted with isopropyl triflate to give the corresponding isopropyl ethers. Allyl triflate was allowed to react similarly with 2,2-dinitropropanol, 2,2,2-trinitroethanol, and 2,2-dinitro-1,3-propanediol to give the allyl ethers.

The high reactivity of the trifluoromethanesulfonate (triflate) group in solvolysis and displacement reactions has been the subject of a number of recent investigations. Thus, methyl and ethyl triflates were reported to undergo solvolysis more than 10^4 times as fast as the corresponding tosylates.[2,3] The use of the triflate leaving group in otherwise unreactive polycyclic systems has extended the range of solvolysis reactions,[4-6] and vinyl triflates have been used extensively in studies of vinyl cations.[7-10] No attempts have been reported, however, to prepare a triflate ester more reactive than the ethyl derivative. Such extremely reactive alkylating agents would be expected to extend the range of weakly nucleophilic reagents that can be alkylated.

The triflates prepared in this work are shown in Table I. Most of these compounds were synthesized from the corresponding alcohols by the commonly used[4] triflic anhydride–pyridine method. Methylene chloride and carbon tetrachloride were used as solvents. Methyl triflate, because of its low boiling point, was prepared conveniently, from dimethyl sulfate by a procedure previously used for the corresponding fluorosulfonate.[11] The reaction of tetrahydrofuran with triflic anhydride gave 1,4-butaneditriflate, a reaction similar to ring openings with mixed sulfonic–carboxylic anhydrides.[12] This ditriflate and 1,2,3-propanetriflate, prepared from glycerol, are the first reported polyfunctional examples.

Allyl triflate, propargyl triflate, and isopropyl triflate were not sufficiently stable for elemental analysis and were characterized by spectral data, described in the Experimental Section. Even pentyl triflate gave only partially acceptable analytical data, and these compounds were generally used as freshly prepared solutions for alkylations. Allyl triflate in carbon tetrachloride solution was completely decomposed in 3 days at ambient temperature. Electron-withdrawing substituents, such as nitro groups or additional triflate groups in the molecule, improved stability; neat 2-fluoro-2,2-dinitroethyl triflate was unchanged after several months at room temperature.

The reactivity of triflates with alcohols of low nucleophilicity was examined using 2,2,2-trinitroethanol, 2,2-dinitro-1,3-propanediol, 2,2-dinitropropanol, and 2-fluoro-2,2-dinitroethanol. With the exception of low yields of methyl ethers of 2,2-dinitropropanol and 2,2-dinitropropanediol prepared by heating the alcohols with dimethyl sulfate,[13] these alcohols have not been previously alkylated under neutral or acidic conditions. In the presence of base, nitronate salts are formed by loss of formaldehyde.[14] With aqueous base, 2-fluoro-2,2-dinitroethanol is the only one of the above alcohols with a sufficient equilibrium concentration of alkoxide ion to react with alkyl sulfates, allyl halides, or epoxides.[13]

Reactions of nitro alcohols with triflates were generally conducted in chlorinated hydrocarbon solvents. To avoid side reactions due to liberated triflic acid, anhydrous potassium carbonate or sodium sulfate was added as a heterogeneous acid scavenger. 2,2,2-Trinitroethanol, 2,2-dinitropropanol, and 2,2-dinitropropanediol could not be alkylated in the presence of potassium carbonate because deformylation took place.

In the presence of potassium carbonate, 2-fluoro-2,2-dinitroethanol reacted at ambient temperature with pentyl triflate, allyl triflate, propargyl triflate, 1,4-butaneditriflate, and 2-(2-fluoro-2,2-dinitroethoxy)-ethyl triflate to give the corresponding 2-fluoro-2,2-dinitroethyl ethers in yields of 43 to 75%.

$$ROSO_2CF_3 + FC(NO_2)_2CH_2OH \xrightarrow{K_2CO_3} ROCH_2CF(NO_2)_2$$

R = C_5H_{11}–, $CH_2{=}CHCH_2$–, $HC{\equiv}CCH_2$–, $-CH_2CH_2CH_2CH_2$–, $FC(NO_2)_2CH_2OCH_2CH_2$–

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TABLE I
PREPARATION OF TRIFLATES

Starting material	Registry no.	Product	Registry no.	Yield, %
n-$C_5H_{11}OH$	71-41-0	n-$C_5H_{11}OSO_2CF_3$	41029-43-0	85
$(CH_3)_2CHOH$	67-63-0	$(CH_3)_2CHOSO_2CF_3$	41029-44-1	82
$CH_2{=}CHCH_2OH$	107-18-6	$CH_2{=}CHCH_2OSO_2CF_3$	41029-45-2	75
$HC{\equiv}CCH_2OH$	107-19-7	$HC{\equiv}CCH_2OSO_2CF_3$	41029-46-3	80
$FC(NO_2)_2CH_2OH$	17003-75-7	$FC(NO_2)_2CH_2OSO_2CF_3$	41828-25-5	42
$FC(NO_2)_2CH_2OCH_2CH_2OH$	25172-17-2	$FC(NO_2)_2CH_2OCH_2CH_2OSO_2CF_3$	41029-48-5	87
$CH_2CH_2CH_2CH_2O$	109-99-9	$CF_3SO_2O(CH_2)_4OSO_2CF_3$	18934-34-4	73
$CH_2(OH)CH(OH)CH_2OH$	56-81-5	$CH_2(OSO_2CF_3)CH(OSO_2CF_3)CH_2OSO_2CF_3$	41029-50-9	98
$(CH_3)_2SO_4$	77-78-1	$CH_3OSO_2CF_3$	333-27-7	81

Application of the same reaction conditions to 2,2,2-trifluoroethanol and pentyl triflate gave an 86% yield of pentyl 2,2,2-trifluoroethyl ether.

$$CH_3(CH_2)_4OSO_2CF_3 + CF_3CH_2OH \xrightarrow{K_2CO_3} CH_3(CH_2)_4OCH_2CF_3$$

The reaction of 2-fluoro-2,2-dinitroethanol with 1,2,3-propanetritriflate in the presence of potassium carbonate gave 3-(2-fluoro-2,2-dinitroethoxy)-2-propenyl triflate. No other products were observed when the reaction was not carried to completion. 1,2,3-Propanetritriflate did not react with potassium carbonate in the absence of 2-fluoro-2,2-dinitroethanol or with 2-fluoro-2,2-dinitroethanol in the presence of sodium sulfate. The product could be formed by displacement of a terminal triflate group followed by rapid elimination of triflic acid, or possibly *via* the initial elimination of triflic acid by the base, fluorodinitroethoxide ion.

$$CF_3SO_3CH_2CH(CF_3SO_3)CH_2(CF_3SO_3) \xrightarrow[K_2CO_3,\ CHCl_3]{FC(NO_2)_2CH_2OH} [FC(NO_2)_2CH_2OCH_2CH(CF_3SO_3)CH_2(CF_3SO_3)] \xrightarrow{-CF_3SO_3H}$$

$$FC(NO_2)_2CH_2OCH_2{-}\underset{\displaystyle OSO_2CF_3}{\underset{|}{CH}}{=}CH_2$$

The reaction of 2-fluoro-2,2-dinitroethyl triflate with 2-fluoro-2,2-dinitroethanol in the presence of potassium carbonate was also attempted. No fluorodinitroethyl ether was formed and the triflate was decomposed. This reaction appears similar to that of 2-fluoro-2,2-dinitroethyl tosylate with alkoxides, which was reported to result in elimination of nitrous acid.[15]

Potassium carbonate functioned in the above reactions not only as a scavenger for triflic acid but also as a heterogeneous base catalyst. In order to study alkylations of neutral alcohols, rather than of the corresponding alkoxide ions, an essentially nonbasic scavenger is required. Sodium sulfate was used for this purpose because sulfuric acid is a weaker acid than triflic acid, and the equilibrium mixture should consist of sodium triflate and sodium bisulfate. Also, the moderately soluble triflic acid should be adsorbed physically.

The use of sodium sulfate instead of potassium carbonate, however, required the use of extended reactions periods or higher temperatures. Thus, under the same experimental conditions that produced a 75% yield of 2-fluoro-2,2-dinitroethyl pentyl ether from 2-fluoro-2,2-dinitroethanol and pentyl triflate, no reaction was observed when sodium sulfate was substituted for potassium carbonate. Sodium sulfate, however, allowed extension of the reaction to base-sensitive alcohols, such as 2,2-dinitropropanol and 2,2,2-trinitroethanol.

Pentyl triflate and 2,2-dinitropropanol reacted in refluxing 1,2-dichloroethane, with sodium sulfate as the acid scavenger, to give a 38% yield of 2,2-dinitropropyl pentyl ethers. This product consisted of 33.5% 1-pentyl ether, 58.8% 2-pentyl ether, and 7.6% 3-pentyl ether, and the products were shown to be stable to the reaction conditions. The potassium carbonate catalyzed reactions of 2-fluoro-2,2-dinitroethanol and pentyl triflate, on the other hand, gave no detectable secondary ethers. The reaction in the presence of sodium sulfate thus has the characteristics of a carbonium ion reaction, even with a relatively nonpolar solvent.

$$CH_3CH_2CH_2CH_2CH_2OSO_2CF_3 \xrightarrow{-CF_3SO_3^-} [CH_3CH_2CH_2CH_2CH_2^+] \xrightarrow{CH_3C(NO_2)_2CH_2OH} CH_3CH_2CH_2CH_2CH_2OCH_2C(NO_2)_2CH_3$$

$$[CH_3CH_2CH_2\overset{+}{C}HCH_3] \longrightarrow CH_3CH_2CH_2\underset{\displaystyle OCH_2C(NO_2)_2CH_3}{\underset{|}{CH}}CH_3$$

$$[CH_3CH_2\overset{+}{C}HCH_2CH_3] \longrightarrow CH_3CH_2\underset{\displaystyle OCH_2C(NO_2)_2CH_3}{\underset{|}{CH}}CH_2CH_3$$

At ambient temperature isopropyl triflate in the presence of sodium sulfate reacted with 2-fluoro-2,2-dinitroethanol, 2,2-dinitropropanol, and 2,2,2-trinitroethanol to give the corresponding isopropyl ethers in yields of 75, 67, and 37%, respectively. Methylene chloride or chloroform was used as solvent, and the reactions were allowed to proceed for 12 hr.

$$(CH_3)_2CHOSO_2CF_3 + XC(NO_2)_2CH_2OH \longrightarrow (CH_3)_2CHOCH_2C(NO_2)_2X$$

X = F, CH_3, NO_2

Allyl triflate was reacted similarly with 2,2-dinitropropanol, 2,2,2-trinitroethanol, and 2,2-dinitro-1,3-propanediol to give allyl 2,2-dinitropropyl ether, allyl 2,2,2-trinitroethyl ether, and 2,2-dinitro-1,3-di(allyloxy)propane in yields of 53, 33, and 28%, respectively. In the latter case, no attempt was made to isolate the monoallyl ether which was undoubtedly also present.

$$CH_2{=}CHCH_2OSO_2CF_3 + CH_3C(NO_2)_2CH_2OH \longrightarrow CH_2{=}CHCH_2OCH_2C(NO_2)_2CH_3$$

$$CH_2{=}CHCH_2OSO_2CF_3 + (NO_2)_3CCH_2OH \longrightarrow CH_2{=}CHCH_2OCH_2C(NO_2)_3$$

$$CH_2{=}CHCH_2OSO_2CF_3 + (NO_2)_2C(CH_2OH)_2 \longrightarrow (CH_2{=}CHCH_2OCH_2)_2C(NO_2)_2$$

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The fact that isopropyl triflate and allyl triflate react at ambient temperature with such a highly electronegatively substituted alcohol as 2,2,2-trinitroethanol is noteworthy. By contrast, 2,2,2-trinitroethanol and methyl triflate gave no methyl 2,2,2-trinitroethyl ether when the reagents were heated in refluxing 1,2-dichloroethane for 45 hr.

The above examples illustrate the use of these alkylating agents where less potent reagents do not react. These reagents should also be useful for alkylating normally reactive hydroxyl groups with other substituents that cannot tolerate acid or base, or that are thermally unstable. The reactivity of isopropyl triflate with normal alcohols was demonstrated using pentanol. A diluted methylene chloride solution of the reactants, stirred for 1 hr with sodium sulfate at ambient temperature, gave a 52% yield of isopropyl pentyl ether.

Thus, alkyl triflates that are too unstable for normal isolation and analysis can be prepared conveniently, diluted in unreactive solvents, and utilized as powerful alkylating agents under neutral conditions.

Experimental Section

General.—Explosive properties of polynitro ethers described below have not been investigated. Adequate safety shielding should be used in all operations. 2-Fluoro-2,2-dinitroethanol[16] is a severe skin irritant and contact should be avoided.

Proton and fluorine nmr spectra were recorded on a Varian T-60 spectrometer using tetramethylsilane and trichlorofluoromethane as the respective internal standards. Gas chromatographic separations were carried out on a Varian 920 instrument using a 12 ft × 3/8 in. aluminum column packed with 12% QF-1 on 60/80 mesh Chromosorb W. Infrared spectra were obtained with a Perkin-Elmer 700 instrument.

Trifluoromethanesulfonic Anhydride.—The published procedure[17] was used with the exception that the amount of phosphorus pentoxide was reduced by 50%. The yield was 73%, bp 82–84°.

Methyl Triflate.—Trifluoromethanesulfonic acid (50 g, 0.030 mol) was added with stirring to 45.5 g (0.36 mol) of dimethyl sulfate. Distillation through a short Vigreux column gave 42.2 g (81%) of methyl triflate, bp 98–99° (reported[18] bp 97°), nmr (CCl_4) δ 4.22 ppm (s).

1,4-Butaneditriflate.—A solution of 2.16 g (0.030 mol) of tetrahydrofuran in 100 ml of methylene chloride was added dropwise to a solution of 9.90 g (0.030 mol) of trifluoromethanesulfonic anhydride in 100 ml of methylene chloride at −78°. The reaction mixture was allowed to warm to room temperature and was washed with water and dried over sodium sulfate. Evaporation of solvent and recrystallization of the residue from methylene chloride gave 7.75 g (73%) of colorless crystals: mp 35–37°; proton nmr ($CDCl_3$) δ 4.63 (m, 4 H, CH_2O), and 2.03 ppm (m, 4 H, CH_2CH_2O); fluorine nmr ϕ 75.1 ppm (s); ir (CCl_4) 1403, 1200, 1138, and 920 cm^{-1} (OSO_2CF_3).

Anal. Calcd for $C_6H_8F_6O_6S_2$: C, 20.34; H, 2.27. Found: C, 20.30; H, 1.90.

Pentyl Triflate.—A solution of 1.76 g (0.020 mol) of pentanol and 1.58 g (0.020 mol) of pyridine in 5 ml of methylene chloride was added, dropwise with stirring, over a 45-min period, to a solution of 6.60 g (0.023 mol) of triflic anhydride in 20 ml of methylene chloride at 0°. After 15 min, the solution was washed with water, dried over sodium sulfate, and distilled to give 3.74 g (85%) of pentyl triflate: bp 53–54° (1 mm); proton nmr ($CDCl_3$) δ 4.55 (t, 2 H, CH_2O), 1.85 (m, 2 H, CH_2CH_2O), 1.45 (m, 4 H, CH_2), and 1.27 ppm (t, 3 H, CH_3): fluorine nmr ϕ 75.3 ppm (s, OSO_2CF_3); ir (CCl_4) 1425, 1200, 1140, and 930 cm^{-1} (OSO_2CF_3).

Anal. Calcd for $C_6H_{11}F_3O_3S$: C, 32.72; H, 5.03; F, 25.90. Found: C, 33.35; H, 4.88; F, 25.44.

Isopropyl Triflate.—A solution of 2.7 g (0.045 mol) of isopropyl alcohol and 3.6 g (0.045 mol) of pyridine in 15 ml of carbon tetrachloride was added dropwise with stirring at 0° to 12.7 g (0.045 mol) of trifluoromethanesulfonic anhydride in 25 ml of carbon tetrachloride. Nmr analysis of the colorless solution indicated a 90 ± 5% yield of isopropyl triflate. In another experiment using methylene chloride as solvent, the organic layer was washed with water, dried, and concentrated. The residue could be vacuum transferred at ambient temperature (5 mm) to give a colorless liquid which darkened rapidly at room temperature. The compound decomposed suddenly on attempted vacuum distillation at 50°: proton nmr (CCl_4) δ 5.16 (septet, J = 7 Hz, 1 H, CH) and 1.50 ppm (d, 6 H, J = 7 Hz, CH_3); fluorine nmr ϕ 76.7 (s).

Allyl Triflate.—A solution of 1.31 g (0.0234 mol) of allyl alcohol and 1.84 g (0.0234 mol) of pyridine in 5 ml of carbon tetrachloride was added dropwise (15 min) with stirring at 0° to a solution of 7.75 g (0.0234 mol) of trifluoromethanesulfonic anhydride in 25 ml of carbon tetrachloride. The insoluble pyridine salt was removed by filtration through sodium sulfate. The resulting colorless solution was analyzed by ir and nmr and used directly for alkylation reactions. Quantitative nmr analysis (chlorobenzene as internal standard) of aliquots indicated yields of 75 ± 5%. Impurities could not be detected by nmr or ir analysis: proton nmr (CCl_4) δ 6.03 (m, 1 H, —CH=), 5.43 (m, 2 H, $=CH_2$), and 4.92 ppm (m, 2 H, CH_2O): fluorine nmr ϕ 74.5 ppm (s); ir (CCl_4) 1625 (C=C), 1405, 1240, 1190, and 1140 cm^{-1} (OSO_2CF_3).

Propargyl Triflate.—A solution of 1.33 g (0.0241 mol) of propargyl alcohol and 1.88 g (0.024 mol) of pyridine in 5 ml of carbon tetrachloride was added dropwise at 0° with stirring to 7.87 g (0.028 mol) of trifluoromethanesulfonic anhydride in 25 ml of carbon tetrachloride. The solution was filtered through sodium sulfate and used directly for alkylation reactions. The yield (nmr) was 80 ± 5%; proton nmr (CCl_4) δ 5.05 (d, 2 H, J = 2 Hz, $C{\equiv}CCH_2O$), and 2.77 ppm (t, 1 H, J = 2 Hz, $C{\equiv}CH$); fluorine nmr ϕ 74.0 ppm (s, OSO_2CF_3); ir (CCl_4) 3290, 2145 ($C{\equiv}CH$), 1410, 1210, 1140 cm^{-1} (OSO_2CF_3).

2-(2-Fluoro-2,2-dinitroethoxy)ethyl Triflate.—A solution of 20.6 g (0.104 mol) of 2-fluoro-2,2-dinitroethyl 2-hydroxyethyl ether[13] and 8.22 g (0.108 mol) of pyridine in 50 ml of methylene chloride was added dropwise over a period of 45 min with stirring to a solution of 29.3 g (0.104 mol) of trifluoromethanesulfonic anhydride in 100 ml of methylene chloride at 0°. After 15 min the mixture was washed with water and dried over sodium sulfate. Evaporation of solvent left a pale yellow oil, which was filtered through silica gel to give 29.1 g (87%) of the triflate: proton nmr ($CDCl_3$) δ 4.70 (d, 2 H, J_{HF} = 17 Hz, $FC{-}CH_2O$) 4.68 (m, 2 H, OCH_2CH_2OTr), and 4.05 ppm (m, 2 H, OCH_2CH_2OTr); fluorine nmr ϕ 110.9 (t, 1 F, J_{HF} = 17 Hz, $F{-}CCH_2{-}$) and 75.4 ppm (s, 3 F, CF_3SO_3O); ir (CCl_4) 1585 (NO_2), 1310, 1210, 1140 cm^{-1} (OSO_2CF_3).

Anal. Calcd for $C_5H_6F_4N_2O_8S$: C, 18.18; H, 1.83; N, 8.48. Found: C, 18.65; H, 1.82; N, 8.16.

1,2,3-Propanetritriflate.—A mixture of 6.14 g (0.067 mol) of glycerol and 16.9 g (0.214 mol) of pyridine was added to a solution of 60.0 g (0.213 mol) of trifluoromethanesulfonic anhydride in 150 ml of methylene chloride over a 30-min period at 0°. Filtration through silica gel and removal of solvent gave 32 g (98% yield) of analytically pure 1,2,3-propanetritriflate: mp 22–23° (from carbon tetrachloride); proton nmr ($CDCl_3$) δ 5.17 (m, 1 H, CH) and 4.67 ppm (d, J = 2.7 Hz, 4 H, CH_2O); fluorine nmr ϕ 74.67 (s, 6 F, $CH_2OSO_2CF_3$) and 74.87 ppm (s, 3 F, $CHOSO_2CF_3$).

Anal. Calcd for $C_6H_5S_3F_9O_9$: C, 14.76; H, 1.03; F, 35.04. Found: C, 14.60; H, 0.86; F, 35.10.

2-Fluoro-2,2-dinitroethyl Triflate.—By the above procedure 15.4 g (0.10 mol) of 2-fluoro-2,2-dinitroethanol and 7.9 g (0.10 mol) of pyridine were treated with 28.2 g (0.10 mol) of trifluoromethanesulfonic anhydride. The crude product was filtered through silica gel and then was distilled to give 12.0 g (42%) of the triflate: bp 36–38° (0.5 mm); proton nmr (CCl_4) δ 5.38 ppm (d, J_{HF} = 14 Hz); fluorine nmr ϕ 81.0 (s, 3 F, OSO_2CF_3) and 111.0 ppm (t, 1 F, J_{HF} = 14 Hz, $F{-}CCH_2$); ir (CCl_4) 1590, 1425, 1300, 1220, 1135, and 1000 cm^{-1} (OSO_2CF_3).

Anal. Calcd for $C_3H_2F_4N_2O_7S$: C, 12.56; H, 0.71. Found: C, 12.43; H, 0.61.

1,2-Bis(2-fluoro-2,2-dinitroethoxy)ethane.—To a stirred solution of 16.5 g (0.050 mol) of 2(2-fluoro-2,2-dinitroethoxy)ethyl triflate and 9.24 g (0.06 mol) of 2-fluoro-2,2-dinitroethanol in 100

(16) V. Grakauskas and K. Baum, *J. Org. Chem.*, **33**, 3080 (1968).

(17) J. Burdon, I. Farazmand, M. Stacey, and J. C. Tatlow, *J. Chem. Soc.*, 2574 (1957).

(18) T. Gramstad and R. N. Haszeldine, *J. Chem. Soc.*, 173 (1956).

ml of methylene chloride was added 34.5 g (0.25 mol) of anhydrous potassium carbonate. Stirring was continued for 16 hr and then the reaction mixture was added to ice–water and the organic phase was washed with 5% aqueous sodium hydroxide solution and dried over sodium sulfate. Removal of solvent gave 13.03 g (78%) of 1,2-bis(2-fluoro-2,2-dinitroethoxy)ethane, bp 117–119° (0.01 mm), which solidified on standing at 0°: mp 28–29°; d^{25} 1.539; nmr ($CDCl_3$) δ 4.57 (d, 4 H, J_{HF} = 16 Hz, FC–CH_2O) and 3.80 ppm (s, 4 H, OCH_2CH_2O); ir ($CDCl_3$) 1590, 1310, and 1120 cm^{-1} (C–O–C).

Anal. Calcd for $C_6H_8F_2N_4O_{10}$: C, 21.56; H, 2.41; N, 16.76. Found: C, 21.19; H, 2.20; N, 16.46.

2-Fluoro-2,2-dinitroethyl Pentyl Ether.—The reaction of 2.20 g (0.010 mol) of pentyl triflate and 1.54 g (0.010 mol) of 2-fluoro-2,2-dinitroethanol by the above procedure gave 1.64 g (73%) 2-fluoro-2,2-dinitroethyl pentyl ether: bp 46–48° (0.04 mm); nmr (CCl_4) δ 4.43 (d, 2 H, J_{HF} = 17 Hz, FC–CH_2O), 3.90 (t, 2 H, J = 6 Hz, OCH_2), 1.27 (broad m, 6 H, CH_2), and 0.87 ppm (m, 3 H, CH_3); ir (CCl_4) 1590, 1305 (NO_2), and 1120 cm^{-1} (C–O–C).

Anal. Calcd for $C_7H_{13}FN_2O_5$: C, 37.49; H, 5.84. Found: C, 37.78; H, 5.46.

Allyl 2-Fluoro-2,2-dinitroethyl Ether.—By the same procedure a solution of 0.03 mol of allyl triflate in carbon tetrachloride (described above) was reacted with 5.39 g (0.035 mol) of 2-fluoro-2,2-dinitroethanol and 13.8 g (0.10 mol) of potassium carbonate in 50 ml of methylene chloride for 3 hr to give 2.75 g (47%) of allyl 2-fluoro-2,2-dinitroethyl ether, bp 34–35° (0.2 mm), which had ir and nmr spectra identical with those of an authentic sample.[13]

2-Fluoro-2,2-dinitroethyl Propargyl Ether.—By the above procedure, 0.0238 mol of propargyl triflate solution, 4.59 g (0.0298 mol) of 2-fluoro-2,2-dinitroethanol and 10 g (0.07 mol) of potassium carbonate in 30 ml of methylene chloride (12 hr) gave 1.93 g (43%) of 2-fluoro-2,2-dinitroethyl propargyl ether, bp 32–34° (0.1 mm), which had ir and nmr spectra identical with those of an authentic sample.[19]

1,4-Bis(2-fluoro-2,2-dinitroethoxy)butane.—A mixture of 3.54 g (0.10 mol) 1,4-butaneditriflate, 6.16 g (0.040 mol) of 2-fluoro-2,2-dinitroethanol, and 23 g (0.167 mol) of potassium carbonate was stirred 18 hr at ambient temperature. The mixture was diluted with water, and the product was extracted with methylene chloride, dried over sodium sulfate, stripped of solvent, and purified by column chromatography on silica gel to give 2.71 g (75%) of 1,4-bis(2-fluoro-2,2-dinitroethoxy)butane, a colorless oil: proton nmr ($CDCl_3$) δ 4.52 (d, 4 H, J_{HF} = 18 Hz, FC–CH_2O), 3.63 (m, 4 H, OCH_2C), and 1.63 ppm (m, 4 H, CH_2CO); fluorine nmr φ 112.6 (t, J_{HF} = 18 Hz); ir (CCl_4) 1590, 1315 (NO_2).

Anal. Calcd for $C_8H_{12}F_2N_4O_{10}$: C, 26.52; H, 3.34; N, 15.46. Found: C, 26.82; H, 3.24; N, 14.93.

Reaction of 2-Fluoro-2,2-dinitroethanol and 1,2,3-Propanetritriflate.—To a stirred solution of 5.0 g (0.0124 mol) of 1,2,3-propanetritriflate and 5.3 g (0.0344 mol) of 2-fluoro-2,2-dinitroethanol in 15 ml of chloroform was added to 5.5 g (0.040 mol) of potassium carbonate, and the mixture was stirred for 16 hr. The mixture was added to 100 ml of ice–water and the product was extracted with 50 ml of methylene chloride and dried over sodium sulfate. Distillation gave 2.6 g (61%) of 3-(2-fluoro-2,2-dinitroethoxy)-2-propenyl triflate, bp 83° (0.2 mm); proton nmr ($CDCl_3$) δ 5.31 (AB quartet, 2 H, CH_2=), 4.77 (d, 2 H, J_{HF} = 18 Hz, FC–CH_2), and 4.25 ppm (s, 2 H, CH_2O); fluorine nmr φ 111.2 (t, 1 F, FC) and 74.8 ppm (s, 3 F, OSO_2CF_3).

Anal. Calcd for $C_6H_6F_4N_2SO_8$: C, 21.06; H, 1.76. Found: C, 21.35; H, 1.88.

Pentyl 2,2,2-Trifluoroethyl Ether.—A mixture of 2.20 g (0.010 mol) of pentyl triflate, 1.10 g (0.010 mol) of 2,2,2-trifluoroethanol, 4.14 g (0.030 mol) of potassium carbonate, and 15 ml of methylene chloride was stirred for 48 hr. The mixture was washed with water, dried over sodium sulfate, and stripped of solvent. Vacuum transfer of the residue gave 1.46 g (86%) of pentyl 2,2,2-trifluoroethyl ether. An analytical sample was isolated by glpc: nmr (CCl_4) δ 3.73 (q, 2 H, J_{HF} = 8 Hz, OCH_2CF_3), 3.57 (t, 3 H, J = 6 Hz, O–CH_2CH_2), 1.92–1.08 (m, 6 H, CH_2), and 0.95 ppm (m, 3 H, CH_3).

Anal. Calcd for $C_7H_{13}F_3O$: C, 49.40; H, 7.70. Found: C, 49.42; H, 7.73.

(19) V. Grakauskas, *J. Org. Chem.*, in press.

Allyl 2,2,2-Trinitroethyl Ether.—A solution of (0.030 mol) of allyl triflate in carbon tetrachloride was added to 5.5 g (0.030 mol) of 2,2,2-trinitroethanol, 100 ml of methylene chloride, and 5 g of sodium sulfate, and the mixture was stirred for 48 hr. The mixture was washed with water and dried over sodium sulfate and the solvent was removed under vacuum. Column chromatography of the dark residue on silica gel gave 1.72 g (33%) of allyl 2,2,2-trinitroethyl ether, a pale yellow oil: nmr ($CDCl_3$) δ 5.83 (m, 1 H, —CH=C<), 5.30 (m, 2 H, $=CH_2$), 4.67 (s, 2 H, $CH_2C(NO_2)_3$), and 4.20 ppm (m, 2 H, OCH_2C=C); ir (CCl_4) 1630 (C=C); 1590, 1300 (NO_2), and 1120 cm^{-1} (–O–).

Anal. Calcd for $C_5H_7N_3O_7$: C, 27.15; H, 3.19; N, 19.00. Found: C, 27.26; H, 3.25; N, 18.88.

Allyl 2,2-Dinitropropyl Ether.—Substitution of 2,2-dinitropropanol for 2,2,2-trinitroethanol in the preceding experiment gave after chromatography, 2.36 g (53%) of allyl 2,2-dinitropropyl ether, a colorless oil: nmr (CCl_4) δ 5.63 (m, 1 H, CH=C), 5.23 (m, 2 H, $=CH_2$), 4.20 ppm (s, 2 H, $(NO_2)_2CCH_2O$), 4.03 (m, 2 H, OCH_2C=), and 2.17 ppm (s, 3 H, $CH_3C(NO_2)_2$); ir (CCl_4) 1630 (C=C), 1580, 1320 (NO_2), and 1100 cm^{-1} (–O–C).

Anal. Calcd for $C_6H_{10}N_2O_5$: C, 37.89; H, 5.30; N, 14.73. Found: C, 37.58; H, 5.27; N, 14.98.

2,2-Dinitro-1,3-di(allyloxy)propane.—By the above procedure, 1.83 g (0.011 mol) of 2,2-dinitro-1,3-propanediol was treated with (0.022 mol) of allyl triflate for 48 hr. The crude solution was washed with 5% sodium hydroxide to remove starting material and monoalkylation product. Chromatography on silica gel gave 0.755 g (28%) of the diallyl ether: nmr (CCl_4) δ 5.77 (m, 2 H, CH=C), 5.43 (m, 4 H, $=CH_2$), 4.27 (s, 4 H, $OCH_2C(NO_2)_2$), and 4.03 ppm (m, 4 H, OCH_2C); ir (CCl_4) 1625 (C=C), 1582, 1320 (NO_2), and 1095 cm^{-1} (C–O–C).

Anal. Calcd for $C_9H_{14}N_2O_6$: C, 43.89; H, 5.73; N, 11.38. Found: C, 43.34; H, 5.69; N, 11.29.

Reaction of 2,2-Dinitropropanol with Pentyl Triflate.—A mixture of 4.0 g (0.0182 mol) of pentyl triflate and 4.1 g (0.0273 mol) of 2,2-dinitropropanol, 5 g of sodium sulfate, and 50 ml of 1,2-dichloroethane was refluxed for 6 hr. The mixture was washed with water and with 5% sodium hydroxide, dried over sodium sulfate, stripped of solvent, and chromatographed on silica gel to give 1.52 g (38%) of a mixture of three 2,2-dinitropropyl pentyl ethers (glpc area ratio 0.13:1:0.57 in the order of retention times).

The major component was 2,2-dinitropropyl 2-pentyl ether: nmr (CCl_4) δ 5.87 (s, 2 H, $C(NO_2)_2CH_2O$), 3.50 (m, 1 H, O–CH–), 2.17 (s, 3 H), $CH_3C(NO_2)_2$), 1.40 (broad m, 4 H, CH_2), 1.15 (d, 3 H, J = 6 Hz, CH_3CHO), and 0.90 ppm (m, 3 H, CH_3); ir (CCl_4) 1560 and 1320 cm^{-1} (NO_2).

Anal. Calcd for $C_8H_{16}N_2O_5$: C, 43.62; H, 7.32. Found: C, 43.21; H, 7.20.

The third component was identified as 2,2-dinitropropyl 1-pentyl ether: nmr (CCl_4) δ 4.17 (s, 2 H, $C(NO_2)_2CH_2$), 3.50 (t, 2 H, J = 6 Hz, OCH_2), 2.15 (s, 3 H, $CH_3C(NO_2)_2$), 1.37 (broad m, 6 H, CH_2), and 0.90 (m, 3 H, CH_3); ir (CCl_4) 1560, 1320, and 1110 cm^{-1} (C–O–C).

Anal. Calcd for $C_8H_{16}N_2O_5$: C, 43.62; H, 7.32; N, 12.72. Found: C, 43.53; H, 7.04; N, 13.02.

The least abundant component was not isolated in sufficient quantity for elemental analysis, but the nmr spectrum indicated that the compound was 2,2-dinitropropyl 3-pentyl ether: nmr (CCl_4) δ 4.20 (s, 2 H, $CH_2C(NO_2)_2$), 3.47 (m, 1 H, CH_2CHCH_2), 2.17 (s, 3 H, $C(NO_2)_2CH_3$), and 1.7–0.7 (broad m, 10 H).

2-Fluoro-2,2-dinitroethyl Isopropyl Ether.—A mixture of 1.54 g (0.010 mol) of 2-fluoro-2,2-dinitroethanol, 1.92 g (0.010 mol) of isopropyl triflate, 3 g of sodium sulfate, and 3 ml of chloroform was stirred for 12 hr at ambient temperature. The solution was washed with water and with 5% sodium hydroxide, dried, and distilled to give 1.45 g (74%) of 2-fluoro-2,2-dinitroethyl isopropyl ether: bp 52° (0.4 mm); proton nmr (CCl_4) δ 4.38 (d, 2 H, J_{HF} = 18 Hz, CH_2), 3.37 (septet, 1 H, J = 7 Hz, CH_2), and 1.11 (d, 6 H, J = 7 Hz, CH_3); fluorine nmr φ 111.5 ppm (t, J_{HF} = 18 Hz).

Anal. Calcd for $C_5H_9FN_2O_5$: C, 30.61; H, 4.62. Found: C, 30.86; H, 4.65.

2,2-Dinitropropyl Isopropyl Ether.—By the above procedure, using methylene chloride as solvent, 7.70 g (0.05 mol) of 2,2-dinitropropanol and (0.040 mol) of isopropyl triflate (12 hr) gave 5.14 g (67%) of 2,2-dinitropropyl isopropyl ether: bp 45–47° (0.07 mm); nmr (CCl_4) δ 4.13 (s, 2 H, $C(NO_2)_2CH_2O$), 3.62 (septet, 1 H, J = 6 Hz), 2.13 (s, 3 H, $CH_3C(NO_2)_2$), and 1.15

ppm (d, 6 H, J = 6 Hz, $(CH_3)_2C$); ir (CCl_4) 1560, 1320 (NO_2), and 1110 cm^{-1} (C–O–C).

Anal. Calcd for $C_6H_{12}N_2O_5$: C, 37.49; H, 6.30. Found: C, 37.62; H, 6.36.

Isopropyl 2,2,2-Trinitroethyl Ether.—Isopropyl triflate (0.040 mol) and 2,2,2-trinitroethanol (9.05 g, 0.050 mol) were allowed to react using the above procedure, except that washing with sodium hydroxide solution was omitted and the crude product was passed through a short column of silica gel to give isopropyl 2,2,2-trinitroethyl ether in 38% yield. The analytical sample was distilled in a molecular still at 0.1 mm, bath temperature 50°: nmr (CCl_4) δ 4.60 (s, 2 H, CH_2), 3.80 (septet, 1 H, J = 7 Hz, CH), and 1.25 ppm (d, 6 H, J = 6 Hz, CH_3); ir (CCl_4) 1565, 1315 (NO_2), and 1120 cm^{-1} (C–O–C).

Anal. Calcd for $C_5H_9N_3O_7$: C, 26.91; H, 4.06. Found: C, 27.30; H, 4.29.

Reaction of Isopropyl Triflate with Pentanol.—A mixture of 0.44 g (0.0050 mol) of pentanol, 0.95 g (0.0050 mol) of isopropyl triflate, 1.0 g of sodium sulfate, and 10 ml of methylene chloride was stirred for 1 hr. The mixture was washed with 30 ml of water, dried, and stripped of solvent. Vacuum transfer of the residue gave 0.57 g of a mixture containing 60% isopropyl pentyl ether (52% conversion) and 40% 1-pentanol, separated by glpc and compared with authentic samples. A reference sample of isopropyl pentyl ether was prepared by the reported method:[20] bp 131–132°; nmr (CCl_4) δ 3.40 (septet, 1 H, J = 6 Hz, CHO), 3.27 (t, 2 H, J = 6 Hz, CH_2O), 1.37 (m, 6 H, CH_2), 1.08 (d, 6 H, J = 6 Hz, $(CH_3)_2C$), and 0.90 ppm (m, 3 H, CH_3).

Registry No.—Trifluoromethanesulfonic anhydride, 358-23-6; 1,2-bis(2-fluoro-2,2-dinitroethoxy)ethane, 41029-52-1; 2-fluoro-2,2-dinitroethyl pentyl ether, 41029-53-2; allyl 2-fluoro-2,2-dinitroethyl ether, 25171-99-7; 2-fluoro-2,2-dinitroethyl propargyl ether, 40696-43-3; 1,4-bis(2-fluoro-2,2-dinitroethoxy)butane, 41029-56-5; 3-(2-fluoro-2,2-dinitroethoxy)-2-propenyl triflate, 41029-57-6; pentyl 2,2,2-trifluoroethyl ether, 41029-58-7; allyl 2,2,2-trinitroethyl ether, 41029-59-8; allyl 2,2-dinitropropyl ether, 41029-60-1; 2,2-dinitro-1,3-di(allyloxy)propane, 41029-61-2; 2,2-dinitropropyl 2-pentyl ether, 41029-62-3; 2,2-dinitropropyl 1-pentyl ether, 41029-63-4; 2,2-dinitropropyl 3-pentyl ether, 41029-64-5; 2-fluoro-2,2-dinitroethyl isopropyl ether, 41029-65-6; 2,2-dinitropropyl isopropyl ether, 41029-66-7; isopropyl 2,2,2-trinitroethyl ether, 41029-67-8; 2,2,2-trifluoroethanol, 75-89-8; 2,2,2-trinitroethanol, 918-54-7; 2,2-dinitropropanol, 918-52-5; 2,2-dinitro-1,3-propanediol, 2736-80-3; isopropyl pentyl ether, 5756-37-6; trifluoromethanesulfonic acid, 1493-13-6; tetrahydrofuran, 109-99-9.

(20) C. Djerassi and C. Fenselau, *J. Amer. Chem. Soc.*, **87**, 5747 (1965).

Stereochemistry in the Solvolytic Ring Contraction of 2,2,4aα-Trimethyl-1-decalyl Methanesulfonate. A Model Reaction Pertaining to Triterpene Biogenesis[1a]

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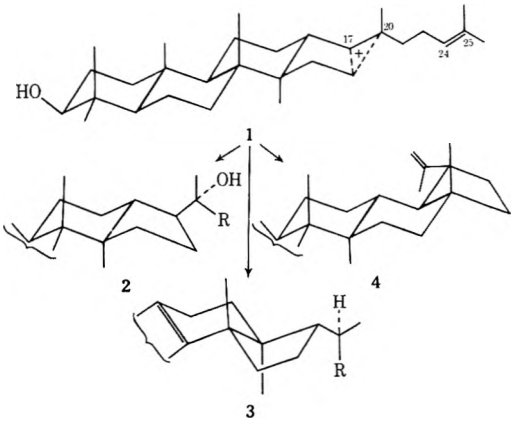
2,2,4aα-Trimethyl-1,2,3,4,4aα,5,6,7,8,8aβ-decahydronaphthalen-1β-ol (**5**-OH) and its 2β-trideuteriomethyl analog (**5**-d_3-OH) were synthesized by reduction-methylation of 4aβ-methyl-2-*n*-butylthiomethylene-3,4,4aβ,-5,6,7,8,8a(α and β)-octahydronaphthalen-1(2*H*)-ones (**8b**) and, after separation of the trans isomer from the mixture of trimethyldecalones (**9** and **10**), lithium–ammonia reduction. Solvolysis of the corresponding methanesulfonates (**5**-OMs and **5**-d_3-OMs) effects efficient ring contraction to 3aα,4,5,6,7,7aβ-hexahydro-3aα-methyl-1β-indanyldimethylcarbinol derivatives (**6**-OR and **6**-d_3-OR). Since the trideuteriomethyl group in the labeled product (**6**-d_3-OR) was equally distributed between the two diastereotopic positions, a bridged species (**21**), akin to a bridged ion (**1**) postulated in triterpene biogenesis, cannot be the sole intermediate in the rearrangement. Intervention of the classical tertiary carbocation (**22**) is presumed to cause the label distribution. Attempts to intercept the intermediate by azide trapping and the use of leaving groups bearing a second nucleophilic site (*o*-carboxysulfonate and *o*-thiocarboxysulfonate) were unsuccessful.

The hypothetical bridged ion **1** (Scheme I)[1c] represents a key branching point in the traditional schemes for the biogenesis of many tetracyclic and pentacyclic triterpenes.[2-4] Three different reaction modes are proposed for this intermediate: (a) direct capture by a water molecule to give dammarenediol I (**2**); (b) 17 → 20 hydride shift followed by a backbone rearrangement to tirucallol (**3**); (c) cyclization into the side chain double

SCHEME I



(1) (a) Taken in part from the Ph.D. Thesis of S. K. C., University of Illinois, 1972. (b) A. P. Sloan Foundation Fellow, 1971–1973. (c) The carbonium ion intermediates in such biogenetic schemes are represented by the bridged type formulation (*e.g.*, **1**) chiefly as a convenient method to correlate and predict the stereochemistry of the individual transformations. The importance of internal stabilization due to delocalization *via* bridging in the course of the biosynthetic transformation remains a matter of speculation.

(2) (a) A. Eschenmoser, L. Ruzicka, O. Jeger, and D. Arigoni, *Helv. Chim. Acta*, **38**, 1890 (1955); (b) G. Stork and A. W. Burgstahler, *J. Amer. Chem. Soc.*, **77**, 5069 (1955); (c) L. Rúzicka, *Proc. Chem. Soc.*, 341 (1959).

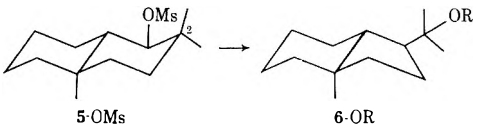
(3) For reviews and discussion see (a) G. Ourisson, P. Crabbé, and O. R. Rodig, "Tetracyclic Triterpenes," Holden-Day, San Francisco, Calif., 1964; (b) T. A. Geissman and D. H. G. Crout, "Organic Chemistry of Secondary Plant Metabolism," W. H. Freeman, San Francisco, Calif., 1969; (c) J. H. Richards and J. B. Hendrickson, "The Biosynthesis of Steroids, Terpenes, and Acetogenins," W. A. Benjamin, New York, N. Y., 1964; (d) K. B. Sharpless, Ph.D. Thesis, Stanford University, 1968.

(4) (a) A biogenetic scheme involving temporary nucleophilic interception of the carbonium ion at certain stages (X group) has recently been suggested. Although different in some stereochemical details, this scheme postulates similar stereoelectronically controlled mechanisms: J. W. Cornforth, *Angew. Chem., Int. Ed. Engl.*, **7**, 903 (1968). (b) A similar bridged ion in the E ring of β-amyrin has been proposed.[2a,c] Recent biosynthetic experiments have verified that the identity of the geminal E ring methyl groups is maintained in the predicted manner in the formation of the E ring of β-amyrin: T. Suga, T. Shishibori, and S. Komoto, *Chem. Lett.*, 313 (1972). That the distinction between these two methyl groups is also preserved in the biosynthesis of lupeol and the related triterpenes, betulin and betulinic acid, has been verified by D. Arigoni and coworkers at the ETH, Zurich: L. Botta, Dissertation No. 4098 (1968); L. Guglielmetti, Dissertation No. 3299 (1962).

bond and either proton loss to lupeol (**4**) or further rearrangement to other pentacyclic triterpenes.

Explicit in this scheme, as in most biogenetic pathways to terpenes, is the assumption that the bridged intermediate will react with a nucleophile (water, migrating hydrogen, or carbon–carbon double bond) from the side opposite the bridging carbon.[1c] It seemed of interest to determine whether or not a carbonium ion such as **1** could be captured stereoselectively in solution in the absence of the biosynthetic enzymes. Stereoselective capture is frequently observed in solvolysis reactions and is one significant criterion for designating the intermediate carbonium ion as nonclassical.[5]

The solvolytic ring contraction of the trans,anti decalyl methanesulfonate **5**-OMs to the trans,anti hydrindan **6** was selected as a model reaction. The **5** → **6** rearrangement, while differing from the well-

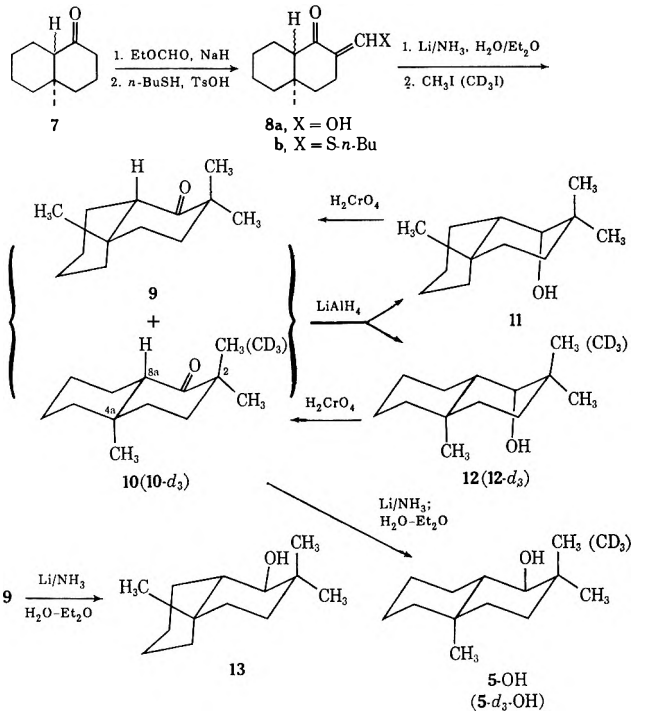


precedented ring A contraction of 4,4-dimethylsterols and triterpenes[6] in producing the natural trans,anti stereochemistry, finds analogy in silver ion assisted transformation of 19α-chloro-β-amyrin into lupeol.[7]

The ring contraction of **5**-OMs must pass through a bridged configuration similar to **1** which, if sufficiently long lived, would undergo substitution at C-2 of the decalin nucleus with net inversion. The stereochemistry of the overall reaction would be revealed by labeling one of the two methyl groups of **5** and determining whether the label appears in one of the two diastereotopic methyl groups in **6**. While the bridged ion might be expected to be less stable than the classical tertiary cation, there is nevertheless precedent for stereoselective capture of potentially symmetrical tertiary carbonium ions.[8]

The requisite decalol **5**-OH was secured by means of the reactions summarized in Scheme II, taking advantage of a new method for regioselective geminal alkylation.[9] Reduction–methylation of the α-*n*-butylthiomethylene derivative (**8b**)[10] of decalone **7** (cis,trans mixture)[11] afforded a mixture (~1:1) of the cis and trans trimethyldecalones (**9** and **10**) in 67% yield. The ketone mixture, after sodium methoxide–methanol equilibration (**9**:**10**, 1:3), was reduced with lithium aluminum hydride to the chromatographically separable axial alcohols **11** (16%) and **12** (68%). Oxidation with aqueous chromic acid afforded the pure cis and trans ketones. The equatorial alcohols **13** and **5**-OH were

SCHEME II



obtained in essentially quantitative yield by reduction with lithium in liquid ammonia.

The deuterium-labeled ketone **10**-d_3 was similarly prepared using deuteriomethyl iodide in the alkylation step. In this case, the excess lithium was first quenched by careful titration with methyl iodide and the *n*-butylmercaptide was consumed by alkylation with isopropyl iodide in order to utilize the labeled reagent more efficiently. With 1.5 equiv of deuteriomethyl iodide the deuterated ketones **9**-d_3 and **10**-d_3 were obtained in comparable yield to the unlabeled compounds.

The trans stereochemistry (**10**) assigned to the major trimethyldecalone is based upon the position of equilibrium (see above) and nmr spectral data. The nmr spectrum of the major isomer exhibits a broadened doublet of doublets (δ 2.30, J = 3, 10 Hz) for the lone α proton (**8a**), while the spectrum of the minor isomer shows a broad singlet (δ 2.30, $W_{1/2}$ = 7 Hz). The α proton of **10**, having a neighboring axial proton, is expected to be more extensively coupled.

The relatively high field position (δ 0.73) for angular methyl in the major ketone is similar to that of *trans*-**7** (δ 0.80)[11] and significantly different from that of the conformationally mobile *cis*-**7** (δ 1.05).[11] The increased proportion of trans isomer in the **9** ⇄ **10** equilibrium (1:3) compared to the *cis*-**7** ⇄ *trans*-**7** equilibrium (1:2)[11] is attributed to destabilization of the alternate conformation of **9** by a 1:3 diaxial dialkyl interaction.

That the deuteriomethyl group was introduced principally (85%) in the 2-axial position of **10**-d_3 was ascertained from the intensities of the geminal methyl peaks in the nmr spectrum. The individual signals for the three methyl groups in **10** (δ 1.17, 0.98, 0.73) may be assigned to the 2-axial, 2-equatorial, and angular methyl groups, respectively, on the basis of benzene solvent shifts ($\Delta\delta$ +0.20, −0.11, +0.11). These shifts are in accord with data for various 2-methyl ($\Delta\delta_{axial}$ +0.2 to 0.3, $\Delta\delta_{equatorial}$ −0.05 to −0.10) and

(5) For leading references see G. D. Sargent, *Quart. Rev., Chem. Soc.*, **20**, 301 (1966); G. A. Olah, *J. Amer. Chem. Soc.*, **94**, 808 (1972).

(6) (a) J. F. King and P. de Mayo in "Molecular Rearrangements," Part 2, P. de Mayo, Ed., Interscience, New York, N. Y., 1964, pp 826, 827. (b) C. W. Shoppee and G. A. R. Johnston, *J. Chem. Soc.*, 3261 (1961). (c) Monocyclic analogs: J. C. Richer and P. Belanger, *Can. J. Chem.*, **47**, 3281 (1969); R. M. Delaney, S. Middleton, and W. F. Norfolk, *Aust. J. Chem.*, **23**, 1015 (1970).

(7) T. G. Halsall, E. R. H. Jones, and G. D. Meakins, *J. Chem. Soc.*, 2862 (1952).

(8) (a) H. L. Goering and S. Chang, *Tetrahedron Lett.*, 3607 (1965); (b) J. A. Berson, R. T. Luibrand, N. G. Kunda, and D. G. Morris, *J. Amer. Chem. Soc.*, **93**, 3075 (1971).

(9) R. M. Coates and R. L. Sowerby, *ibid.*, **93**, 1027 (1971).

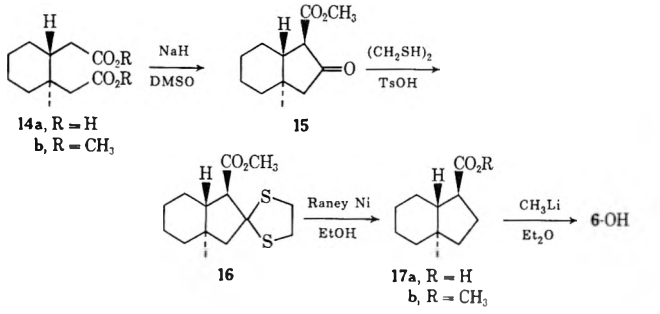
(10) R. E. Ireland and J. A. Marshall, *J. Org. Chem.*, **27**, 1615 (1962).

(11) J. A. Marshall and A. R. Hochstetler, *J. Amer. Chem. Soc.*, **91**, 648 (1969).

3-methyl ($\Delta\delta_{axial}$ +0.2) cyclohexanones.[12,13] The substantial preference for axial methylation in this case is in line with the trend[14] that substitution on an enolate enhances the extent of axial alkylation.[12,14,15] The long-range steric effect of the angular methyl group may also contribute to this stereoselectivity. The stereochemistry of the hydroxyl group in the four decalols follows from the extent of coupling of the protons on carbon-bearing oxygen (**11** and **12**, s; **13** and **5**-OH, d, J = 10 Hz).

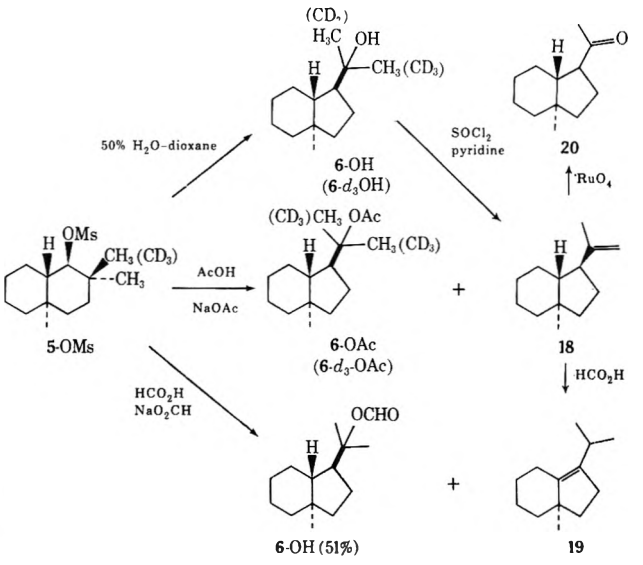
The trans fused hydrindanyl carbinol **6**-OH was independently synthesized from *trans*-1-methylcyclohexane-1,2-diacetic acid (**14a**)[16] (Scheme III). Dieckmann cyclization of the diester **14b** with sodium hydride in dimethyl sulfoxide[17] furnished a crystalline keto ester (68%) which must have structure and stereochemistry **15** judging from the nmr coupling of the proton on carbon bearing the ester group (d, J = 12.7 Hz). The ketone group was then removed by Raney nickel desulfurization of the thioketal **16**, and the resulting ester **17b** (68%) was converted to **6**-OH by reaction with methyllithium.[18]

SCHEME III



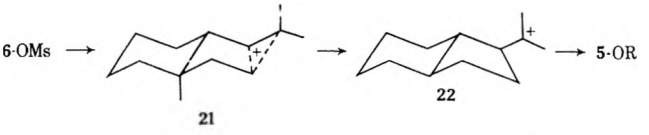
Solvolysis of **5**-OMs under various conditions effected efficient ring contraction to hydrindanyl derivatives (Scheme IV). The tertiary alcohol produced (80%) by hydrolysis in 50% aqueous dioxane was identical with synthetic **6**-OH. The acetate (**6**-OAc) and formate (**6**-OCHO) obtained from acetolysis and formolysis were identified by conversion to **6**-OH. The rearranged olefin **19**, the major product from formolysis of **6**-OMs, is evidently formed by secondary isomerization of the isopropenyl hydrindan **18**.

SCHEME IV



Hydrolysis of the labeled sulfonate **5**-d_3-OMs gave rise to **6**-d_3-OH in which the two methyl groups had become equivalent. The nmr spectrum of **6**-d_3-OH in the presence of europium trisdipivaloylmethane revealed two separate, equally intense resonances (δ 2.94 and 3.04) for the diastereotopic side chain methyl groups. Similarly the acetate (**6**-d_3-OAc) obtained from acetolysis of **5**-d_3-OMs had the deuterium label equally distributed between the geminal methyl groups.

The complete scrambling of the methyl groups in the solvolyses of **5**-d_3-OMs establishes that the bridged ion **21** cannot be the sole carbonium ion intermediate in the ring contraction rearrangement. Evidently the bridged species **21**, which must exist along the reaction pathway either as a transition state or a transient intermediate, proceeds to the more stable, classical tertiary ion **22**



prior to solvent capture. The distinction between the two diastereotopic methyl groups may then be lost either by rapid rotation about the exocyclic single bond, or a nonspecific reaction of **22** with a solvent molecule from its two nonequivalent faces.

In view of the documented examples of stereoselective capture of potentially symmetrical tertiary carbonium ions,[8] we investigated other means for faster interception of the carbonium ion intermediate. One approach involved rearrangement in the presence of the highly nucleophilic azide ion. Since the efficiency of azide trapping with *tert*-butyl chloride is relatively high

(12) (a) R. S. Mathews, S. J. Girgenti, and E. A. Folkers, *Chem. Commun.*, 708 (1970); (b) B. J. L. Huff, F. N. Tuller, and D. Caine, *J. Org. Chem.*, **34**, 3070 (1969).

(13) (a) S. Bory, M. Fétizon, P. Laszlo, and D. H. Williams, *Bull. Soc. Chim. Fr.*, 2541 (1965); (b) M. Fétizon, J. Goré, P. Laszlo, and B. Waegell, *J. Org. Chem.*, **31**, 4047 (1966); (c) P. Laszlo, *Progr. Nucl. Magn. Resonance Spectrosc.*, **3**, 348 (1967); (d) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, pp 159–170.

(14) H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, New York, N. Y., 1972, pp 586–595.

(15) Since the cis,trans mixture of decalones **9**-d_3 and **10**-d_3 was equilibrated with base prior to the nmr analysis, it is not possible to determine the stereoselectivity of methylation of the individual cis and trans enolate intermediates. However, in view of the high proportion of **10**-d_3 with an axial CD_3, the minimum stereoselectivity for methylation from the face opposite to the angular methyl group in one of the two isomeric enolates is 2:1 (*i.e.*, if methylation of its isomer were stereospecific in the same sense).

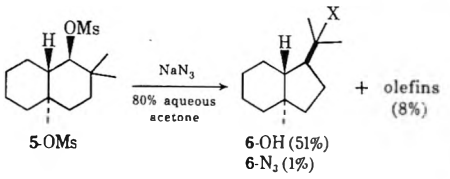
(16) (a) R. L. Kronenthal and E. I. Becker, *J. Amer. Chem. Soc.*, **79**, 1095 (1957); (b) G. Stork and S. D. Darling, *ibid.*, **86**, 1761 (1964).

(17) I. J. Bolton, R. G. Harrison, and B. Lythgoe, *J. Chem. Soc. C*, 2950 (1971).

(18) The following less efficient and nonstereospecific routes were also investigated. (a) Ketalization of methyl 4aα-methyl-2-oxo-1α,2,3,4aα,-5,6,7,8,8aβ-decahydronaphthoate[19a] followed by lithium aluminum hydride reduction, oxidation with Collins reagent,[19b] and ketal hydrolysis with 1% hydrochloric acid in aqueous methanol gave 1-hydroxymethylene-4aα-methyl-3,4,5aα,5,6,7,8,8aβ-octahydronaphthalen-2(1*H*)-one (62% overall). Irradiation of the diazo ketone resulting from reaction with tosyl azide and triethylamine in methylene chloride (45%)[19c] in aqueous tetrahydrofuran containing sodium bicarbonate[19d] afforded an 80:20 mixture of **17b** and its 1α epimer (43%). (b) The diazo transfer reaction[19c] carried out as above with **8a** (trans:cis 57:43) provided mainly the cis fused diazo ketone (60%), photolysis of which furnished the epimeric cis isomers of **17b** (82%; 4:1 cis,syn:cis,anti). For details see Ph.D. Thesis of S. K. Chung, University of Illinois, Urbana, Ill., 1972.

(19) (a) G. Stork, P. Rosen, N. Golman, R. V. Coombs, and J. Tsuiji, *J. Amer. Chem. Soc.*, **87**, 275 (1965); (b) R. Ratcliffe and R. Rodehorst, *J. Org. Chem.*, **35**, 4000 (1970); (c) M. Regitz and J. Ruter, *Chem. Ber.*, **101**, 1263 (1968); (d) M. Regitz and J. Ruter, *ibid.*, **102**, 3877 (1969).

(k_{N_3}/k_{H_2O} = 74),[20] we hoped that with high concentrations of azide the carbonium ion would be captured as the hydrindanyl azide 6-N_3. In practice, however, hydrolysis of 5-OMs in 50% aqueous acetone containing 2 *M* sodium azide gave only 5% of 6-N_3. The value of

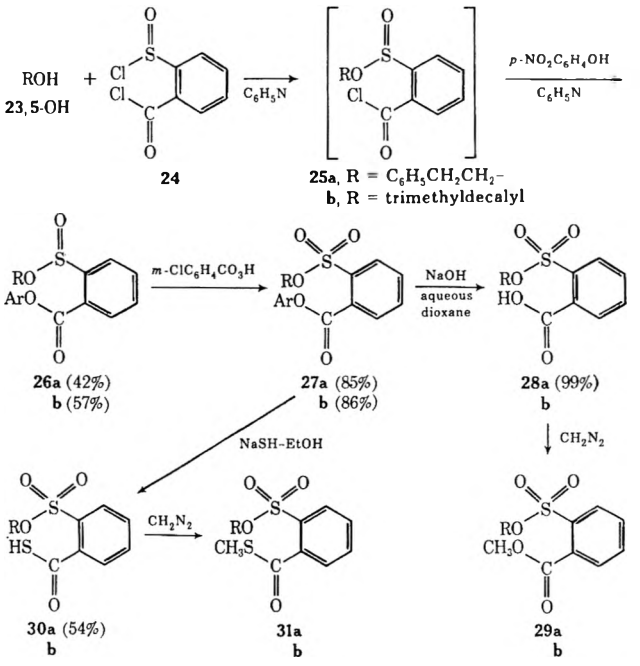


k_{N_3}/k_{H_2O} (determined with 0.1 *M* sodium azide) is 2.5, considerably less than the value for *tert*-butyl chloride cited above. The large decrease is probably attributable to the change in leaving group and indicates once again that azide trapping may involve ion pair intermediates.[20,21]

Another method which has been employed for more rapid interception of carbonium ions involves the use of a leaving group bearing a second, more nucleophilic site.[22] We considered that the *o*-carboxybenzenesulfonate or *o*-thiocarboxybenzenesulfonate might be successful in the present case in view of the proximity of the relatively nucleophilic carboxylate or thiocarboxylate group to the carbonium ion site. Since the hydroxyl group in 5-OH is too sterically hindered to permit direct conversion to the tosylate with tosyl chloride,[23] an indirect, three-step route *via* a mixed sulinate carboxylate diester was developed in order to introduce these bidentate leaving groups (Scheme V).

The reaction between 1 equiv of either 2-phenylethanol (23) or the trimethyldecalol 5-OH and *o*-chlorosulfinylbenzoyl chloride (24)[26] in the presence of *pyridine* occurs selectively at the sulfinyl function. The resulting *o*-(alkoxysulfinyl)benzoyl chlorides (25) are converted directly to the *p*-nitrophenyl esters (26) by treatment with *p*-nitrophenol. The sulfinates are then oxidized[27] to the *o*-carboxysulfonates (27), which upon alkaline hydrolysis in aqueous dioxane or sulfhydrolysis with sodium hydrosulfide in ethanol[28,29] liberate the *o*-carboxybenzenesulfonates (28) and *o*-thiocarboxybenzenesulfonates (30), respectively.[30] The latter were reesterified with diazomethane for characterization.

SCHEME V



The ready loss of the *p*-nitrophenyl group in the hydrolyses of 27 and the incorporation of the sulfhydryl group in the sulfhydrolyses provides proof that the alkoxy group (RO) from the original alcohols is in fact bound to sulfur. Hydrolysis or sulfhydrolysis of the isomer of 27 (R and Ar exchanged) at the ester function would give a carboxylic acid retaining the *p*-nitrophenyl moiety. In the alternative event of aryl oxygen cleavage at the sulfonate group of the isomer, a common, presumably water soluble, sulfonic acid would have been formed from both hydrolysis and sulfhydrolysis.

The greater reactivity of the chlorosulfinyl group over the acyl chloride function of 24 is noteworthy. The facile formation of the *o*-carboxysulfonate of the hindered trimethyldecalol 5-OH indicates that the method is relatively insensitive to steric hindrance.

Acetolysis of the carboxysulfonate **28b** in the presence of sodium acetate afforded 6-OAc (13%) and olefin **18** (51%) as the major products (Scheme VI). Similarly hydrolysis of the thiocarboxysulfonate **30b** led to the ring-contracted alcohol 6-OH (51%) and olefin **18** (17%). It is clear from these results that the major reaction pathway is a normal solvolysis of both **28b** and **30b**. Although relatively small amounts of the internal return isomers **31** could have been formed in these reactions, the amount would have been insufficient for a deuterium-labeling experiment to be feasible. Evidently ion pair dissociation is faster than internal return. The possibility that the major products are formed by subsequent ionization of an intermediate hydrindanyl benzoate (**31**) is rendered unlikely by control experiments. *tert*-Butyl benzoate was recovered from the acetolysis medium while *tert*-butyl thiolbenzoate was stable for a prolonged period in 50% aqueous dioxane at 105°. Since the σ values for the sulfonate anion are quite small (σ_m = 0.05, σ_p = 0.09),[31] the presence of the sulfonate group in **31** should not unduly alter the reactivity, unless there is a special proximity effect due to its ortho position.

(20) D. J. Raber, J. M. Harris, R. E. Hall, and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **93**, 4821 (1971).

(21) C. D. Ritchie, *ibid.*, **93**, 7324 (1971); D. Kovačević, Z. Majeraski, S. Borčić, and D. E. Sunko, *Tetrahedron*, **28**, 2469 (1972).

(22) (a) *m*-Carboxysulfonate: E. J. Corey, J. Casanova, Jr., P. A. Vatakencherry, and R. Winter, *J. Amer. Chem. Soc.*, **85**, 169 (1963). (b) Thiocarboxylate: S. G. Smith and J. P. Petrovich, *J. Org. Chem.*, **30**, 2882 (1965), and succeeding paper. (c) Thiocyanate: L. A. Spurlock and Y. Mikuriya, *ibid.*, **36**, 1549 (1971). (d) Sulfinate: D. Darwish and E. A. Preston, *Tetrahedron Lett.*, **No. 2**, 113 (1964).

(23) Symmetrical esters of *o*-sulfobenzoic acid have been prepared previously by reaction of the *o*-chlorosulfonylbenzoyl chloride with alcohols.[24] Acyl-type monoesters are formed in the reaction of *o*-sulfobenzoic anhydride with alcohols.[25] Alkylation of the silver salt of these monoesters offers a route to unsymmetrical diesters.[26] Few, if any, *o*-(alkoxysulfonyl)benzoic acids seem to have been prepared in the literature.

(24) B. Loev and M. Kormendy, *J. Org. Chem.*, **27**, 2448 (1962).

(25) H. G. Rule and G. Smith, *J. Chem. Soc.*, 1482 (1931).

(26) I. B. Douglass and B. S. Farah, *J. Org. Chem.*, **26**, 351 (1961).

(27) R. M. Coates and J. P. Chen, *Tetrahedron Lett.*, 2705 (1969).

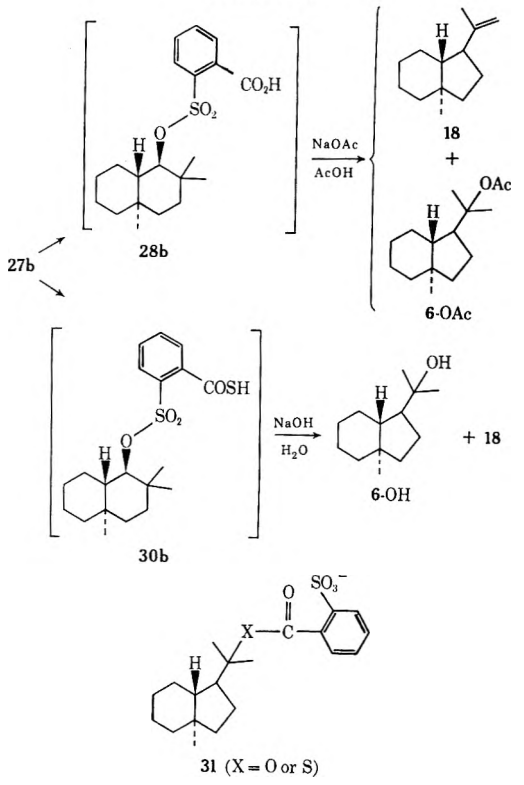
(28) Y. Hirabayashi, M. Mizuta, and T. Mazume, *Bull. Chem. Soc. Jap.*, **37**, 1002 (1964).

(29) H. Staudinger and H. Freudenbeger, "Organic Syntheses," Collect Vol. II, Wiley, New York, N. Y., 1943, p 573.

(30) Attempts to prepare the *o*-(alkoxysulfinyl)benzoic acids by hydrolysis of the acid chloride group of *o*-(alkoxysulfinyl)benzoyl chlorides (**3**) afforded *o*-(hydroxysulfinyl)benzoic acid as the only acidic product. Evidently hydrolysis of the sulfinate is very rapid owing to intramolecular assistance by the neighboring free carboxyl group.

(31) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," Wiley, New York, N. Y., 1963, p 173.

SCHEME VI



In closing it is appropriate, albeit highly speculative, to consider briefly means by which the biosynthetic enzyme(s) could maintain the stereospecifity expressed in Scheme I. One obvious possibility is for the active site to fix the side chain in a particular conformation and thus restrict rotation about the 17,20 bond until either reaction with a water molecule or cyclization into the terminal double bond occurs. A specific, clockwise, 90° rotation of the side chain would set the stage for 17 → 20 hydride shift and backbone rearrangement to **3**. Temporary attachment to a nucleophilic site (X) within the active site as suggested by Cornforth[4a] offers a second possible mechanism for stereochemical control. This explanation would require either formal front-side nucleophilic attack by the X group on **1** (*i.e.*, from the bridged face) followed by a "normal" inversion or "normal" back-side attack on **1** followed by a formal front-side replacement of the X group.

A recent investigation (subsequent to the original submission of this manuscript)[32] has established that the related ring contraction rearrangement of 4β-dueteriomethyl-4α-methylandrostane-3β,17β-diol 17-acetate (phosphorus pentachloride in hexane) and the corresponding tosylate (sodium acetate, acetic acid) to 3-isopropylidene-*A*-norandrostan-17β-ol acetate proceeds stereospecifically, maintaining the integrity of the geminal methyl groups in the overall reactions. As noted above, this well-known rearrangement[6] differs significantly from the bicyclic model examined here; the dimethylandrostane precursors possess a 1,3-diaxial steric interaction in ring A not present in **5**-OMs and the intermediate (or incipient) carbonium ion(s) from the androstane precursors has a trans,syn stereochemistry of positions 10, 5, and 3 of the *A*-norandrostane ring system. Nevertheless, it is surprising that these reactions are stereospecific. Perhaps the proton elimination occurs earlier along the reaction coordinate (*e.g.*, ion pair) while the substitution reaction giving **6**-OAe occurs later (*e.g.*, dissociated ions).

(32) S. Iwasaki, K. Okaniwa, and S. Okuda, *Tetrahedron Lett.*, 4601 (1972).

Experimental Section[33]

4aβ-Methyl-2-*n*-butylthiomethylene-3,4,4aβ,5,6,7,8a(α and β)-octahydronaphthalen-1(2*H*)-ones (8b).—A solution of 41.5 g (250 mmol) of the isomeric decalones **7** in 800 ml of benzene was slowly added with stirring to hexane-washed sodium hydride (24 g of 60% oil dispersion, 600 mmol).[10] After 30 min, ethyl formate (55 g, 750 mmol) and 20 drops of methanol were slowly introduced. After 14 hr at room temperature (nitrogen atmosphere), water (300 ml) and ether (300 ml) were added. The organic layer was separated and washed four times with 5% sodium hydroxide. The combined aqueous phase was acidified and thoroughly extracted with ether. The ether extracts were washed, dried, and evaporated to give 45.7 g (94%) of the hydroxymethylene derivative **8a** as a yellow, viscous oil: ir 1130 1580, 1635, 1710, 2500–3500 cm^{-1}; nmr δ 0.88 (cis) and 0.98 (trans) (2 s, total 3 H, C-4 CH_3), 8.04 (cis), and 8.64 (trans) (2 s, total 1 H, =CHOH). The ratio of cis/trans was 43:57 (by nmr).

A solution of 45 g (231 mmol) of **8a**, 21.6 g (240 mmol) of *n*-butanethiol, and 3 g of *p*-toluenesulfonic acid in 500 ml of benzene was refluxed with removal of water (Dean–Stark separator) for 3 hr.[10] After cooling, the benzene solution was successively washed with 800 ml of 5% sodium hydroxide, water, and brine, dried, and evaporated to give 58.5 g (95%) of the *n*-butylthiomethylene derivative **8b** as a dark yellow oil: ir 1545, 1660 cm^{-1}; nmr δ 0.85 and 1.0 (2 s, 3 H total), 7.25–7.40 (m, 1 H).

2,2,4a(α and β)-Trimethyl-2,3,4,4aβ,5,6,7,8-octahydronaphthalen-1(8aβ*H*)-ones (9 and 10).—A solution of 17 g (64 mmol) of **8b** and 2.34 g (130 mmol) of water in 300 ml of ether was added to a refluxing solution of 2.7 g (384 mmol) of lithium in 1.2 l. of liquid ammonia over 40 min with efficient stirring.[9] After an additional 1 hr, 57 g (400 mmol) of methyl iodide in 300 ml of ether was added and the stirring was continued for 30 min before the addition of 25 g of ammonium chloride. Evaporation of ammonia followed by a standard extractive work-up[33] with ether gave 13 g of tan-colored oil. The crude product was equilibrated in a solution of 3 g of sodium methoxide in 200 ml of methanol over 11 hr at room temperature. An extractive work-up[33] followed by column chromatography on silica gel afforded 8.35 g (67%) of an epimeric mixture of decalones **9** and **10** (eluted with 3% ether in hexane). The ratio of trans/cis at equilibrium was 3:1 in favor of trans by nmr and glpc (column D, 160°) analyses. For further characterization see below.

2α,4a(α and β)-Dimethyl-2β-trideuteriomethyl-2,3,4,4aβ,5,6,7,8-octahydronaphthalen-1(8aβ*H*)-ones (9-d_3 and 10-d_3).—A solution of 6.6 g (24.8 mmol) of **8b** and 894 mg (49.6 mmol) of water in 100 ml of ether was added to a refluxing solution of 1.04 g (148 mmol) of lithium in 500 ml of ammonia as above. After an ad-

(33) Melting points were taken in open capillary tubes on a Thomas-Hoover melting point apparatus and are uncorrected. Spectra were recorded on the following instruments: Perkin-Elmer Model 137 or 521 ir spectrophotometers; Varian Associates Model A-60A, A-56/60, HA-100, or HR 220 nmr spectrophotometers; Atlas CH_4, MAT CH-5, or MAT-SM-1B mass spectrometers. All nmr spectra were determined in deuterated chloroform unless otherwise specified and chemical shifts are reported as δ values using tetramethylsilane as internal standard. Refractive indices were measured on an Abbe refractometer. Combustion analyses were performed in the University of Illinois Microanalytical Laboratory. The gas chromatographic (glpc) analyses were performed with a Hi-Fe Model 600-D or a Varian Aerograph Model A90-P3 instrument using the following columns: A, 5 ft × 0.125 in., 5% SE-30 on 60/80 mesh DMCS Chromosorb W; B, 5 ft × 0.125 in., 5% Carbowax 20M on 60/80 mesh SMCS Chromosorb W; C, 5 ft × 0.125 in., 5% Apiezon L on 60/80 mesh SMCS Chromosorb W; D, 5 ft × 0.125 in., 5% FFAP on 60/80 mesh DMCS Chromosorb W; E, 5 ft × 0.375 in., 15% FFAP on 60/80 mesh DMCS Chromosorb W; F, 6 ft × 0.375 in., 20% SE-30 on 60/80 mesh DMCS Chromosorb W; G, 6 ft × 0.375 in., 15% Apiezon L on 60/80 mesh DMCS Chromosorb W. The standard extractive work-up procedure consisted of pouring into a large amount of water, extracting with the organic solvent indicated, washing the combined extracts successively with water and brine, drying the extract on anhydrous sodium sulfate, and evaporating the solvent.

ditional 15 min, the blue color of the solution was titrated by very careful addition of methyl iodide, and then 4.22 g (24.8 mmol) of isopropyl iodide in 50 ml of ether was added in one portion. After 1 hr, 5.4 g (37.2 mmol) of trideuteriomethyl iodide in 50 ml of ether was added. The solution was stirred for 20 min and the same isolation and purification procedure as described above was followed, yielding 3.5 g (72%) of the labeled ketone mixture 9-d_3 and 10-d_3.

2,2,4aβ-Trimethyl-1,2,3,4,4aβ,5,6,7,8,8a(α and β)-decahydronaphthalen-1α-ol (11 and 12).—The epimeric mixture of 9 and 10 (10.6 g, 54.6 mmol) was reduced with 4.15 g (108.5 mmol) of lithium aluminum hydride in 400 ml of ether over 2.5 hr at room temperature and 1 hr at reflux temperature. The excess hydride was destroyed by cautious addition of 5% hydrochloric acid and the alcohol mixture (10.6 g) isolated by ether extraction was chromatographed on 300 g of silica gel. The trans-axial alcohol (12, 7.29 g, 68%) was first eluted with 3% ether in hexane and was immediately followed by the cis-axial alcohol (11, 1.7 g, 16%): nmr δ 0.94 (s, 3 H, C-4a CH_3), 0.98 [s, 6 H, $C(CH_3)_2$], 3.64 (br s, 1 H, CHOH).

The less polar alcohol (12) had the following spectral properties: nmr δ 0.96 [s, 6 H, $C(CH_3)_2$], 1.03 (s, 3 H, C-4a CH_3), 3.17 (s, 1 H, CHOH); ir 3500 cm^{-1}; mass spectrum *m/e* (rel intensity 196 (M^+, 11), 178 (20), 163 (18), 125 (81), 109 (100).

Anal. Calcd for $C_{13}H_{24}O$: C, 79.53; H, 12.32. Found: C, 79.56; H, 12.21.

2,2,4aα-Trimethyl-2,3,4,4aα,5,6,7,8-octahydronaphthalen-1-(8aβH)-one (10).—To a solution of 7.29 g (37 mmol) of decalol 12 in 15 ml of acetone was added 14.3 ml of Jones reagent.[34] After 30 min at room temperature, a standard extractive work-up[33] with ether gave 7.21 g (100%) of the liquid ketone 10. An analytical sample was obtained by preparative glpc (column E, 170°): $n^{24.5}D$ 1.4782; ir 1705 cm^{-1}; nmr (CCl_4) δ 0.73 (s, 3 H, C-4a CH_3), 0.98 (s, 3 H, equatorial C_2 CH_3), 1.17 (s, 3 H, axial C_2 CH_3); nmr (C_6H_6) δ 0.62 (s, 3 H, C-4a CH_3), 0.97 (s, 3 H, axial C_2 CH_3), 1.09 (s, 3 H, equatorial C_2 CH_3).

Anal. Calcd. for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 80.22; H, 11.13.

2,2,4aβ-Trimethyl-2,3,4,4aβ,5,6,7,8-octahydronaphthalen-1-(8aβH)-one (9) was similarly obtained from 11 and displayed the following properties after preparative glpc (column E, 170°): $n^{24.5}D$ 1.4810; ir 1700 cm^{-1}; nmr (CCl_4) δ 1.0 (s, 3 H, equatorial C_2 CH_3), 1.13 (s, 6 H, C-4a CH_3 and axial C_2 CH_3); nmr (C_6H_6) δ 0.94 (s, 6 H, C-4a CH_3 and axial C_2 CH_3), 1.09 (s, 3 H, equatorial C_2 CH_3).

Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 80.22; H, 11.05.

2,2,4aβ-Trimethyl-1,2,3,4,4aβ,5,6,7,8,8aβ-decahydronaphthalen-1β-ol (13).—Reduction of 9 with lithium in ammonia as described below for 10 afforded the cis-fused decalol 13: mp 62–64°; ir 3500 cm^{-1}; nmr δ 0.85 (s, 3 H), 1.0 (s, 6 H), 3.47 (d, J = 10 Hz, 1 H, CHOH).

Anal. Calcd for $C_{13}H_{24}O$: C, 79.53; H, 12.32. Found: C, 79.33; H, 12.12.

2,2,4aα-Trimethyl-1,2,3,4,4aα,5,6,7,8,8aβ-decahydronaphthalen-1β-ol (5-OH).—A solution of 7.1 g (36.8 mmol) of 10 and 1.4 g (77.5 mmol) of water in 300 ml of ether was added to a refluxing solution of 1.03 g (147 mmol) of lithium in 1 l. of ammonia over 20 min with rapid stirring. After an additional 30 min, 8 g (149 mmol) of ammonium chloride was cautiously added. Evaporation of the ammonia followed by the standard extractive work-up with ether[33] gave 7.1 g (98%) of the alcohol 5-OH: mp 66–68°; ir 3500 cm^{-1}; nmr δ 0.83 (s, 3 H, C-4aα CH_3), 0.88 (s, 3 H, axial C_2 CH_3), 1.00 (s, 3 H, equatorial C_2 CH_3), 3.10 (d, J = 10 Hz, 1 H, CHOH).

Anal. Calcd for $C_{13}H_{24}O$: C, 79.53; H, 12.32. Found: C, 79.25; H, 12.19.

2,2,4aα-Trimethyl-1,2,3,4,4aα,5,6,7,8,8aβ-decahydronaphthalen-1β-ol Methanesulfonate (5-OMs).—A solution of 1.76 g (15.3 mmol) of methanesulfonyl chloride in 50 ml of benzene was slowly added to a solution of 3 g (15.3 mmol) of 5-OH and 1.62 g (16 mmol) of triethylamine in 50 ml of benzene at 0°.[35] After 2 hr at room temperature the precipitate was filtered and washed with benzene; the combined benzene filtrate was washed with 5% hydrochloric acid, water, and brine and then dried and evaporated to give 3.9 g (93%) of methanesulfonate 5-OMs as a viscous oil: nmr δ 0.88 (s, 3 H, C-4aα CH_3), 0.98 (s, 3 H, axial C_2 CH_3), 1.08 (s, 3 H, equatorial C_2 CH_3), 3.02 (s, 3 H, OSO_2CH_3), 4.42 (d, J = 11 Hz, 1 H, $CHOSO_2CH_3$).

2α,4aα-Dimethyl-2β-trideuteriomethyl-1,2,3,4,4aα,5,6,7,8,8aβ-decahydronaphthalen-1β-ol methanesulfonate (5-d_3-OMs) was prepared from the labeled mixture of ketones 9 and 10 in the same way as described for the nonlabeled compounds. The nmr spectra of the labeled compounds are the same as those of the nonlabeled ones except for the intensities of the C-2β CH_3 peaks: 10-d_3 (equatorial C_2 CH_3:axial C_2 CH_3 ~2.5H:0.5H); 5-d_3-OH (equatorial C_2 CH_3:axial C_2 CH_3 ~2.5H:0.5H); 5-d_3-OMs (equatorial C_2 CH_3:axial C_2 CH_3 ~2.5H:0.5H).

4aβ-Methyl-3,4,4aβ,5,6,7,8,8aα-octahydronaphthalen-2(1H)-one was prepared from 4a-methyl-4,4a,5,6,7,8-hexahydronaphthalene-2(3H)-one[36a] according to a literature procedure[36b] in 95% yield: bp 76–78° (0.2 mm) [lit.[36b] bp 73–80° (0.1 mm)]; ir 1715 cm^{-1}; nmr (CCl_4) δ 1.05 (s, 3 H).

Dimethyl-*trans*-1-methylcyclohexane 1,2-Diacetate (14b).[37a,b]—Concentrated nitric acid (230 ml) was heated to boiling (~110°), and 23.2 g (0.142 mol) of 4aβ-methyl-3,4,4aβ,5,6,7,8,-8aα-octahydronaphthalen-2(1H)-one was very slowly added. During the addition period, the oil bath was removed, and the temperature was kept over 90°[37c] by controlling the rate of addition. Ten minutes was allowed at reflux temperature after addition was over. Water (100 ml) was added, and the solution was refluxed for 30 min. A crystalline product was obtained upon cooling the mixture in an ice bath. Recrystallization from 50% aqueous acetic acid gave 11 g (37%) of *trans*-1-methylcyclohexane-1,2-diacetic (14a) acid, mp 190–195° (lit.[37a] mp 192–194°).

The dimethyl ester 14b was prepared by treatment with diazomethane in ether: ir 1725 cm^{-1}; nmr (CCl_4) δ 0.92 (s, 3 H), 3.60 (s, 3 H), 3.61 (s, 3 H).

Methyl 3aα-Methyl-2-oxo-3aα,4,5,6,7,7aβ-hexahydroindan-1β-carboxylate (15).—A slurry of 38 g (0.157 mol) of diester 14b and 18.8 g (0.47 mol) of 60% sodium hydride (hexane washed) in 2 l. of DMSO was heated at 85° for 4 hr.[17] After cooling, the mixture was acidified with concentrated hydrochloric acid and thoroughly extracted with ether. The combined extracts were treated with diazomethane, dried, and evaporated, and the resulting solid was recrystallized from hexane to yield 22.5 g (68%) of β-keto ester 15: mp 70–74°; ir 1720, 1750 cm^{-1}; nmr δ 0.95 (s, 3 H, CH_3), 2.18 (s, 2 H), 2.98 (d, J = 12.7 Hz, 1 H, C-1α H), 3.74 (s, 3 H, CO_2CH_3).

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.52; H, 8.56.

Methyl 3aα-Methyl-3aα,4,5,6,7,7aβ-hexahydroindan-1β-carboxylate (17b).—A solution of 30 g (0.143 mol) of keto ester 15, 19 g (0.202 mol) of ethanedithiol, and 14 g of *p*-toluenesulfonic acid in 220 ml of acetic was stirred for 26 hr at room temperature. A standard extractive work-up with ether[33] gave 38.7 g (94%) of oily thioketal 16 which slowly solidified: mp 75–77° (recrystallized from hexane); ir 1725 cm^{-1}; nmr δ 0.99 (s, 3 H, CH_3), 2.24 (d, J = 13 Hz, C-1α H), 2.8–3.5 (m, 4 H, $-SCH_2CH_2S-$), 3.70 (s, 3 H, CO_2CH_3).

A mixture of 38.6 g (0.135 mol) of 16 and 160 g of freshly prepared W-2 Raney nickel[38] in 750 ml of ethanol was stirred for 2 hr at room temperature and for 5 hr at reflux temperature. The slurry was filtered and washed with ethanol. The combined filtrate and washing was concentrated, and the residue was redissolved in ether. The ether solution was washed with water and brine, dried, and evaporated to give a crude oily product. Chromatography on silica gel effected separation of ester 17b (18 g, 68%, elution with 10% ether–hexane) from a more polar material (9 g) corresponding in R_f value to starting ketal.

Further purification was carried out on ester similarly obtained from a small scale, preliminary desulfurization. Since glpc analysis indicated the presence of two minor impurities (~10% each), the analytical specimen of ester 17b was purified by preparative glpc (column E, 160°): ir 1720 cm^{-1}; nmr δ 0.77 (s, 3 H, CH_3), 3.66 (s, 3 H, CO_2CH_3). The appearance of small

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extraneous signals [δ 0.85 (s), 3.66 (s), 5.68 (2 d, J = 1.5 Hz, 6), 5.97 (2 d, J = 2.5 Hz; 6)] in the nmr spectrum of this collected sample, however, reveals the presence of a minor (~15–20%) contaminant.

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.29; H, 10.06.

3aα,4,5,6,7aβ-Hexahydro-3aα-methyl-1β-indanyldimethylcarbinol (6-OH).—Methyllithium (3 mmol) in ether was added to ester **17b** (~60 mg, 0.32 mmol) in 4 ml of ether and the solution was heated under reflux for 5 hr. Addition of saturated ammonium chloride solution followed by an extractive work-up with ether gave ~68 mg (97%) of oily alcohol **6-OH** which compared satisfactorily with a sample obtained from hydrolysis of **5-OMs** [nmr, tlc, and glpc (column D, 150°) comparisons]. For characterization data, see below.

Solvolyses of Methanesulfonates 5-OMs and 5-d_3-OMs. A. Hydrolyses.—A solution of 600 mg (2.2 mmol) of **5-OMs** in 300 ml of aqueous dioxane (1:1 by volume) containing 1.0 g (10 mmol) of calcium carbonate was heated under reflux for 24 hr. After cooling, the solution was saturated with sodium chloride. The mixture, obtained after a standard extractive work-up with ether,[33] was chromatographed on 35 g of silica gel. The hydrocarbon mixture (10% yield) was eluted with hexane and found to consist of predominantly olefin **18**: ir 3100, 1640, 890 cm^{-1}; nmr δ 0.79 (s, 3 H, CH_3), 1.6 (t, J = 1 Hz, 3 H, $=CCH_3$), 4.60 (q, J = 1 Hz, 2 H, $=CH_2$).

The alcohol **6-OH** (80%) was eluted with 5% ether in hexane: ir 3620 cm^{-1}; nmr δ 0.80 (s, 3 H, C-3a CH_3), 1.19 [s, 6 H, C-$(CH_3)_2$]; nmr (with 0.2 molar equiv of europium trisdipivalomethane) δ 1.12 (s, 3 H, C-3a CH_3), 2.94 and 3.04 [2 s, 3 H, $C(CH_3)_2$].

Anal. Calcd for $C_{13}H_{24}O$: C, 79.53; H, 12.32. Found: C, 79.30; H, 12.17.

The *p*-nitrobenzoate of **6-OH** had mp 95–97°; nmr δ 0.87 (s, 3 H, C-3a CH_3), 1.6 (s, 6 H), 8.1–8.5 (quartet, 4 H, ArH).

Hydrolysis of the labeled substrate (**5-d_3-OMs**) was performed in exactly the same manner as described for **5-OMs**. The nmr spectrum of the resulting tertiary alcohol **6-d_3-OH** in the presence of 0.2 molar equiv of europium trisdipivalomethane showed the diastereotopic methyl peaks at δ 2.95 and 3.04 with essentially equal intensities (94:100).

B. Acetolyses.—A solution of 500 mg (1.82 mmol) of **5-OMs** in 50 ml of acetic acid containing 820 mg (10 mmol) of sodium acetate was kept at ~75° for 5 hr 20 min. A standard extractive work-up[33] followed by chromatography on 12 g of silica gel gave a hydrocarbon mixture (72 mg, 22%, eluted with hexane) consisting of olefins **18** and **19** (83:17 by glpc) and acetate **6-OAc** (160 mg, 37%, eluted with 2% ether in hexane): ir 1725 cm^{-1}; nmr δ 0.79 (s, 3 H, C-4a CH_3), 1.40 and 1.42 [each s, 3 H, C-$(CH_3)_2$], 2.08 (s, 3 H, OAc). The acetate was treated with $LiAlH_4$, and the resulting alcohol was identical with **6-OH** by glpc (column D) and nmr analyses.

A solution of 548 mg (2 mmol) of the labeled methanesulfonate **5-d_3-OMs** in 50 ml of acetic acid containing 820 mg (10 mmol) of sodium acetate was kept at ~75° for 5 hr (acetolysis was not complete). Work-up identical with that discussed above gave a hydrocarbon mixture (120 mg, 34%) and the acetate (115 mg, 24%). The ester was cleaved with $LiAlH_4$ and the nmr spectrum of the alcohol was determined in the presence of the europium shift reagent as described above. Again the intensities of the shifted methyl signals were essentially equal (91:100).

C. Formolysis.—A solution of 548 mg (2 mmol) of **5-OMs** in 50 ml of formic acid (0.04 M concentration) containing 680 mg (10 mmol) of sodium formate was stirred for 80 min at room temperature. A standard extractive work-up with ether,[33] followed by treatment with 5% methanolic potassium hydroxide (1 hr at reflux), and a silica gel chromatography gave mainly hydrocarbon (46%) and alcohol **6-OH** (17%). The structure of the hydrocarbon was assigned as **19** based on nmr: δ 0.93 and 0.98 [each d, J = 7 Hz, 3 H, $CH(CH_3)_2$], 0.98 (s, 3 H, C-4a CH_3). The same olefin **19** was obtained from **18** by treatment with formic acid containing sodium formate at room temperature for 90 min in *ca.* 70% yield.

3aα,4,5,6,7,7aβ-Hexahydro-3aα-methyl-1β-indanyl Methyl Ketone (20).—To a solution of 2 g (10.2 mmol) of **6-OH** in 13.5 ml of pyridine was added 2.48 g (20.4 mmol) of thionyl chloride at 0°. The solution was stirred for 13 min at 0° and poured into 135 ml of ice–water. The standard extractive work-up with petroleum ether[33] (bp 30–60°) followed by chromatography on silica gel gave 1.25 g (68%) of colorless oil (eluted with hexane). The major product (88%) was separated from two minor products (12%) by preparative glpc (column G, 135°) and identified as **18** by nmr comparison.

The olefin mixture (500 mg, 2.8 mmol) in 25 ml of acetone and 2 ml of carbon tetrachloride was added slowly to a yellow solution of ruthenium dioxide dihydrate (475 mg, 2.80 mmol) and sodium periodate (3 g, 14 mmol) in 60 ml of water.[39] Two additional 3-g portions of periodate were added to the reaction at 12 and 17 hr, then at 18 hr isopropyl alcohol (~30 ml) was added. After 1 hr with stirring the precipitate was filtered and washed with acetone and ether. The filtrate was concentrated and diluted with ether, and the product (350 mg) was isolated by a standard extractive work-up. Chromatography on silica gel afforded the methyl ketone **20** (250 mg, 50%): nmr δ 0.80 (s, 3 H, C-3a CH_3), 2.14 (s, 3 H, $COCH_3$).

Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.87; H, 11.15.

Hydrolysis of 5-OMs in the Presence of Sodium Azide. A.—A solution of 274 mg (1 mmol) of **5-OMs** and 650 mg (10 mmol) of freshly recrystallized sodium azide[20] in 100 ml of 80% aqueous acetone (water–acetone 20–80, v/v before mixing) was heated under reflux for 46 hr. The acetone solvent was partially evaporated and a standard extractive work-up with ether was followed.[33] The oily product was chromatographed in 12 g of silica gel, affording 17 mg of a mixture of olefins (8%) and alkyl azide **6-N_3** (1%) (eluted with hexane). From glpc analysis (column B, 100°) the relative ratio of alkyl azide:olefins:tertiary alcohol was estimated as 1.9:13.4:84.7, and the ratio of $k_{N_3^-}/k_{H_2O} \cong 2.5$.[20]

B.—A solution of 274 mg (1 mmol) of **5-OMs** and 6.5 g (100 mmol) of freshly recrystallized sodium azide in 50 ml of 50% aqueous acetone was heated under reflux for 6.7 hr and worked up as described in A. The ir (2100 cm^{-1}) absorbance of the alkyl azide was about 5.6 times stronger than that above. A pure sample of azide **6-N_3** was obtained by preparative glpc (column E, 162°): ir 2100 cm^{-1}; nmr δ 0.78 (s, 3 H, C-3 CH_3), 1.20 and 1.27 [each s, 3 H, $C(CH_3)_2$]; mass spectrum m/e (rel intensity) 179 ($M^+ - N_3$, 4), 178 ($M^+ - HN_3$, 4), 137 [$M^+ - N_3C(CH_3)_2$, 26], 95 (62), 81 (100).

***o*-Chlorosulfinylbenzoyl chloride (24)** was prepared according to the literature procedures[26] in 96% yield, mp 58–62° (lit. mp 62–64°). The dichloride decomposes upon storage.

2-Phenylethyl [*o*-Carbo(*p*-nitrophenoxy)]benzenesulfonate (27a).—A solution of 3.67 g (30 mmol) of freshly distilled 2-phenylethanol (**23**), 2.37 g (30 mmol) of pyridine, and 6.7 g (30 mmol) of the sulfinyl chloride **24** in 60 ml of ether was stirred for 35 min at 0°; then 2.37 g (30 mmol) of pyridine and a solution of 4.17 g (30 mmol) of *p*-nitrophenol in 40 ml of ether were added successively. The mixture was stirred for 2 hr at 0°, then diluted with chloroform. The solution was washed with 5% potassium carbonate, saturated sodium bicarbonate, and water, then dried (Na_2SO_4) and evaporated. The resulting oil crystallized from acetone to give 5.1 g (42%) of the sulfinate **26a**: mp 120–123°; ir 1700, 1620, 1590, 1530, 1495, 1355 cm^{-1}; nmr δ 2.87 (t, J = 7 Hz, 2 H, $PhCH_2$), 3.7–4.4 (m, 2 H, CH_2OSO_2Ar), 7.23 and 8.21 (each d, J = 9.5 Hz, 2 H, *p*-nitrophenyl), 7.4–8.0 (m, 4 H, ArH).

Anal. Calcd for $C_{21}H_{17}NSO_6$: C, 61.31; H, 4.14; N, 3.41; S, 7.79. Found: C, 60.91; H, 4.33; N, 3.25; S, 7.91.

A solution of sulfinate **26a** (4.11 g, 10 mmol) and 85% *m*-chloroperoxybenzoic acid (2.22 g, 11 mmol) in 85 ml of methylene chloride was allowed to stand for 5 hr at room temperature.[27] After extraction with 5% potassium carbonate and water, the solution was dried (Na_2SO_4) and evaporated. The initially oily sulfonate **27a** (85%) crystallized upon storage overnight in a refrigerator: mp 74–78° (from acetone); ir 1710, 1620, 1595, 1530, 1495, 1365, 1345 cm^{-1}; nmr (CCl_4) δ 2.90 (t, J = 7 Hz, 2 H, $PhCH_2$), 4.26 (t, J = 7 Hz, 2 H, CH_2OSO_2Ar), 7.01 (br s, 5 H, phenyl), 7.30 and 8.12 (each d, J = 10 Hz, 2 H, *p*-nitrophenyl), 7.4–8.0 (m, 4 H, ArH).

2,24aα-Trimethyl-1,2,3,4,4aα,5,6,7,8,8aβ-decahydronaphthalen-1β-yl [*o*-Carbo(*p*-nitrophenoxy)]benzensulfonate (27b).—To a solution of 1.96 g (10 mmol) of decalol **5-OH** and 791 mg (10 mmol) of pyridine in 50 ml of ether at 10° was added 2.7 g (12 mmol) of freshly prepared sulfinyl chloride **2** in one portion. The mixture was stirred for 1 hr at room temperature, and then

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791 mg (10 mmol) of pyridine and 1.3 g (10 mmol) of *p*-nitrophenol were added in succession. The reaction mixture was stirred vigorously for an additional 2 hr at room temperature. The precipitate was filtered and washed with ether. The combined ether solution was washed with 0.1 *N* sodium carbonate and saturated sodium bicarbonate until no yellow color was observed in the washing, and then with water and brine. The ether solution was dried and evaporated and the residue was chromatographed on 100 g of silica gel, yielding 2.75 g (57%) of the amorphous sulfinate **26b** (eluted with 20% ether in hexane): ir 1740, 1580, 1608, 1520, 1340, 1132 cm^{-1}; nmr (CCl_4) δ 0.83 (s, 3 H), 0.88 (s, 3 H), 1.0 (s, 3 H), 3.90 [d, J = 10 Hz, 1 H, CHOS(O)-Ar], 7.42 and 8.31 (each d, 2 H, *p*-nitrophenyl), 7.3–8.4 (m, 4 H, ArH).

A solution of 1.16 g (5.7 mmol) of 85% *m*-chloroperbenzoic acid in 30 ml of methylene chloride was added to a solution of 2.75 g (5.7 mmol) of sulfinate **4b** in 20 ml of methylene chloride at 0°.[27] The resulting solution was stirred for 12 hr at room temperature and then chilled to 0° to induce precipitation. After filtration, the filtrate was evaporated and redissolved in hexane and ether. The organic phase was successively washed with 0.1 *N* sodium carbonate, saturated sodium bicarbonate, and water, dried, and evaporated at room temperature to give 2.45 g (86%) of the crystalline sulfonate **27b**: mp 101–103°; ir 1750 (C=O), 1607, 1580 (aromatic), 1518, 1340 (NO_2), 1355, 1170 cm^{-1} (SO_3); nmr δ 0.78 (s, 3 H), 0.84 (s, 3 H), 0.87 (s, 3 H), 4.61 (d, J = 10.5 Hz, 1 H, $CHOSO_2Ar$), 7.35–8.64 (m, 8 H, ArH).

Anal. Calcd for $C_{25}H_{31}O_7SN$: C, 62.28; H, 6.19; S, 6.39. Found: C, 61.93; H, 6.29; S, 6.48.

***o*-(2-Phenylethoxy)sulfonylbenzoic Acid (28a).**—A solution of 429 mg (1 mmol) of *p*-nitrophenyl ester **5a** in 40 ml of dioxane and 40 ml (4 mmol) of 0.1 *N* sodium hydroxide was stirred for 10 min at room temperature. The progress of saponification was followed by tlc and the starting material was observed to disappear after 10 min. The solution was poured into a large amount of water and any neutral material was removed by ether extraction. The aqueous phase was acidified and extracted with ether, and the ether extract was dried (Na_2SO_4) and evaporated. The resulting oily material (*ca.* 400 mg, 99%) proved to be a 1:1 mixture of *p*-nitrophenol and carboxylic acid **28a**: ir 1730, 3400–2800, 1590–1610, 1360 cm^{-1}; nmr δ 2.96 (t, J = 7 Hz, 2 H, $PhCH_2$) 4.34 (t, J = 7 Hz, 2 H, CH_2OSO_2Ar), 7.09 (br s, 5 H, Ph), 7.35–7.80 (m, 4 H, ArH).

Esterification with diazomethane afforded the methyl ester **29a** contaminated by a small amount of *p*-nitroanisole: ir 1735, 1360 cm^{-1}; nmr δ 2.96 (t, J = 7 Hz, 2 H, $PhCH_2$), 3.85 (s, 3 H, CO_2CH_3), 4.32 (t, J = 7 Hz, CH_2OSO_2Ar), 7.09 (br s, 5 H, Ph), 7.35–7.80 (m, 4 H, ArH).

Anal. Calcd for $C_{16}H_{16}SO_5$: C, 60.00; H, 5.00. Found: C, 60.45; H, 5.17.

***o*-(2-Phenylethoxy)sulfonylthiobenzoic Acid (30a).**—To a solution of 1.71 g (4 mmol) of *p*-nitrophenyl ester **5a** in 40 ml of ethanol and 60 ml of dioxane was added 20 ml (20 mmol) of 1 *N* sodium hydrogen sulfide in ethanol prepared by saturating 1 *N* sodium ethoxide in ethanol with hydrogen sulfide.[28,29] The mixture was stirred for 30 min at room temperature. Tlc analysis showed no starting material left after 30 min. Neutral material (~600 mg) was removed by chloroform extraction, the aqueous solution was acidified and extracted with chloroform, and the chloroform extract was washed with water twice, dried, and evaporated. The residual oil (0.99 g) was a 1:1 mixture of *p*-nitrophenol and the thio acid **30a** (54%): ir 1700, 1670, 1595, 1340 cm^{-1}; nmr δ 3.0 (t, J = 7 Hz, 2 H, $PhCH_2$), 4.34 (t, J = 7 Hz, 2 H, CH_2OSO_2Ar), 7.12 (br s, 5 H, Ph), 7.4–8.0 (m, 4 H, ArH).

Exposure of the acid to diazomethane effected conversion to the *S*-methyl ester **31a**, which was further purified by preparative tlc: ir 1670, 1360, 1180 cm^{-1}; nmr δ 2.50 (s, 3 H, $COSCH_3$), 3.16 (t, J = 7 Hz, 2 H), 4.34 (t, J = 7 Hz, 2 H), 7.20 (br s, 5 H), 7.5–8.2 (m, 4 H).

Anal. Calcd for $C_{16}H_{16}S_2O_4$: C, 57.14; H, 4.76. Found: C, 57.38; H, 4.98.

Saponification of 2,2,4aα-Trimethyl-1,2,3,4,4aα,5,6,7,8,8aβ-decahydronaphthalen-1β-yl [*o*-Carbo(*p*-nitrophenoxy)]benzenesulfonate (27b).—A solution of 501 mg (1 mmol) of *p*-nitrophenyl ester **27b** in 120 ml of dioxane and 20 ml of 0.1 *N* sodium hydroxide was stirred for 2.5 hr at room temperature. During this period the tlc spot for **27b** disappeared and a very polar spot appeared, and the pH of the solution became almost neutral. The reaction mixture was poured into ice–water, acidified with concentrated hydrochloric acid, saturated with sodium chloride, and extracted with ether. The extracts were combined, washed with cold brine, and dried.

About one third of the dried extract was treated with diazomethane in ether and then washed with 0.1 *N* ammonium hydroxide, saturated sodium bicarbonate, and water, successively dried, and evaporated to give 140 mg of an oily material which was a 43:57 mixture of *p*-nitroanisole [67%; nmr δ 3.90 (s, 3 H), 6.96 and 8.17 (AB doublet, J_{AB} = 9.3 Hz)] and methyl ester **29b** (88%) according to the following nmr data: δ 0.78 (s, 3 H), 0.90 (s, 3 H), 0.98 (s, 3 H), 3.98 (s, 3 H, CO_2CH_3), 4.56 (d, J = 10.5 Hz, 1 H, $CHOSO_2Ar$), 7.3–8.3 (m, 4 H). A sample of methyl ester **29b** obtained free of *p*-nitroanisole in another run had spectral data identical with the preceding data obtained from the spectrum of the mixture. Another one third of the extract was evaporated at 10° to give an oil, which decomposed rapidly at room temperature.

Acetolysis of *o*-Carboxybenzenesulfonate 28b.—The *p*-nitrophenyl ester **27b** (501 mg, 1.00 mmol) was saponified and worked up as described above. The volume of the ether extract was reduced to 5 ml at 10°, and then diluted with 50 ml of high-boiling petroleum ether. After the concentration–dilution was repeated twice (to remove residual dioxane), the volume was finally reduced to *ca.* 1 ml. The solution was diluted with 100 ml of glacial acetic acid containing 820 mg (10 mmol) of sodium acetate, heated at 60° for 30 min, poured into ice–water, and extracted with ether. The combined ether extracts were washed successively with 0.2 *N* sodium carbonate, saturated sodium bicarbonate, and brine, dried, and evaporated to give *ca.* 210 mg (~97%) of oil, which was found by glpc analyses to consist of olefin **18** and **19**, alcohol **6-OH**, and acetate **6-OAc** in the ratio 40:12:34:14. Alcohol **6-OH** apparently arises from partial hydrolysis of **24** under the conditions of saponification and/or the isolation procedure prior and/or subsequent to acetolysis. Aliquots taken at various times from another acetolysis at 25° and processed as described above indicated that the amount of **6-OAc** was increasing with time while the amount of **6-OH**, which was present from the beginning, was decreasing, albeit with some irregularity.

Sulfhydrolysis of *p*-Nitrophenyl Ester 27b.—Sodium hydrogen sulfide (5 ml of 1 *N*) in ethanol, prepared by saturating 1 *N* sodium ethoxide in ethanol with hydrogen sulfide,[28,29] was added to a solution of 510 mg (1 mmol) of *p*-nitrophenyl ester **27b** in 120 ml of dioxane. After 40 min at room temperature (**23** consumed according to tlc analysis) the mixture was poured into ice–water, the pH was adjusted to about 9 by addition of potassium carbonate, and a small amount of neutral material (66 mg, mostly **6-OH**) was removed by ether extraction. The aqueous solution was acidified and extracted with ether. The extracts were washed with cold water, dried, and concentrated to *ca.* 4 ml. A part (1 ml) of the concentrated extract was treated with diazomethane, washed with saturated sodium bicarbonate and water, dried, and evaporated, giving an 85:15 mixture of the *S*-methyl ester **31b** and *p*-nitroanisole, containing a trace of the tertiary alcohol **6-OH**. The nmr data for **31b** are as follows: δ 0.75 (s, 3 H), 0.88 (s, 3 H), 0.98 (s, 3 H), 2.50 (s, 3 H, $COSCH_3$), 4.33 (d, J = 11 Hz, 1 H, $CHOSO_2Ar$), 7.5–7.6 and 7.8–8.2 (m, total 4 H, ArH).

Hydrolysis of *o*-Thiocarboxybenzenesulfonate 30b.—The *p*-nitrophenyl ester **27b** (250 mg, 0.5 mmol) was subjected to sulfhydrolysis as described above. The concentrated ether solution of the thio acid was diluted with 10 ml of 0.1 *N* sodium hydroxide and 20 ml of water and then heated for 70 min at 70°. A standard extractive work-up followed by chromatography on silica gel afforded olefin **18** (15 mg, 17%) and the ring-contracted alcohol **6-OH** (50 mg, 51%).

Control Experiments. A.—A solution of *tert*-butyl benzoate (K & K Laboratories, 182 mg, 1.02 mmol) in 75 ml of acetic acid containing 821 mg (10 mmol) of sodium acetate was heated at 60° for 30 min. The solution was diluted with water and extracted three times with pentane. The combined pentane extracts were washed once each with water and saturated sodium bicarbonate, then dried ($MgSO_4$) and evaporated. The remaining oil (128 mg, 98%) had ir and nmr spectra identical with those of the starting *tert*-butyl ester.

B.—Benzoyl chloride (11.7 ml, 14.1 g, 0.10 mol) was added slowly (5–10 min) with stirring to a cooled (0°) solution of *tert*-butyl mercaptan (9.0 g, 0.10 mol) in 24 ml of pyridine.[40] The

(40) R. L. Buckson and S. G. Smith, *J. Org. Chem.*, **32**, 634 (1967).

suspension was allowed to warm to room temperature over a 5–10-min period, diluted with ether, and extracted once each with water, 10% sulfuric acid, saturated sodium bicarbonate, and saturated brine. The dried ($MgSO_4$) ethereal solution was evaporated, a 1.4-g crop of yellow crystals (from petroleum ether, bp 60–68°) was separated by filtration, and the concentrated filtrate was distilled under reduced pressure. *tert*-Butyl thiolbenzoate (8.7 g, 45%) was obtained as a water-white liquid: bp ~135–145°(15–25 mm) [lit.[41] bp 127° (11 mm)]; ir (all s) 687, 772, 908, 1060, 1205, 1655 cm^{-1} (C=O); nmr δ 1.55 (s, 9 H), 7.2–7.4 (m, 3 H), 7.7–7.9 (m, 2 H).

A solution of the thiolbenzoate (99 mg, 0.51 mmol) in ~30 ml 50% aqueous dioxane (v/v before mixing) was heated at 105° for 12 days in a sealed ampoule. The ester (83 mg, 84%), recovered by extraction with pentane, had unchanged ir and nmr spectra.

Acknowledgment.—We thank the National Institutes of Health for financial assistance and the National Science Foundation for funds used in the purchase of a Varian HR 220 nmr spectrometer.

(41) H. Reinholt, F. Mott, and E. Motzkers, *J. Prakt. Chem.*, **134**, 274 (1932).

Registry No.—**5**-OH, 40599-63-1; **5**-OMs, 40599-64-2; **5**-d_3-OMs, 40625-59-0; **6** (R = H), 40599-65-3; **6** (R = H) *p*-nitrobenzoate, 40599-66-4; **6**-d_3 (R = H) (R*), 40599-67-5; **6**-d_3 (R = H) (S*), 40625-60-3; **6** (R = Ac), 40599-68-6; **6** (X = N_3), 40625-61-4; *cis*-**7**, 32166-40-8; *trans*-**7**, 21370-71-8; *cis*-**8a** (X = OH), 40599-69-7; *trans*-**8a** (X = OH), 40599-70-0; *cis*-**8b** (X = S-*n*-Bu), 40599-71-1; *trans*-**8b** (X = S-*n*-Bu), 40599-72-2; **9**, 40599-73-3; **9**-d_3, 40625-62-5; **10**, 40599-74-4; **10**-d_3, 40625-63-6; **11**, 40599-75-5; **12**, 40724-84-3; **13**, 40599-77-7; **14a**, 40599-78-8; **14b**, 40599-79-9; **15**, 40599-80-2; **16**, 40599-81-3; **17b**, 40599-82-4; **18**, 40599-83-5; **19**, 40599-84-6; **20**, 40599-85-7; **23**, 60-12-8; **24**, 40625-64-7; **26a**, 40599-86-8; **26b**, 40599-87-9; **27a**, 40599-88-0; **27b**, 40599-89-1; **28a**, 40599-90-4; **28b**, 40599-91-5; **29a**, 40599-92-6; **29b**, 40599-93-7; **30a**, 40599-94-8; **30b**, 40599-95-9; **31a**, 40599-96-0; **31b**, 40599-97-1; *n*-butanethiol, 109-79-5; methanesulfonyl chloride, 124-63-0; 4α,β-methyl-3,4,4aβ,5,6,7 8,8aα-octahydronaphthalen-2(1*H*)-one, 938-07-8; sodium azide, 12136-89-9; *p*-nitrophenol, 100-02-7.

Triterpenes of *Datura innoxia* Mill. Structure of Daturadiol and Daturaolone

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Two new pentacyclic triterpenes, daturadiol and daturaolone, have been isolated from *Datura innoxia* Mill. seeds (Solanaceae). The structures—3β,6β-dihydroxyolean-12-ene and 3-oxo-6β-hydroxyolean-12-ene—were established by chemical degradation and supported by the spectral properties.

Two new pentacyclic triterpenes have been isolated from *Datura innoxia* Mill. (Solanaceae), a known source of tropane alkaloids.[1] A mixture of these two compounds crystallized from the oil extracted from the seeds.[2] The determination of their structure is presented below.

The pmr spectrum of the more polar *Datura* triterpene—daturadiol **1a**—shows the presence of two secondary hydroxyl groups and a trisubstituted double bond (Table I). The spectrum shows also the presence of eight tertiary methyl groups. The latter observation, combined with the shape and position of the olefinic proton signal [triplet δ 5.22 (J = 3 Hz)], suggested that the compound was most probably a diol of the β-amyrin type. Acetylation at room temperature gave the monoacetate **1d**; its pmr spectrum (Table I) showed that only the triplet-like signal, ascribed to the 3α-H, was shifted downfield with a slight change in shape. The molecular rotation change caused by the acetylation ($\Delta[M]_D$ = −57°) is consistent with similar values for 3β-hydroxytriterpenes (*e.g.*, β-amyrin −33°, α-amyrin, −29°, lupeol −69°, taraxasterol −67°, and ψ-taraxasterol −53°).

The low reactivity of the second secondary hydroxyl group, and the shape of the signal corresponding to the HCOH [broad singlet at δ 4.54 ($W_{1/2}$ = 10 Hz)] indicated that it was axially oriented. Prolonged reaction time at boiling temperature with pyridine–acetic anhydride or acetic anhydride–boron trifluoride etherate at room temperature led to daturadiol diacetate **1c**.

This diacetate, when oxidized with a stoichiometric amount of selenium dioxide, gave a derivative typical for a β-amyrin, that is the 11,13(18)-diene[3] **2**, with characteristic uv absorption. Prolonged oxidation with an excess of selenium dioxide led to a second characteristic product[4] **3**, showing typical uv and ir absorption.

To assure the presence of the β-amyrin skeleton the axial hydroxyl group was removed by the following series of reactions. The monoacetate **1d** was oxidized with Jones reagent to the keto acetate **1e**. The latter underwent Wolff–Kishner reduction only under drastic conditions (anhydrous hydrazine, sodium in ethylene glycol), yielding β-amyrin in 25% yield.

Evidence for the location of the second hydroxyl group is provided by the pmr spectrum of keto acetate **1e** (Table I). The broad singlet of the equatorial proton was replaced by a slightly broadened doublet at δ 2.51 (J = 12.5 Hz) and a singlet at δ 2.23. Thus the fragment $\geqslant CCHCOCH_2C\leqslant$ should be present in the keto acetate. In β-amyrin there is only one such possible location for a carbonyl group, *i.e.*, position 6.

The second new triterpene, daturaolone **1b**, was less polar than daturadiol. Its ir spectrum showed the presence of hydroxyl and carbonyl groups. As in the case of daturadiol, an olefinic proton signal and a broad singlet of 6α-H are present (Table I), as well as a one-proton multiplet (doublet of triplets) at 2.76 ppm. In addition, eight tertiary methyl group signals are

(1) H. G. Boit, "Ergebnisse der Alkaloid Chemie bis 1960," 1961.

(2) C. K. Atal, *et al.*, Indian Pharmaceutical Congress, Hajderabad, 1967.

(3) "Elsevier Encyclopedia," 14th Suppl., 1952, pp 945–1064.

(4) H. Budzikiewicx, J. M. Wilson, and C. Djerassi, *J. Amer. Chem. Soc.*, **85**, 3688 (1963).

TABLE I

100-MHz SPECTRAL DATA OF *Datura* TRITERPENES AND THEIR DERIVATIVES[a]

Compd	2β-H	3α-H	5α-H	6α-H	7α-H	12-H	23	24	25	26	27	28	29,30	CH_3COO-
							Methyl group signals, the most probable assignment[b]							
1a		3.15 t (7.5)		4.54 b s		5.21 t (3)	1.08	1.18	1.32	1.27	1.10	0.84	0.88	
1b	2.76 m			4.48 b s		5.23	1.17	1.42	1.51	1.33	1.10	0.85	0.88	
1c		4.44 q (10, 7)		5.55 b s		5.23 t (3)	0.93	1.03	1.33	1.14	1.10	0.81	0.87	2.03 (two)
1d		4.45 q (10, 6)		4.45 b s		5.23 t (3)	0.95	1.26	1.35	1.26	1.10	0.83	0.87	2.04
1e		4.41 q	2.21 s		2.51 d (12.5)	5.23 t (3)	1.01	1.31	0.98	0.94	1.26	0.81	0.88	2.04
1g			2.12		2.52 d (12.2)	5.20 t (3)	1.00	1.27	0.93	0.93	1.27	0.81	0.88	
5α-1h	2.79 m		2.47 s		2.52 d (12)	5.24 t (3)	1.25	1.52	1.12	1.08	1.25	0.82	0.88	
5β-1h			2.40 s		2.50 d (12)	5.27 t	(1.23,	1.20,	1.16,	1.13,	1.04)	0.82	0.88	
4				5.58 t, 4.2		5.24 t (3)	(1.27,	1.24,	1.13,	1.04,	0.93)	0.85	0.88	

[a] In $CDCl_3$, δ values (*J* in hertz). [b] The following values of the "6-substitution effect" (close to those given in ref 4) were used.

6β-OH	0.08	0.39	0.40	0.27	−0.03	0	0
6β-OAc	0.07	0.17	0.37	0.18	−0.03	−0.01	0.01
6-Oxo	0.14	0.45	0.03	−0.02	0.12	−0.03	0.01

clearly visible. Oxidation of daturaolone with Jones reagent led to the same diketone **1h** as obtained from daturadiol. Therefore daturaolone must have the structure **1b** (3-oxo-6β-hydroxyolean-12-ene). The one-proton multiplet in the pmr spectrum of daturaolone is ascribed to the 2β(axial)-H. It is also visible at the same position in the spectrum of daturadione **1h**, which in addition shows the signals of the 5α and 7α protons. The 5α-H signals in the spectra of **2e** and **1h** are shifted downfield by 0.09 and 0.35 ppm, respectively, compared with the position in the spectrum of the 6-oxo compound **1h** described below, an observation which provides additional evidence for the close vicinity of both oxygen functions.

Daturadione **1h**, when refluxed with base, underwent epimerization to the more polar 5β epimer to the extent of approximately 10%. The mass spectrum of the latter was very similar to that of the 5α epimer (Table II), but its pmr spectrum, with shifted methyl and 2-, 5-, and 7-H signals, reflected the change in configuration (Table I). When the epimerization was carried out with D_2O and NaOD in monoglyme, five deuterium atoms were incorporated, as shown by the change in the molecular ion from *m/e* 438 to 443 (Table II).

TABLE II

MASS SPECTRAL DATA OF *Datura* TRITERPENES

Compd	Molecular ion *m/e*	Molecular ion %	189,[a] %	203,[a] %	218, %	258, %
1a	442	3.2	14	38	100	4.8
1b	440	4.1	11	37	100	4.2
1c	526	1.3	6	34	100	15
1d	484	2.6	7	18	100	4.6
1e	482	5.1	7	30	100	3.9
1f	426	5.0	16	51	100	8.1
1g	424	2.1	7	21	100	5.1
5α-1h	438	9.5	12	51	100	3.1
5β-1h	438	12	10	63	100	5.5
1h-d_5	443	3.4	9	48	100	3.3
	442	1.9				
	441	0.3				
	422	27	24	52	100	18

[a] Ions *m/e* 189 and 203 are formed from the ion *m/e* 218 by elimination of *m/e* 15 and 29: K. Takahashi, K. Kanayama, Y. Tanabe, and M. Takani, *Chem. Pharm. Bull.*, **20**, 2106 (1972).

The mass spectra of all compounds are fully consistent with 3,6 substitution of the oleane skeleton. For Δ^{12} compounds the dominating fragmentation process is the formation of the ion 218 in the retrodiene reaction which represents the base peak in all compounds and is derived from ring D and E.[4] A second retrodiene reaction starting with the formation of the 5(6) double bond is also present[5,6] (ion *m/e* 258 for **1** and **4**, shifted to 256 for **2**). This process is more pronounced in the spectra of daturadiol diacetate **1c** and anhydrodaturaolone **4** (Table II).

Tables I and II give properties of some other products derived from the new *Datura* triterpene. 6β-Hydroxy- and 6-oxoolean-12-ene (**1f** and **1g**) were obtained by Wolff–Kishner reduction of daturaolone and daturadiol, respectively. The latter reaction demonstrates the great steric hindrance of the 6-keto function, similar to the situation in the case of sumaresinolic acid[7] and astilbic acid.[8]

An independent proof of the daturaolone structure is the formation of the anhydro compound **4** from daturaolone by treatment with thionyl chloride in pyridine. The pmr spectrum of this product demonstrates the presence of only two olefinic proton signals, the triplet of H-12 at 5.24 (J = 3 Hz) and the triplet of H-6 at 5.58 ppm (J = 4.2 Hz).

Daturadiol and daturaolone are members of the rare class of 6β-hydroxylated β-amyrin derivatives.

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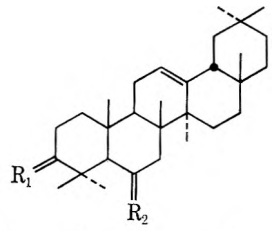
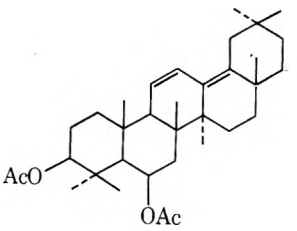
(6) I. Kitagawa, A. Inada, I. Yosioka, R. Somanathan, and M. U. S. Sultanbawa, *Chem. Pharm. Bull.*, **20**, 633 (1972).

(7) C. Djerassi, G. N. Thomas, and O. Jeger, *Helv. Chim. Acta*, **38**, 1304 (1955).

(8) H. Hikino, S. Nabetani, and T. Takemoto, *Yakugaku Zasshi*, **92**, 891 (1972).



1	R_1	R_2
a	β-OH, α-H	β-OH, α-H
b	O	OH, H
c	β-OAc, α-H	β-OAc, α-H
d	β-OAc, α-H	β-OH, α-H
e	β-OAc, α-H	O
f	H_2	β-OH, α-H
g	H_2	O
h	O	O



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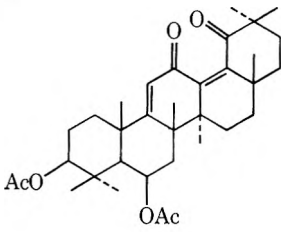

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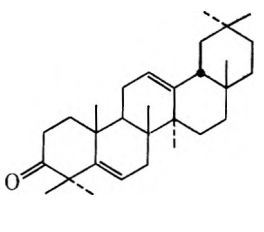

4

The only other known examples are sumaresinolic acid,[7] its 3-keto derivative[5] (3β,6β-dihydroxy- and 3-oxo-6β-hydroxyolean-12-en-28-oic acid, respectively), and protobassic acid[6] (2β,3β,6β,23-tetrahydroxyolean-12-en-28-oic acid). Recently also 6β-hydroxylation of oleanolic acid by a soil bacterium[8] has been observed and the new acid astilbic acid[9] (3β,6β-dihydroxyolean-12-en-27-oic) has been described. The *Datura* triterpenes represent the parent compounds of the above group.

Experimental Section

Melting points were measured on a micro hot plate. Optical rotations were measured at 0.5% concentration in chloroform. Pmr spectra were determined with a Jeol 100-MHz spectrometer in $CDCl_3$ solution (accuracy of chemical shift measurements, ±0.5 Hz). Mass spectra were carried out on an LKB 9000 apparatus, ionization energy 70 eV.

Extraction and Purification of 1b and 1a.—Coarsely powdered *Datura innoxia* seeds (5 kg) were extracted with petroleum ether (bp 60–80°). The oil obtained (400 ml) was kept at 10° for 10 days, during which time a crystalline solid (4.5 g) separated. It was chromatographed on 150 g of alumina. Elution with benzene gave 3.5 g of daturaolone **1b**, which was crystallized from benzene and a mixture of chloroform and methanol: mp 276–279°; $[\alpha]_D$ +48.5°; ν_{max} (KBr) 3500, 1690 cm^{-1}.

Anal. Calcd for $C_{30}H_{48}O_2$: C, 81.76; H, 10.98. Found: C, 81.64; H, 10.72.

Subsequently 0.8 g of daturadiol **1a** was eluted with benzene–chloroform (9:1). It was recrystallized from benzene–chloroform and chloroform–methanol and had mp 260–261°, $[\alpha]_D$ +48.9°, ν_{max} (KBr) 3500 cm^{-1}.

Anal. Calcd for $C_{30}H_{50}O_2$: C, 81.39; H, 11.4. Found: C, 81.44; H, 11.31.

Daturadione 1h.—Oxidation of both of the above compounds with Jones reagent in acetone at room temperature for 5 min yielded the same compound **1h** (melting point, mixture melting point, ir, and R_f value) which was recrystallized from methanol–chloroform and had mp 198–201°, $[\alpha]_D$ +50.3°, ν_{max} (KBr) 1705 cm^{-1}.

Anal. Calcd for $C_{30}H_{46}O_2$: C, 82.13; H, 10.6. Found: C, 82.23; H, 10.45.

5-Epidaturadione.—Daturadione refluxed with 5% NaOH in ethylene glycol for 4 hr was transformed in about 10% yield to a more polar compound, which was separated by chromatography on silica gel with benzene as solvent and crystallized from dilute alcohol: mp 187–191°.

Deuteration of Daturadione.—Daturadione **1h** (25 mg) was refluxed for 1 hr with 5% NaOD in D_2O (2 ml) and 5 ml of monoglyme. When the hot solution was diluted with D_2O, 19 mg of a mixture of both epimers (9:1, tlc) separated and was purified by washing with D_2O: mp 168–182°; ν_{max} (KBr) 2250, 2140, 1705 cm^{-1}. Bands at 1440 and 1280 cm^{-1} in the spectrum of daturadione were no longer present.

Monoacetate of Daturadiol 1d.—**1a** (224 mg) was kept in 5 ml of pyridine and 1 ml of acetic anhydride for 4 days at room temperature. The usual work-up and chromatography on silica gel with benzene yielded pure monoacetate which was crystallized from dilute alcohol: 190 mg; mp 227–236°; ν_{max} (KBr) 3520, 1704, 1265 (C_2Cl_4), 3600, 1730, 1240 cm^{-1}.

Anal. Calcd for $C_{32}H_{52}O_3$: C, 79.28; H, 10.81. Found: C, 79.07; H, 10.82.

Daturadiol Diacetate 1c.—Daturadiol **1a** (142 mg) was refluxed in pyridine–acetic anhydride mixture for 4 hr. The two products formed were separated on a silica gel column with benzene as solvent. After the monoacetate **1d** (26 mg) was eluted, further elution gave the pure diacetate, which was crystallized from dilute alcohol: 54 mg; mp 141–144°; $[\alpha]_D$ +34.2°; ν_{max} (KBr) 1735, 1245 cm^{-1}.

Anal. Calcd for $C_{34}H_{54}O_4$: C, 77.52; H, 10.33. Found: C, 78.10; H, 10.23.

Acetylation of daturadiol with acetic anhydride in the presence of boron trifluoride etherate gave only the diacetate (same R_f value and melting point) accompanied by a small amount of nonpolar products.

3β,6β-Diacetoxyolean-11,13(18)-diene (2).—Daturadiol diacetate **1c** (66.5 mg) was refluxed with 20 mg of selenium dioxide in 5 ml of acetic acid for 3 hr. Chromatography of the products with benzene on a silica gel column yielded 40 mg of pure diene, which was crystallized from dilute methanol: yield 32 mg; mp 242°; ν_{max} (KBr) 1735, 1250, 1620 (w), 815 (w), 800 (w), 785 cm^{-1} (w); λ_{max} (ethanol) 242.5, 250.0, 260.0 nm (log ε 4.37, 4.40, 4.20); mass spectrum *m/e* (rel intensity) 524 (43, M^+), 509 (11), 464 (100), 449 (11), 404 (16), 389 (29), and 256 (21).

3β,6β-Acetoxy-12,19-dioxoolean-9(11),13(18)-diene (3).—Daturadiol diacetate **1c** (12 mg) was refluxed overnight with 100 mg of selenium dioxide in 5 ml of acetic acid. Chromatography of the products on a small silica gel column with benzene–ethyl acetate (9:1) gave the pure yellow product, which was crystallized from methanol: yield 7 mg; mp 252–256°; ν_{max} (KBr) 1730, 1685, 1610, 1590, 1240 cm^{-1}; λ_{max} (ethanol) 278 nm (log ε 3.96); mass spectrum *m/e* (rel intensity) 552 (100, M^+), 537 (5), 524 (4), 492 (13), 482 (79), 464 (6), 432 (5), 422 (25), 417 (8), 363 (31), 347 (12).

6-Oxo-3β-acetoxyolean-12-ene (1e).—The monoacetate **1d** (85 mg) was oxidized with excess Jones reagent in acetone for 15 min, diluted with water, extracted into ether, and crystallized from dilute ethanol to give 78 mg of the pure keto acetate: mp 251°; $[\alpha]_D$ +62.5°; ν_{max} (KBr) 1730, 1700, 1245 cm^{-1}.

Anal. Calcd for $C_{32}H_{50}O_3$: C, 79.62; H, 10.44. Found: C, 79.53; H, 10.22.

Reduction of 1e to β-Amyrin.—The above keto acetate (53 mg) was refluxed at 135–140° for 2 days with 25 ml of ethylene glycol in which 1 g of sodium and 5 ml of anhydrous hydrazine were dissolved. Then the mixture was distilled until the temperature reached 200° and refluxed for an additional 6 hr; 10.7 mg of β-amyrin was obtained by chromatography of the products over silica gel with benzene as eluting solvent. The product was crystallized from dilute alcohol, melting point and mixture melting point identical with that of authentic β-amyrin, 196.5–198°. The ir spectra (KBr) were identical.

6β-Hydroxyolean-12-ene (1f).—Daturaolone **1b** (102 mg) was refluxed with 2.5 g of KOH, 2.0 ml of hydrazine hydrate, and 0.5 ml of hydrochloric acid in 12 ml of diethylene glycol for 4 hr; then the temperature of the mixture was adjusted to 210° by distillation of hydrazine and refluxed for an additional 4 hr.[10] The usual work-up and crystallization from dilute alcohol yielded

(9) K. Takahashi, K. Kanayama, Y. Tanabe, and M. Takani, *Chem. Pharm. Bull.*, **20**, 2106 (1972).

(10) W. Nagata and N. Itazaki, *Chem. Ind. (London)*, 1194 (1964).

82 mg of pure product: mp 178–182°; $[\alpha]_D$ +74°; ν_{max} (KBr) 3620 cm^{-1}.

Anal. Calcd for $C_{30}H_{50}O$: C, 84.44; H, 11.81. Found: C, 84.42; H, 11.75.

6-Oxoolean-12-ene (1g).—Daturadione 1h (95 mg) was reduced in the same manner to give 69 mg of the product: mp 174–176°; $[\alpha]_D$ +88°; ν_{max} (KBr) 1705 cm^{-1}.

Anal. Calcd for $C_{30}H_{48}O$: C, 84.84; H, 11.4. Found: C, 84.74; H, 11.60.

Oxidation of the alcohol 1f with Jones reagent yielded the same ketone, as proved by ir and mixture melting point.

3-Oxoolean-5,12-diene (4).—Daturaolone (205 mg) in 5 ml of pyridine was treated with 1 ml of thionyl chloride in an ice bath. The usual work-up and crystallization from dilute alcohol yielded 173 mg of pure product: mp 169–171°; ν_{max} (KBr) 1700, 1660, 840 cm^{-1}.

Anal. Calcd for $C_{30}H_{46}O$: C, 85.24; H, 11.0. Found: C, 85.16; H, 11.15.

Registry No.—1a, 41498-79-7; 1b, 41498-80-0; 1c, 41579-25-3; 1d, 41498-81-1; 1e, 41498-82-2; 1f, 41498-83-3; 1g, 41498-84-4; 5α-1h, 41498-85-5; 5β-1h, 41498-86-6; 1h-d_5, 41499-07-4; 2, 41498-87-7; 3, 41498-88-8; 4, 41498-89-9.

Cyclotrichosantol, a New C_{31} 31-Nortriterpene

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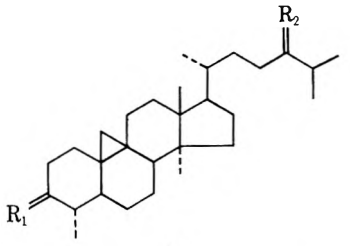
Isolation of cycloeucalenol 1a and a novel methylsterol—cyclotrichosantol (2a, 4α,14α-dimethyl-24-ethyl-9:19-cyclocholest-25-en-3β-ol)—from the leaves of *Trichosantes palmata* L., Cucurbitaceae, is described. The structure was established on the basis of mass and nmr spectra with the use of Eu(dpm)$_3$. The probably biogenetic significance of cyclotrichosantol is discussed.

Although the biogenesis of C-29 plant sterols containing a 24-ethyl group by way of the precursors (24-methylenecycloartenol, cycloeucalenol, obtusifiol, and citrostadienol) has been well established,[1] it seems probable that this is not the only possible biogenetic pathway. It is also possible that certain minor Δ^{25} sterols, widely distributed in some plants,[2a] especially in those of the Cucurbitaceae family,[2b,c] are markers of an alternative pathway for the introduction of a 24-ethyl group, just as similarly 24-ethylidenesterols, *e.g.*, Δ^5 and Δ^7 avenasterols, are considered to be markers of such a pathway.

In the present paper we describe the structure elucidation of a new cyclopropane methylsterol, cyclotrichosantol 2a, which was isolated from the leaves of *Trichosantes palmata* L. (Cucurbitaceae), an Indian medicinal plant, together with cycloeucalenol 1a.

The so-called "methylsterol" fraction was isolated from the saponified petroleum ether (bp 30–60°) extract of the dry leaves by chromatography and crystallization subsequent to treatment of the whole saponified extract with urea to remove the aliphatic alcohols which mask the minute methylsterol fraction. Only two components were present as shown by tlc, and they were separated by preparative tlc, the less polar in 0.005 and the more polar in 0.009% yield based on the weight of dry leaves. The compound with lower R_f value was easily identified as cycloeucalenol 1a on the basis of its properties (melting point, ir, mass spectrum, and pmr). This was confirmed by preparation of the acetate 1b, the 3 ketone 1c, and the 28 norketone 1d, the properties of which were in good agreement with reported data.[3]



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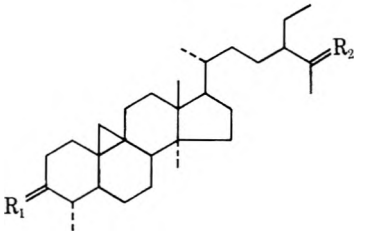

2

	R_1	R_2
a	β-OH, α-H	=CH_2
b	β-OAc, α-H	=CH_2
c	=O	=CH_2
d	β-OH, α-H	=O

The second compound—cyclotrichosantol—like cycloeucalenol 1a exhibited the presence of cyclopropane and methylene groups in its ir and pmr spectra. Both compounds melted at nearly the same point (for cycloeucalenol mp 144–145°, for cyclotrichosantol mp 143–144°), and practically no depression was noted for the mixture, a circumstance which demonstrated the close relationship of the two compounds. Cyclotrichosantol gave an acetate 2b, a 3 ketone 2c, and a 26 norketone 2d, the latter by oxidation with OsO_4–KIO_4.

Molecular ions in the mass spectra of all these compounds corresponded to the formula $C_{31}H_{52}O$ for the parent alcohol. The two previously known triterpenes having this composition, 24-methylenecycloartenol and cyclolaudenol, were excluded, as both melt at distinctly lower temperature (122 and 125°, respectively[4]).

Structure 2a for cyclotrichosantol could, however,

(1) L. J. Goad in "Natural Substances Formed Biologically from Mevalonic Acid," T. W. Goodwin, Ed., Academic Press, New York, N. Y., 1970.

(2) (a) W. Sucrow, *Chem. Ber.*, **99**, 3559 (1966); M. Manzoor-i-Khuda, *Tetrahedron*, **22**, 2377 (1966); T. Sedane and T. Villacorta, *An. Real. Soc. Espan. Fis. Quim. Ser. B*, **66**, 1315 (1970); L. M. Belger, N. N. Rees, E. L. Ghisalberti, L. J. Goad, and T. W. Goodwin, *Tetrahedron Lett.*, 3043 (1970); S. C. Pakrashi and B. Achari, *ibid.*, 365 (1971). (b) R. R. Gonzales and F. M. Panizo, *An. Real. Soc. Espan. Fis. Quim. Ser. B*, **63**, 1123 (1967); W. Sucrow and A. Reimerdes, *Z. Naturforsch. B*, **23**, 42 (1968). (c) I. Belič, T. Čerin, and D. Stucin, *Vestn. Slov. Kem. Drûs.*, **18**, 1 (1971).

(3) J. S. C. Cox, F. F. King, and T. J. King, *J. Chem. Soc.*, 514 (1959).

(4) "Rodd's Chemistry of Carbon Compounds," Vol. IIC, 1969, p 423.

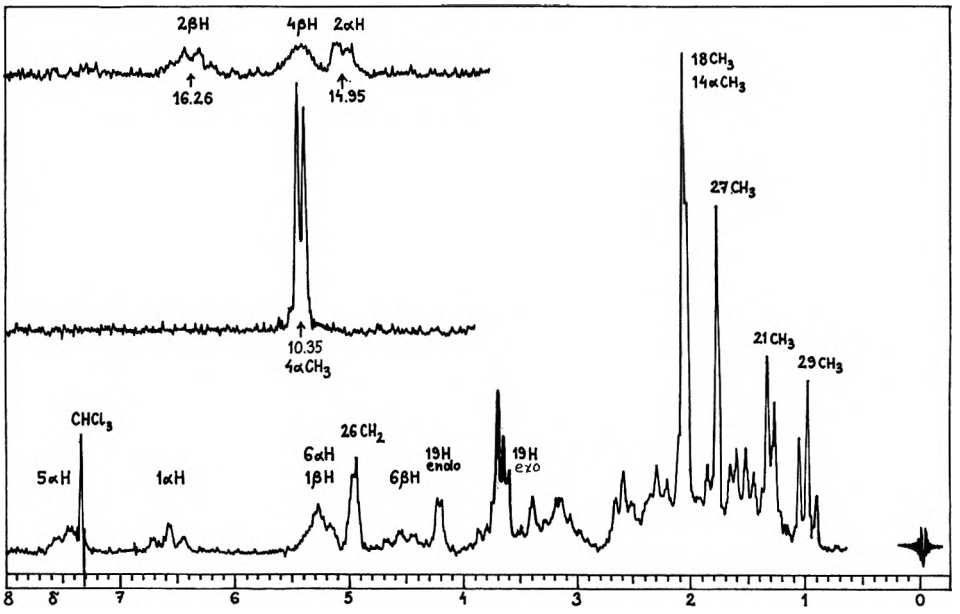

Figure 1.—100-MHz pmr spectrum of cyclotrichosantol (**2a**) in $CDCl_3$ with added $Eu(dpm)_3$; concentration ratio 1.02.

be deduced by comparing the mass spectra of **2a**, **2b**, **2c**, and **2d**.

Mass spectra of **2a**, **2b**, and the norketone **2d** showed a peak corresponding to the elimination of 55 mass units from the ion M − 18 (or M − 60); this process is also observed in the case of **1a**, **1b**, and **1d**, and is typical for 4-methyl-9:19-cyclosterols.[5] The fragment 55 represents carbon atoms 2, 3, and 4 and 4-Me. The second characteristic process involving elimination of ring A, for which two alternative mechanisms have been proposed,[5,6] was also visible in the spectra: M − 126 in **2a** and **2d**, also in **1a** and **1d**, and M − 168 in **2b** and **1b**. In the 3 ketones the analogous elimination of *m/e* 124 was observed. These facts are consistent with the presence of one methyl group at C-4 of cyclotrichosantol, as in the case of cycloeucalenol.

Cyclotrichosantone and cycloeucalenone (**2c** and **1c**) exhibited nearly the same value of $\Delta\epsilon_{285}$ in their CD spectra (1.08 and 1.11, respectively). This value is typical for 4α-methyl-3-ones.[7]

The presence of the $C_{10}H_{19}$ side chain was evident from the appearance of the ion M − 139 in the spectra of **2a–c** which was displaced to M − 141 in the spectrum of **2d**. Because the ion M − 139 − 2 was very weak, the side chain unsaturation should be distant from the nucleus.[8] The elimination of part of the side chain in a McLafferty process was also visible, especially in the spectrum of **2c** (M − 84), and the corresponding elimination of *m/e* 86 was present in the spectrum of **2d**. The pmr spectrum of **2a** or its acetate **2b** showed the presence of a methyl group connected with the double bond (broadened singlet at δ 1.60). Therefore any other arrangement of the side chain was excluded.

The use of the $Eu(dpm)_3$ shift reagent provided further confirmation for the ring skeletal identity of **1a** and **2a** and revealed the presence of an ethyl group whose signal was invisible in the normal pmr spectrum of **2a** (Figure 1).

That the carbocyclic skeletons of **1a** and **2a** are identical is clearly seen by inspection of Table I, which shows that the shifts of the methyl groups in the two compounds are nearly the same; furthermore at high Eu-complex concentration all ring A protons signals were visible, and these parts of both spectra were nearly identical. The spectrum of cyclotrichosantol was decoupled for all axial–axial and geminal couplings; the most shifted methyl group signal, the doublet of 4α-Me, which is absent from the spectra of similar 4,4-dimethyl derivatives,[9] is coupled to the broad signal at 15.32 ppm which must therefore be the resonance of 4α-H. The remaining signals could then be identified as shown in Figure 1.

This example demonstrates the utility of shift reagents for a comparison of closely related compounds which differ from each other at locations far from the complexing group, a situation which is encountered frequently in sterols and terpenes.[10,11]

Cyclotrichosantol **2a** thus possesses a ten-carbon-atom side chain, like all "finished" plant sterols. In comparison with the initial cyclic plant sterol precursor, cycloartenol, **2a** lacks only one methyl group, namely, the one at C-4 (if the presence of the "extra" ethyl group at C-24 is neglected). Therefore, if cyclotrichosantol **2a** is not a side product of sterol biosynthesis in *Trichosantes palmata*, but a sterol precursor, the hypothetical "25-methylene" path differs from the "24-ethylidene" path not only in the manner of 24-alkylation, but also in the order of skeletal demethylation and double bond formation.

Recently another methylsterol was isolated from *Echinocystis lobata*, a member of the Cucurbitaceae, and the structure 4α-methylstigmasta-7,25-dien-3β-ol was proposed for it as the most likely possibility.[2c] This methylsterol thus represents the 25(26) isomer of

(5) H. E. Audier and B. C. Das, *Tetrahedron Lett.*, 4341 (1966).
(6) R. T. Aplin and G. M. Hornby, *J. Chem. Soc. B*, 1078 (1966).
(7) L. H. Zalkow, R. Hale, K. French, and P. Crabbé, *Tetrahedron*, **26**, 4948 (1970).
(8) S. C. Wyllie and C. Djerassi, *J. Org. Chem.*, **33**, 305 (1968).
(9) J. St. Pyrek, unpublished work.
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(11) Unpublished work.

TABLE I

CHEMICAL SHIFTS, δ, AND RELATIVE PARAMAGNETIC SHIFTS, ΔEu, CAUSED BY Eu(dpm)$_3$ IN $CDCl_3$[a]

Cyclotrichosantol (2a)			Cycloeucalenol (1a)		
	δ	ΔEu		δ	ΔEu
30-Me (4α-Me)	d 1.00	100	30-Me (4α-Me)	d 1.00	100
18-Me (13β-Me)	s 1.01	11.9	18-Me (13β-Me)	s 1.01	11.6
32-Me (14α-Me)	s 0.92	12.2	32-Me (14α-Me)	s 0.94	12.0
21-Me	d 0.88	4.6	21-Me	d 0.94	4.5
27-Me	b s 1.60	2.0	26,27-Me_2	d 1.08	1.6
26-CH_2 (25 =CH_2)	4.78	2.4	28-CH_2 (24 =CH_2)	4.73	2.5
	4.71			4.77	
29-Me	t 0.81	1.8			
3α-H	b 3.23	225	3α-H		213

[a] Shifts are normalized assuming a 4α-Me shift value of 100.

citrostadienol and should be regarded as the last sterol precursor in the proposed biosynthetic scheme. A methylsterol with the same skeleton as cyclotrichosantol, but with a methyl group at C-24, *i.e.*, a nine-carbon side chain, 31-norcyclolaudenol, has been isolated from the rhizomes of *Polypodium vulgare* L.,[12] and the corresponding ketone has been found in *Musa sapientum* L.[13] Cycloneolitsin and cyclolabanone, two "abnormal" 24-methylation products, should be mentioned also; these C_{32} triterpenes possess two geminal methyl groups at C-24 and a 25(26) double bond.[14]

The sterol fraction of *Trichosantes palmata* L. leaves were examined also. The main sterol component was identified as α-spinasterol, but by tlc chromatography and mass spectrometry trace amounts of stigmastanol and C-29 sterols with 7 or 7,25 or 7,22,25 double bonds were shown to be present also.

Experimental Section

Isolation of Methylsterols.—The petroleum ether extract, 48 g, of dry *Trichosantes palmata* L. leaves, 1.5 kg, was saponified with 20 g of NaOH in 50 ml of water, 400 ml of ethanol, and 100 ml of benzene under a nitrogen atmosphere at reflux temperature for 4 hr. The mixture was acidified with acetic acid, diluted with 500 ml of water, and extracted with ether. The residue from the ether extract was dissolved in 200 ml of ethyl acetate and 400 ml of methanol, and 100 g of urea was added with boiling. The clathrates were separated and the solvent was again removed. The residue was extracted with ether and washed with water and alkali; evaporation gave 32.5 g of oily residue which was chromatographed on 550 g of alumina grade IV–V with petroleum ether as solvent. The methylsterol fraction was crystallized from hexane and chromatographed on silica gel plates containing 30% of $AgNO_3$ with benzene as developing solvent.

Cycloeucalenol (1a).—1a (130 mg) was obtained after crystallization from dilute alcohol: mp 144–145° (lit.[3] mp 138–139°); ν_{max} (KBr) 3400, 1640, 885 cm^{-1}; nmr (100 MHz, $CDCl_3$) δ 4.77 (1 H, b s), 4.73 (1, H, b s), 3.25 (1 H, b), 1.08 (6 H, d, J = 6 Hz), 1.01 (3 H, s), 0.94 (3 H, d, J = 6 Hz), 0.94 (3 H, s), 0.1–0.4 (2 H, q, J = 4 Hz); mass spectrum m/e (rel intensity) 426 (45), 411 (58), 408 (100), 393 (70), 383 (10), 356 (6), 353 (9), 342 (6), 327 (10), 324 (7), 309 (10), 301 (30), 300 (40). Acetate **1b** had mp 105–109°; $[\alpha]_D$ +61.6° (*c* 0.66, $CHCl_3$) (lit.[3] mp 110°, $[\alpha]_D$ +63°); ν_{max} (KBr) 1730, 1640, 1243, 900 cm^{-1}; nmr δ (100 MHz, CCl_4) 4.75 (1 H, b s), 4.71 (1 H, b s), 4.43 (1 H, b), 2.00 (3 H, s); mass spectrum m/e (rel intensity) 468 (12), 453 (9), 425 (5), 408 (100), 393 (52), 365 (5), 353 (9), 325 (7), 324 (5), 300 (12), 283 (14), 281 (10).

Cycloeucalenone (1c).—Cycloeucalenol (1a) was oxidized with excess CrO_3 in pyridine and purified by preparative tlc and crystallization from methanol: mp 83–84° (lit.[3] mp 84°); $\Delta\epsilon_{285}$ (*c* 0.2, MeOH) +1.11; mass spectrum m/e (rel intensity) 409 (18), 424 (45), 381 (19), 341 (17), 340 (18), 328 (13), 327 (13), 326 (12), 325 (10), 300 (18), 299 (36).

28-Norcycloeucalenol (1d).—Cycloeucalenol (7 mg) was oxidized with excess KIO_4 in 2 ml of 80% acetic acid and in the presence of 2 mg of OsO_4. The more polar product was purified by preparative tlc and crystallization from dilute methanol: yield 5 mg; mp 114–116° (lit.[3] 110–111°); $\Delta\epsilon_{285}$ (*c* 0.2, MeOH) −0.185; mass spectrum m/e (rel intensity) 428 (48), 413 (50), 410 (100), 395 (80), 385 (4), 367 (6), 355 (18), 342 (7), 302 (47), 301 (27), 283 (27).

Cyclotrichosantol (2a).—Cyclotrichosantol (70 mg) was obtained after crystallization from dilute alcohol: mp 143–144°; $[\alpha]_D$ +42°; λ_{max} (EtOH) 195 nm (log ε 3.85); ν_{max} (KBr) 3450, 1640, 1040, 885 cm^{-1}; nmr (100 MHz, $CDCl_3$) δ 4.78 (1, H, b s), 4.71 (1 H, b s), 3.23 (1 H, b), 1.60 (3 H, b s), 1.01 (3 H, s), 0.92 (3 H, s), 0.88 (3 H, d, J = 6 Hz), 0.1–0.4 (2 H, q, J = 4 Hz); mass spectrum m/e (rel intensity) 440 (55), 425 (74), 422 (100), 407 (75), 367 (17), 314 (45), 301 (32). The acetate **2b** melted at 113°; $[\alpha]_D$ +58°; ν_{max} (KBr) 1735, 1640, 1250, 895 cm^{-1}; nmr (CCl_4, 100 MHz) δ 4.72 (1 H, b s), 4.64 (1 H, b s), 4.40 (1 H, b), 2.00 (3 H, s), 1.59 (3 H, s); mass spectrum m/e (rel intensity) 482 (17), 467 (11), 422 (100), 407 (61), 367 (10), 343 (7), 314 (13), 283 (23).

Cyclotrichosantone (2c).—Cyclotrichosantol (2a) was oxidized with excess CrO_3 in pyridine and purified by preparative tlc and crystallization from methanol: mp 121–122°; λ_{285} (*c* 0.15, MeOH) +1.08; mass spectrum m/e (rel intensity) 438 (51), 423 (20), 395 (5), 354 (12), 341 (11), 328 (18), 314 (12), 299 (69), ... 55 (100).

26-Norcyclotrichosantol (2d).—Cyclotrichosantol was oxidized as before with KIO_4–OsO_4 but a longer reaction time was required as compared with cycloeucalenol. The product was purified by preparative tlc and crystallization from dilute methanol: mp 125–127°; λ_{285} (*c* 0.1, MeOH) −0.07;[15] mass spectrum m/e (rel intensity) 442 (7), 427 (13), 424 (29), 409 (35), 369 (8), 356 (5), 316 (13), 301 (20), 283 (18), ... 55 (100).

Acknowledgment.—We are very much indebted to Professor P. C. Dutta, Indian Association for Cultivation of Science, Calcutta, India, as well as Professor Cz. Belzecki and Dr. W. Sobotka of our institute, for supplying the plant material.

Registry No.—1a, 469-39-6; 1b, 10376-42-8; 1c, 1255-12-5; 1d, 15371-62-7; 2a, 41507-26-0; 2b, 41507-27-1; 2c, 41507-28-2; 2d, 41507-29-3.

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(15) This value of Δε cannot be used for determination of the absolute configuration at C-24.

Aminocyclitols. 30.[1] Unambiguous Synthesis of Seven Aminocyclopentanetetrols

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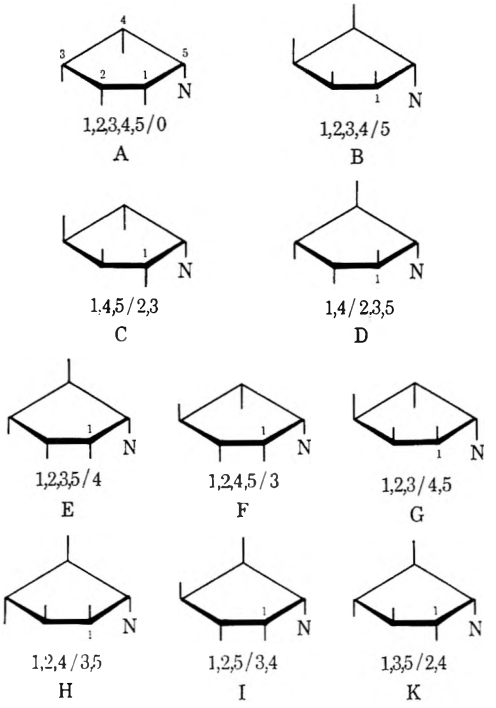
Pentaacetyl and other derivatives of 5-amino-1,2,3,4-cyclopentanetetrols with 1,2,3,5/4 (**14**), 1,2,3,4/5 (**15**), 1,4,5/2,3 (**16**), 1,3,5/2,4 (**17**), and 1,2,4/3,5 configuration (**18**) were prepared from readily accessible derivatives (**3** and **4**) of the 1,4/2,3,5 isomer. The synthetic routes involved displacement of sulfonyloxy group of the mono-*O*-sulfonyl (**1**, **5**, **11**–**13**) and di-*O*-sulfonyl derivatives (**8**–**10**) by water. In an analogous reaction sequence the pentaacetyl derivatives of 1,2,4,5/3 (**33**) and the all-cis configuration (**34**) were prepared from mesylates (**31** and **32**) of the 1,4,5/2,3 isomer.

Though none of the ten possible 5-amino-1,2,3,4-cyclopentanetetrols (*cf.* Chart I) has been encountered in nature so far, their chemistry has received considerable attention,[3-5] deriving its main stimulus from the occurrence of certain aminocyclopentanepolyol systems as components in some antibiotics, *i.e.*, aristeromycin[6] and pactamycin.[7] While it might be surmised from the structural features of these antibiotics that aminocyclopentanepolyols as such may lack biological relevance, their preparation and establishment of configuration, nevertheless, was deemed prerequisite for further transformations, *i.e.*, conversions into nucleosides. As a consequence, in this paper we wish to report the preparation and configurational elucidation of seven diastereomers of pentaacetyl derivatives of 5-amino-1,2,3,4-cyclopentanetetrols, of which five had not been previously prepared, thus providing now a synthetic route to any one of the ten isomers.

CHART I

THE TEN DIASTEREOMERIC AMINOCYCLOPENTANETETROLS[a]



[a] Isomers A–D, having a plane of symmetry, are meso forms. Of the six racemic diastereomers E–K, the enantiomer has been depicted which allows clockwise assignment of positional numbers as in A.

DL-(1,2,3,5/4)-5-Amino-1,2,3,4-cyclopentanetetrol (E).—While the readily available 2,3-*O*-cyclohexylidene-(1,4/2,3,5)-5-acetamido-1,2,3,4-cyclopentanetetrol (**3**)[4,5] could be converted into the corresponding 1,4-di-*O*-mesyl derivative (**1**) in good yield (Chart II), selective mono-*O*-mesylation could not be achieved. Treatment of **3** with 1.1–1.4 molar equiv of mesyl chloride in each case yielded mixtures of the mono-*O*- and di-*O*-mesyl compounds (**2** and **1**) ranging in ratios from 1:1 to 3:2. After removal of the major portion of **1** formed, the resulting mixture of **1** and **2** was subjected to displacement of the sulfonyloxy group by heating in water in the presence of sodium acetate, and subsequently acetylated. On separation by column chromatography the crystalline 1,4-di-*O*-acetyl-2,3-*O*-cyclohexylidene-(1,2,3,5/4)-5-acetamido-1,2,3,4-cyclopentanetetrol (**7**) was obtained. Mild acid hydrolysis of **7** followed by acetylation afforded (1,2,3,5/4)-5-acetamido-1,2,3,4-cyclopentanetetrol tetraacetate (**14**), mp 123–124°.[8] The 1,2,3,5/4 configuration for **7** and **14** rests on the following evidence. First, compound **7** exhibited three and compound **14** five distinct acetyl resonances in the τ 8 region (*cf.* Table I), clearly indicating the presence of an unsymmetrical configuration (E–K, Chart I). Second, on displacement of the mesyloxy group of **2**, the 2,3 positions being sterically fixed by the cyclohexylidene group, configurational changes may occur at C-1 (or at C-4) and hence configuration E is left as the only choice for compounds **7** and **14**. This configurational assignment is further supported by the fact that the de-*O*-acetylated product of **14** (**19**) yields two distinct mono-*O*-isopropylidene derivatives (**20** and **21**) on acetonation. Formation of intermediary oxazolinium ions with participation of the vicinal trans acetamido groups and their cis opening by water were proposed as the reaction mechanism.[5]

(1,2,3,4/5)-5-Amino-1,2,3,4-cyclopentanetetrol (B).—On treatment of 1,4-di-*O*-acetyl-(1,4/2,3,5)-5-acetamido-1,2,3,4-cyclopentanetetrol (**4**)[5] with mesyl or tosyl chloride, in pyridine, the 2,3-di-*O*-mesyl (**8**) and 2,3-di-*O*-tosyl (**9**) derivatives were obtained. Each, on

(1) Part 29: T. Suami, S. Ogawa, H. Uchino, and M. Uchida, *Bull. Chem. Soc. Jap.*, in press.

(2) On leave of absence from Institut für Organische Chemie, Technische Hochschule Darmstadt, Germany.

(3) A. Hasegawa and H. Z. Sable, *J. Org. Chem.*, **31**, 4154 (1966).

(4) R. Ahluwalia, S. J. Angyal, and B. M. Luttrell, *Aust. J. Chem.*, **23**, 1819 (1970).

(5) T. Suami, Y. Sakota, K. Tadano, and S. Nishiyama, *Bull. Chem. Soc. Jap.*, **44**, 2222 (1971).

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(8) The melting point previously reported for **14** (116°)[5] must be corrected, since further purification raised it to 123–124°.

CHART II

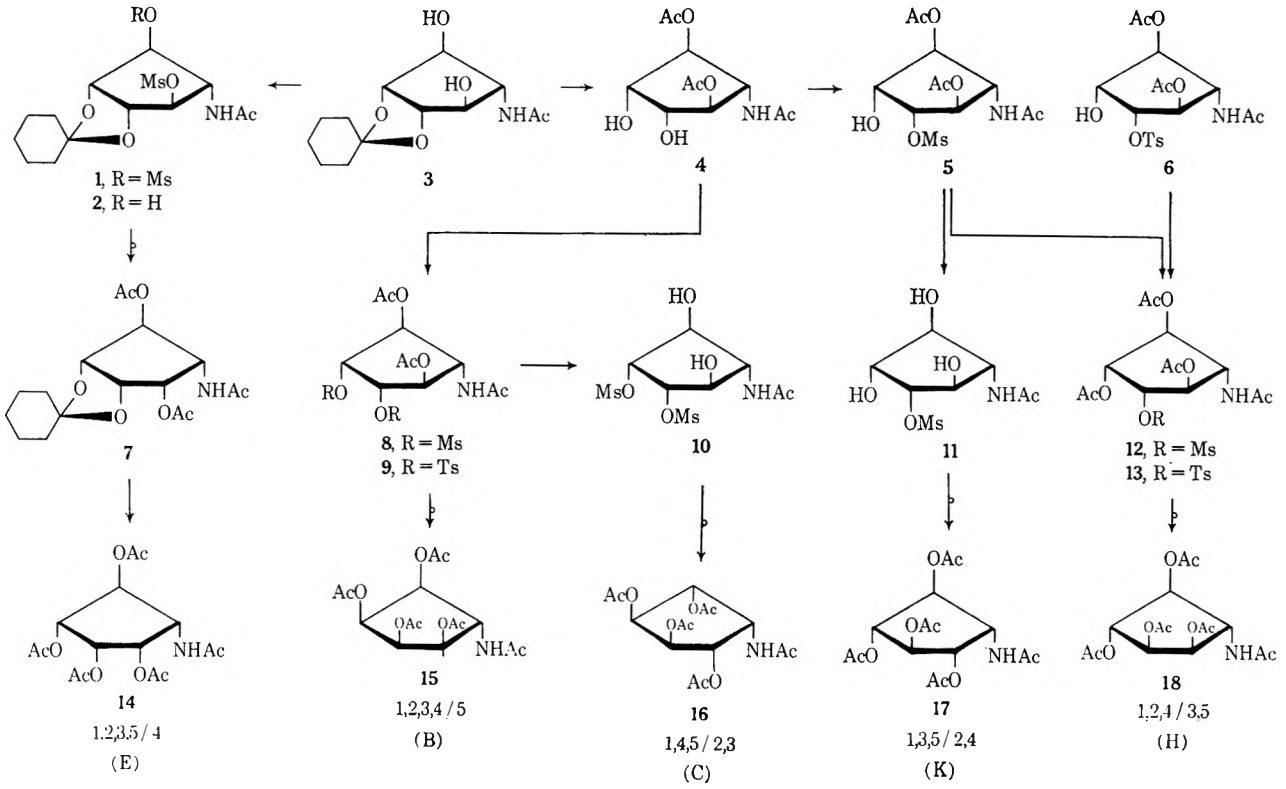
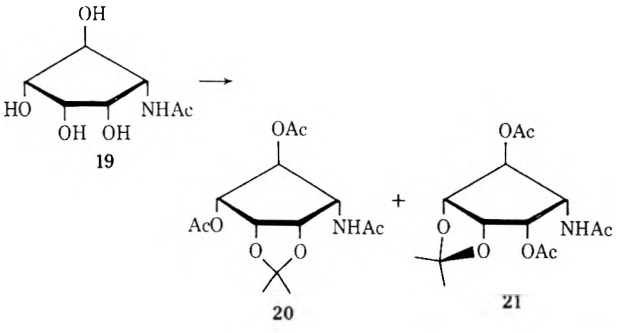


TABLE I

CHEMICAL SHIFT OF ACETYL RESONANCES IN $CDCl_3$ AND MELTING BEHAVIOR OF THE TEN 5-ACETAMIDO-1,2,3,4-CYCLOPENTANETETROL TETRAACETATES

Configuration		Acetyl resonances (τ value) (number of OAc groups)				
Formula	Fractional notation	OAc		NHAc[a]	Mp, °C	Ref
A (34)	1,2,3,4,5/0	7.91 (2)	7.92 (2)	8.03	174–175	5
B (15)	1,2,3,4/5	7.87 (2)	7.94 (2)	7.96	145–146	
C (16)	1,4,5/2,3	7.87 (2)	7.95 (2)	7.97	176.5	4
					173.5–174	5
D	1,4/2,3,5	7.92 (2)	7.95 (2)	8.05	147	3
					138.5–140	4
					148.5–149.5	5
E (14)	1,2,3,5/4	7.90, 7.94, 7.96, 7.99		8.04	123–124	
F (33)	1,2,4,5/3	7.85, 7.88, 7.93, 7.99		8.00	162–163.5	
G	1,2,3/4,5	7.88, 7.89, 7.93, 7.94		8.01	192	3
					189.5–190.5	5
H (18)	1,2,4/3,5	7.92, 7.94, 7.95, 7.96		8.04	111–112°	
I	1,2,4/3,4				119	3
K (17)	1,3,5/2,4	7.87, 7.90, 7.93 7.94		8.04	161.5–162.5	

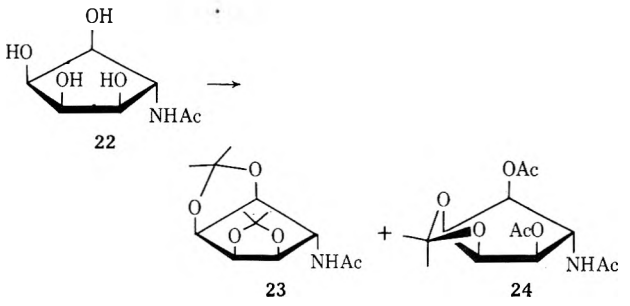
[a] Assignment of the *N*-acetyl resonance of the D isomer was established by measurement of the *O*-trideuterioacetyl derivative,[5] and those of the other isomers were carried out by analogy with that of the D isomer.



displacement of the sulfonyloxy group with water–sodium acetate, evidently proceeding *via* cyclic acetoxonium ions by participation of the vicinal trans acetoxy groups and their respective cis opening by water,[9] and subsequent acetylation afforded the pentaacetyl derivative (**15**), mp 145–146°. The 1,2,3,4/5 configuration for this compound was established on the basis of the following findings. The nmr spectrum of **15** revealed three sharp signals with 2:2:1 relative intensities for the five acetyl groups, clearly indicating the presence of a symmetrical structure (A–D). Three of the four compounds had been described[3–5] (A, C, and D) and compound **15** was not identical with any one of the known pentaacetyl derivatives by comparing their melting point, nmr, and ir spectra. Therefore, configuration B is given to compound **15**. The assign-

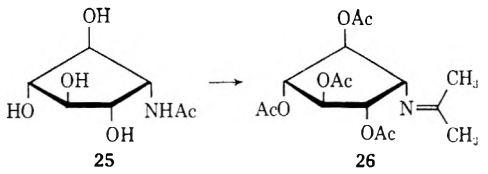
(9) H. Paulsen, *Advan. Carbohyd. Chem.*, **26**, 133 (1971).

ment of the configuration is consistent with the fact that the de-*O*-acetylated product of **15** (**22**) yielded mono-*O*-isopropylidene (**24**) and di-*O*-isopropylidene derivative (**23**) on acetonation.

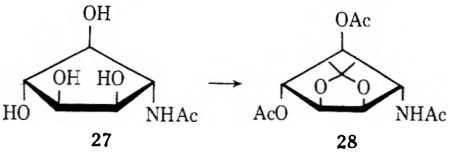


(1,4,5/2,3)-5-Amino-1,2,3,4-cyclopentanetetrol (C).—In contrast to reactions of **8** and **9** → **15**, the analogous reaction with the de-*O*-acetylated product of **8** (**10**) took —not unexpectedly—a different course. By participation of the neighboring hydroxyl groups, the reaction proceeded *via* oxirane intermediates. The oxirane rings were opened in the trans arrangement by intramolecular attack of the vicinal acetamido groups, forming oxazolinium ions, which were further attacked by water to give *cis*-acetamido alcohol. Thus the pentaacetyl derivative of the 1,4,5/2,3 configuration (**16**) was obtained on acetylation as the main product, identical with a sample prepared by another route.[4]

DL-(1,3,5/2,4)-5-Amino-1,2,3,4-cyclopentanetetrol (K).—Mesylation of **4** gave a mixture of the mono-*O*-mesyl (**5**) and di-*O*-mesyl (**8**) compounds, which were successfully separated. De-O-acetylation of **5** yielded the mono-*O*-mesyl derivative (**11**), which on treatment in water–sodium acetate and subsequent acetylation afforded the (1,3,5/2,4)-5-acetamido-1,2,3,4-cyclopentanetetrol tetraacetate (**17**), mp 161.5–162.5°. The nmr spectrum of **17** exhibited five sharp acetyl resonances in the τ 8 region, thus establishing an unsymmetric configuration (E–K). Comparisons of ir data and melting behavior with that of four other pentaacetyl derivatives (configuration E–H) showed **17** to be not identical with any of the four compounds, and formation of a compound with configuration I could not be conceived in the reaction employed. Therefore, **17** was reasonably assigned the 1,3,5/2,4 configuration. This assignment was supported by the fact that an *N*-isopropylidene derivative (**26**) was formed but no *O*-isopropylidene derivative was formed on treatment of the de-O-acetylated product of **17** (**25**) with 2,2-dimethoxypropane in the presence of *p*-toluenesulfonic acid and subsequent acetylation. The analogous reaction mechanism *via* oxirane intermediates as described above was proposed in this reaction.



DL-(1,2,4/3,5)-5-Amino-1,2,3,4-cyclopentanetetrol (H).—By comparison with the stereochemical course of other reactions in acetamidocyclopentanetetrol series, *i.e.*, conversions of **8** and **9** → **15**, **31** → **33**, **32** → **34**, and other examples,[5] displacement of the mesyloxy group in **5** would be expected to yield a product of 1,2,4/3,5 configuration (H). The same would have to be anticipated for the tosyl analog (**6**) and their fully acetylated products (**12** and **13**). Indeed, when subjecting either of them to the displacement reaction by water–sodium acetate, followed by acetylation, the pentaacetyl derivative (**18**), mp 111–112°, was obtained as the exclusive product. The ease with which the reactions of **5**, **6**, **12**, and **13** took place to give **18**, together with the fact that no other isomeric products were detectable by tlc in the reaction mixture, already appears to be convincing proof of the validity of the mechanistic rationalizations advanced above, and hence of the 1,2,4/3,5 configuration of **18**. Corroborative evidence is provided by the nmr pattern of acetyl resonances, exhibiting five sharp signals in the τ 8 region (Table I) to indicate an unsymmetrical configuration (E–K), and by the nonidentity of **18** with any one of the eight other pentaacetyl derivatives in our hands (A–G and K) with respect to ir, melting point, and mixture melting point data.[10] Thus, **18** can unequivocally be assigned the 1,2,4/3,5 configuration. A formation of a mono-*O*-isopropylidene derivative (**28**) from the de-O-acetylated



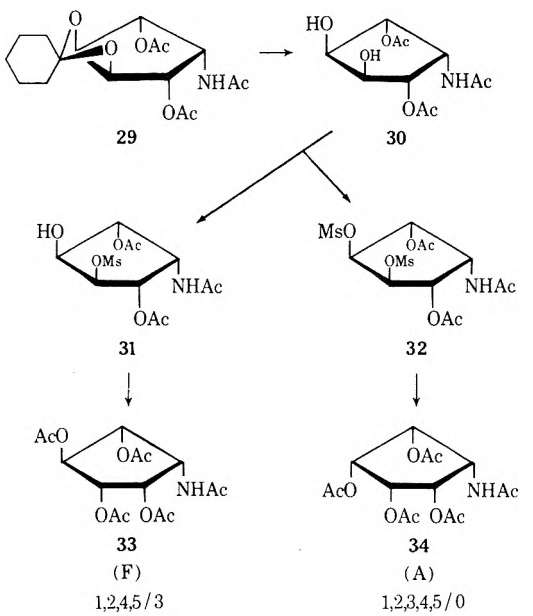
product of **18** (**27**) provided further evidence for the assigned configuration. In fact, a pentaacetyl derivative of the 1,2,4/3,5 configuration with mp 123–124° was reported by Hasegawa and Sable[3] (compound XXVIb). Although the melting point of our product **18** (111–112°) is rather close, the two compounds were found to be not identical with respect to ir and mixture melting point.[11] In addition, an analogous comparison of XXVIb[3] with the above-described **14** showed no depression of the mixture melting point (123–124°) and exhibited only minor differences in their ir spectra.[11] Since the configurational proof for **14** and **18** is unequivocal, it appears likely that the configuration of compound XXVIb[3] will have to be revised to 1,2,3,5/4 arrangement of substituents.

DL-(1,2,4,5/3)- (F) and (1,2,3,4,5/0)-5-Amino-1,2,3,4-cyclopentanetetrol (A).—Application of the reaction sequences similar to those used for the conversions **4** → **5** → **18** and **4** → **8** → **15** to compound **30** available from **29**[4] could give the known isomer **34**[5] and its C-3 epimer **33**. Mesylation of **30** yielded the expected mixture of mono-*O*- and di-*O*-mesyl derivatives (**31** and **32**, respectively), which was subjected to displacement of

(10) The pentaacetyl derivative obtained (**18**) might be surmised to have the 1,2,5/3,4 configuration (I), the only isomer not at hand for direct comparison. Its reported melting point (119°[3] *vs.* 111–112° of **18**; *cf.* Table I) is very similar; it would feature an analogous pattern of acetyl resonances and also could give a mono-*O*-isopropylidene compound, although a di-*O*-isopropylidene derivative would be more likely. However, a product with a configuration as in I cannot intelligibly be conceived to arise from compounds of a 1,4/2,3,5 arrangement of substituents as in **5**, **6**, **12**, and **13**.

(11) Dr. H. Z. Sable, School of Medicine, Case Western Reserve University, Cleveland, Ohio 44106, kindly performed these comparative measurements.

the mesyloxy group with water–sodium acetate and subsequent acetylation to give a mixture of **33** and **34**.



Separation was achieved by column chromatography and afforded the major product, the F isomer **33**, mp 162–163.5°, while the A isomer **34** was isolated as the minor product, which was identified with an authentic sample.[5] The 1,2,4,5/3 configuration for **33** clearly followed from its nmr pattern of acetyl resonance signals (Table I), from its nonidentity with eight of the other nine isomers (A–E, G, H, and K)—the mixture melting point of **33** with **16**, **17**, and **34** showed strong depression—and from the fact that a compound of configuration F is the only reasonable product to be expected in this reaction.

Experimental Section

General.—Melting points were determined in capillary tubes and are corrected. Solutions were evaporated under diminished pressure. Acetylations were carried out with acetic anhydride in pyridine in the usual manner. Ir spectra were determined for potassium bromide disks with a Hitachi EPI-2 spectrophotometer. Nmr spectra were measured at 60 and 100 MHz on a Varian A-60D and a Varian HA-100D spectrometer in deuteriochloroform with reference to tetramethylsilane as an internal standard and the peak positions are given in τ values. Tlc was performed on silica gel plates (Wakogel B-10) with 5:1 benzene–ethanol as a solvent system, if not indicated otherwise. Elemental analyses were performed by Mr. Saburo Nakada, to whom our thanks are due.

A. Derivatives of (1,4/2,3,5)-5-Amino-1,2,3,4-cyclopentanetetrol (5, 6, and 8–13). 1,4-Di-*O*-acetyl-2- (or 3-) *O*-mesyl-(1,4/2,3,5)-5-acetamido-1,2,3,4-cyclopentanetetrol (5).—To a solution of 1,4-di-*O*-acetyl-(1,4/2,3,5)-5-acetamido-1,2,3,4-cyclopentanetetrol (**4**)[6] (1.00 g, 3.6 mmol) in pyridine was added mesyl chloride (0.40 ml, 5.2 mmol). The solution was left overnight at room temperature and poured into ice water to give di-*O*-mesyl derivative **8** (0.44 g) as a crystalline precipitate, which was collected by filtration. The filtrate was extracted with chloroform and the chloroform solution was evaporated. The residue was crystallized from ethanol, giving **5** (0.50 g, 39%), mp 141–145°. Recrystallization from ethyl acetate yielded the analytical sample, mp 151–152°.

Anal. Calcd for $C_{12}H_{19}NO_9S$: C, 40.77; H, 5.44; N, 3.96; S, 9.06. Found: C, 40.60; H, 5.19; N, 4.04; S, 8.96.

1,4-Di-*O*-acetyl-2,3-di-*O*-mesyl-(1,4/2,3,5)-5-acetamido-1,2,3,-4-cyclopentanetetrol (8).—To a solution of 4 (0.61 g, 2.2 mmol) in pyridine (8.0 ml), mesyl chloride (0.65 ml, 8.3 mmol) was added with cooling and stirring. The mixture was then kept at room temperature overnight and stirred into ice water to give crystalline precipitate. Collection by filtration, washing with cold water, and drying afforded **8** (0.62 g, 65%) as colorless crystals, mp 173–176°. Extraction of the aqueous filtrate with ethyl acetate gave another crop (0.20 g, 21%): nmr (5:1 $CDCl_3$–pyridine-d_6) τ 8.03 (s, 3 H, NHAc), 8.01 (s, 6 H, 2 OAc), 6.73 (s, 6 H, 2 OMs).

Anal. Calcd for $C_{13}H_{21}NO_{11}S_2$: C, 36.18; H, 4.92; N, 3.25; S, 14.84. Found: C, 36.13; H, 4.96; N, 3.40; S, 14.79.

Tosylation of 1,4-Di-*O*-acetyl-(1,4/2,3,5)-5-acetamido-1,2,3,4-cyclopentanetetrol (4).—To a solution of **4** (0.50 g, 1.8 mmol) in pyridine (12 ml), a mixture of tosyl chloride (1.73 g, 9.1 mmol) and pyridine (3.5 ml) was added under ice cooling with agitation. After stirring for 4 hr, the solution was poured into ice water, which subsequently was extracted with chloroform. Evaporation of the extract gave a mixture of **6** and **9**, which was fractionated on a silica gel column (Wakogel C-200, 30 g) with 8:1 benzene–ethanol.

Di-*O*-tosylate 9.—The fractions containing **9** according to tlc (R_f 0.6 in the same solvent system as above) were pooled and evaporated. The residue crystallized on trituration with ethyl acetate–petroleum ether (bp 30–60°) to give needles (0.32 g 30%), mp 144–145°. Recrystallization from chloroform–petroleum ether gave the analytically pure sample: mp 150–151°; nmr τ 8.09 (s, 3 H, NHAc), 8.05 (s, 6 H, 2 OAc), 7.53 (s, 6 H, aryl CH_3).

Anal. Calcd for $C_{25}H_{29}NO_{11}S_2$: C, 51.44; H, 5.01; N, 2.40; S, 10.97. Found: C, 51.70; H, 4.89; N, 2.43; S, 11.39.

Mono-*O*-tosylate 6.—The appropriate fractions containing **6** (R_f 0.5 in the same solvent system as above) were combined and evaporated to dryness. The residue was crystallized from ethyl acetate–petroleum ether to afford **6** (0.30 g, 38%): mp 153–154°; nmr τ 8.09 (s, 3 H, NHAc), 7.90 (s, 6 H, 2 OAc), 7.54 (s, 3 H, aryl CH_3).

Anal. Calcd for $C_{18}H_{23}NO_9S$: C, 50.33; H, 5.41; N, 3.26; S, 7.46. Found: C, 50.47; H, 5.28; N, 3.25; S, 7.08.

2,3-Di-*O*-mesyl-(1,4/2,3,5)-5-acetamido-1,2,3,4-cyclopentanetetrol (10).—Compound **8** (1.44 g) was dissolved in methanolic ammonia (40 ml) and the solution was stored in a refrigerator overnight. Evaporation and recrystallization of the residue from ethanol afforded **10** (0.92 g, 79%), mp 137–138°.

Anal. Calcd for $C_9H_{17}NO_9S_2$: C, 31.11; H, 4.93; N, 4.03; S, 18.44. Found: C, 30.87; H, 4.97; N, 4.02; S, 18.22.

2- (or 3-) *O*-Mesyl-(1,4/2,3,5)-5-acetamido-1,2,3,4-cyclopentanetetrol (11).—De-O-acetylation of **5** (0.49 g) in methanolic ammonia (12 ml) and work-up as described for **10** gave 0.28 g (76%) of crude product, which after recrystallization from ethanol melted at 177–178°.

Anal. Calcd for $C_8H_{15}NO_7S$: C, 35.67; H, 5.61; N, 5.20; S, 11.89. Found: C, 36.00; H, 5.52; N, 5.20; S, 11.36.

1,3,4-Tri-*O*-acetyl-2-*O*-mesyl-(1,4/2,3,5)-5-acetamido-1,2,3,4-cyclopentanetetrol (12).—Acetylation of **5** (97 mg) in the usual manner and recrystallization of the crude product (mp 149–151°) from ethanol afforded **12** (58 mg, 54%) as colorless crystals: mp 151–152°; nmr τ 8.02 (s, 3 H, NHAc), 7.89 (s, 3 H, OAc), 7.88 (s, 6 H, 2 OAc), 6.90 (s, 3 H, OMs), 3.65 (d, 1 H, J = 7 Hz, NH).

Anal. Calcd for $C_{14}H_{21}NO_{10}S$: C, 42.54; H, 5.36; N, 3.54; S, 8.11. Found: C, 42.33; H, 5.10; N, 3.58; S, 8.30.

1,3,4-Tri-*O*-acetyl-2-*O*-tosyl-(1,4/2,3,5)-5-acetamido-1,2,3,4-cyclopentanetetrol (13).—Acetylation of tosylate **6** (200 mg) and recrystallization of the crude product from acetone–ethyl acetate afforded **13** (0.15 g, 68%): mp 188–191°; nmr τ 8.07 (s, 3 H, NHAc), 8.04, 7.98, and 7.92 (three s, 3 H, 3 OAc), 7.54 (s, 3 H, aryl CH_3).

Anal. Calcd for $C_{20}H_{25}NO_{10}S$: C, 50.93; H, 5.35; N, 2.97; S, 6.79. Found: C, 50.93; H, 5.13; N, 3.21; S, 6.90.

B. Derivatives of DL-(1,2,3,5/4)-5-Amino-1,2,3,4-cyclopentanetetrol (7, 14, and 19–21). 1,4-Di-*O*-acetyl-2,3-*O*-cyclohexylidene-DL-(1,2,3,5/4)-5-acetamido-1,2,3,4-cyclopentanetetrol (7).—2,3-*O*-Cyclohexylidene-(1,4/2,3,5)-5-acetamido-1,2,3,4-cyclopentanetetrol (**3**)[5] (950 mg, 3.5 mmol) was treated with mesyl chloride (0.41 ml, 5.3 mmol) in pyridine (12 ml) for 30 min under ice cooling and agitation. The mixture was left at room temperature for 1.5 hr and poured into ice water (100 ml) to give the 1,4-di-*O*-mesylate (**1**)[6] as a crystalline precipitate, which was collected by filtration (394 mg). Extraction of the filtrate with chloroform, followed by washing of the organic layer with water, drying, and evaporation, gave an oily residue (831 mg) comprising according to tlc an approximately 3:2 mixture of monomesylate **2** and dimesylate **1**. This mixture was treated with boiling water

in the presence of sodium acetate (0.98 g) for 1.5 hr and subsequently evaporated to dryness. Upon acetylation of the residue, the mixture was separated on a silica gel column (Wakogel C-200, 75 g, 35 × 1.8 cm) by elution with 10:1 benzene–ethanol. The fractions containing **7** according to tlc were pooled and evaporated to dryness. Trituration with ether afforded 288 mg (23%) of **7** as colorless crystals: mp 98–100°; nmr τ 8.45 and 8.30 (two m, 4 H and 6 H, cyclohexylidene protons), 8.02 (s, 3 H, NHAc), 7.92 and 7.86 (two s, 3 H, 2 OAc).

Anal. Calcd for $C_{17}H_{25}NO_7$: C, 57.45; H, 7.09; N, 3.94. Found: C, 57.29; H, 6.94; N, 3.89.

Tetra-*O*-acetyl-DL-(1,2,3,5/4)-5-acetamido-1,2,3,4-cyclopentanetetrol (14).—The cyclohexylidene compound **7** (100 mg) was refluxed in 80% aqueous acetic acid for 70 min and the solution was subsequently evaporated to dryness. Acetylation of the residue as usual and recrystallization of the crude product from ether afforded **14** (54 mg, 54%) as needles, mp 123–124°.[8] Nmr data (*cf.* Table I) were identical with those of the compound described previously.[5]

Anal. Calcd for $C_{15}H_{21}NO_9$: C, 50.13; H, 5.89; N, 3.90. Found: C, 50.11; H, 6.02; N, 3.90.

DL-(1,2,3,5/4)-5-Acetamido-1,2,3,4-cyclopentanetetrol (19).—De-O-acetylation of **14** (400 mg) with methanolic ammonia overnight and evaporation of the reaction mixture followed by two recrystallizations from ethanol afforded 145 mg (68%) of colorless crystals, mp 123–124°.

Anal. Calcd for $C_7H_{13}NO_5$: C, 44.22; H, 6.75; N, 7.18. Found: C, 43.98; H, 6.85; N, 7.33.

3,4-Di-*O*-acetyl-1,2-*O*-isopropylidene- (20) and 1,4-di-*O*-acetyl-2,3-*O*-isopropylidene-DL-(1,2,3,5/4)-5-acetamido-1,2,3,4-cyclopentanetetrol (21).—To a solution of acetamidotetrol **19** (85 mg) in 12 ml of 1:1 acetone–methanol, Drierite (0.3 g) and a drop of concentrated sulfuric acid were added. The mixture was stirred for 46 hr and then neutralized with sodium bicarbonate solution, followed by extraction with chloroform and evaporation of the extract. The residue was acetylated to give a syrup (172 mg) comprising according to tlc an approximately 4:1 mixture of two products (R_f 0.67 and 0.54, respectively). Separation was achieved on a silica gel column (Wakogel C-200, 35 g, 30 × 2 cm) by elution with 5:1 benzene–ethanol. The appropriate fractions were pooled and evaporated to dryness. The major product (113 mg) was recrystallized from ether and again from ether–light petroleum to give 40 mg (29%) of an isopropylidene di-*O*-acetate (tentative structure **21**): mp 136–138°; nmr τ 8.69 and 8.48 [two s, 3 H, $C(CH_3)_2$], 8.02 (s, 3 H, NHAc), 7.94 and 7.90 (two s, 3 H, 2 OAc).

Anal. Calcd for $C_{14}H_{21}NO_7$: C, 53.32; H, 6.71; N, 4.44. Found: C, 53.44; H, 6.58; N, 4.36.

The minor product (25 mg, mp 154–156°) was recrystallized from ether to give 10 mg (7%) of di-*O*-acetylisopropylidene derivative **20** (tentatively): mp 155–156°; nmr τ 8.68 and 8.48 [two s, 3 H, $C(CH_3)_2$], 8.02 (s, 3 H, NHAc), 7.93 and 7.85 (two s, 3 H, 2 OAc).

Anal. Calcd for $C_{14}H_{21}NO_7$: C, 53.32; H, 6.71; N, 4.44. Found: C, 53.52; H, 6.76; N, 4.30.

C. Derivatives of (1,2,3,4/5)-5-Amino-1,2,3,4-cyclopentanetetrol (14 and 22–24). Tetra-*O*-acetyl-(1,2,3,4/5)-5-acetamido-1,2,3,4-cyclopentanetetrol (15). 1. From Dimesylate 8.—A suspension of **8** (0.61 g) in 30 ml of water containing 0.23 g of sodium acetate was refluxed for 10 hr. The solution was then evaporated and the residue was acetylated as usual. Crystallization of the product from ethyl acetate gave 0.28 g (55%), mp 141–145°. Recrystallization from chloroform–ether raised the melting point to 145–146° (0.11 g, 22%). A mixture melting point with tetra-*O*-acetyl-(1,4/2,3,5)-5-acetamido-1,2,3,4-cyclopentanetetrol[4] showed a remarkable depression.

Anal. Calcd for $C_{15}H_{21}NO_9$: C, 50.11; H, 5.90; N, 3.90. Found: C, 50.38; H, 5.95; N, 3.98.

2. From Ditosylate 9.—Refluxing **9** (400 mg) in 30 ml of 30% aqueous ethanol containing 0.12 g of sodium acetate for 24 hr, followed by acetylation and work-up as described under 1, gave 61 mg (25%) of **15**, identical in all respects with the product obtained above.

(1,2,3,4/5)-5-Acetamido-1,2,3,4-cyclopentanetetrol (22).—Compound **15** (0.19 g) was dissolved in methanolic ammonia (10 ml) and kept overnight. The solution was evaporated and the residue was triturated in ethyl acetate to give a crude product. Recrystallization from ethanol afforded **22** (77 mg, 76%), mp 173–176°. Admixture with the 1,4/2,3,5 isomer (mp 169.5–171°[5]) showed considerable depression of the melting point.

Anal. Calcd for $C_7H_{13}NO_5$: C, 43.96; H, 6.86; N, 7.33. Found: C, 43.64; H, 6.80; N, 7.21.

1,2:3,4-Di-*O*-isopropylidene- (23) and 1,4-Di-*O*-acetyl-2,3-*O*-isopropylidene-(1,2,3,4/5)-5-acetamido-1,2,3,4-cyclopentanetetrol (24).—To a solution of **22** (100 mg) in 66 ml of acetone–methanol (10:1), Drierite (0.30 g) and a drop of concentrated sulfuric acid were added. The mixture was stirred for 46 hr and then neutralized with sodium hydrogen carbonate solution, followed by extraction with chloroform and evaporation of the extract. The residue resisted crystallization despite several purifications *via* alumina columns. The product **23** of the tentative structure was characterized as a syrup (84 mg, 59%), exhibiting the presence of two isopropylidene functions (two s, 6 H at 8.68 and 8.42) and an acetamido group (s, 3 H at 8.03) in the nmr spectrum. The aqueous layer was evaporated to dryness, followed by acetylation of the residue and usual work-up. Crystallization was achieved from chloroform–ether to give the mono-*O*-isopropylidene derivative of the tentative structure **24** as needles (33 mg, 22%): mp 204–205°; nmr τ 8.67 and 8.45 [two s, 3 H, $C(CH_3)_2$], 8.04 (s, 3 H, NHAc), 7.87 (s, 6 H, 2 OAc).

Anal. Calcd for $C_{14}H_{21}NO_7$: C, 53.32; H, 6.71; N, 4.44. Found: C, 53.06; H, 6.58; N, 4.73.

D. Derivatives of (1,4,5/2,3)-5-Amino-1,2,3,4-cyclopentanetetrol (16 and 30–32). Tetra-*O*-acetyl-(1,4,5/2,3)-5-acetamido-1,2,3,4-cyclopentanetetrol (16).—A solution of dimesylate **10** (500 mg) and sodium acetate (0.22 g) in water (20 ml) was heated under reflux for 56 hr. Evaporation of the solution and acetylation of the residue gave a syrup which crystallized from ethyl acetate–petroleum ether: 150 mg (26%) of **16** as colorless crystals; mp 171–173°; for nmr *cf.* Table I. The product was identical on the basis of mixture melting point and ir data with the corresponding pentaacetyl derivative prepared by the method of Ahluwalia, *et al.*[4]

1,4-Di-*O*-acetyl-(1,4,5/2,3)-5-acetamido-1,2,3,4-cyclopentanetetrol (30).—A 0.55-g portion of 1,4-di-*O*-acetyl-2,3-*O*-cyclohexylidene-(1,4,5/2,3)-5-acetamido-1,2,3,4-cyclopentanetetrol[4] (**29**) was hydrolyzed in boiling 80% aqueous acetic acid (20 ml) for 100 min and then evaporated. The residue showed a major component (R_f 0.3) and a minor one (R_f 0.3) on tlc, and was fractionated on a silica gel column (Wakogel C-200, 30 g) with 5:1 benzene–ethanol. The main component was collected and evaporated to give 0.21 g (53%) of a colorless sirup.

Mixture of 1,4-Di-*O*-acetyl-2,3-di-*O*-mesyl- (32) and 1,4-Di-*O*-acetyl-2- (or 3-) *O*-mesyl-(1,4,5/2,3)-5-acetamido-1,2,3,4-cyclopentanetetrol (31).—To a solution of **30** (0.21 g, 0.8 mmol) in pyridine (3.0 ml) was added mesyl chloride (0.14 ml, 1.8 mmol) under ice cooling and the mixture was kept overnight at room temperature. The solution was poured into ice water and deionized with Amberlite MB-3. The solution was evaporated and the residue was chromatographed on a silica gel column (Wakogel C-200, 30 g) in 5:2 benzene–methanol. The two major components were collected and evaporated to give a mixture of **31** and **32** (0.27 g) as an amorphous solid.

E. Derivatives of DL-(1,3,5/2,4)-5-Amino-1,2,3,4-cyclopentanetetrol (17, 25 and 26). Tetra-*O*-acetyl-DL-(1,3,5/2,4)-5-acetamido-1,2,3,4-cyclopentanetetrol (17).—Refluxing **11** (0.25 g) with sodium acetate (0.12 g) in water (15 ml) for 17 hr, followed by evaporation and acetylation, afforded a product which crystallized from ethyl acetate (0.17 g, 51%, mp 159–161°). Recrystallization from ethyl acetate–petroleum ether gave analytically pure **17**, mp 161.5–162.5°; for nmr *cf.* Table I.

Anal. Calcd for $C_{15}H_{21}NO_9$: C, 50.11; H, 5.90; N, 3.90. Found: C, 49.77; H, 5.71; N, 3.88.

DL-(1,3,5/2,4)-5-Acetamido-1,2,3,4-cyclopentanetetrol (25).—Compound **17** (138 mg) was de-O-acetylated as described for **22**, and the crude product was recrystallized from ethanol to give **25** (49 mg, 52%), mp 166–167°, showing a single spot on tlc in chloroform–methanol (7:3).

Anal. Calcd for $C_7H_{13}NO_5$: C, 43.98; H, 6.85; N, 7.33. Found: C, 44.31; H, 7.01; N, 7.38.

Tetra-*O*-acetyl-*N*-isopropylidene-DL-(1,3,5/2,4)-5-amino-1,2,3,4-cyclopentanetetrol (26).—To a solution of **25** (30 mg) in *N*,*N*-dimethylformamide (2 ml), 2,2-dimethoxypropane (0.1 ml) and *p*-toluenesulfonic acid (3 mg) were added and the mixture was kept for 3 hr at room temperature. Neutralization by addition of Amberlite IRA-400 (OH^-) followed by evaporation and acetylation as usual gave a syrup which crystallized on trituration with ether: 35 mg (63%) of colorless crystals; mp 194–196°; nmr τ 8.47 and 8.28 [two s, 3 H, $C(CH_3)_2$], 7.97 and 7.94 (two s, 6 H, 4 OAc).

Anal. Calcd for $C_{16}H_{23}NO_8$: C, 53.77; H, 6.48; N, 3.92. Found: C, 53.50; H, 6.22; N, 4.07.

F. Derivatives of DL-(1,2,4/3,5)-5-Amino-1,2,3,4-cyclopentanetetrol (18, 27, and 28). Tetra-*O*-acetyl-DL-(1,2,4/3,5)-5-acetamido-1,2,3,4-cyclopentanetetrol (18). 1. From 6 or 5.—A mixture of 0.23 g (0.55 mmol) of 6 (or the molar equivalent of mesylate 5) and sodium acetate (0.1 g) was refluxed in water (10 ml) for 2 hr and evaporated. The residue was acetylated and the product was crystallized in ether to give 0.12 g (63%) of 18, mp 108–110°. Recrystallization from the same solvent raised the melting point to 111–112°. Mixture melting points with the pentaacetyl derivatives of configuration 1,2,3,5/4 (14, mp 123–124°), as well as 1,2,3,4/5 (15, mp 145–146°) and 1,4/2,3,5 (mp 148.5–149°) showed marked depression in each case; for nmr *cf.* Table I.

Anal. Calcd for $C_{15}H_{21}NO_9$: C, 50.11; H, 5.90; N, 3.90. Found: C, 50.53; H, 6.02; N, 3.84.

2. From 12 or 13.—A mixture of 0.85 g (1.41 mmol) of 13 (or the molar equivalent of 12), sodium acetate (0.3 g), and water (40 ml) was refluxed for 17 hr. Evaporation, acetylation, and work-up in the same manner as described under 1 afforded 0.44 g (67%) of 18, identical in all respects with the product described above.

DL-(1,2,4/3,5)-5-Acetamido-1,2,3,4-cyclopentanetetrol (27).—Compound 18 was de-O-acetylated with methanolic ammonia as described for 22 and the syrupy product obtained after evaporation was extracted with hot ethyl acetate. Only part of the residue which was insoluble in ethyl acetate, showing a single spot on tlc, could be induced to crystallization on trituration with 4:1 2-propanol–ethanol; 36 mg (43%) of colorless crystals, mp 142–144°, was obtained.

Anal. Calcd for $C_7H_{13}NO_5$: C, 43.83; H, 6.86; N, 7.28. Found: C, 44.31; H, 7.01; N, 7.38.

3,4-Di-*O*-acetyl-1,2-*O*-isopropylidene-DL-(1,2,4/3,5)-5-acetamido-1,2,3,4-cyclopentanetetrol (28).—Compound 27 (70 mg) was treated in *N*,*N*-dimethylformamide (3.5 ml) with 2,2-dimethoxypropane (0.20 ml) and *p*-toluenesulfonic acid (3 mg) for 3 hr at room temperature. Neutralization, acetylation, and work-up as described above for 26 gave a syrup which crystallized from ether: 50 mg (44%) of colorless crystals; mp 135–136°; nmr τ 8.71 and 8.43 [two s, 3 H, $C(CH_3)_2$], 8.01 (s, 3 H, HNAc), 7.94 and 7.92 (two s, 3 H, 2 OAc).

Anal. Calcd for $C_{14}H_{21}NO_7$: C, 53.32; H, 6.71; N, 4.44. Found: C, 53.37; H, 6.63; N, 4.45.

G. Tetra-*O*-acetyl-(1,2,3,4,5/0)-5-acetamido-1,2,3,4-cyclopentanetetrol (34).—A mixture (0.25 g) of the mono- and di-*O*-mesyl derivatives (31 and 32), as obtained on mesylation of 30 (*cf.* section C), was heated in water (10 ml) in the presence of sodium acetate (0.12 g) for 8 hr and subsequently evaporated. The residue was acetylated to give a syrupy mixture of 33 and 34, which was chromatographed on a silica gel column (Wakogel C-200, 30 g) in 5:1 benzene–ethanol. Fractions showing R_f 0.39 (tlc) were combined and evaporated to dryness. The residue was crystallized in ethanol to give 34 (17 mg, 6% from 30), mp 173–174°. The product was identified by a comparison of ir spectra and a mixture melting point determination with an authentic sample of 34, prepared by another route.[5]

H. Tetra-*O*-acetyl-DL-(1,2,4,5/3)-5-acetamido-1,2,3,4-cyclopentanetetrol (33).—Those fractions of the above column separation exhibiting a spot at R_f 0.41 (tlc) were pooled and evaporated to dryness. The residue was crystallized in ethyl acetate–petroleum ether to give 33 (60 mg, 22% from 30), mp 160–161°. Recrystallization from the same solvent yielded the analytically pure sample, mp 162–163.5°. Admixture with the 1,3,5/2,4 analog 17 (mp 161.5–162.5°) showed a distinct depression of the melting point.

Anal. Calcd for $C_{15}H_{21}NO_9$: C, 50.11; H, 5.90; N, 3.90. Found: C, 50.35; H, 5.80; N, 3.97.

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Synthesis of Some 17-Substituted 3,10-Ethano-5α-estranes[1]

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Several 17-substituted derivatives of 3-hydroxy-3,10-ethano-5α-estrane were prepared. The synthetic sequence centers about the transformation of dehydroisoandrosterone 3-acetate (4a) into a 19a-methylandrostane-3,17,19-trione (7e). Treatment of 7e with ethanolic potassium hydroxide effected an internal condensation of the 19a-methyl ketone with the 3-ketone moiety to give 3,10-[2′-oxoethano]-5α-estran-3-ol-17-one (9b). Selective reduction of 9b with lithium tri-*tert*-butoxyaluminum hydride afforded 3,10-[2′-oxoethano]-5α-estran-17-ol (9c). Wolff–Kishner reduction of 9c under forcing conditions gave 3,10-ethano-5α-estrane-3,17-diol (10a) which served as starting material for the synthesis of the 17-substituted 3,10-ethano-5α-estranes. The circular dichroism properties of the 3,10-[2′-oxoethano]-5α-estranes with various 17 substituents were studied. The sign of the Cotton effect can be explained if both the back and front octants are considered.

The literature contains but one report on the synthesis of 3,10-ethanoestranes, and this was by Birch and coworkers.[2] In order to more fully investigate the chemical and physical properties of these steroid derivatives, as well as to study their biological effects, we undertook the synthesis of the parent steroid and several 17-substituted derivatives. The Birch synthesis of 3,10-ethanoestranes, shown in Chart I, was accomplished by first isomerizing 1,4-dihydroestradiol 3-methyl ether (1) to a mixture of 1,4- and 1,2-dihydroestradiol 3-methyl ether (1 and 2), followed by a Diels–Alder reaction on the conjugated diene steroid 2 with methyl vinyl ketone to furnish the ethanoestrane adduct 3.[2]

Our initial synthetic efforts followed the precedent set down by Birch and coworkers.[2] We found that the isomerization of 1 to 2 using Triton B catalyst in dimethyl sulfoxide was superior to the method reported by Birch; however, we were unsuccessful in obtaining

(1) This investigation was supported by Contract NIH-71-2457 from the Contraceptive Development Branch Center for Population Research, National Institute of Child Health and Human Development, National Institutes of Health.

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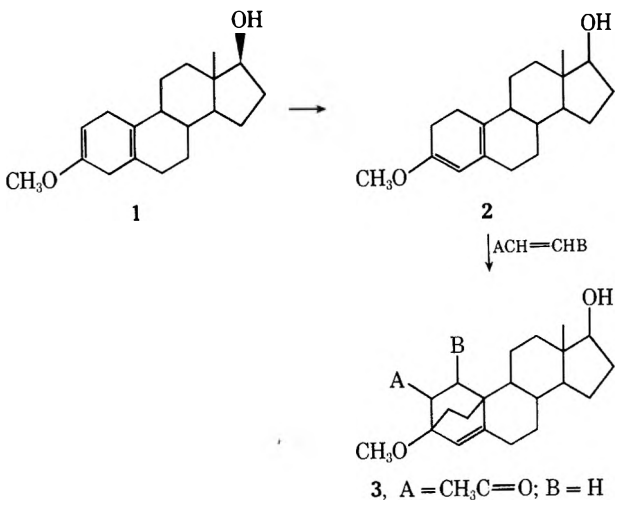
CHART I



Diels–Alder adducts from the diene mixture. Attempts to thermally isomerize 1,4-dihydroestradiol (**1**) to 1,2-dihydroestradiol (**2**) in a sealed tube in the presence of a dienophile as a trapping agent were also unsuccessful.

An alternate, although longer sequence, which started with dehydroisoandrosterone 3-acetate (**4a**) was devised. The sequence involved the conversion of **4a** to a 19a-methyl-3,19-diketo derivative which could be internally condensed to yield the desired A-ring bicyclo[2.2.2]octanone compound. Thus, dehydroisoandrosterone (**4a**) was converted into the known bromohydrin[3] **5** with *N*-bromoacetamide in aqueous dioxane and perchloric acid. Compound **5** was then photolyzed at reflux in benzene or carbon tetrachloride with iodine and lead tetraacetate to furnish the 6,19 ether **6a** in high yield.[4] For convenience as well as to include the possibility of manipulating various ketones later in the synthetic sequence, **6a** was converted to the ketal derivative **6b**. It was necessary to reacetylate after the ketalization, since the appearance of 3500 cm^{-1} hydroxy absorption in the infrared spectrum and only a weak singlet at 2.06 ppm in the pmr spectrum indicated that some of the 3 acetate was lost in the reaction. In our initial attempts to convert the 19,6 ether **6b** to the olefinic alcohol **4b** employing published procedures,[5] we noticed that the singlet at 2.00 ppm for the 3 acetate integrated for too few protons, indicating that formation of **4c** by cleavage of the 3 acetate was occurring. Alternatively, it was found that **6b** could be converted to **4b** in 82% yield by treating **6b** with either acid-washed zinc dust or zinc–copper couple[6] for 10 min in refluxing 2-propanol. Attempts to oxidize the 19 alcohol **4b** to the 19 aldehyde **4d** with chromium trioxide in pyridine gave poor yields. However, employing the Collins reagent,[7] which uses methylene chloride as the reaction solvent, we were able to consistently oxidize **4b** to pure aldehyde **4d** in high yield (70–80%). The pmr spectrum in chloroform-d_1 shows two absorptions at 9.60 and 9.61 ppm in a ratio of 1:2 for the aldehydic proton. This probably represents two geometric configurations of the 19 aldehyde.

Methyllithium addition to the 19 aldehyde of **4d** occurred with concomitant cleavage of the acetate and furnished the diol **4e**. An inspection of the pmr spectra indicated that the product was a mixture of diastereoisomers, most probably resulting from stereospecific addition of methyllithium to the two aldehyde geometric isomers. The 18-methyl groups of mixture **4e** appeared as two absorptions in a ratio of 2:1. In addition, the 19a-methyl absorptions appeared as two doublets centered at 1.37 and 1.40 ppm, respectively, with J = 6 Hz for both isomers in a ratio of 2:1. No attempt was made to separate these isomers, but rather the sample was subjected directly to hydrogenation. The olefinic diol **4e** was nearly inert to reduction; however, after various catalysts and solvents were tried, it was determined that 20% palladium hydroxide on carbon in 2-propanol–ethanol gave optimum yields of material in which the $\Delta^{5,6}$ double bond had been reduced. The appearance of a 1750-cm^{-1} absorption in the infrared spectrum of the crude product indicated that some hydrolysis of the 17-ketal group had occurred during hydrogenation. The reduction product was reketalized to furnish **7a**, and then, without prior purification, oxidized with the Collins reagent to the crude diketo ethylene ketal compound **7b**. Thin layer chromatography of this initial material indicated that at least two major compounds were present. Column chromatography of the mixture furnished both **7b** and **7c**.

The structure of **7b** was readily established from its infrared and pmr spectra. Absorptions at 1715 and 1695 cm^{-1} were observed for both the 3 and 19 ketones, and the presence of a singlet at 2.12 ppm in the pmr spectrum for the 19a-methyl confirmed the structure assignment.

The structure of **7c** was also established by examination of the infrared and pmr sepctra. The infrared spectrum of **7c** showed only a 1690-cm^{-1} carbonyl absorption; however, this did not accurately establish whether the 3 or 19 ketone function was now missing. A singlet at 2.28 ppm in the pmr spectrum for the 19a-methyl of **7c** clearly indicated that the 3 ketone function was missing. As well, the absence of other functional groups and the elemental analysis of **7c** indicated that hydrogen replacement of the 3 functionality had occurred. Compound **7c** could have been formed by catalytic isomerization of the $\Delta^{5,6}$ olefin to the $\Delta^{4,5}$ position, hydrogenolysis of the 3-hydroxyl, and then reduction of the $\Delta^{4,5}$ double bond. Alternatively, **7c** could have been formed by reduction of a solvolytic intermediate such as **8** or its products.

Treatment of **7b** with alcoholic potassium hydroxide for 5 min resulted in the quantitative formation of a new product whose infrared spectrum showed a new 3500- and a 1710-cm^{-1} absorption. As well, the singlet at 2.12 ppm for the 19a-methyl was not present in the pmr spectrum of the new compound. These data were consistent with the formulation of the new product as 3,10-[2′-oxoethano]-5α-estran-3-ol-17-one 17-ethylene ketal (**9a**).

Experimentally it proved simpler to deketalize rather than reketalize the crude product from reduction of

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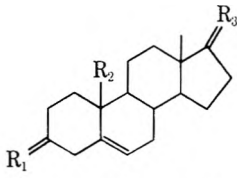
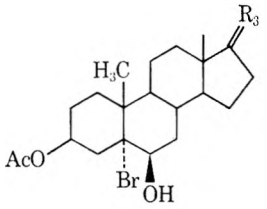
4e. This product, without purification, was directly oxidized to a mixture of triketone **7e** and diketone **7f**. Triketone **7e** could then be directly isolated by crystallization. Chromatography of the filtrates afforded additional quantities of **7e** and also the hydrogenolysis product **7f**. The infrared spectrum of **7e** showed absorptions at 1735, 1715, and 1695 cm^{-1} while **7f** showed only absorptions at 1735 and 1690 cm^{-1}. Analogous to the reaction of **7b**, treatment of **7e** with alcoholic potassium hydroxide afforded a near quantitative conversion to 3,10-[2′-oxoethano]-5α-estran-3-ol-17-one (**9b**).

Since the 17-ketal function was removed, it was necessary to manipulate either the 2′ or 17 ketone functions of **9b** so that the 2′ ketone could then be selectively removed. Examination of molecular models of **9b** indicated that the 2′-oxo position was extremely sterically hindered and quite probably a 17-keto functionality could be easily manipulated in its presence. Indeed, we found that the product **9c** from treatment of **9b** with



4a, R_1 = H,OAc; R_2 = CH_3; R_3 = O
b, R_1 = H,OAc; R_2 = CH_2OH; R_3 = OCH_2CH_2O
c, R_1 = H,OH; R_2 = CH_2OH; R_3 = OCH_2CH_2O
d, R_1 = H,OAc; R_2 = CHO; R_3 = OCH_2CH_2O
e, R_1 = H,OH; R_2 = $HOCHCH_3$; R_3 = OCH_2CH_2O



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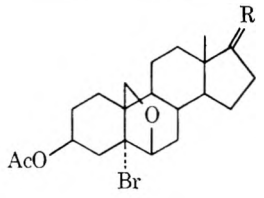
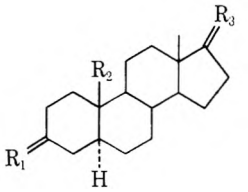
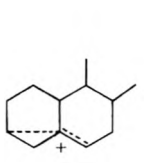


6a, R = O
b, R = OCH_2CH_2O



7a, R_1 = H,OH; R_2 = $HOCHCH_3$; R_3 = OCH_2CH_2O
b, R_1 = O; R_2 = O=CCH_3; R_3 = OCH_2CH_2O
c, R_1 = H,H; R_2 = O=CCH_3; R_3 = OCH_2CH_2O
d, R_1 = H,OH; R_2 = $HOCHCH_3$; R_3 = O
e, R_1 = O; R_2 = O=CCH_3; R_3 = O
f, R_1 = H,H; R_2 = O=CCH_3; R_3 = O



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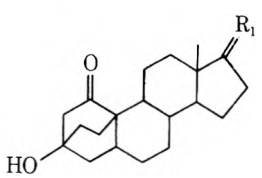
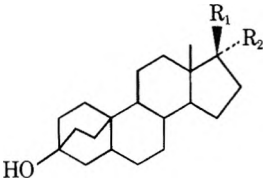


9a, R_1 = OCH_2CH_2O
b, R_1 = O
c, R_1 = α-H,β-OH

1 equiv of lithium tri-*tert*-butoxyaluminum hydride had no 1735-cm^{-1} absorption, but did retain the 1710-cm^{-1} peak in its infrared spectrum. In fact, the 2′ ketone function is so sterically hindered that selective reduction of the 17 ketone to furnish the 17-hydroxy compound **9c** can be accomplished with no reduction of the 2′-oxo moiety even when a large excess of reducing agent is employed.

Initial attempts to reductively convert the 2′ ketones **9a** or **9c** to the corresponding methylene unit by formation of the tosylhydrazone followed by reduction with sodium borohydride were unsuccessful. The 2′-oxo position is so severely sterically hindered that the tosylhydrazone derivatives could not be formed under forcing conditions. Wolff–Kishner reduction of **9c**, employing the Huang-Minlon method for reduction of sterically hindered 11-keto steroids,[8] afforded a high yield of the ethanoestrane **10a**. Since Nagata and Itazaki[8] had successfully reduced steroid 11-keto groups in the presence of a 17-ketal moiety using the indicated conditions, we treated the ketal **9a** under similar conditions. However, the only product isolated from this reaction was 3,10-ethano-5α-estran-3-ol (**10b**). Oxidation of **10a** afforded a high yield of ketone **10c**. Ethynylation of ketone **10c** with lithium acetylide–ethylenediamine complex afforded the bicyclic 17α-ethynyl-17β-hydroxy compound **10d**.



10a, R_1 = OH; R_2 = H
b, R_1 = R_2 = H
c, R_1 = R_2 = O
d, R_1 = OH; R_2 = C≡CH

The ORD and/or CD properties of only a few optically active bicyclo[2.2.2]octanones have been reported in the literature.[9-11] The back octant rule method[12] has been used to explain the sign of the Cotton effect in some cases[10,11] while other examples were explained by their antioctant behavior or the Horeau method.[9] Since no generally accepted method for the correlation of the sign of the Cotton effect exhibited by bicyclo[2.2.2]octanones and their absolute stereochemistry is yet available, we wish to report our observations with steroid A-ring bicyclo[2.2.2]octanones.

The CD spectra of **9a**, **9b**, and **9c** are shown in Figure 1. As shown in these curves, the long-wavelength Cotton effect due to the bicyclo carbonyl n–π^* transitions are all weakly negative. In the case of compound **9b** this effect is obscured by the large positive Cotton effect due to the 17-carbonyl moiety. The octant rule can be used to explain this observation.

If one considers the cyclohexanone ring formed by carbons 1, 1′, 2, 2′, 3, and 10 in these compounds, then

(8) W. Nagata and H. Itazaki, *Chem. Ind. (London)*, 1194 (1964).
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(11) P. Crabbé, L. H. Zalkow, and N. N. Girotra, *J. Org. Chem.*, **30**, 1678 (1965).
(12) W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne, and C. Djerassi, *J. Amer. Chem. Soc.*, **83**, 4013 (1961).

the observed negative Cotton effect is inconsistent with the octant rule when only the back octants are considered. Carbon atom 5 is severely skewed in a positive octant and is enhanced by carbon atom 6, also in a positive octant. These contributions are only partly canceled by carbon atom 1 in a negative octant. However, an examination of the geometry of these steroid A-ring bicyclo[2.2.2]octanones with Dreiding molecular models indicates that it is necessary to also consider the front octants.[12] Since carbon atoms 7, 14, 15, and 16 fall into a negative front octant and are only partly canceled by carbon atoms 11 and 12 in a positive front octant, one would predict a relatively large negative front octant effect. This negative front octant effect would be only partially canceled by the smaller positive back octant effects, and one would then predict that the 3,10-[2′-oxoethano]-5α-estranes **9a** and **9c** would show small negative n–π* Cotton effects. Thus, the compounds **9a** and **9c** give an excellent example of the use of the front octant method to explain the observed Cotton effect.[13]

In addition to the relatively strong negative Cotton effect exhibited by compounds **9a** and **9c**, one also observes two weaker Cotton effects at lower wavelengths. No satisfactory explanation has been found for this observation, and only tentative interpretation, such as solvation, may be suggested.

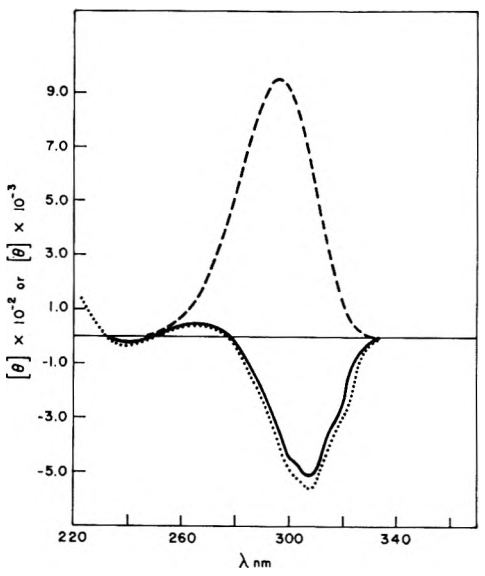

Figure 1.—The CD spectra of **9a** (——) and **9c** (· · · ·), ordinate = $[\theta] \times 10^{-2}$, and **9b** (- - - -), ordinate = $[\theta] \times 10^{-3}$, in methanol.

Experimental Section

Melting points were taken on a Kofler hot-stage microscope and are uncorrected. Infrared spectra were measured with a Perkin-Elmer 221 spectrophotometer. Ultraviolet spectra were run in methanol on a Cary Model 14 recording spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian Model A-100, using tetramethylsilane (TMS) as an internal standard. Chemical shifts are expressed in δ units. Rotations were determined with a Perkin-Elmer Model 141 polarimeter. CD measurements were made with a Jasco Model-20 spectropolarimeter at ambient temperature. Microanalyses were carried out by Micro-Tech Laboratories, Skokie, Ill.

3β-Acetoxy-19-hydroxyandrost-4-en-17-one Ethylene Ketal (4b).—Steroid **6b**[5] (40 g, 0.085 mmol) was treated with Zn–Cu couple[6] for 10 min in refluxing 2-propanol. The hot solution was immediately filtered, and the residue was washed with chloroform. After evaporation of the solvent, the residue was taken up in chloroform and water, and washed with saturated ammonium chloride and then with water. The solution, after drying ($MgSO_4$), was evaporated, and the residue was recrystallized from acetone–hexane to yield 27.3 g (82%) of pure **4b**, mp 143–144° (lit.[5] mp 143.5–144.5°).

3β-Acetoxy-19-oxoandrost-4-en-17-one Ethylene Ketal (4d).—Chromium trioxide (47 g) was slowly added to a mechanically stirred solution of pyridine (80 ml) in methylene chloride (1500 ml) under nitrogen.[7] After the solution was stirred for 15 min, steroid **4b** (28 g, 0.072 mol) in methylene chloride (100 ml) was rapidly added dropwise; then the solution was stirred for an additional 15 min. After the methylene chloride layer was decanted, the tarry residue was leached with ether (4 × 300 ml) and the combined organic layers were washed with water (2 × 400 ml), 2% sodium hydroxide (4 × 200 ml), and water until neutral. The organic layer was dried (Na_2SO_4), filtered through Celite, and evaporated to dryness at reduced pressure. The crude product was recrystallized from acetone–water to yield 21.5 g (77%) of pure **4d**: mp 149–151° (lit.[5] mp 148°); ir (KBr) 1725 (CHO) and 1745 cm^{-1} (RCO_2R); nmr ($CDCl_3$) δ 0.84 (s, 3, CH_3), 2.10 [s, 3, $OC(=O)CH_3$], 3.86 (m, 4, $-OCH_2CH_2O-$), 5.85 (m, 1, =CH), and 9.61 ppm (d, 1, CHO).

3,19-Dihydroxy-19-methylandrost-5-en-17-one 17-Ethylene Ketal (4e).—Methyllithium (30 ml, 1.6 *M*) was added dropwise to a magnetically stirred dry ether (100 ml) suspension of aldehyde **4d** (5.6 g, 0.014 mol) under nitrogen. On completion of the addition, the ether solution was refluxed for an additional 30 min, then stirred overnight.

The excess methyllithium was decomposed by dropwise addition of water. Ethyl acetate (200 ml) and water (100 ml) were added to dissolve the residue, and the aqueous phase was extracted with additional ethyl acetate (2 × 200 ml). The combined extracts were washed with water (2 × 100 ml), dried (Na_2SO_4), evaporated, and recrystallized (methylene chloride–hexane) to give 4.8 g (94%) of **4e**: mp 179–180°; ir ($CHCl_3$) 3500 cm^{-1} (OH); nmr ($CDCl_3$) δ 0.91 and 0.93 (s, 3, 18-CH_3), 1.37 (d, ~2, J = 6 Hz, 19a-CH_3), 1.40 (d, ~1, J = 6 Hz, 19a-CH_3), 3.4 (m, 4, $-OCH_2CH_2O-$), and 5.63 ppm (m, 1, =CH). Nmr indicated the presence of two isomers.

Anal. Calcd for $C_{22}H_{34}O_4$: C, 72.88; H, 9.45. Found: C, 72.77; H, 9.52.

19a-Methyl-5α-androstane-3,17,19-trione 17-Ethylene Ketal (7b).—A solution of **4e** (10.5 g, 0.029 mol) in 2-propanol (150 ml) and absolute ethanol (100 ml) was stirred with palladium hydroxide on carbon (2.5 g, 35%) under hydrogen for 1 hr. The catalyst was removed by filtration and the filtrate was evaporated to dryness: ir ($CHCl_3$) 1750 cm^{-1}; nmr indicates no vinyl hydrogens.

The residue and *p*-toluenesulfonic acid (250 mg) were dissolved in ethylene glycol (60 ml) and benzene (150 ml) and refluxed with water removal employing a Dean–Stark trap. After cooling, the reaction was diluted with water (500 ml) and extracted with ethyl acetate. The combined organic layers were washed with dilute bicarbonate and water, then dried (Na_2SO_4) and evaporated to dryness under reduced pressure to give crude **7a** (10.1 g).

Compound **7a** was dissolved in methylene chloride (15 ml) and added to a well-stirred solution of chromium trioxide (48 g) in methylene chloride (1.2 l.) and pyridine (60 ml), then stirred for 1 hr. The methylene chloride solution was decanted from the tarry residue, which was then thoroughly washed with methylene chloride. The combined methylene chloride solutions were repeatedly washed with water until the water washings were no longer dark. After drying (Na_2SO_4), the methylene chloride was removed at reduced pressure to give a light brown solid (8.8 g). The residue was chromatographed on alumina (activity III, 800 g). After washing with benzene (1 l.), the column was eluted with 5% ethyl acetate to furnish 19a-methyl-5α-androstane-17,19-dione 17-ethylene ketal (**7c**) (1.55 g, 15.4%): mp 93–94° [petroleum ether (bp 30–60°)]; ir ($CHCl_3$) 1690 cm^{-1} (19-C=O); nmr ($CDCl_3$) δ 0.98 (s, 3,18-CH_3), 2.12 (s, 3,19a-CH_3), and 3.86 ppm (b, m, 4, $-OCH_2CH_2O-$).

(13) In the steroid A-ring bicyclooctanones the ring containing the carbonyl moiety is a cyclohexane ring in the boat conformation. Therefore, since the octant rule has been based mainly for cyclohexanones in the chair conformation, this explanation will have to be considered tentative until additional information becomes available concerning the application of the octant rule to cyclohexanes in nonchair conformations.

Anal. Calcd for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.22; H, 10.01.

Further elution with 7.5% ethyl acetate gave 19a-methyl-5α-androstane-3,17,19-trione 17-ethylene ketal (**7b**) (5.3 g, 50.8%): mp 148–151° (acetone–hexane); ir ($CHCl_3$) 1695 (19-C=O), 1715 cm^{-1} (3-C=O); nmr ($CDCl_3$) δ 0.80 (s, 3, 18-CH_3), 2.28 (s, 3, 19a-CH_3), and 3.86 ppm (d, 4, $-OCH_2CH_2O-$).

Anal. Calcd for $C_{22}H_{32}O_4$: C, 73.29; H, 8.95. Found: C, 73.41; H, 9.22.

3,10-[2′-Oxoethano]-5α-estran-3-ol 17-Ethylene Ketal (9a).—A solution of **7b** (200 mg, 0.55 mmol) and potassium hydroxide (30 mg, 0.55 mmol) in absolute ethanol (4 ml) was boiled on a steam bath for 5 min, cooled, diluted with water (10 ml), and extracted with ethyl acetate. After drying (Na_2SO_4), the ethyl acetate was removed at reduced pressure to give a white solid (197 mg). Crystallization from acetone–hexane gave 178 mg (89%) of pure **9a**: mp 205–207°; ir (KBr) 3600, 3420 (OH), and 1710 cm^{-1} (2′-C=O); nmr ($CDCl_3$) δ 1.00 (s, 3, 18-CH_3), 1.71 (s, 2, CH_2C=O), and 3.86 ppm (d, 4, $-OCH_2CH_2O-$).

Anal. Calcd for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95. Found: C, 73.24; H, 8.98.

19a-Methylandrostane-3,17,19-trione (7e).—Steroid **4e** (12 g, 0.033 mol) in 2-propanol (150 ml) and ethanol (100 ml) was stirred with 35% palladium hydroxide on carbon (3.0 g) under hydrogen until hydrogen uptake ceased (~1.5 hr). The catalyst was filtered and the filtrate was evaporated to dryness (nmr indicated that the reduction was complete). The residue was dissolved in a mixture of acetone (250 ml), hydrochloric acid (5 ml), and water (5 ml), and the solution was stirred overnight. After dilution with water (500 ml) and extraction with ethyl acetate, the extracts were washed with bicarbonate solution and water, then dried (Na_2SO_4). Evaporation of the solvent gave crude steroid **7d** (11.5 g).

Crude dihydroxy steroid **7d** in methylene chloride (15 ml) and pyridine (5 ml) was added to a mechanically stirred solution of chromium trioxide (48 g) in methylene chloride (900 ml) and pyridine (60 ml). The solution was stirred for 1 hr. After the methylene chloride was decanted, the tarry residue was thoroughly washed with methylene chloride (3 × 300 ml). The combined organic extracts were washed with 5% sodium hydroxide, 5% hydrochloric acid, and water and then dried ($MgSO_4$). Evaporation of the solvent and recrystallization of the residue from acetone–hexane gave **7e** (4.5 g), mp 171–172°.

The filtrate was concentrated and chromatographed (alumina III) by first eluting with benzene (1 l.). Further elution with 5% ethyl acetate gave **7f** (2.8 g, 28%): mp 161–162°; ir ($CHCl_3$) 1690 (19-C=O) and 1735 cm^{-1} (17-C=O); nmr ($CDCl_3$) δ 1.03 (s, 3, 18-CH_3) and 2.13 ppm (s, 3, 19a-CH_3).

Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.43; H, 10.00. Found: C, 79.59; H, 10.16.

Elution with 7.5% ethyl acetate solution gave an additional 1.5 g of **7e** (6 g total, 58%): ir ($CHCl_3$) 1695 (19-C=O), 1714 (3-C=O), 1735 cm^{-1} (17-C=O); nmr ($CDCl_3$) δ 0.82 (s, 3, 18-CH_3) and 2.31 ppm (s, 3, 19a-CH_3).

Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.80; H, 8.97.

3,10-[2′-Oxoethano]-5α-estran-3-ol-17-one (9b).—A solution of steroid **7e** (0.2 g, 0.69 mmol), potassium hydroxide (30 mg), and ethanol (4 ml) was refluxed on a steam bath for 30 min, then cooled, diluted with water (10 ml), and extracted with ethyl acetate. The ethyl acetate extract was washed with water, dried (Na_2SO_4), and evaporated at reduced pressure to give **9a** (197 mg) as a white solid.

Recrystallization from acetone–hexane gave pure **9b** (182 mg, 91%): mp 215–216°; ir (KBr) 3600, 3420 (broad, OH), and 1710 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.00 (s, 3, 18-CH_3), 1.71 (s, 2, CH_2C=O), and 3.86 ppm (m, 4, $-OCH_2CH_2O-$).

Anal. Calcd for $C_{20}H_{28}O_3$: C, 73.30; H, 8.95. Found: C, 73.24; H, 8.98.

3,10-[2′-Oxoethano]-5α-estrane-3,17-diol (9c).—Steroid **9b** (3.5 g, 11.0 mmol) in dry tetrahydrofuran (100 ml), magnetically stirred at 0° under nitrogen, was treated portionwise with lithium tri-*tert*-butoxyaluminum hydride and then stirred for 2 hr more. Water was added dropwise to destroy the excess hydride; then 10% acetic acid (350 ml) was added. The precipitated steroid **9c** (2.88 g), after filtration and drying, had mp 247–248°. An additional quantity of **9c** (0.51 g, 97% total yield) was obtained by removing the tetrahydrofuran from the filtrate at reduced pressure: mp 249–249.5°; ir ($CHCl_3$), 1717 cm^{-1} (2′-C=O); nmr (DMSO-d_6) δ 0.73 (s, 3, 18-CH_3), 4.34 (d, 1, J = 5 Hz, 17-OH), and 4.61 ppm (s, 1, 3-OH).

Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.28; H, 9.52.

3,10-Ethano-5α-estrane-3,17-diol (10a).—A mixture of keto steroid **9c** (3.0 g, 9.4 mmol), hydrazine (19 ml, 97%), hydrazine dihydrochloride (7.5 g), and triethylene glycol (203 ml) was heated at 100° for 11 hr. Potassium hydroxide (11.25 g) was added, and the temperature was gradually raised to 240° with distillation of lower boiling material. The reaction was maintained at 240° for 7 hr, then cooled and diluted with water. The solid was collected, dried, and recrystallized from methanol to give steroid **10a** (2.03 g, 71%), mp 195–197°. The analytical sample prepared by recrystallization from methanol had mp 197–198°; ir (KBr) 3400 cm^{-1} (OH); nmr (DMSO-d_6–$CDCl_3$) δ 0.71 (s, 3, 18-CH_3), 3.94 (s, 1, 3-OH), and 4.2 ppm (d, 1, J = 5 Hz, 17-OH).

Anal. Calcd for $C_{20}H_{32}O_2$: C, 78.89; H, 10.60. Found: C, 78.47; H, 10.88.

3,10-Ethano-5α-estran-3-ol (10b).—The ketal **9a** (0.36 g, 10 mmol) was reduced under exactly the same conditions as described for **10a**. The crude product obtained was chromatographed on alumina (activity III) using benzene–ethyl acetate (9:1) as the eluent. The product fractions were combined, concentrated, and recrystallized from hexane to give 0.175 g (61%) of **10b**: mp 156–158°; ir ($CHCl_3$) 3600 and 3420 cm^{-1} (OH); nmr ($CDCl_3$) δ 0.67 ppm (18-CH_3).

Anal. Calcd for $C_{20}H_{32}O$: C, 83.32; H, 11.20. Found: C, 83.17; H, 11.47.

3,10-Ethano-5α-estran-3-ol-17-one (10c).—A solution of **10a** (1.2 g, 3.9 mmol) in methylene chloride (5 ml) and pyridine (11 ml) was added dropwise to a mechanically stirred solution of chromium trioxide (2.4 g) in methylene chloride (85 ml) and pyridine (4 ml) and stirred for 1 hr. The methylene chloride was decanted from the tarry residue, which was then washed thoroughly with methylene chloride. After the combined organic extracts were washed with 5% sodium hydroxide, 5% hydrochloric acid, and water, the methylene chloride solution was dried (Na_2SO_4) and evaporated at reduced pressure to give **10c** (1.03 g, 86%), mp 163–164°. The analytical sample, recrystallized from acetone–hexane, had mp 165–166°; ir ($CHCl_3$) 3600, 3420 (OH), and 1735 cm^{-1} (17-C=O).

Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 9.99. Found: C, 79.25; H, 10.12.

17α-Ethynyl-3,10-ethano-5α-estrane-3,17β-diol (10d).—Steroid **10c** was ethynylated with lithium acetylide–ethylenediamine complex in dioxane by a method used for other five-membered ketones.[14] Several recrystallizations from methanol–water and chloroform gave pure **10d**: mp 290–291° (sealed capillary, sublimes); ir (KBr) 3450 (OH) and 3260 cm^{-1} (C≡CH); nmr ($CDCl_3$–CD_3OD) δ 0.78 (s, 3, 18-CH_3) and 2.55 ppm (s, 1, C≡CH).

Anal. Calcd for $C_{22}H_{32}O_2$: C, 80.44; H, 9.83. Found: C, 80.16; H, 9.81.

Registry No.—**4b**, 41563-98-8; **4d**, 4119-21-5; **4e**, 41564-00-5; **7a**, 41564-01-6; **7b**, 41564-02-7; **7c**, 41564-03-8; **7e**, 24124-71-8; **7f**, 41564-05-0; **9a**, 41564-06-1; **9b**, 41564-07-2; **9c**, 41564-08-3; **10a**, 41564-09-4; **10b**, 41564-10-7; **10c**, 41564-11-8; **10d**, 41564-12-9.

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Alkaloids of the Papaveraceae. XX. 2,9-Dimethoxy-3-hydroxypavinane, a New Alkaloid from *Argemone munita* subsp. *rotundata*[1]

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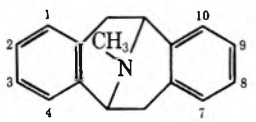
Received June 5, 1973

A new alkaloid ($C_{19}H_{21}NO_3$, mp 197–198°, $[\alpha]^{27}D$ −254°) was isolated from *Argemone munita* Dur. & Hilg. subsp. *rotundata* (Rydb.) G. B. Owmb. and was shown to be 2,9-dimethoxy-3-hydroxypavinane (I) by total synthesis. The synthesis was accomplished by formation of the Reissert compound from 7-methoxyisoquinoline and 3-methoxy-4-benzyloxybenzyl chloride, conversion to the benzylisoquinoline, N-methylation, reduction to the 1,2-dihydroisoquinoline, and cyclization to I with HCOOH and H_3PO_4. If the latter three steps were carried out on 1-(4-methoxybenzyl)-6,7-dimethoxyisoquinoline, the final product under the HCOOH and H_3PO_4 conditions was not a pavinane alkaloid, but instead the rearranged product 3-(4-methoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-*N*-methylisoquinoline.

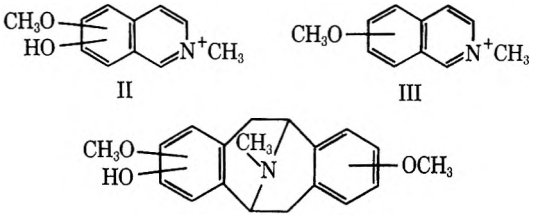
From a large-scale extraction of plants of *Argemone munita* subsp. *rotundata* we isolated (see Experimental Section) an alkaloid with the following properties: $C_{19}H_{21}NO_3$ (by combustion analysis and mass spectrum), mp 197–198°, $[\alpha]^{27}D$ −254° (*c* 1.59, CH_3OH). The high optical rotation and preliminary interpretation of the nmr, uv, and mass spectra indicated that the alkaloid belonged to the pavinane[2] group (I). Since



I

elemental analysis and mass spectrum showed the presence of only three oxygens in the molecule, whereas all previously known pavinanes have contained four oxygens, the isolated alkaloid represented a new compound.

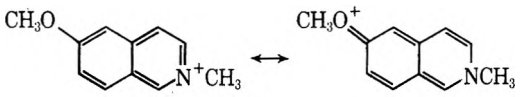
The nmr showed the presence of two methoxy methyl groups and one *N*-methyl group. The mass spectrum showed intense peaks at *m/e* 190 and 174, which could (in analogy with previous work[3]) be assigned structures II and III, respectively. Part structure IV could therefore be assigned to the unknown.



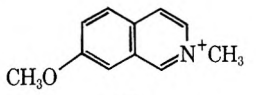
II III

IV

Known natural pavinanes either contain oxygenated substituents only at the 2, 3, 8, and 9 positions (*e.g.*, argemonine, bisnorargemonine) or contain at least one of these substituents at the 4 or 10 position (munitagine, platycerine). In the case of tetrasubstituted derivatives, a clear choice can be made between the two possibilities, since the bridgehead protons of the central ring appear downfield from the normal position if an oxygenated substituent is in the 4 or 10 position and, in addition, ultraviolet spectra in cyclohexane show characteristic differences[3] in the two cases. The uv and nmr spectra of the unknown were characteristic of pavinanes containing substituents only in the 2, 3, 8, and/or 9 positions. Since oxygenated substituents at the 1 and 7 positions are probably unlikely from biogenetic considerations,[3] then four possible structures remain for the unknown alkaloid: 2,9-dimethoxy-3-hydroxy-, 2,8-dimethoxy-3-hydroxy-, 3,9-dimethoxy-2-hydroxy-, or 3,8-dimethoxy-2-hydroxypavinane. Differentiation among these possibilities seemed difficult if not impossible without total synthesis. However, two considerations allowed us to at least make a rational choice as to which of the isomers might be the best target for the initial synthesis. First, it was noted that the *m/e* 190 peak in the mass spectrum was the base peak while the *m/e* 174 peak was 63% relative intensity. An explanation for the lowered intensity of the *m/e* 174 peak might reside in its lower stability if it had structure VI rather than V (where charge de-



V



VI

localization is possible). Secondly, some biogenetic arguments can be made. The trisubstituted unknown was isolated as 150 mg of a total alkaloid isolate of 252 g, with bisnorargemonine (2,9-dimethoxy-3,8-dihydroxypavinane) and munitagine (2,9-dimethoxy-3,10-dihydroxypavinane) representing 92% of the alkaloid content.[3a] If the unknown trisubstituted alkaloid could arise from biosynthetic removal of a phenolic group at position 8 of bisnorargemonine or from position 10 of munitagine, the resultant structure would be VII. The high negative rotation should be reasonable evidence for the absolute configuration indicated, since this is known[4] for several very similar pavinanes. The alternative would be to propose a complete separate biosynthetic path from a trisub-

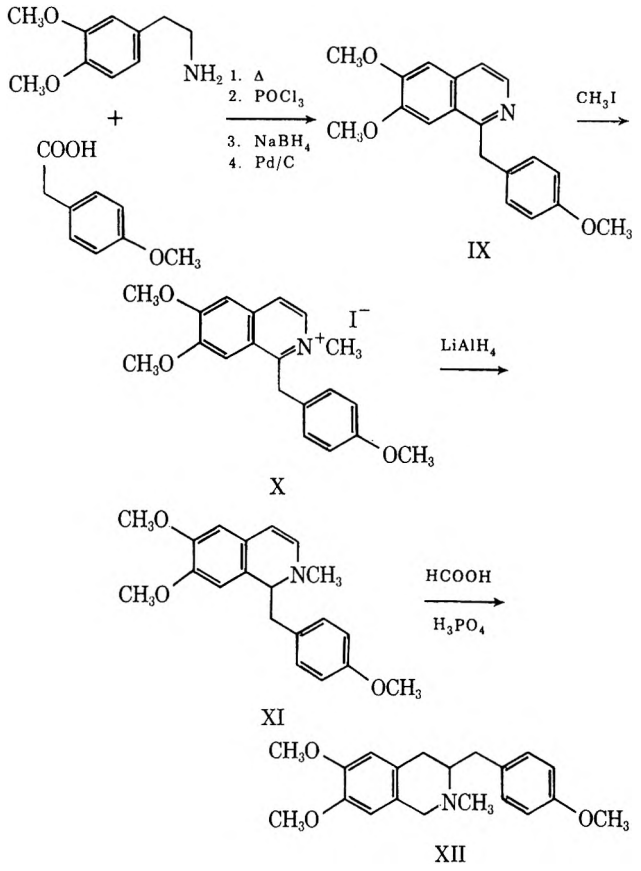
(1) Part XIX: F. R. Stermitz, K. A. Larson, and D. K. Kim, *J. Med. Chem.*, in press. This work was supported in part by NIH Research Grants GM 15424 and GM 19234 from the National Institute of General Medical Science.

(2) C. H. Chen and T. O. Soine, *J. Pharm. Sci.*, **61**, 55 (1972).

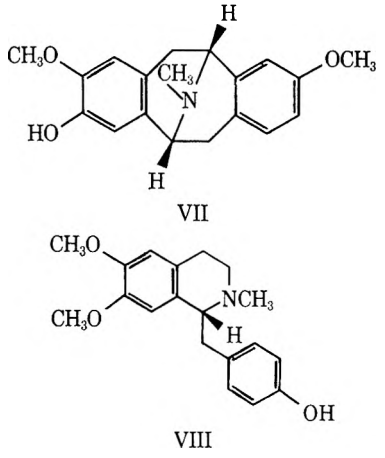
(3) (a) F. R. Stermitz and J. N. Seiber, *J. Org. Chem.*, **31**, 2925 (1966); (b) F. R. Stermitz and K. D. McMurtrey, *ibid.*, **34**, 555 (1969).

(4) A. C. Barker and A. R. Battersby, *J. Chem. Soc. C*, 1317 (1967).

SCHEME I



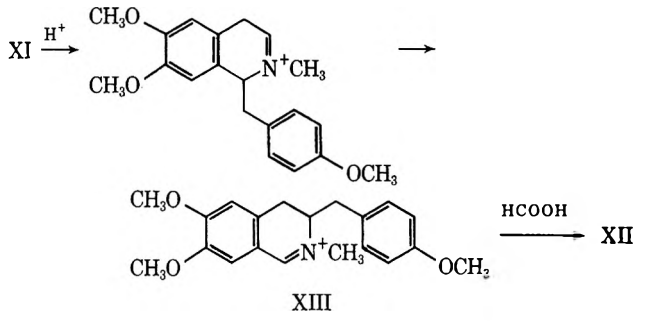
stituted tetrahydrobenzylisoquinoline. We have recently isolated[5] (+)-armepavine (VIII) as the first



trisubstituted tetrahydrobenzylisoquinoline from an *Argemone* species. The precursor necessary for (+)-armepavine formation would have the proper absolute configuration and oxygenated substituent pattern to be a precursor of VII as well as VIII. Thus, two possible biogeneses and a tenuous suggestion from the mass spectrum each pointed to VII as the best candidate for the structure of the unknown.

Because of the ready availability of starting materials, we elected first to synthesize the completely methylated VII, which could then be compared with the methylated unknown alkaloid. However, the standard pavinane synthesis of Scheme I did not yield a pavinane, but instead the rearranged tetrahydrobenzylisoquinoline XII. The formation of XII can be accounted for by Scheme II. Although such a rearrangement has been observed[6] when 1,2-dihydroisoquinolines similar to XI have been treated with mild acid (acetic acid) conditions, this is the first report of a rearrangement under conditions of the pavinane synthesis. In addition,

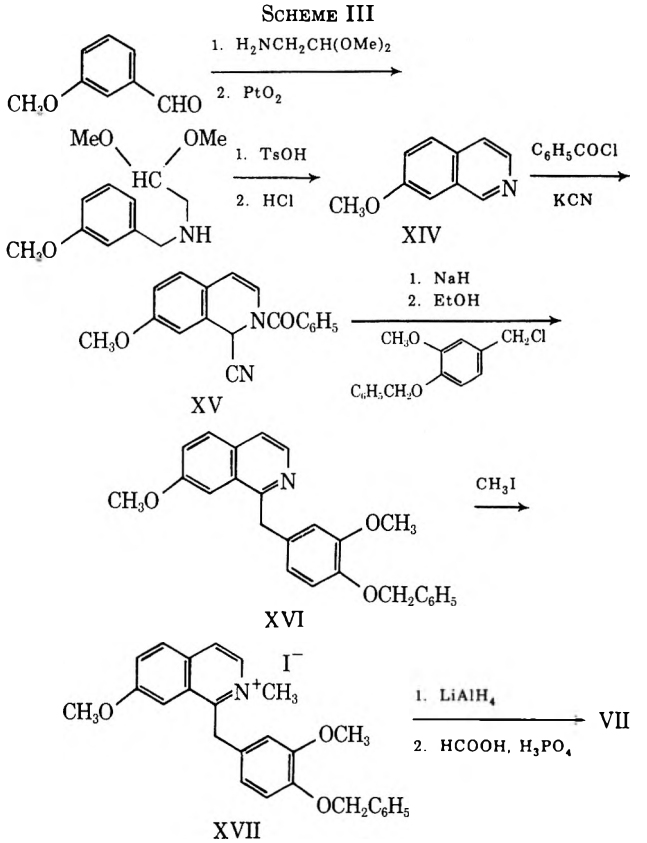
SCHEME II



rearrangements with mild acid[6] lead only to the iminium salt XIII, whereas in our case this salt would have been reduced to XII by the HCOOH present. The failure of this attempt to form a pavinane can be attributed to the fact that cyclization must take place meta to a methoxy group and such cyclizations (for example, in the Bischler–Napieralski reaction) are prevented if a methoxy group is in a position meta to the point of cyclization and no ortho or para activating groups are present.

In order to avoid the above problem, we turned to the alternate mode of synthesis given in Scheme III.

SCHEME III



(5) F. R. Stermitz, D. K. Kim, and K. A. Larson, *Phytochemistry*, in press.

(6) J. Knabe, R. Dorr, S. F. Dyke, and R. G. Kinsman, *Tetrahedron Lett.*, 5373 (1972), and references cited therein.

This approach was successful and culminated in the preparation of (±)-2,9-dimethoxy-3-hydroxypavinane (VII) which was identical, with the exception of optical rotation and melting points, with the natural alkaloid.

Experimental Section

Isolation.—Dried and powdered, largely above-ground plant parts (125 kg) of *Argemone munita* Dur. & Hilg. subsp. *rotundata* (Rydb.) G. B. Owmb., collected 3 miles east of Nephi, Utah, in July 1967, were extracted by our standard[3] technique and yielded a total of 252 g (0.22%) of crude alkaloids as a brown solid. This crude solid was crystallized from 500 ml of MeOH to yield 54 g of bisnorargemonine. The residue from the mother liquor was dissolved in 1 *M* H_2SO_4 and this solution was extracted with $CHCl_3$ after successive pH adjustments to pH 1, 12.5, 11, and 9. At pH 12.5, the solution was extracted with 2 l. of $CHCl_3$ and evaporation of the $CHCl_3$ yielded 17 g of crude alkaloids, which proved to be mainly cryptopine and muramine.[3a] The pH 12.5 aqueous solution was extracted with an additional 2 l. of $CHCl_3$, but evaporation of this extract yielded a residue (0.5 g) which contained alkaloids other than those of the first pH 12.5 extract. The major alkaloid had R_f 0.45 (tlc on Brinkman silica gel F_{254} with 3:2 benzene–methanol as eluting solvent). The crude alkaloid residue was chromatographed on a column of silica gel and yielded (eluting solvent 90:10 $CHCl_3$–MeOH) 150 mg of pure alkaloid: mp 197–198°; $[\alpha]^{27}D$ −254° (*c* 1.59, MeOH); ν_{max} (KBr disk) 2920, 1625, 1530, 1505, 1460, 1430, 1330, 1260, 1120, 1020, 875 cm^{-1}; nmr (from TMS) δ 2.46 (s, 3 H, NCH_3), 2.35–4.06 (m, 6 H, two ABX-type patterns[3a] for bridgehead and CH_2 protons), 3.73 (s, 6 H, two OCH_3 groups), 6.45–6.80 (m, 5 H, aromatic H); mass spectrum *m/e* (rel intensity) 311 (55), 190 (100), 174 (63).

Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.71; H, 6.59; N, 4.45.

1-(4-Methoxybenzyl)-6,7-dimethoxyisoquinoline (IX).—An equal molar mixture of 25 g of 2-(3,4-dimethoxyphenyl)ethylamine (Aldrich Chemical Co.) and 22.5 g of 4-methoxyphenylacetic acid (Aldrich Chemical Co.) was heated (170–175°) on an oil bath for 3 hr under N_2. The reaction product was cooled and dissolved in benzene and the solution was washed with 1 *N* HCl, 5% $NaHCO_3$, and then water. The organic layer was dried and evaporated to yield 41.7 g of *N*-(3,4-dimethoxyphenethyl)-2-(4-methoxyphenyl)acetamide, mp 124–125° after crystallization from ethanol (lit.[7] mp 126–128°). To a stirred and refluxing solution of 40 g of the amide in 400 ml of dry acetonitrile was added 36 g of $POCl_3$ over 30 min. The mixture was refluxed under N_2 for 1.5 hr and cooled, and the solvent was evaporated. The residue was dissolved in EtOAc, washed with saturated $NaHCO_3$ solution, dried, and evaporated to yield 35.8 g of cyclized imine which was used in the next step without further purification.

To a stirred and cooled (0°) solution of 10 g of the above imine in 150 ml of methanol was cautiously added 2.8 g of $NaBH_4$. After the mixture had stirred for 2 hr at room temperature, the solvent was evaporated and the residue was taken up in water and extracted with $CHCl_3$. The combined dried $CHCl_3$ solution was evaporated to give a yellow oil which crystallized from MeOH to yield 8.9 g of 1-(4-methoxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline, mp 89–90.5°. The HCl salt had mp 183–184.5° (lit.[8] mp 182°). A mixture of 1 g of this tetrahydroisoquinoline and 75 mg of 10% Pd/C in 50 ml of tetralin was heated (180°) under N_2 for 28 hr. Most of the solvent was distilled under vacuum and the residue was taken up in $CHCl_3$ and filtered to remove the catalyst. The organic washes were evaporated to give a drak brown oil which readily crystallized from ethanol to yield 805 mg of 1-(4-methoxybenzyl)-6,7-dimethoxyisoquinoline (IX) as a white solid: mp 121.5–122.5°; uv (EtOH) λ_{max} 320 and 333 nm; nmr (from TMS) δ 3.68 (s, 6 H), 3.87 (s, 3 H), 3.93 (s, 3 H), 4.55 (s, 2 H), 6.72–7.50 (m, 7 H), 8.40 (d, 1 H, *J* = 6 Hz); HCl salt mp 207° dec.

Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.46; H, 6.37; N, 4.33.

1-(4-Methoxybenzyl)-6,7-dimethoxyisoquinoline Methiodide (X).—IX (5.0 g) was heated at reflux for 2 hr in 15 ml of MeOH to which 10 ml of MeI had been added. The solution was evaporated to half its volume and cooled to give a quantitative yield of X, mp 221–223°.

Anal. Calcd for $C_{20}H_{22}NO_3I \cdot H_2O$: C, 51.18; H, 5.16; N, 2.98. Found: C, 51.36; H, 4.93; N, 2.48.

3-(4-Methoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-*N*-methylisoquinoline (XII).—To a cooled (0°) and stirred dispersion of 1.26 g of X in 100 ml of dry Et_2O was added dropwise a slurry of 0.45 g of $LiAlH_4$ in 25 ml of dry Et_2O. The slurry was stirred for 4 hr at room temperature and then quenched with 10% aqueous NaOH. The mixture was filtered and washed with ether. The combined organic layers were dried and evaporated to give the dihydro derivative XI (nmr showed a vinyl H doublet at δ 5.23) which was used immediately in the next step. A solution of XI in 3 ml of 85% H_3PO_4 and 7 ml of 90% formic acid was heated at reflux overnight. After it had cooled, the mixture was diluted with 10 ml of H_2O and extracted with ether. The aqueous layer was adjusted to pH 8 and extracted with $CHCl_3$. The $CHCl_3$ layers were combined, washed with water, dried, and evaporated to yield a brown oil. This was chromatographed on silica gel to yield 595 mg of XII as a colorless oil which crystallized from ethanol as a white powder: mp 96–97° (picrate mp 176–177°, HCl salt mp 193–194°); nmr (60 MHz, from TMS) δ 2.32–3.26 (m, 8 H, including a singlet at 2.52 for NCH_3), 3.67–3.88 (11 H, 3 OCH_3 absorptions appeared as singlets at δ 3.77, 3.80, and 3.83 but the total integration showed 11 H), 6.55 (s, 2 H, aromatic), 6.84 (d, 2 H, J_{ab} = 4.5 Hz), 7.12 (d, 2 H, J_{ab} = 4.5 Hz); mass spectrum *m/e* (rel intensity) 206 (100), 204 (15) 121 (8.5).

Anal. Calcd for $C_{20}H_{25}NO_3 \cdot HCl$: C, 66.01; H, 7.20; N, 3.85. Found: C, 66.26; H, 7.07; N, 3.55.

That XII did not have a pavinane structure was evident from the mass spectrum and nmr. Whereas pavinanes exhibit molecular ions at about 50% rel intensity, no molecular ion was observable for XII. The only peak above 15% rel intensity was that at *m/e* 206, while a dimethoxypavinane would exhibit the base peak at *m/e* 204 for the methoxylated ion corresponding to II. The nmr did not show the typical ABX pattern[3] of the pavinane central ring protons and included six rather than five aromatic protons. Structure XII is isomeric with a 1-benzyltetrahydroisoquincline, which compounds often lack or show only a small molecular ion. However, in our structure proof[5] of armepavine from *Argemone turnerae* we had prepared 1-(4-methoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-*N*-methylisoquinoline, mp 63–64° (lit.[9] mp 63–64°), by $NaBH_4$ reduction of X and it was found to be nonidentical with XII. The main spectral key to the structure of XII was the two-proton nmr singlet for the C-1 protons, which could be resolved out from the methoxy region when the nmr was taken at 100 MHz.

7-Methoxyisoquinoline (XIV).—An adaptation of the method of Birch and Jackson[10] was used. Intermediates to XIV were isolate as crudes, but not purified. A mixture of *m*-methoxybenzaldehyde (30 g) and 10% excess aminoacetaldehyde dimethylacetal was heated in benzene at reflux using a Dean–Stark trap until the calculated amount of water collected. Excess aminoacetal was removed by washing with water and distillation *in vacuo*. The residue was reduced to the amine with 1% by weight PtO_2 in ethanol at 50 psi hydrogen in a Parr apparatus. The catalyst was filtered off and the ethanol was removed to yield a residue which was treated with *p*-toluenesulfonyl chloride in pyridine to yield the *N*-tosylate. The *N*-tosylate (30 g) was added to a mixture of 115 ml of 6 *N* HCl and 400 ml of dioxane and heated at reflux in the dark under N_2 for 6 hr. Work-up[10] of this reaction mixture yielded 10.4 g (81%) of 7-methoxyisoquinoline (XIV), mp 48° (lit.[10] mp 48°).

***N*-Benzoyl-1,2-dihydro-7-methoxyisoquinoline-1-carbonitrile (XV).**—Benzoyl chloride (0.10 mol) was added dropwise to a stirred solution of 10 g (0.062 mol) of XIV and 0.15 mol of KCN in 75 ml of water at 10°. Stirring was continued until the product separated as a brown solid. This was removed by filtration, washed with water and dilute aqueous HCl, and then crystallized from EtOH to yield 11.9 g (66%) of XV: mp 144–146°; nmr δ 3.83 (s, 3 H, OCH_3), 6.00 (d, 1 H, vinyl, *J* = 4 Hz), 6.53 (d, 1 H, vinyl, *J* = 4 Hz), 6.53 (s, 1 H, C-1 H), 7.50–6.80 (m, 8 H, aromatic).

(7) G. J. Kopadia, N. Shah, and R. Highet, *J. Pharm. Sci.*, **53**, 1431 (1964).

(8) H. Kondo and T. Kondo, *J. Pharm. Sci. Jap.*, **48**, 324 (1928).

(9) K. Fujitani and T. Kishimoto, *Yakugaku Zasshi*, **84**, 329 (1964); *Chem. Abstr.*, **61**, 1830*d* (1965).

(10) A. J. Birch, A. H. Jackson, and P. V. R. Shannon, *Tetrahedron Lett.*, **47**, 4789 (1972).

Anal. Calcd for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.36; H, 4.76; N, 9.53.

1-(3-Methoxy-4-benzyloxybenzyl)-7-methoxyisoquinoline Methiodide (XVII).—The nitrile XV, 11.0 g (0.038 mol), was dissolved in 100 ml of DMF at 0° and was treated under N_2 with a threefold excess of NaH. After 10 min, a twofold excess of 4-benzyloxy-3-methoxybenzyl chloride in 50 ml of DMF was added. The mixture was stirred overnight, excess EtOH was added to destroy remaining NaH, and the mixture was allowed to stir for an additional 24 hr. Benzene and water were added and the benzene layer was separated and washed with water and then with 6 *M* HCl. The acidic layer was made basic with NaOH and extracted with $CHCl_3$. The organic extracts were combined, dried, and evaporated to yield 10.8 g (68%) of 1-(3-methoxy-4-benzyloxybenzyl)-7-methoxyisoquinoline (XVI) as a crude brown oil. To this oil was added 50 ml of iodomethane and 50 ml of MeOH and the solution was heated at reflux for 6 hr. The solvent was then removed *in vacuo* to leave a yellow solid, which was recrystallized from ethanol to give 9 g (60%) of 1-(3-methoxy-4-benzyloxybenzyl)-7-methoxyisoquinoline methiodide (XVII), mp 201°.

Anal. Calcd for $C_{26}H_{26}NO_3I$: C, 59.30; H, 4.97; N, 2.67. Found: C, 58.95; H, 4.98; N, 2.35.

(±)-2,9-Dimethoxy-3-hydroxypavinane (VII).—XVII (5 g) was dried and pulverized and then added to a slurry of 1 g of $LiAlH_4$ in anhydrous ether. The mixture was stirred for 3 hr at room temperature and the excess hydride was decomposed by addition of wet ether followed by a saturated solution of sodium potassium tartrate. The ether layer was separated and evaporated to yield 2.0 g (55%) of the crude 1,2-dihydroisoquinoline as a yellow oil. To this was then added 35 ml of 7:3 HCOOH–H_3PO_4 and the solution was heated at reflux for 18 hr. The solution was diluted with water and washed with $CHCl_3$. The aqueous layer was made basic and extracted with $CHCl_3$. The extracts were combined, dried, and evaporated to a crude oil which was 65% VII by nmr and tlc. Column chromatography on Florisil with benzene as eluting solvent yielded pure (±)-2,9-dimethoxy-3-hydroxypavinane (VII), mp 162°, whose ir, nmr, uv, and mass spectra, and tlc R_f values were identical with those of the natural alkaloid.

Registry No.—VII, 41498-94-6; (±)-VII, 41498-95-7; IX, 41498-25-3; IX hydrochloride, 41498-26-4; X, 41498-27-5; XI, 41498-28-6; XII, 41498-29-7; XII picrate, 41498-30-0; XII hydrochloride, 41498-31-1; XIV, 39989-39-4; XV, 41498-33-3; XVI, 41498-34-4; XVII, 41498-35-5; *N*-(3,4-dimethoxyphenethyl)-2-(4-methoxyphenyl)acetamide, 4078-65-3; 1-(4-methoxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline, 41498-37-7.

Interconversions of Hexofuranosyl Nucleosides. V. Synthesis and Reexamination of the Structure of 9-(6-Deoxy-α-L-mannofuranosyl)adenine[1]

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Received May 23, 1973

9-(6-Deoxy-α-L-mannofuranosyl)adenine (**3**) has been prepared by several synthetic procedures and completely structure proofed. It was concluded that the substance previously reported to be **3** really could not have been, based upon the differences in physical properties and the present structure proof. The most successful synthesis required conversion of 6-deoxy-1,5-di-*O*-benzoyl-2,3-*O*-isopropylidene-L-mannofuranose into 6-deoxy-1,2,3,5-tetra-*O*-benzoyl-L-mannofuranose in two steps, conversion of this into the glycosyl chloride with ethereal hydrogen chloride, and condensation of the latter with 6-benzamidochloromercuripurine in hot xylene. Removal of the blocking groups with sodium methoxide and purification *via* a picrate gave an 18% yield of **3**. Other coupling procedures, such as the titanium tetrachloride method, gave rather complex, colored mixtures, which required extensive column chromatography to purify **3**, and consequently lower yields. Attempts to prepare **3** following acetolysis of 6-deoxy-1,5-di-*O*-acetyl-2,3-*O*-isopropylidene-L-mannofuranose (**4**) resulted in the isolation of 9-(6-deoxy-β-L-glucofuranosyl)adenine (**5**) and 9-(6-deoxy-β-L-mannopyranosyl)adenine (**6**) in addition to **3**. Considerable yields of **5** occurred even under acetolysis reaction conditions that are reportedly not supposed to cause epimerization at C-2. Acetolysis of **4** in 1:1 acetic acid–acetic anhydride with 3% sulfuric acid, followed by nucleoside formation by the titanium tetrachloride procedure, afforded **5**, **3**, and **6** in a ratio of 1.5:2.2:1.0 and acetolysis of **4** in 3:7 acetic acid–acetic anhydride with 5% sulfuric acid changed this ratio to 0.1:1.5:1.0.

The synthesis of hexofuranosyl nucleosides has been a subject of investigation by the author for a number of years.[2-5] Such studies have received occassional impetus from reports in the literature concerning the biological or enzymatic activity of compounds like these.[6] The purpose of the current investigations was to improve upon the synthesis of hexofuranosyl nucleosides by causing the inversion of configuration at one or more hydroxyl groups of the preformed nucleosides, thereby precluding the necessity of preparing rare sugars to be used in *de novo* synthesis of such compounds.[3]

In the previous two articles,[4,5] reasons were presented for the synthesis of 9-(5,6-dideoxy-β-D-*erythro*-hex-4-enofuranosyl)adenine (**1**) (Chart I). Because of the difficulties encountered in the removal of the isopropylidene blocking group of **2** without complete degradation of the nucleoside, it was thought to be desirable to prepare 9-(6-deoxy-α-L-mannofuranosyl)adenine (**3**, 9-α-L-rhamnofuranosyladenine) in large quantity and, starting from this source, to prepare a derivative of **3** having a blocking group at the 2′,3′ position which could be more easily removed after the 4′,5′ double bond was formed. In an attempt to prepare **3** from 6-deoxy-1,5-di-*O*-acetyl-2,3-*O*-isopropylidene-L-mannofuranose (**4**), the latter compound was subjected to acetolysis conditions which are now known to cause epimerization at C-2, and, as a result, two nucleosides were formed from the uncharacterized syrup upon condensation with 6-benzamidochloromercuripurine. The main product was 9-(6-deoxy-β-L-glucofuranosyl)adenine (**5**) and the other was 9-(6-deoxy-α-L-mannopyranosyl)adenine (**6**).[5] Conditions were sought for the acetolysis of **4** not accompanied by epimerization and

(1) The present work was supported by Grant No. CA13802 from the National Cancer Institute, National Institutes of Health.

(2) (a) L. M. Lerner and P. Kohn, *J. Org. Chem.*, **31**, 339 (1966); (b) P. Kohn, R. H. Samaritano, and L. M. Lerner, *ibid.*, **31**, 1503 (1966); (c) L. M. Lerner, B. D. Kohn, and P. Kohn, *ibid.*, **33**, 1780 (1968); (d) ref 3–5.

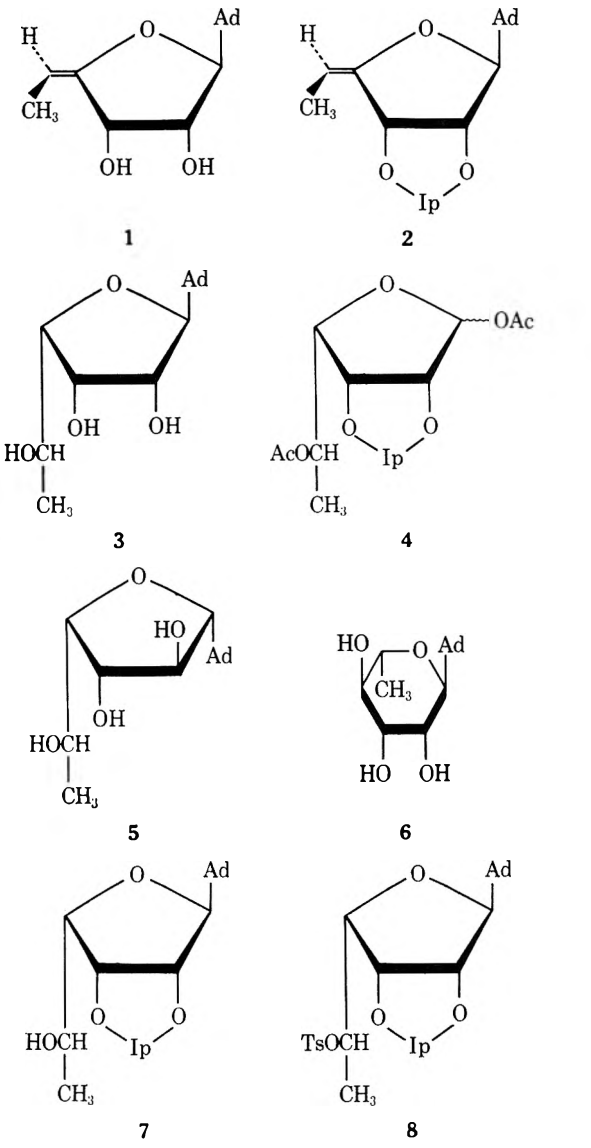
(3) L. M. Lerner, *J. Org. Chem.*, **37**, 470 (1972); **37**, 473 (1972).

(4) L. M. Lerner, *J. Org. Chem.*, **37**, 477 (1972).

(5) L. M. Lerner, *J. Org. Chem.*, **37**, 4386 (1972).

(6) For examples, see A. Hampton, P. J. Harper, and T. Sasaki, *Biochemistry*, **11**, 4736 (1972); J. F. Henderson, A. R. P. Paterson, I. C. Caldwell, B. Paul, M. C. Chan, and K. F. Lau, *Cancer Chemother. Rep.*, [2] **3**, 71 (1972); I. C. Caldwell and J. F. Henderson, *ibid.*, **2**, 237 (1971); and J. F. Henderson, J. F. Gadd, R. E. A. Palser, and M. Hori, *Can. J. Biochem.*, **48**, 573 (1970).

CHART I



Ad = adenyl, Ip = $C(CH_3)_2$

the products of nucleoside synthesis were separated by chromatography on an anion-exchange resin column.[7] When this was done, a new peak arose from the column which had not previously been observed. This substance crystallized from water as a monohydrate, and, later, a sample was crystallized from ethanol in an anhydrous form. Although this substance had physical properties unlike that reported earlier,[8] it is now evident that it is, indeed, 9-(6-deoxy-α-L-mannofuranosyl)-adenine (**3**) and some doubt must now be cast upon the identity of the previously reported material.[9] The purpose of this article is to (a) present evidence for the structure of **3**, (b) report the results obtained when the synthesis of Baker and Hewson[8] was repeated, (c) discuss other procedures used for the synthesis of **3**, and (d) report on the results obtained when **4** was subjected to acetolysis under different conditions.

Baker and Hewson[8] reported that **3** had a melting point of 132–135° and a specific rotation of −18° after crystallization from a mixture of ethanol and methyl ethyl ketone. The compound gave an elemental analysis which indicated to these workers that the ketone and some water were firmly bound to the crystals, and the ir spectrum confirmed the presence of a carbonyl group. However, very little evidence identifying the compound as **3** was actually presented. The nucleoside upon which the following structural evidence is presented was obtained from any of the procedures described below for its synthesis, or from the acetolysis studies. The monohydrate prismatic crystals were chosen only because they had crystallized first and the structural studies were already in motion when the anhydrous crystals were obtained from ethanol. The latter were shown to be readily recrystallized from water to form the monohydrate, which has a double melting point of 155 and 196°. The specific rotation of −72° was the first indication that this substance was really different from that reported previously and, since there was no reason to believe that a change at the C-6′ position from a hydroxyl group to a hydrogen would affect the value of the optical rotation to any great extent, it appeared that this substance may actually be the "real" **3**. Table I shows a comparison of the optical rotations of some hexofuranosyl nucleosides which differ only at C-6′ and which gave the first clue to the identity of **3**.

TABLE I

OPTICAL ROTATIONS OF SOME HEXOFURANOSYL NUCLEOSIDES

Hexofuranose config	[α]D, degree 6′-CH_3	6′-CH_2OH
β-D-allo	−74[a]	−57[b]
β-D-gluco	−60[c]	−58[d]
α-L-talo	−35[e]	−32[b,f]
α-L-manno	−72 (−18[h])	−75[f,g]

[a] E. J. Reist, L. Goodman, R. R. Spencer, and B. R. Baker, *J. Amer. Chem. Soc.*, **80**, 3962 (1958). [b] Reference 2b. [c] E. J. Reist, R. R. Spencer, and B. R. Baker, *J. Org. Chem.*, **23**, 1753 (1958). [d] E. J. Reist, R. R. Spencer, and B. R. Baker, *ibid.*, **23**, 1958 (1958). [e] E. J. Reist, L. Goodman, and B. R. Baker, *J. Amer. Chem. Soc.*, **80**, 5775 (1958). [f] The number reported is the absolute value, with a change of sign to conform to the expected value for the unknown enantiomer. [g] Reference 2a. [h] Reference 8.

The uv spectrum of **3** had a maximum at 260 nm, suggesting that the substitution was at N-9 of the purine. The nucleoside consumed 1 mol equiv of periodate in <10 min which was evidence that the ring was in a furanose form and that the hydroxyl groups at C-2′ and C-3′ were oriented cis to each other. Hydrolysis of **3** in hot acid afforded crystalline adenine, which was identified by melting point, ir spectroscopy, and paper chromatography, and a sugar which did not crystallize. The sugar was identified as 6-deoxy-L-mannose (L-rhamnose) by paper chromatography and by conversion into a phenylosazone. Since 6-deoxy-L-glucose yields the same osazone, chromatographic systems were used which would separate the two sugars. It was fairly obvious at this point that the compound was a 9-(6-deoxy-L-mannofuranosyl)adenine, but the anomeric configuration still had to be solved.

(7) C. A. Dekker, *J. Amer. Chem. Soc.*, **87**, 4027 (1965).

(8) B. R. Baker and K. Hewson, *J. Org. Chem.*, **22**, 966 (1957).

(9) L. M. Lerner and Y. Y. Cheng, *Carbohyd. Res.*, **14**, 297 (1970), reported a small yield of a substance, obtained by acid hydrolysis of a crude sample of **7** whose physical properties were somewhat close to those of the previously reported compound[8] and it was assumed to be the same. Unfortunately, this particular sample has been exhausted, but other samples obtained from similar experiments have now been found to be identical with nucleoside **3** as crystallized from ethanol.

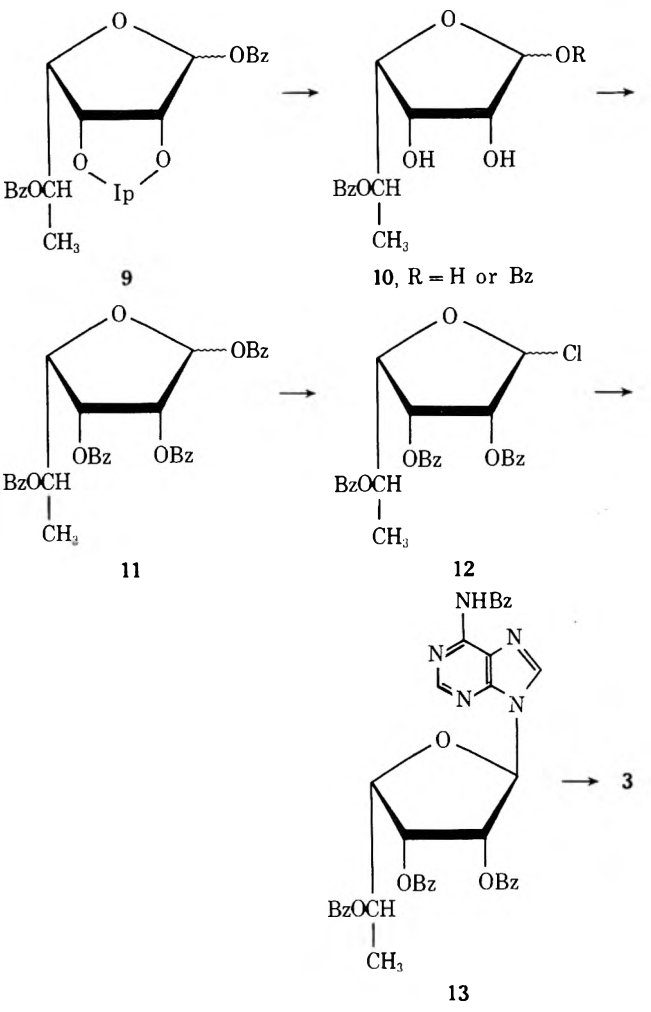
Baker and Hewson[8] never proved the anomeric configuration of their nucleoside, but instead they used the argument that the major product obtained from the condensation of a heavy metal salt of a purine and a glycosyl halide would have a configuration in which the purine was situated trans to the hydroxyl group at C-2′.[10] To determine the anomeric configuration of **3**, the nmr spectrum of two compounds related to **3** were examined. Previously, 9-(6-deoxy-2,3-*O*-isopropylidene-α-L-mannofuranosyl)adenine (**7**)[4,9] and 9-(6-deoxy-2,3-*O*-isopropylidene-5-*O*-*p*-toluenesulfonyl-α-L-mannofuranosyl)adenine (**8**)[4] were prepared and their structural relationship was shown by detosylation of **8** to **7**. Furthermore, the anomeric configuration of compound **2**, which was obtained from **8** by elimination of a molecule of *p*-toluenesulfonic acid, was shown to be α by nmr spectroscopy.[4] This would imply that **3** also had an α configuration if the structural relationship of these molecules could be confirmed. Therefore, a pure sample of **7**, obtained from the previous work,[4] was carefully treated with 9:1 trifluoroacetic acid–water to remove the isopropylidene group, and this resulted in the crystallization of **3**, first in its anhydrous form, then as a monohydrate after recrystallization from water. A sample of nucleoside **3**, obtained in the present work, was treated with acetone, using *p*-toluenesulfonic acid as a catalyst, and a good yield of **7** was obtained. In addition, the nmr spectrum of **7** revealed a singlet at τ 3.95, which is consistent with a trans orientation of H-1′ and H-2′. These data established the structure of **3** as 9-(6-deoxy-α-L-mannofuranosyl)adenine.

In their original work, Baker and Hewson[8] prepared what they believed to have the structure of **3** by two different routes. In the first of these,[8] what was believed to be 6-chloro-9-(6-deoxy-2,3,5-tri-*O*-benzoyl-α-L-mannofuranosyl)purine[11] was treated with hot methanolic ammonia and, in the second,[8] the reactions illustrated in Scheme I were used. The route shown has now been carefully reinvestigated and found to give **3** in an overall yield of 18%, having all of the properties associated with the compound described in the present paper. Comments concerning the individual reactions from **9** → **3** are presented in the Experimental Section.

In an effort to improve the synthesis of **3**, changes in the various steps illustrated in Scheme I were considered and these are described in detail in the Experimental Section. It is somewhat ironic that the best synthesis of **3** was accomplished by coupling the intermediate chloride **12** with 6-benzamidochloromercurpurine under the conditions originally described by Baker and Hewson.[8] The procedure was especially advantageous because the products were much cleaner and **3** could be crystallized without the necessity of extensive and time-consuming column chromatography.

At the outset of this investigation, it was hoped that **3** would be obtainable by the general scheme used previously[5] in which 6-deoxy-1,5-di-*O*-acetyl-2,3-*O*-isopropylidene-L-mannofuranose (**4**) was subjected to acetolysis and the products, consisting mainly of peracetylated 6-deoxy-L-mannofuranose, could then be coupled directly to the base by the titanium tetrachloride procedure. Reports in the literature indicated that the extent of epimerization occurring at C-2 was related to the relative concentrations of acetic acid to acetic anhydride and that a mixture of 1:1 acetic acid–acetic anhydride containing about 3% concentrated sulfuric acid did not cause epimerization,[12,13] or, at least if it did, only trace amounts of the epimerized product could be observed.[14] Most studies concerned with isomerizations occurring as a result of treatment of sugars with acetolysis mixtures have examined the identity of sugars obtained after hydrolysis of the acetate groups and have used paper chromatographic techniques.[14-16] However, the present author was interested primarily in a good, rapid preparation of **3**, and so a number of acetolysis studies were carried out with the products being immediately converted to adenine nucleosides and the identity and distribution of the nucleosides were determined. This study was greatly aided by the highly reproducible technique of column chromatography on an anion-exchange column worked out by Dekker.[7] It is important to realize that the different sugar acetates may have reacted to a different

SCHEME I



(10) B. R. Baker in Ciba Foundation Symposium, "Chemistry and Biology of Purines," G. E. W. Wolstenholme and C. M. O'Connor, Ed., Little, Brown and Co., Boston, Mass., 1957 p 120.

(11) B. R. Baker, K. Hewson, H. J. Thomas, and J. A. Johnson, *J. Org. Chem.*, **22**, 954 (1957).

(12) E. J. Reist, D. E. Gueffroy, and L. Goodman, *J. Amer. Chem. Soc.*, **86**, 5658 (1964).

(13) J. A. Montgomery, K. Hewson, A. G. Laseter, and M. C. Thorpe, *J. Amer. Chem. Soc.*, **94**, 7176 (1972).

(14) W. Sowa, *Can. J. Chem.*, **49**, 3292 (1971).

(15) P. Jerkeman, *Acta Chem. Scand.*, **17**, 2769 (1963).

(16) G. J. G. Chittenden, *Carbohyd. Res.*, **22**, 491 (1972).

extent with the nitrogenous base and that the yields reported for the nucleosides may not be representative of the true ratio of 6-deoxy-L-mannose to 6-deoxy-L-glucose or, for that matter, of 6-deoxy-L-mannofuranose to pyranose tetraacetates, resulting from the acetolysis mixtures. The ratio of nucleosides obtained are shown in Table II in comparison with the amount of 9-(6-deoxy-L-mannopyranosyl)adenine (**6**) found. Although the yields of **3** were generally lower than desirable and it was necessary to purify the products by chromatography, the results shown are quite interesting, especially in regard to **5**. The data clearly show a trend in which the degree of C-2 epimerization decreased considerably as the concentration of acetic acid was reduced, verifying an observation noted previously.[14] A change in the concentration of sulfuric acid did not seem to significantly change the results and is also in agreement with previous conclusions.[14] What is striking here is that, under conditions which are not supposed to give epimerization, namely, 1:1 acetic acid–acetic anhydride, a considerable amount of **5** was isolated after nucleoside formation. Even when the concentration of acetic acid was reduced further, such as with 3:7 acetic acid–acetic anhydride, **5** could still be isolated and crystallized. Furthermore, these results indicate that it cannot be assumed that epimerization has not occurred in any acetolysis mixtures, unless for some unexplained reason these results are peculiar only to 6-deoxy-L-mannose. It should be recalled that this isomerization only seems to occur in those cases where the sugar is in the furanose ring form and the hydroxyl groups in the ring are oriented in a cis relationship.[5,14,15] In a similar manner, Chittenden[16] has rexamined the acetolysis conditions used by Guthrie and Smith[17] (3:4 acetic acid–acetic anhydride) for the preparation of D-ribofuranose tetraacetate and found a ratio of D-ribose to D-arabinose of 6:1. In a recent communication, Montgomery, *et al.*,[13] claimed that a 1:1 mixture of acetic acid–acetic anhydride did not cause epimerization of ethyl 5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*ribo*-heptofuranuronate, but that the acid-catalyzed fusion with a purine did, resulting in a mixture of nucleosides. Moreover, in a footnote, they called attention to an experiment in which the usual method of glycosyl chloride formation with ethereal hydrogen chloride also was responsible for epimerization in one case. In agreement with these authors, it is also suggested here that nucleosides and other deivatives of sugars obtained after exposure of their precursors to *any* acid conditions be scrutinized carefully and their structures unequivocally proved.

TABLE II

NUCLEOSIDES OBTAINED AFTER ACETOLYSIS OF 6-DEOXY-1,5-DI-*O*-ACETYL-2,3-*O*-ISOPROPYLIDENE-L-MANNOFURANOSE (**4**)[a]

	Ratio		
Nucleoside	10:1[b-d]	1:1[b,e]	3:7[b,d]
6	1.0	1.0	1.0
3	Not detected	2.2	1.5
5	3.9	1.5	0.1

[a] Results are reported as comparisons of the yield of nucleoside to **6**. [b] Ratio of acetic acid:acetic anhydride. [c] Reference 5. [d] 5% sulfuric acid. [e] 3% sulfuric acid.

(17) R. D. Guthrie and S. C. Smith, *Chem. Ind. (London)*, 547 (1968).

Experimental Section[18]

All of the structural information reported below was obtained using the monohydrate crystals of **3**. Because of the repetitive nature of many of the experiments with regard to the isolation and characterization of the nucleosides **3**, **5**, and **6**, the phrase "identical in every respect" is used to indicate that the compounds isolated were identical by melting point, mixture melting point, ir, and paper chromatography in solvents A, B, and C. In most cases, the optical rotation was also checked and found to agree within experimental limitations.

Paper chromatography was run on 24-in.-long Whatman No. 1 sheets for 18–24 hr by a descending technique. The solvents used were (A) 5% aqueous disodium hydrogen phosphate, (B) 86:14 1-butanol–water, (C) 5:1:2 1-butanol–acetic acid–water, (D) 8:2:1 ethyl acetate–pyridine–water, (E) 2:1:2 ethyl acetate–pyridine–water, (F) 40:11:19 1-butanol–ethanol–water, and (G) 1:5:3:3 benzene–1-butanol–pyridine–water. The expression R_{Ad} refers to the ratio of the distance the nucleoside migrated to the distance which adenine migrated. Chromatographic data for the nucleosides **3**, **5**, **6**, and **7** are presented in Table III.

TABLE III

R_{Ad} VALUES FOR ADENINE NUCLEOSIDES

	R_{Ad}		
Compd	A[a]	B[a]	C[a]
3	1.66	0.72	0.89
5	1.47	1.20	1.15
6	1.39	0.39	0.71
7	1.59	2.29	1.59

[a] Solvent.

Periodate Uptake.—The consumption of periodate was determined by a spectrophotometric procedure as described by Rammler and Rabinowitz.[19] **3** consumed 0.96 mol equiv of periodate in <10 min and this amount remained unchanged after 6 and 24 hr.

Composition of 3.—A sample of **3** (59 mg) was dissolved in 4 ml of 0.1 *N* sulfuric acid and heated at reflux for 2 hr. The solution was cooled to room temperature, adjusted to pH 7 with dilute ammonium hydroxide, and concentrated by evaporation to approximately 1.5–2.0 ml, whereupon crystals began forming. The crystals were redissolved by heating the flask on a steam bath and the flask was kept in a refrigerator for several hours. Filtration of the crystals produced 16 mg of adenine, identified by its high melting point, >320° (slow decomposition), ir spectrum, which was identical with that of authentic adenine, and paper chromatography in solvent systems A, B, and C.

The mother liquor was passed through an Amberlite MB-3 column (8 × 1 cm) and the column was washed with water. Evaporation of the water resulted in a gum which was used for paper chromatography and its mobility was compared against that of samples of authentic 6-deoxy-L-mannose (Pfanstiehl) and 6-deoxy-L-glucose.[5] The chromatograms were sprayed with aniline oxalate reagent and heated at 110° for 10 min.[20] The results are reported in Table IV as R_g values, which represent

TABLE IV

PAPER CHROMATOGRAPHIC DATA FOR 6-DEOXYHEXOSES

	R_g		
Solvent	L-Rhamnose	6-Deoxy-L-glucose	Hydrolysis product
B	3.92	3.57	4.04
D	3.60	3.03	3.55
E	2.00	1.89	2.05
F	1.92	1.92	1.92
G	2.00	1.92	2.01

(18) General methods and instrumentation used in these investigations have been described.[3] Moist organic solutions were dried over anhydrous magnesium sulfate. Evaporations were performed under reduced pressure at bath temperatures between 40–45°, unless stated otherwise.

(19) D. H. Rammler and J. C. Rabinowitz, *Anal. Biochem.*, **4**, 116 (1962).

(20) S. M. Partridge, *Biochem. Soc. Symp.* (Cambridge, Engl.), **3**, 52 (1949).

the ratio of the distances that the sugars migrated to the distance that D-glucose migrated.

The phenylosazone of the sugar (~0.03 g) was prepared by mixing 0.06 g of phenylhydrazine hydrochloride, 0.09 g of anhydrous sodium acetate, and 2 ml of water, and this mixture was heated on a steam bath for 15 min. The turbid solution slowly crystallized: mp 178–180°. An authentic sample of 6-deoxy-L-mannose, when treated in the same manner, gave crystals, mp 176–178° (lit.[21] mp 178–179°). The ir spectra of the two samples were identical and there was no depression of melting point when the samples were mixed.

9-(6-Deoxy-2,3-*O*-isopropylidene-α-L-mannofuranosyl)adenine (7).—To 100 mg of **3** monohydrate suspended in 30 ml of acetone was added 3 ml of 2,2-dimethoxypropane and 0.64 g of *p*-toluenesulfonic acid monohydrate. The nucleoside went into solution after a few minutes and the mixture was stirred for 3 hr at room temperature, protected from moisture. The yellow mixture was poured into a stirring solution of 1 g of sodium bicarbonate in 10 ml of water. The precipitate was removed by filtration and washed well with acetone. The solvents were evaporated, leaving a white residue, which was triturated with 50 ml of chloroform. The solid portion was filtered off and the chloroform was evaporated. The residue was dissolved in 3 ml of boiling methanol, 4 ml of hot water was slowly added, and the solution was put aside. Crystals formed slowly during the next 3 days to give 88 mg (81%) of **7**: mp 226–229° (lit.[4,9] mp 225–228°); $[\alpha]^{27}D$ −26.1° (*c* 0.64, methanol) {an optical rotation obtained on a previously prepared sample[5] was found to be $[\alpha]^{25}D$ −25.5° (c 0.54, methanol)}; nmr τ 1.75, 2.12 (both s, 1 proton each, H-2, H-8), 3.27 (s, 2, NH_2), 3.95 (s, 1, H-1′), 4.4–4.8 (m, 2, H-2′, H-3′), 5.78–5.85 (broad unresolved m, 2, H-4′, H-5′), 8.41 (d, 3, C-6′ CH_3), 8.67, 8.73 (both s, 6, *gem*-dimethyl).

9-(6-Deoxy-L-mannofuranosyl)adenine (3). Method A.—To 222 mg of **7**, obtained during a previous study,[4] was added 3 ml of 9:1 trifluoroacetic acid–water.[22] The nucleoside derivative dissolved after stirring for ~5 min, the solution was kept at room temperature for an additional 7 min, and the solvents were evaporated *in vacuo* at 35°. The residue was dissolved in 20 ml of water, the pH was adjusted to neutrality with Bio-Rad AG1-X2 (OH^-) resin, and the resin was filtered off. The residue obtained after evaporation was triturated with hot ethanol and some insoluble material was removed by filtration. The solution was concentrated to about 1–2 ml and allowed to crystallize at room temperature. A second crop of crystals was obtained in a similar manner to give a total of 55 mg (30%), mp 118–124 and 194–196°, identical in every respect with the anhydrous form of **3** prepared in method D. The first crop of crystals was recrystallized from water to give **3** as the monohydrate, mp 157 and 192–196°, identical in every respect with **3** prepared by method B.

Method B.—The procedure for this synthesis was the one described by Baker and Hewson.[8] The instructions were carefully adhered to, except that a smaller amount of 6-deoxy-1,5-di-*O*-benzoyl-2,3-*O*-isopropylidene-L-mannofuranose (**9**, 5.65 g) was used. **9** was treated with refluxing 70% aqueous acetic acid for 3 hr and the products were partitioned between water and 1:1 ethyl acetate–benzene. The organic soluble substance (**10**) was benzoylated to give **11**, 4.63 g of which was converted to chloride **12** and coupled with 6-benzamidochloromercuripurine in refluxing xylene. When the blocking groups of **13** were removed with sodium methoxide and the product was isolated *via* the picrate, an attempt was made to crystallize the product from ethanol and methyl ethyl ketone, as described earlier.[8] Only a portion of the substance separated and this had mp 145–157° and a second melting point above 170°; $[\alpha]^{26}D$ −63° (*c* 0.57, H_2O). The material was all recombined, dissolved in hot water, and allowed to stand for several days. Prismatic crystals of **3** formed: 301 mg; mp 155–156.5°, slowly crystallizing again above 160°, and melting at 195–196°; $[\alpha]^{23}D$ −72.3° (*c* 0.65, H_2O); uv $\lambda_{max}^{pH\ 1}$ 257 (ε 14,900), $\lambda_{max}^{H_2O}$ 260 (ε 14,900), $\lambda_{max}^{pH\ 13}$ 260 nm (ε 15,300).

Anal. Calcd for $C_{11}H_{15}N_5O_4 \cdot H_2O$: C, 44.14; H, 5.73; N, 23.40. Found: C, 44.15; H, 5.86; N, 23.41.

The mother liquor was chromatographed on a column (45 × 1 cm) of Bio-Rad AG1-X2 (OH^-, 200–400 mesh) using 30% aqueous methanol and 7-ml fractions were collected. Tubes 60–101 yielded another 89 mg of **3**, mp 155 and 197–198.5° (total yield 430 mg, 18%). Two other uv absorbing peaks were observed. The peak at tubes 6–24 afforded 43 mg of **6** from ethanol–water, identical in every respect with the authentic compound.[5] Tubes 48–55 contained only 8 mg of a substance that was not identified.

Method C.—**9**[8] (13.9 g) was dissolved in 120 ml of 9:1 trifluoroacetic acid–water and kept for 15 min at room temperature. The solvents were evaporated under reduced pressure at 35°, resulting in a slightly greenish syrup containing crystals, presumably benzoic acid formed by hydrolysis of the anomeric benzoate. The syrup was dissolved in 85 ml of 1:1 ethyl acetate–benzene, washed with 60 ml of water and twice with 50-ml portions of cold saturated sodium bicarbonate solution, and dried. The syrup obtained after evaporation of the solvents weighed 7.6 g: ir ν_{max} 3410 (strong OH), 1724 (C=O of benzoate), and 712 cm^{-1} (monosubstituted phenyl). The original water layer contained 0.8 g of a chloroform-soluble, benzene-insoluble substance, which was not 6-deoxy-L-mannose as determined by tlc on silica gel plates (HF, Merck) using 9:1 chloroform–methanol.

The syrup **10** (7.6 g) was dissolved in 100 ml of dry pyridine and the solution was chilled in an ice bath while 60 ml of acetic anhydride was slowly added. The reaction was allowed to proceed at room temperature for 21 hr and then poured into 400 ml of an ice–sodium bicarbonate mixture. This was stirred for 1 hr, the product was extracted with chloroform (150 ml), and the chloroform solution was washed with saturated sodium bicarbonate (2 × 200 ml) and water (200 ml) and dried. Evaporation of the chloroform and coevaporation with toluene three times gave 14.7 g of an amber-colored syrup. This material (14.1 g) was added to a mixture of 6-benzamidochloromercuripurine (18.7 g), Celite-545 (18.7 g), titanium tetrachloride (5.5 ml), and 1,2-dichloromethane (1250 ml) and the mixture was refluxed for 24 hr, cooled to room temperature, and stirred for 2 hr with 700 ml of saturated sodium bicarbonate solution. The mixture was filtered through a Celite pad and the filter cake was washed thoroughly with warm 1,2-dichloroethane (~200 ml). After evaporation, the syrup was dissolved in 250 ml of chloroform, washed with 30% aqueous potassium iodide solution (2 × 200 ml) and water (300 ml), and dried. Evaporation of the chloroform afforded a hard gum (14.8 g) which was dissolved in methanol and treated with 16 ml of 1 *N* methanolic sodium methoxide. The solution was refluxed for 1.25 hr, cooled to room temperature, and neutralized with acetic acid. The solvents were evaporated, the residue was partitioned between 175 ml of water and 75 ml of chloroform, and the aqueous layer was further washed with chloroform (3 × 35 ml). Filtration and evaporation gave a residue which was dissolved in 65 ml of methanol and 75 ml of 10% methanolic picric acid was added. The flask was placed in an ice bath for 2 hr and the yellow crystals were filtered off and washed with cold methanol, then cold water. The wet picrate was suspended in 800 ml of water and enough Bio-Rad AG1-X8 (CO_3^{2-}) resin was added in portions over 3 hr to the stirring mixture to discharge the yellow color. The water was evaporated and attempts to crystallize the orange product or to remove the yellow color with charcoal failed. Therefore, the material was dissolved in 20 ml of water and placed on a column (27 × 2 cm) of Bio-Rad AG1-X2 (OH^-, 200–400 mesh) resin and the column was eluted with 30% aqueous methanol. Ten-milliliter fractions were collected. The major peak in tubes 51–104 were pooled and the product was crystallized from water to give 0.751 g of **3**. An additional 0.033 g was obtained from the mother liquor (yield 7%), mp 153–155 and 195–197°. This substance was identical in every respect with **3** prepared by method B.

Method D.—The acetate (7.86 g), prepared by method C, was heated with 6-benzamidochloromercuripurine (10.4 g), Celite-545 (10.4 g), titanium tetrachloride (3.0 ml), and 1,2-dichloroethane (800 ml) at reflux and processed as described above to give 8.86 g of a light brown foam. This material was fractionated on a column (10 cm long × 8 cm wide) of silicic acid (Mallinckrodt, 100 mesh, activated at 130° for 16 hr). The column was prepared in chloroform and washed with 9:1 chloroform–ethyl acetate and 1050 ml collected to give 1.84 g of unreacted sugar derivatives. Elution of the column with 19:1 chloroform–methanol followed, the first 500 ml was discarded, and the next 900 ml contained 7.0 g of blocked nucleosidic material. The blocking groups were removed in a refluxing mixture of 200 ml of methanol and 12 ml of 1 *N* methanolic sodium methoxide. The methanol was evaporated and the residue was dissolved in 100 ml of water and neutralized with IR-120 (H^+) resin. After filtration, the aqueous solution was washed with chloroform (2 × 50 ml) and treated with

(21) Khr. Akhtardzhiev and D. Kolev, *Pharm. Zentralh.*, **100**, 14 (1961); *Chem. Abstr.*, **55**, 15829*i* (1961).

(22) J. E. Christensen and L. Goodman, *Carbohyd. Res.*, **7**, 510 (1969).

a little Norit A, and the water was evaporated. Since the resulting gum did not crystallize, it was purified on an anion-exchange column (29 × 2.4 cm) as described in method C and 10-ml fractions were collected. The main peak was at tubes 32–100, which yielded 1.3 g (23%). Recrystallization from ethanol gave 691 mg (12%), mp 121–123°, solidifying above 160° and melting again at 193–195°. The analytical sample was prepared by further recrystallization and required drying at 100° under high vacuum over P_2O_5: mp 121–124 and 194–196°; $[\alpha]^{25}D$ −76° (*c* 0.79, H_2O).

Anal. Calcd for $C_{11}H_{15}N_5O_4$: C, 46.96; H, 5.41; N, 24.90. Found: C, 46.88; H, 5.41; N, 25.11.

When a small sample of this substance was recrystallized from water, the crystals which formed (mp 157–159 and 196–198°) were identical in every respect with **3** monohydrate.

Tubes 4–20 afforded a tan powder which was rechromatographed on a column (43 × 1 cm) by the same procedure as above. The main uv-absorbing peak was isolated to give a substance (165 mg) which did not crystallize from most common solvents. It did, however, afford a white precipitate from ethanol–methyl ethyl ketone, mp 131–137°, and from acetone, mp 90–150°. It is interesting to note that Baker and Hewson reported[8] mp 132–135 and 50–135° for their compound from these same solvents, respectively. However, the optical rotation $[\alpha]^{25}D$ −40° (*c* 0.37, H_2O) differed greatly. Paper chromatography in solvent C showed this substance to have a mobility very different from that of **3** or **6**, but identical with that of **7** which it obviously was not. Uv showed λ_{max} 258 (pH 1), 259 (H_2O), and 259 nm (pH 11). Although isolated from several preparations, including some as performed in method C, this substance has not yet been identified.

Method E.—This procedure gave the poorest results and is of no synthetic use. Tetrabenzoate **11** (4.4 g) was dissolved in 10 ml of methylene chloride and treated with 23 ml of 32% hydrogen bromide in acetic acid (Eastman) at room temperature for 45 min. The mixture was poured into 50 ml of ice–water and the product was extracted with 50 ml of chloroform. The aqueous layer was extracted once more with 20 ml of chloroform, and the solutions were combined and washed three times with 50-ml portions of ice-cold water. The solvent was evaporated and small portions of toluene were coevaporated two times to eliminate traces of acetic acid. The halide was treated with 4.4 g of 6-benzamidochloromercuripurine as described in method B. All of the subsequent steps were as described in method B and the nucleoside was isolated *via* the picrate and chromatography on the anion-exchange column. The only major peak yielded 30 mg (1.4%) of **3** from ethanol, mp 118–120 and 196–197°, identical in every respect with the substance prepared by method D.

Acetolysis of 6-Deoxy-1,5-di-*O*-acetyl-2,3-isopropylidene-L-mannofuranose (4).[9]—The data reported in Table II for a 10:1 mixture of acetic acid–acetic anhydride was obtained earlier.[5] The 1:1 acetic acid–acetic anhydride mixtures contained 3% concentrated sulfuric acid and were run according to the directions of Reist, *et al.*[12] Acetolyses conducted in 3:7 acetic acid–acetic anhydride were run exactly as described for that above using 5% sulfuric acid, the concentration of acid that had been previously used in the 10:1 acetic acid–acetic anhydride mixtures. The syrups obtained were used directly for nucleoside synthesis.

Nucleosides Obtained after Coupling of Acetolysis Products. From 1:1 Acetic Acid–Acetic Anhydride.—The reaction mixture consisted of 3.4 g of the sugar acetate mixture, 5.8 g of 6-benzamidochloromercuripurine, 5.8 g of Celite-545, 1.7 ml of titanium tetrachloride, and 600 ml of 1,2-dichloroethane. After work-up, a pale yellow foam was obtained, 4.47 g. Removal of the ester groups with hot methanolic sodium methoxide and treatment with a little charcoal gave a syrup which was fractionated on a column (28 × 2.4 cm) of Bio-Rad AG1-X2 (OH^-, 200–400 mesh).[7] The column was packed with water and the sample was added dissolved in water. Development was carried out with 30% aqueous methanol and 9-ml fractions were collected. The contents of tubes 15–58 were pooled and the product was crystallized from ethanol–water to give 145 mg (5%) of **6**, mp 215–217°, identical in every respect with an authentic sample of **6**. The contents of tubes 144–250 were pooled and the product was crystallized from water to afford 323 mg (10.5%) of **3** in two crops, mp 156–158.5°, resolidifying above 165° and melting again at 198–200°. This compound was identical in every respect with **3** as reported in method B. Crystallization from ethanol of the nucleoside collected in tubes 277–440 afforded 208 mg (6%) of **5** in two crops, mp 119–122°, identical in every respect with an authentic sample.[6]

From 3:7 Acetic Acid–Acetic Anhydride.—The reaction mixture consisted of 3.2 g of the sugar acetate, 5.5 g of Celite-545, 1.5 ml of titanium tetrachloride, and 680 ml of 1,2-dichloroethane. The steps followed and the column chromatography were run exactly as described above. Tubes 21–37 yielded **6** (210 mg, 8%, mp 216–218.5°) and tubes 77–220 afforded **3** (305 mg, 11%, mp 157–160 and 197–200°). The eluent was changed to 60% aqueous methanol at tube 334 and the peak at tubes 355–397 yielded 27 mg (0.9%) of **5**, mp 118–121°. These nucleosides were identical with the previous preparations in every respect.

Acknowledgment.—The author appreciates the effort made by Dr. John Montgomery of the Southern Research Institute to locate the original sources of the data reported in ref 8.

Registry No.—**3**, 29847-43-6; **4**, 29847-40-3; **7**, 29847-42-5; **9**, 41507-10-2; 2,2-dimethoxypropane, 77-76-9; *p*-toluenesulfonic acid, 104-15-4.

Crystalline Transitions of Carbohydrates

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Several types of transitions which precede the melting of crystalline carbohydrate compounds have been investigated by thermal analysis and the existence and interconversion of different stable and metastable forms have been confirmed by recording their X-ray powder diffraction pattern. The observed phenomena include dehydration, plastic crystal transition, and monotropic and enantiotropic polymorphism. Because of the possibility for these transitions, melting point and X-ray diffraction provide convenient but not necessarily unequivocal methods for characterization of crystalline organic compounds.

The melting point of crystalline materials determined by visual methods has been traditionally considered as a characteristic constant and criterion of purity for organic compounds in general and carbohydrates in particular. However, since the fusion process could be accompanied or preceded by other transitions and transformations, the visual determination of the melting point often provides partial or inadequate description of the changes which are taking place. Wide range and multiple melting points or melting points accompanied by decomposition, sintering, and sublimation are common examples. During the investigation of model compounds for thermal decomposition and combustion of cellulosic materials,[1,2] it was found that thermal analysis provides convenient and comprehensive description of the transitions and transformations which precede or accompany the fusion. Some of these phenomena, such as the plastic crystal transition of 1,6-anhydro-β-D-hexopyranoses,[3-5] simultaneous melting and thermal anomerization of reducing sugars,[6,7] and the consecutive melting and decomposition of phenyl 2-acetamido-2-deoxy-β-D-glucopyranosides,[8] have been already reported. This article provides further examples of dehydration, plastic crystal phase transition, and monotropic and enantiotropic polymorphism of carbohydrates, which hitherto have received little or no attention.

Results and Discussion

Dehydration.—The crystal lattice of carbohydrates often contains molecules of water or organic solvents which are removed on drying or heating. Since the crystalline materials are generally analyzed after drying and melting points are determined with anhydrous forms, the original form of the crystalline material and its transformations before melting could easily escape detection. In some cases, when the dehydration process takes place before the melting of the anhydrous form and, depending on the prevailing conditions, it may or may not be accompanied by a separate fusion, there could be considerable confusion about the accuracy of melting point data.

Thermal analysis instruments provide useful tools for investigating the transformation of the carbohydrates and determining the cause of such confusions. The amount and rate of solvent loss under different conditions could be determined by thermogravimetric analysis (tga) and derivative thermogravimetry (dtg), while the changes in crystalline structure, melting, and crystallization and the accompanying changes in enthalpy and entropy could be determined by differential thermal analysis (dta) and differential scanning calorimetry (dsc).

Phenyl β-D-glucopyranoside,[9] phenyl 2-amino-2-deoxy-β-D-glucopyranoside,[8] and *p*-aminophenyl β-D-glucopyranoside,[10] which have been investigated in this laboratory, show sharp tga, dtg, and dta signals for dehydration before melting. The first compound was originally reported in 1879 as anhydrous material,[11] in a subsequent preparation crystallization from water gave a dihydrate,[12] and a commercial sample recently analyzed in this laboratory was found to be a monohydrate. The reported melting point of this compound has varied within the range of 174–175° for the anhydrous compound[12] to 176° for the monohydrate[12a] and 144–145° for the dihydrate.[12b]

Tga analysis of a sample freshly crystallized from aqueous ethanol in a covered pan showed the loss of 11.3% water at 85°, which corresponds nearly to the theoretical value of 12.3% for the dihydrate. Loss of moisture from the dihydrate at room temperature and lower water vapor pressure (humidity) gave a monohydrate. The monohydrate has a different X-ray diffraction from the dihydrate and, as shown in Figure 1, loses 6.6% water, corresponding exactly to 1 mol, at about the same temperature as the dihydrate. The rate of dehydration, as expected, depends on the temperature and the ambient vapor pressure.

Figure 2 shows the dsc data for phenyl β-D-glucopyranoside monohydrate.[9] Heating under conditions which prevent (Figure 2a) or limit (Figure 2b) the loss of water from the system gives two sharp endotherms at 85 and 176° for the dehydration of the monohydrate and melting of the anhydrous crystals, respectively. Since there is no exotherm between the two transitions, the anhydrous crystals must be formed simultaneously with the dehydration of the original

(1) F. Shafizadeh, *Advan. Carbohyd. Chem.*, **23**, 419 (1968).
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(3) F. Shafizadeh, G. D. McGinnis, C. W. Philpot, and R. A. Susott, *Carbohyd. Res.*, **13**, 184 (1970).
(4) F. Shafizadeh, G. D. McGinnis, R. A. Susott, and C. W. Philpot, *Carbohyd. Res.*, **15**, 165 (1970).
(5) G. W. Smith and F. Shafizadeh, *J. Chem. Soc. B*, 908 (1971).
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(11) A. Michael, *Amer. Chem. J.*, **1**, 305 (1879).
(12) (a) E. Fischer and E. F. Armstrong, *Chem. Ber.*, **34**, 2885 (1901); (b) A. Robertson and R. B. Waters, *J. Chem. Soc.*, 2729 (1930); (c) B. Helferich and E. Schmitz-Hillebrecht, *Chem. Ber.*, **66**, 378 (1933).

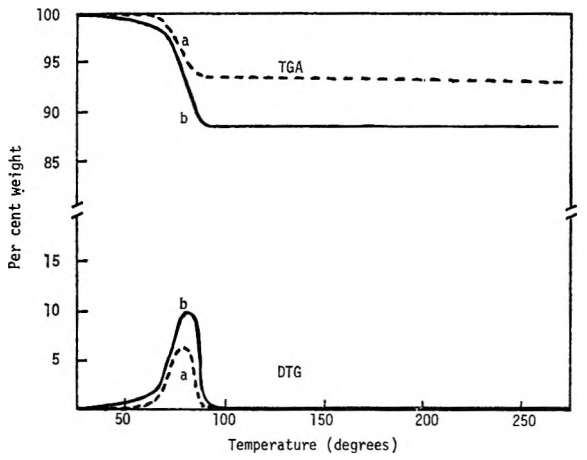

Figure 1.—Tga and dtg of phenyl β-D-glucopyranoside: a, monohydrate; b, dihydrate.

materials. Visual observation indicated that dehydration is not accompanied by fusion. When the water vapor is allowed to escape freely, as in an open pan (Figure 2c) or under vacuum (Figure 2d), the dehydration process takes place gradually with development of a broad endotherm at about 60°. This process gives a solid material which lacks sharp X-ray diffraction but changes to a crystalline, anhydrous form with a sharp X-ray pattern after minor exotherms at 100 and 120°. The anhydrous, crystalline material then melts with a sharp endotherm at 176°. The X-ray powder diffraction patterns obtained for the different phases of these transitions are listed in Table I.

TABLE I
DIFFERENT PHASES OF DEHYDRATION AND MELTING OF PHENYL β-D-GLUCOPYRANOSIDE AND TREHALOSE ON HEATING AND REMOVAL OF WATER

Temp, °C	Phase present	X-Ray diffraction
	Phenyl β-D-Glucopyranoside	
20	Dihydrate crystal	14.8 (24), 8.15 (100), 4.91 (31), 4.66 (41), 4.22 (17)
20	Monohydrate crystal	7.89 (74), 4.74 (100), 4.23 (68), 4.01 (59), 3.75 (60)
80	Solid intermediate	18.8 (100) very broad 4.93 (62) very broad
145	Anhydrous crystals	20.2 (45), 18.7 (100), 15.5 (47), 4.62 (35), 3.68 (32)
176	Isotropic liquid	
	Trehalose	
25	Dihydrate crystals	5.39 (38), 5.34 (39), 3.78 (100), 3.46 (42), 2.11 (43)
125	Amorphous glass	No diffraction peaks
135	Supercooled liquid	
200	Anhydrous crystals	5.10 (100), 4.32 (64), 3.96 (80), 3.93 (48), 3.54 (67)
215	Isotropic liquid	

The broad endothermic peak at 215° in Figure 2d is due to vaporization. Under vacuum, phenyl β-D-glucopyranoside vaporizes without decomposition, while in a covered pan it could be completely decomposed.[8,9] The different end results show the care which must be taken in selecting proper conditions for investigating the decomposition and thermal properties of carbohydrates.

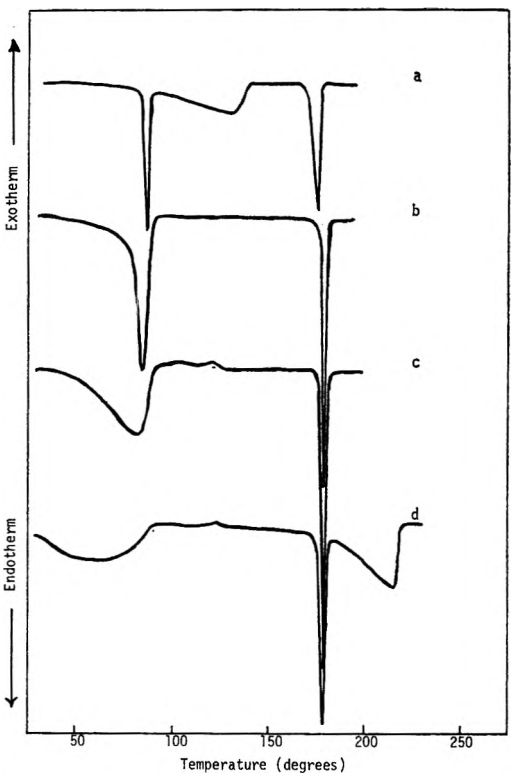

Figure 2.—Dsc of phenyl β-D-glucopyranoside under different conditions: a, hermetically sealed; b, covered pan; c, open pan; d, open and vacuum (1 mm).

Trehalose provides another interesting example.[7] It forms a dihydrate which has been widely reported to melt at 100 ± 3°.[13,14] Further investigation has shown that in a tightly packed capillary tube it melts at the above temperature, but, when the capillary contains single crystals and is gently heated, it melts at 135°.[14] Furthermore, heating on a microscope melting block shows sintering and loss of birefringence at 100° and melting at 135°. It has also been shown that, when the dihydrate is heated at 130°, it forms anhydrous crystals which melt according to the earlier reports at about 205°[13,15] and according to a later report at 216–218°.[14]

The thermal analysis data for trehalose shown in Figure 3 indicate that when the dihydrate is heated in a closed system which prevents the free evaporation of water (Figure 3a), two sharp endotherms appear at 100 and 215°. At the first endotherm, the dihydrate melts and simultaneously forms anhydrous crystals which remelt at 215°. The situation is quite different when water is allowed to escape freely (Figure 3d). Under this condition, dehydration starts at lower temperatures and proceeds gradually. Consequently, it gives a broad endotherm at about 60°, and leaves an amorphous glass which liquefies with a minor endotherm at 133°. The liquid material then crystallizes with a broad exotherm at 185° and the resulting anhydrous, crystalline form melts with a sharp endotherm at 215°. The sequence of events (in Figure 3d) involving conversion of the crystalline dihydrate to an amorphous glass, an intermediate or supercooled liquid,

(13) E. Mitscherlich, *Justus Liebigs Ann. Chem.*, **106**, 15 (1858).
(14) H. J. Reisener, H. R. Goldschmid, G. A. Ledingham, and A. S. Perlin, *Can. J. Biochem. Physiol.*, **40**, 1248 (1962).
(15) E. O. von Lippmann, *Chem. Ber.*, **45**, 3431 (1912).

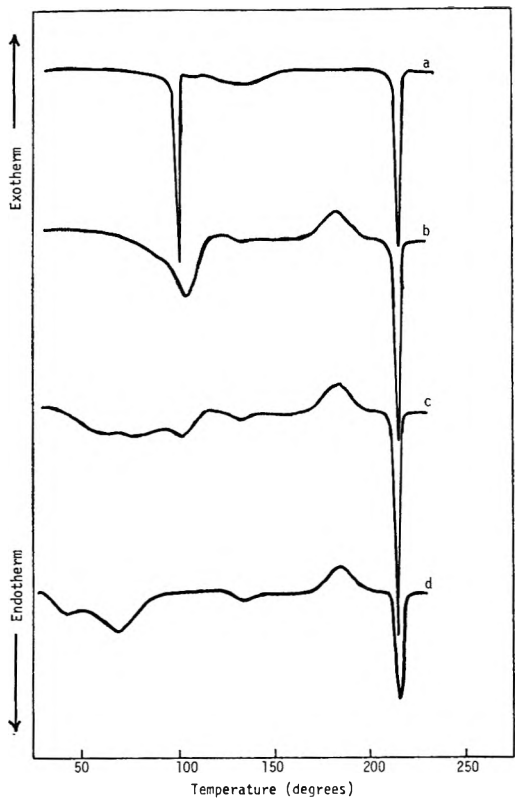

Figure 3.—Dsc of α,α-trehalose under different conditions: a, hermetically sealed; b, covered pan; c, open pan; d, open pan and vacuum (1 mm).

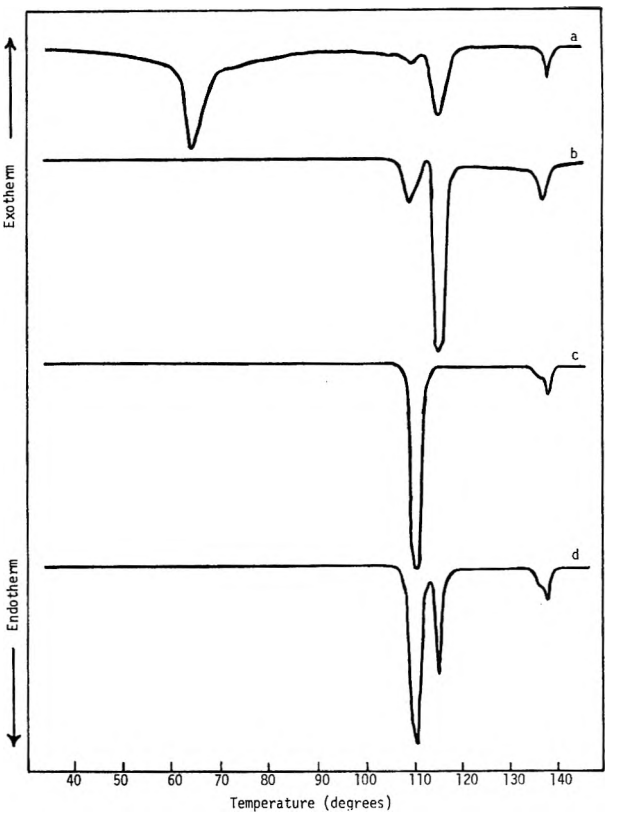

Figure 4.—Dsc of different samples of 1,6-anhydro-β-D-altropyranose: a, monohydrate; b, finely powdered anhydrous crystals; c and d, anhydrous single crystals from tetrahydrofuran at 50°.

an anhydrous crystalline form, and a final liquid phase has been confirmed by X-ray powder diffraction data of the solids and the visual observation of the liquids. The X-ray data presented in Table I show the highly crystalline patterns of the dihydrate and the anhydrous crystalline forms and amorphous nature of the glass phase.

According to these data, the commonly reported sharp melting of the dihydrate at 100 ± 3° is observed under high ambient vapor pressure, when the moisture is kept within the system, and the reported alternate melting at 135° is due to the softening or liquefaction of the amorphous glass which is formed on gradual dehydration under lower ambient vapor pressure.

Plastic Crystal Transition.—Normally the melting process involves loss of crystal coherence owing to diffusional motion accompanied by isotropy or randomized orientation of the molecule. In the previous studies in this program, it was found that 1,6-anhydrohexopyranoses show a transition in which the orientation of the molecule is randomized but the crystal coherence is maintained until melting at a higher temperature. Wide-line nmr investigation of crystalline 1,6-anhydro-β-D-glucopyranose, which melts at 180°, showed that before transition at 112° it possessed a rigid lattice and after the transition the molecules begin to reorient about their center of gravity and show increased self-diffusion as the temperature is raised further. The transition affects the heat capacity, hardness, X-ray diffraction, hydrogen bonding, vapor pressure, and ir spectra of the crystalline material.[2-5] This phenomenon, known as plastic crystal phase transition, is readily detected by thermal analysis because the major changes of enthalpy and entropy take place at the transition rather than melting.[16]

The thermogram of 1,6-anhydro-β-D-altropyranose,[2,4] in addition to a major endotherm for the transition at 115° (ΔS_t = 11.1 eu) and a minor endotherm at 137° (ΔS_f = 1.3 eu) for melting, showed another minor endotherm before the transition (ΔS_t = 1.5 eu) which remained unaccounted for. The situation was further complicated by the fact that 1,6-anhydro-β-D-altropyranose has been also reported to melt at 58–59°[17] and later has been found to form a monohydrate.[18] Investigation of these transformations initially increased the confusion and complexity of the problem because the thermal analysis data (Figure 4) did not seem to be reproducible. However, the key to the problem was found when it was recognized that there are at least four different crystalline forms of the anhydro sugar: the monohydrate form, which dehydrates with an endotherm at about 62° (see Figure 4a), two types of pretransition anhydrous forms IIa and IIb, and finally the plastic crystal form I. The X-ray powder diffraction of these forms and their transformation temperatures are given in Table II. The forms IIa and IIb that could exist as a mixture have different plastic crystal transition temperatures. The transition for IIa is at 115° and for IIb at 110°. Heating of the monohydrate (Figure 4a) and finely powdered anhydrous crystals (Figure 4b) produce a minor transition endotherm at 110° and a major transition endotherm at

(16) J. Timmermans, *J. Chim. Phys.*, **35**, 331 (1938); *Phys. Chem. Solids*, **18**, 1 (1961).
(17) F. H. Newth and L. F. Wiggins, *J. Chem. Soc.*, 1734 (1950).
(18) I. Johansson and N. K. Richtmyer, *Carbohyd. Res.*, **10**, 322 (1969).

TABLE II
DIFFERENT PHASES AND TRANSFORMATIONS OF 1,6-ANHYDRO-β-D-ALTROPYRANOSE

Phase	Transformation Temp, °C	Form	Characteristics
Monohydrate	62 →	IIb	8.50 (84), 6.10 (66), 5.55 (45), 4.23 (57), 2.81 (100)[a]
IIb	110 →	IIa	5.54 (100), 4.66 (93), 4.39 (80), 3.66 (26), 2.77 (32)
IIb	110 →	I	
IIa	80 →	I	
IIa	115 →	I	12.6 (25), 5.23 (100), 4.92 (40), 4.83 (27), 4.67 (32), 3.37 (27)
I	138 ⇄ 134	Liquid	Plastic crystal

[a] X-Ray powder diffraction pattern.

115°. Large anhydrous single crystals prepared by recrystallization from tetrahydrofuran solution at 50° produce the major endotherm at 110° (Figure 4c) and sometimes also a minor endotherm at 115° (Figure 4d). The immediate dehydration product and the crystalline material formed on reversing the transition at 75° both show the IIb X-ray diffraction pattern of the large, anhydrous, single crystals obtained by direct recrystallization from tetrahydrofuran. The X-ray pattern for the IIa form could only be obtained from samples which are heated beyond 110° without major transition. These data suggest that IIa is formed as a thermodynamically stable form from minor rearrangements of IIb (see Table II).

Polymorphism.—The phenyl glycosides[6,8,9] investigated in this laboratory as model compounds for pyrolysis and combustion of cellulosic materials provide interesting and highly complex examples of polymorphism in carbohydrates which, with the notable exception of recent X-ray studies on three forms of mannitol,[19,20] has received very little attention.

The dsc data on transition of *p*-methoxyphenyl β-D-glucopyranoside[9] and phenyl and *p*-methoxyphenyl 2-acetamidotri-*O*-acetyl-2-deoxy-β-D-glucopyranoside[8] are shown in Figure 5. These transitions are generally characterized by an endothermic peak which is closely followed by an exotherm. They could not be easily reversed and show some variation for different preparations, sample sizes, and the heating rates. Table III shows the X-ray pattern for each phase and the temperature of its transition to the next phase. These transitions can be classified as monotropic[21] resulting from the conversion of a metastable crystalline phase to a stable crystalline phase. The succession of endothermic and exothermic peaks shows that the transformation involves melting of the metastable form and subsequent crystallization of the stable form.

The transitions of *p*-methoxyphenyl β-D-glucopyranoside (Figure 5a) and phenyl 2-acetamidotri-*O*-acetyl-2-deoxy-β-D-glucopyranoside (Figure 5b) are quite similar and rather simple. In both cases, the liquid formed on melting of the stable phase can be supercooled considerably below the transition temperature. The supercooled liquid always crystallizes in the stable form even when seeded with the metastable form. On

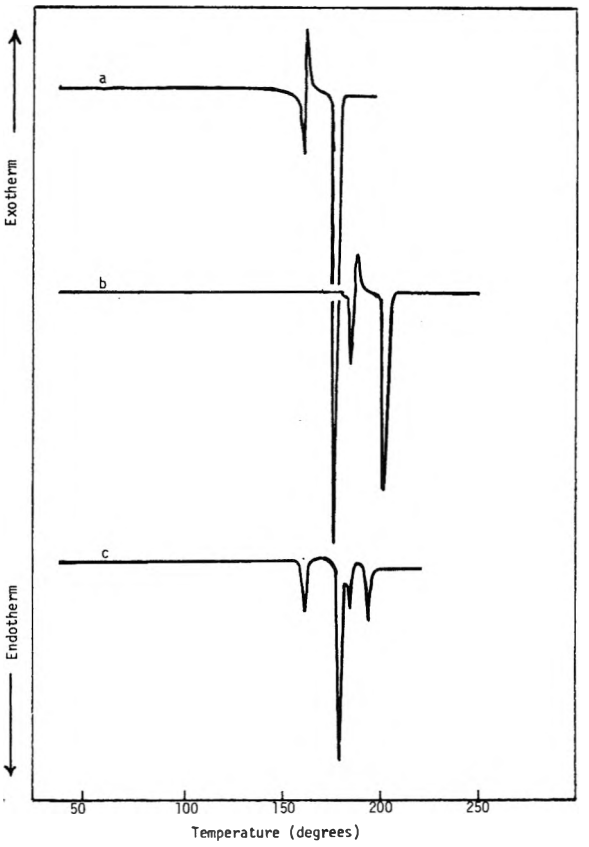

Figure 5.—Dsc of polymorphic glycosides: a, *p*-methoxylphenyl β-D-glucopyranoside; b, phenyl 2-acetamidotri-*O*-acetyl-2-deoxy-β-D-glucopyranoside; c, *p*-methoxyphenyl 2-acetamidotri-*O*-acetyl-2-deoxy-β-D-glucopyranoside.

TABLE III
MONOTROPIC POLYMORPHISM OF PHENYL GLUCOSIDES

Phase	Transformation Temp, °C	Form	Characteristics
p-Methoxyphenyl β-D-Glucopyranoside			
II	161 →	I	14.0 (60), 5.97 (100), 4.82 (37), 4.59 (67), 4.21 (76)[a]
I	176 ⇄ 30	Liquid	19.6 (71), 4.94 (67), 4.54 (75), 4.09 (70), 3.66 (100)
Phenyl 2-Acetamidotri-*O*-acetyl-β-D-glucopyranoside			
II	185 →	I	12.0 (100), 10.5 (29), 8.39 (36), 4.15 (36), 3.84 (28)
I	201 ⇄ 160	Liquid	12.2 (100), 5.74 (39), 4.81 (51), 4.41 (90), 4.21 (38)
p-Methoxyphenyl 2-Acetamidotri-*O*-acetyl-β-D-glucopyranoside			
IV	158 →	III	11.0 (100), 8.69 (62), 7.20 (59), 3.89 (78), 3.58 (78)
III	177 →	II	11.4 (100), 9.31 (81), 4.73 (50), 3.99 (41), 3.62 (64)
II	183 →	I	11.0 (100), 4.98 (40), 4.35 (48), 4.04 (46), 3.95 (42)
I	183 → 192	Liquid	10.8 (100), 4.98 (77), 4.37 (62), 4.26 (49), 4.13 (44)

[a] X-Ray powder diffraction pattern.

(19) H. M. Berman, G. A. Jeffrey, and R. D. Rosenstein, *Acta Crystallogr., Sect. B*, **42**, 442 (1968).
(20) H. S. Kim, G. A. Jeffrey, and R. D. Rosenstein, *Acta Crystallogr., Sect. B*, **42**, 1449 (1968).
(21) J. E. Ricci, "The Phase Rule and Heterogeneous Equilibrium," Van Nostrand, Princeton, N. J., 1951.

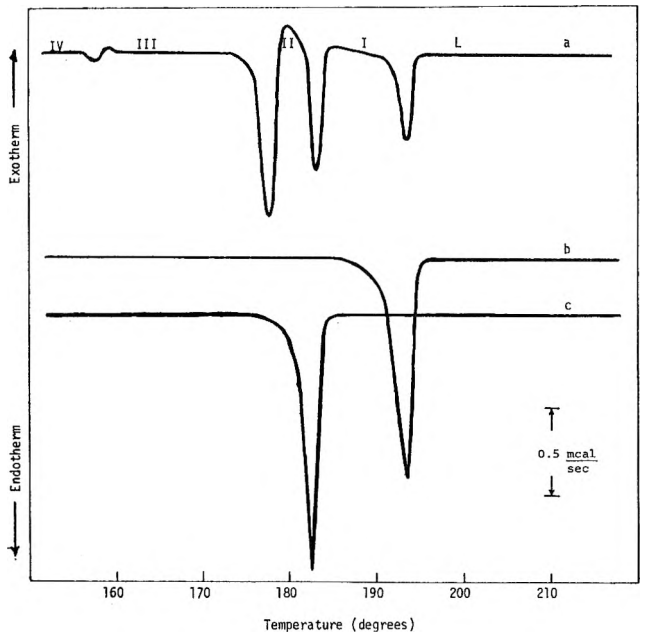

Figure 6.—Dsc of *p*-methoxyphenyl 2-acetamidotri-*O*-acetyl-2-deoxy-β-D-glucopyranoside: a, complete transition from phase IV to the final liquid L; b, fusion of phase I formed after melting of phase II at 183°; c, fusion of phase II formed after melting of phase I at 192°.

the other hand, crystallization from ethanolic solutions always gives the metastable form even when the solution is seeded with the stable form.

The transitions of *p*-methoxyphenyl 2-acetamidotri-*O*-acetyl-2-deoxy-β-D-glucopyranoside (Figure 5c) are more complex and involve crystalline phases of IV to I and the final liquid phase L. Figure 6 shows a more detailed dsc analysis of these transitions, when the heating rate is 5°/min instead of 15°/min employed in the previous experiments. Under this condition, the successive transitions (phases IV to L) of a sample that has not been heated before show more pronounced exotherms (compare Figure 6a with Figure 5c). This phenomenon indicates that crystallization of the new forms, which is an exothermic process, is more complete when the sample is heated slowly. Figure 6b shows the melting endotherm at 192° for a sample that has been previously melted at 183° and recrystallized in phase I.

It is interesting to note that cooling and recrystallization of the final liquid phase L, formed on melting at 192°, gives phase II rather than phase I. Figure 6c shows the melting endotherm at 183° for a sample of phase II which is formed after the fusion of phase I at 192°. However, recrystallization from aqueous methanol at 0° gives IV and at room temperature gives a mixture of III and IV crystalline forms.

Another type of polymorphism is observed for phenyl β-D-xylopyranoside[6] and *p*-bromophenyl and *p*-iodophenyl 2-acetamidotri-*O*-acetyl-2-deoxy-β-D-glucopyranosides.[8] The transitions of these compounds are signaled by the minor endotherms shown in Figure 7. Unlike the previous cases of monotropic polymorphism, these transitions are readily reversible on cooling. The enthalpy and entropy of the transition and fusion of these compounds measured by dsc are given in Table IV. According to these data, the entropy of transition, ΔS_t (0.37–1.5 eu), is considerably smaller than the

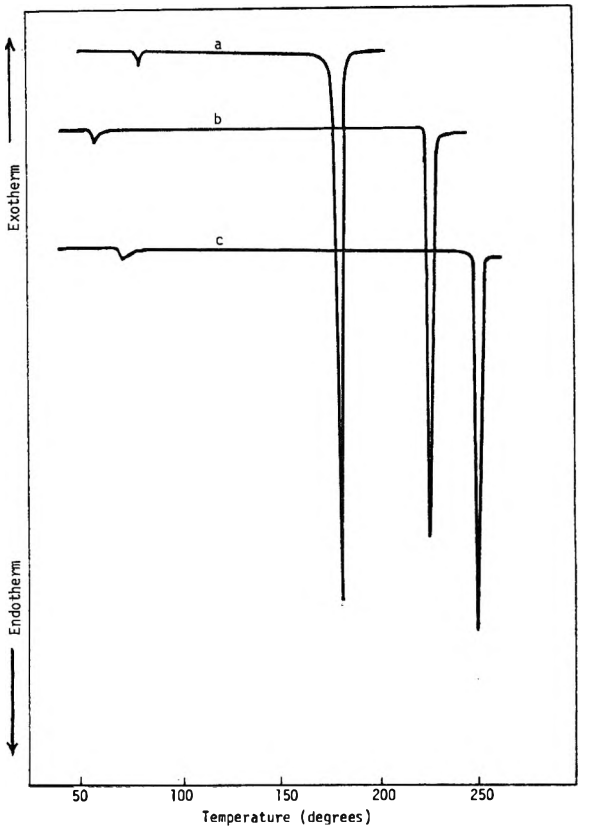

Figure 7.—Dsc of polymorphic glycosides: a, phenyl β-D-xylopyranoside; b, *p*-bromophenyl 2-acetamidotri-*O*-acetyl-2-deoxy-β-D-glucoside; c, 3, *p*-iodophenyl 2-acetamidotri-*O*-acetyl-2-deoxy-β-D-glucoside.

TABLE IV

THERMODYNAMIC FEATURES OF THE ENANTIOTROPIC TRANSITION AND FUSION OF PHENYL GLYCOSIDES

Compd	T_t, °C	ΔH_t, kcal/mol	ΔS_t, cal/mol deg	T_f, °C	ΔH_f, kcal/mol	ΔS_f, cal/mol deg
Phenyl β-D-xyloside	81	0.13	0.37	181	7.47	16.5
p-Bromophenyl 2-acetamido-2-deoxy-β-D-glucoside triacetate	61	0.51	1.5	229	10.7	21.4
p-Iodophenyl 2-acetamido-2-deoxy-β-D-glucoside triacetate	72	0.47	1.4	253	12.9	24.5

entropy of fusion, ΔS_f (16.5–24.5 eu), indicating minor changes in the solid state. As noted before, the situation is reversed for the plastic crystal phase transition, which involves major changes of entropy on transition.[16] These considerations point out to an enantiotropic inversion,[21] involving the reversible transition of two stable crystalline forms.

Experimental Section

Dynamic Thermal Analysis.—The dta and dsc scans were obtained with a Du Pont 990 thermal analyzer and calorimeter cell programmed at 5 or 15°/min. These experiments were carried out with a 2-mg sample in a nitrogen atmosphere. The ΔH determinations were made on a Perkin-Elmer DSC-1B instrument

calibrated against the heat of fusion of indium at 156.6°, ΔH_f = 6.75 cal/g.

X-Ray Diffraction.—The X-ray powder diffraction spectra were obtained with a North American Philips Co. diffractometer and a recording geiger counter using Cu Kα radiation. Different crystalline forms were obtained by crystallization from solvent or controlled heating in the thermal analysis equipment. Lightly ground samples of each form (~10 mg) were scanned at 1° 2 θ min^{-1}. More severe grinding was avoided to prevent possible distortion of the soft crystals and decreased resolution of the pattern. The d spacing in Å (with relative intensity in parentheses) is given in Tables I–III for the most intense lines.

Acknowledgment.—The authors thank the National Science Foundation for supporting this work under the RANN Program, Grant No. GI-33645x.

Registry No.—Phenyl β-D-glucopyranoside, 1464-44-4; trehalose, 99-20-7; 1,6-anhydro-β-D-altropyranose, 10339-41-0; *p*-methoxyphenyl β-D-glucopyranoside, 6032-32-2; phenyl 2-acetamidotri-*O*-acetyl-β-D-glucopyranoside, 13089-21-9; *p*-methoxyphenyl 2-acetamidotri-*O*-acetyl-β-D-glucopyranoside, 38229-72-0; phenyl β-D-xyloside, 4756-31-4; *p*-bromophenyl 2-acetamido-2-deoxy-β-D-glucoside triacetate, 38229-74-2; *p*-iodophenyl 2-acetamido-2-deoxy-β-D-glucoside triacetate, 38229-75-3.

Stereochemistry of the Exhaustive Methylation of Alcohols with Trimethylaluminum

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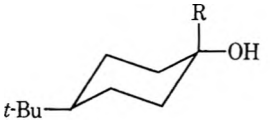
Exhaustive methylation of the pair of epimeric 4-*tert*-butyl-1-cyclohexanols with 1-ethyl and 1-vinyl substituents using trimethylaluminum proceeds with the loss of stereochemistry at the new quaternary carbon center. Axial and equatorial cyclohexanols give the same mixture of axially and equatorially methylated products with a preference for axial methylation. Methylation occurs *via* a common intermediate, which is not the olefin (the major side product of exhaustive methylation), since separate experiments show that methylalumination of olefin is not important under reaction conditions. A carbonium ion pair intermediate containing an oligomeric aluminum oxide counterion is proposed. Under forcing conditions, methylalumination of the olefins occurs with a strong preference for equatorial methylation. Exhaustive methylation of the allylic cyclohexanols proceeds with predominant rearrangement. Unrearranged products are formed nonstereospecifically as with the saturated analog. However, a common allylic carbonium ion intermediate cannot alone account for all the products.

Exhaustive methylation of tertiary alcohols given in eq 1 can be achieved with trimethylaluminum.[1] Since

$$R_3COH \xrightarrow{(CH_3)_3Al} R_2CCH_3 \qquad (1)$$

the quaternization of carbon centers is a useful synthetic objective, we examined the stereochemistry of the replacement of the hydroxyl function by a methyl group in the stereoisomeric alcohols, *cis*- and *trans*-4-*tert*-butyl-1-ethylcyclohexanol (**1c** and **1t**)[2] and *cis*- and *trans*-4-*tert*-butyl-1-vinylcyclohexanol (**2c** and **2t**).[3]



1t, R = C_2H_5
2t, R = C_2H_3

1c, R = C_2H_5
2c, R = C_2H_3

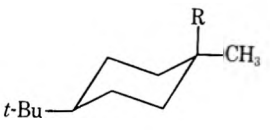
Results

Each of the *tert*-butyl-substituted cyclohexanols (ROH) reacted vigorously with trimethylaluminum (TMA) on mixing at room temperature to afford a mixture of alkoxydimethylalanes and methane (eq 2).

$$ROH + (CH_3)_3Al \longrightarrow ROAl(CH_3)_2 + CH_4 \qquad (2)$$

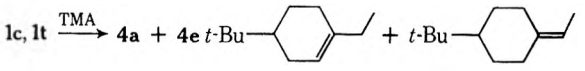
Heating the benzene solution of the alkoxydimethylalanes with a threefold excess of trimethylaluminum and a small amount of water in sealed tubes afforded the expected methylated products as a mixture of cis and trans isomers. Significant amounts of elimination

4a, R = C_2H_5
7a, R = C_2H_3

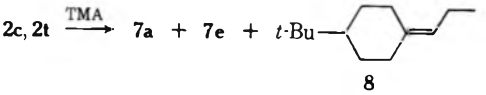


4e, R = C_2H_5
7e, R = C_2H_3

products **5** and **6** shown in eq 3 were also formed. The

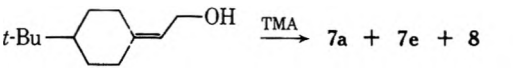


(3)



(4)

allylic isomer of **2c** and **2t**, the cyclohexylidene alcohol **3**, also afforded in eq 5 the same products as those



(5)

derived from **2c** and **2t**, although in different isomeric ratios, as shown in Table I.

The structures of the axial and equatorial methylation products (**4a** and **4e**) were assigned by an analysis of the nmr spectra of isolated samples. The C-1 methyl resonance (δ 0.77) in **4e** appears at higher field than the corresponding methyl resonance (δ 0.80) in **4a** owing to steric deshielding of the axial methyl by the axial 3 and 5 hydrogens.[4] These assignments were confirmed by

(1) A. Meisters and T. Mole, *J. Chem. Soc., Chem. Commun.*, 595 (1972).
(2) G. D. M. Meakins, R. K. Percy, E. E. Richards, and R. N. Young, *J. Chem. Soc. C*, 1106 (1968).
(3) R. J. Ouellette, K. Liptak, and G. E. Booth, *J. Org. Chem.*, **31**, 546 (1966).
(4) G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists," Wiley-Interscience, New York, N. Y., 1972, p 43.

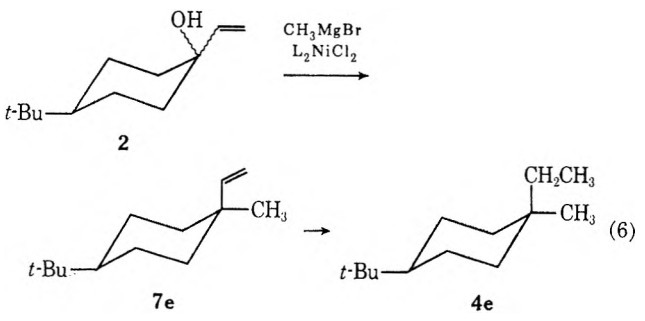
TABLE I

EXHAUSTIVE METHYLATION OF *tert*-BUTYLCYCLOHEXANOLS

Reactant	Temp, °C	Methylation products, Relative yield, % 4a	4e	8	Overall yield, %	Elimination products yield, % 5 + 6
1c[a]	150	70	30		49	34
1t[b]	150	67	33		14	16
		7a	7e	8		
2c	150	6	7	88	23	
	115	11	11	78	32	
2t	150	6	7	87	29	
	115	11	12	77	30	
3	115	3	80	17	75	

[a] Average of six runs. [b] Average of three runs.

an independent synthesis of **4e** by hydrogenation of the corresponding olefin (**7e**), the major product[5] of



exhaustive methylation of a mixture of the epimeric alcohols (**2**)[6] with methylmagnesium bromide in the presence of bis(triphenylphosphine)nickel dichloride.[7] The elimination products 4-*tert*-butyl-1-ethylcyclohexene (**5**) and 4-*tert*-butyl-1-ethylidenecyclohexane (**6**) were identified by comparison with authentic samples,[8] as were the methylation products **7a**, **7e**, and **8**.[5]

The overall yields from the saturated alcohols **1c** and **1t** varied considerably from run to run, but the product ratios of **4a** and **4e** were reasonably constant. The unreacted alcohol accounted for the remainder of the material balance shown in Table I and was recovered unisomerized from each epimer.

Heating of either 4-*tert*-butyl-1-ethylidenecyclohexane (**6**) or 4-*tert*-butyl-1-ethylcyclohexene (**5**) with 1 equiv of dimethyl methyoxyaluminate and excess trimethylaluminum in benzene at 175° for 60 hr gave mostly unreacted olefin and less than 3% of a mixture of **4e** and **7e**. No trace of **4a** was detected in the reaction mixtures.

(5) (a) M. Joly-Goudket, Thesis, University of Paris-Sud Centre d'Orsay, 1972. (b) These structural assignments were based on the synthesis of **7a** and **7e** from the corresponding 4-*tert*-butyl-1-methylcyclohexylacetic acids whose structures were established (C. Amsterdamsky, Thesis, Universite de Paris-Sud Centre d'Orsay, 1969) by the Barbier–Wieland degradation to the corresponding methyl 4-*tert*-butyl-1-methylcyclohexanecarboxylates, since the axial acid, *cis*-4-*tert*-butyl-1-methylcyclohexanecarboxylic acid, was known [H. O. House and T. M. Bare, *J. Org. Chem.*, **33**, 943 (1968)]. In addition, it was shown that the methyl ester of the equatorial acid is saponified much more readily than the hindered axial epimer. These esters also exhibit infrared bonds characteristic of equatorial (1253 cm^{-1}) and axial (1170, 1195, 1220 cm^{-1}) esters [*cf.* M. Fetizon and S. Bory, *Bull. Soc. Chim. Fr.*, 570 (1964)].

(6) K. W. Egger and A. T. Cocks, *J. Amer. Chem. Soc.*, **94**, 1810 (1972), and references cited therein.

(7) C. Chuit, H. Felkin, C. Frajerman, G. Roussi, and G. Swierczewski, *Chem. Commun.*, 1604 (1968).

(8) (a) E. J. Corey and G. T. Kwiatkowski, *J. Amer. Chem. Soc.*, **88**, 5652 (1966); (b) D. J. Pasto and F. M. Klein, *J. Org. Chem.*, **33**, 1468 (1968).

Discussion

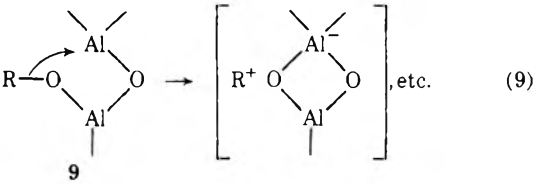
Exhaustive methylation of the stereoisomeric saturated tertiary alcohols **1c** and **1t** affords methylation products **4e** and **4a** by a nonstereospecific substitution. A mechanism which incorporates a common intermediate such as a carbonium ion would accommodate the experimental results. The axial alcohol **1c** is more reactive than the equatorial isomer **1t**, and suggests that acceleration due to release of steric strain accompanies a rate-determining cleavage of the C–O bond. Preferential delivery of the methyl group to the resulting tertiary cyclohexyl carbonium ion intermediate from the axial direction is preferred, since torsional interactions of the ethyl substituent with the equatorial hydrogens on C-2 and C-6 (which develop during equatorial bond formation) hinder "equatorial" delivery of a methyl group.[9] In addition, the counterion in an ion-pair intermediate (*vide infra*) could shield one side of the cyclohexane ring. The "equatorial" ion pair would be favored over the more sterically congested "axial" ion pair, resulting in preferential shielding of the "equatorial" side of the cyclohexane ring.

It was previously noted that the temperature and the time required for exhaustive methylation may be lowered significantly by the addition of a few mole per cent of water.[1] This observation could indicate the formation of oxygen-bridged polynuclear aluminum alkoxides such as **9**, as reactive intermediates in the following manner.

$$ROAl(CH_3)_2 + H_2O \longrightarrow ROAl(CH_3)OH + CH_4 \quad (7)$$

$$ROAl(CH_3)OH + (CH_3)_3Al \xrightarrow{-CH_4} \underset{\mathbf{9}}{ROAl(CH_3)OAl(CH_3)_2}, \text{ etc.} \quad (8)$$

The lack of epimerization of the aluminum alkoxides during the reaction indicates that C–O bond cleavage is irreversible. Thus, if the reaction involves heterolysis of the C–O bond, the resulting oxyanion must be a relatively poor nucleophile. The effect of water as well as the nonnucleophilicity of the postulated anionic aluminum oxide leaving group would be explained by the concerted (anchimerically assisted) formation of a polynuclear aluminum anion.[10] from an oxygen-bridged polynuclear aluminum alkoxide as shown in eq 9. Thus, instead of forming an oxy anion by simple

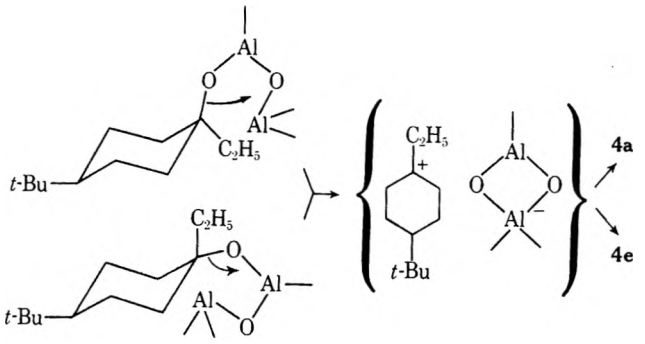


C–O heterolysis, a neighboring aluminum atom may act as an internal Lewis acid catalyst. The sequestering of the oxygen atoms of the resulting aluminum

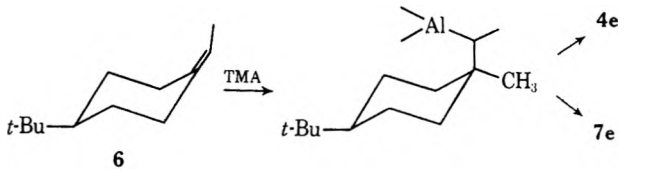
(9) (a) F. R. Jensen, L. H. Gale, and J. E. Rodgers, *J. Amer. Chem. Soc.*, **90**, 5793 (1968); (b) S. D. Elakovich and J. G. Traynham, *J. Org. Chem.*, **38**, 873 (1973).

(10) (a) The partial structure indicated in the scheme for this anion is only one of many possibilities. The actual structure may even be polymeric and several structurally different species may be involved. (b) Alternatively, Dr. E. C. Ashby has kindly suggested ionization of the dimer, *e.g.*, $[ROAl(CH_3)_2]_2 \rightleftharpoons R^+ + OAl_2(CH_3)_4OR^-$, etc.

oxide anion by chelation would lead to their diminished nucleophilic reactivity.



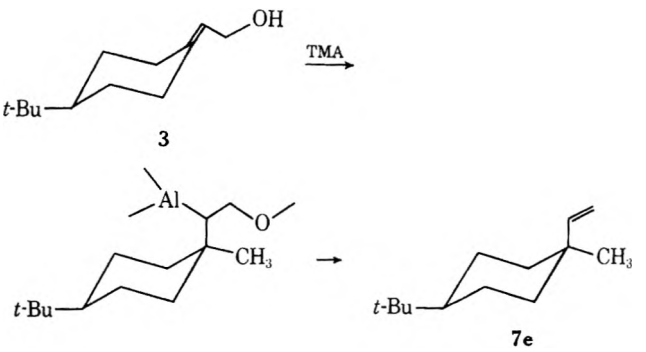
Olefins **5** and **6** are the major side products of the exhaustive methylation reaction. The possibility that methylation of **1c** and **1t** might proceed indirectly *via* methylalumination of **5** and **6** was examined. Under the conditions of the exhaustive methylation (*i.e.*, 150°) no reaction was detected. Under more forcing conditions (*i.e.*, 175°), a low yield of **4e** but no **4a** was observed. A small amount of **7e** was also formed,



6

presumably by dehydroalumination of an alkylaluminum intermediate. Methylalumination of **5** and **6** must vary in importance during the course of the exhaustive methylation, being favored at higher temperatures and as the concentrations of these olefins build up.

Both stereoisomeric allylic alcohols (**2c** and **2t**) produce the same relative yields of unrearranged quaternary methylation products (**7a** and **7e**). As with the saturated analogs, the lack of stereospecificity suggests a common intermediate prior to the formation of these products. The relative yield of **7a** and **7e** from the exhaustive methylation of the alcohol **3** is much different from that observed from the alcohols **2c** and **2t**. Moreover, exhaustive methylation of the allylic alcohols **2c**, **2t**, and **3** proceeds with predominant allylic rearrangement. A common intermediate from **2c**, **2t**, and **3**, such as an allylic carbonium ion, cannot alone account for all of the products. The preferential formation of the equatorially methylated **7e** from the hydroxyethylidenecyclohexane **3** is reminiscent of the preferential formation of **4e** by methylalumination of the ethylidenecyclohexane **6**. A preference for "equatorial" methylalumination of **3** or **6** is expected since "axial" methylalumination would be sterically hindered by axial hydrogens. Neighboring heteroatoms are known to facilitate alkylmetalation of olefins.[11] Thus methylalumination of **3** followed by elimination is a reasonable mechanism for production of **7e**. A similar mechanism may be operative for the production of **8** from **2c** or **2t**. Other mechanisms, such as SN2′ or SNi processes, may also be operative.



3 **7e**

Experimental Section

Materials.—Trimethylaluminum was obtained from the Ethyl Corp. and used as such. The stereoisomeric alcohols *cis*- and *trans*-4-*tert*-butyl-1-ethylcyclohexanol (**1c** and **1t**) and *cis*- and *trans*-4-*tert*-butyl-1-vinylcyclohexanol (**2c** and **2t**) were prepared by known procedures.[2,3] 4-*tert*-Butyl-1-(2′-hydroxyethylidene)-cyclohexane (**3**) was prepared by the lithium aluminum hydride reduction of ethyl-4-*tert*-butylcyclohexylidene acetate.[12]

Preparative gas chromatography (vpc) was carried out with a Varian A-90 chromatograph. Analytical vpc utilized a Varian Hy Fi instrument. Trimethylaluminum was vacuum transferred into a cooled receiver. Benzene was distilled from sodium benzophenone ketyl under nitrogen. Nmr spectra were recorded with a Varian A-60 spectrometer. Mass spectra were measured with a Varian CH7 instrument. Microanalyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich.

Exhaustive Methylation.—The appropriate alcohol (200 mg, 1.09 mmol) was combined with a solution of trimethylaluminum in benzene (1.4 ml of a 3 *M* solution) with judicious cooling. Water (2 μl) was added cautiously and the mixture was sealed in a heavy-walled glass tube (about 20 ml volume). The mixture was then heated in a steel bomb using benzene as an external solvent for pressure equalization. The reaction mixture was cooled with liquid nitrogen and carefully opened (methane produced). After dilution with pentane (50 ml) followed by hydrolysis with 5% hydrochloric acid (20 ml), the clear pentane extract was washed with saturated aqueous $NaHCO_3$, dried with $MgSO_4$, and concentrated by distillation of the solvent through a 20-cm Vigreux column. Product yields from **1c** and **1e** were determined (after addition of *n*-tetradecane as internal standard) by vpc on a 10 ft × 0.125 in. column packed with 20% FFAP on 60/80 AW Chromosorb W. Relative retention times follow: **4e**, 0.73; **4a**, 0.79; **6**, 0.87; **5**, 0.90; *n*-tetradecane, 1.00. Products were isolated by vpc on a 10 ft × 0.25 in. column packed with Apiezon J on firebrick at 160°, on which the olefins **5** and **6** have shorter retention times than the hydrocarbons **4e** and **4a**. The sample of **4e** thus obtained was further purified by vpc on 9 ft × 0.25 in. column packed with 15% FFAP on Chromosorb W. The products **4e**, **5**, and **6** were identified by comparison with authentic samples. In addition, **4e** and **4a** were characterized by elemental analysis.

4-*tert*-Butyl-*cis*-1-ethyl-*trans*-1-methylcyclohexane (4e).—*Anal.* Calcd for $C_{13}H_{26}$: C, 85.63; H, 14.37. Found: C, 85.76; H, 14.27.

4-*tert*-Butyl-*trans*-1-ethyl-*cis*-1-methylcyclohexane (4a).—*Anal.* Calcd for $C_{13}H_{26}$: C, 85.63; H, 14.37. Found: C, 85.74; H, 14.42.

Product yields from **2c**, **2t**, and **3** were determined (after addition of *n*-pentylbenzene as internal standard) by vpc on the above FFAP column. Relative retention times follow: **7e**, 0.53; **7a**, 0.62; **8**, 0.82; *n*-pentylbenzene, 1.00. The mass spectra of these products as well as their vpc retention times were identical with those of authentic samples prepared by known procedures.[5]

4-*tert*-Butyl-*trans*-1-methyl-*cis*-1-vinylcyclohexane (7e).—The title compound was prepared by bis(triphenylphosphine)nickel(II) dichloride catalyzed exhaustive methylation of a mixture of *cis*- and *trans*-4-*tert*-butyl-1-vinylcyclohexanols (**2**)[6] with methyl-

(11) (a) J. K. Crandall, and A. C. Clark, *J. Org. Chem.*, **37**, 4236 (1972), and references cited therein. (b) A. H. Veefkind, J. v. d. Schaff, F. Bickelhaupt, and G. W. Klumpp, *Chem. Commun.*, 722 (1971), and references cited therein.

(12) H. O. House, W. L. Respess and G. M. Whitesides, *J. Org. Chem.*, **31**, 3128 (1966).

magnesium bromide.[7] Distillation of the product mixture under reduced pressure yielded a sample of the title compound (**7e**) as the major component of the reaction mixture (about 90% pure), bp 74–76° (0.6 mm).[5]

Hydrogenation of the Olefin 7e.—The olefin was stirred under a blanket of hydrogen in methyl acetate solution with a suspension of 5% Pd/C to afford a hydrocarbon whose nmr spectrum and vpc retention time were identical with that of the equatorially methylated isomer **4e**.

Methylalumination of 5 and 6.—The olefins **5** or **6** plus 1 equiv of methanol were substituted for the tertiary alcohols in the exhaustive methylation procedure described above. A component of the reaction mixture in each case had a vpc retention time identical with that of **4e** and **7e**. The mass spectrum of this component resembled that obtained by the superposition of spectra of authentic samples of **4e** and **7e**.

4-*tert*-Butyl-1-(2′-hydroxyethylidene)cyclohexane (3).—Ethyl-4-*tert*-butylcyclohexylidene acetate[3] was reduced in the usual manner with $LiAlH_4$ in ether, giving **3**, bp 82–83° (0.4 mm), in 86.4% yield.

Anal. Calcd for $C_{12}H_{22}O$: C, 79.06; H, 12.16. Found: C, 78.97; H, 12.21.

Acknowledgment.—We wish to thank the National Science Foundation for financial support of this work, the Ethyl Corporation for a gift of trimethylaluminum, and Dr. Hugh Felkin for results concerning the vinyl alcohols (**2a** and **2e**) and methyl derivatives (**7a** and **7e**) prior to publication.

Registry No.—**1c**, 17328-78-8; **1t**, 25143-76-4; **2c**, 7103-35-7; **2t**, 7103-36-8; **3**, 41498-18-4; **4a**, 41498-76-4; **4e**, 41498-77-5; **7e**, 41498-78-6; trimethylaluminum, 75-24-1; methyl bromide, 74-83-9.

Preparation of Organometallic Complexes by Reduction of Magnesium Alkyls with Alkali Metals

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Received March 7, 1973

The reduction of dialkylmagnesium compounds in hydrocarbon solution by alkali metals was studied and found to yield organometallic complexes of definite stoichiometries involving magnesium and alkali metals. In most cases, the reduction appeared to occur according to the stoichiometry below, *i.e.*, a 1:1 complex was formed: $2M + 3R_2Mg \rightarrow 2R_3MgM + Mg\downarrow$. Lithium reacted to form both the 1:1 complex and a 3:1 complex, R_5MgLi_2. Results with sodium were not so straightforward, but it appeared that this metal reduced dialkylmagnesium compounds to form a 1:2 complex (R_5Mg_2Na) as well as the 1:1 complex. Potassium, rubidium, and cesium also reduced dialkylmagnesium compounds to yield 1:1 complexes. These intermetallic reagents are viewed as complexes between alkali metal alkyls and magnesium alkyls; this complex formation solubilizes and stabilizes the alkali metal alkyls. The latter compounds, with the exception of lithium alkyls, had previously been known only as insoluble, relatively unstable species. A structure for the hydrocarbon-soluble 1:1 complexes was proposed in which a di-*sec*-butylmagnesium unit in the di-*sec*-butylmagnesium dimer is replaced by an organoalkali compound.

In 1951 Wittig,[2] Meyer, and Lange reported that reaction of diphenylmagnesium and phenyllithium resulted in the formation of a 1:1 complex in ether (eq 1). After the addition of xylene, the complex

$$PhLi + Ph_2Mg \longrightarrow Ph_3MgLi \quad (1)$$

precipitated as a crystalline compound, mp 212°. Recently there has been considerable interest in the preparation of additional examples of intermetallic complexes involving magnesium and alkali metals illustrated for the general case with magnesium in eq 2, where R is alkyl, aryl, or hydrogen and M is alkali metal.

$$nR_2Mg + RM \longrightarrow [R_2Mg]_n \cdot [RM] \quad (2)$$

The preparation of "lithium *n*-butyldimethylmagnesium" complex was reported by Coates and Heslop.[3] Removal of solvent after reaction of *n*-butyllithium with dimethylmagnesium in diethyl ether yielded a viscous liquid of stoichiometry [*n*-BuLi]·[Me_2Mg]·[OEt_2]. Coates and Heslop also attempted to prepare alkali metal–alkylmagnesium hydride complexes analogous to $NaEt_2BeH$[4] and $NaH \cdot 2Et_2Zn$.[5] These attempts were unsuccessful owing to cleavage of the solvent ether by the alkali metal hydride.

More recently, Ashby and Arnott[6] have reported the preparation and characterization of several complexes between alkali metal hydrides and dialkylmagnesium compounds. Their initial attempts to prepare these species by reaction of magnesium alkyls in ether with alkali metal hydrides resulted in extensive ether cleavage, consistent with the results of earlier work by Coates and Heslop.[3] However, Ashby and Arnott were able to isolate one stable complex from an ether solution by reaction of diphenylmagnesium with potassium hydride at room temperature. The complex precipitated from the ethereal reaction mixture and analysis showed it to be $KH \cdot 2Ph_2Mg$. By reaction of the hydrocarbon-soluble di-*sec*-butylmagnesium[7] with solid potassium hydride, a relatively stable solution of a 1:1 complex was obtained which was soluble in cyclohexane and benzene. Reaction of sodium hydride with di-*sec*-butylmagnesium resulted in the formation of [NaH]·2[*sec*-Bu_2Mg], but lithium hydride would not react.

Seitz and Brown[8] have studied organometallic exchange reactions by lithium-7 and proton nuclear magnetic resonance, and have reported that alkyllithium

(1) Correspondence should be addressed to D. B. Malpass, Texas Alkyls, Inc., P. O. Box 600, Deer Park, Texas 77536.

(2) G. Wittig, F. J. Meyer, and G. Lange, *Justus Liebigs Ann. Chem.*, **571**, 167 (1951).

(3) G. E. Coates and J. A. Heslop, *J. Chem. Soc. A*, 514 (1963).

(4) G. E. Coates and G. F. Cox, *Chem. Ind. (London)*, 269 (1962).

(5) W. E. Becker and P. Kobetz, *Inorg. Chem.*, **2**, 859 (1963).

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compounds form complexes with dialkylmagnesium compounds in ether, as in eq 3, in which n = 1, 2, or 3 depending on the nature of the R groups.

$$n\text{RLi} + \text{R}_2\text{Mg} \longrightarrow [\text{RLi}]_n \cdot [\text{R}_2\text{Mg}] \quad (3)$$

We wish to report the preparation of organometallic complexes involving alkali metal and magnesium by direct reaction of magnesium alkyls with alkali metals.

Results and Discussion

The reduction of dialkylmagnesium compounds with alkali metals has been studied. Dispersions of the alkali metals in excess were stirred with hydrocarbon solutions of di-*n*-butylmagnesium, di-*sec*-butylmagnesium, and di-*tert*-butylmagnesium; a limited amount (2–3%) of ether was present with the di-*n*-butylmagnesium reagent. Periodically the supernatant solutions were analyzed for total base, magnesium, and alkali metal. In every case it was apparent that the magnesium alkyl was being reduced; the black, amorphous metal appeared as a precipitate in the reaction mixture. However, also in every case, it appeared that this reduction either stopped or markedly slowed after an intermetallic complex of some specific stoichiometry was formed, generally with no more than one alkali metal atom per atom of magnesium, *e.g.*, as in eq 4. An organoalkali compound is a likely

$$3\text{R}_2\text{Mg} + 2\text{M} \longrightarrow 2\text{R}_3\text{MgM} + \text{Mg}\downarrow \quad (4)$$

intermediate in the overall reaction, resulting from reduction or "metal–metal" exchange (eq 5). The

$$\text{R}_2\text{Mg} + 2\text{M} \longrightarrow 2\text{RM}\downarrow + \text{Mg}\downarrow \quad (5)$$

organoalkali compound (RM) generated *in situ* is complexed by unreacted dialkylmagnesium reagent (eq 6).

$$\text{R}_2\text{Mg} + \text{RM} \longrightarrow \text{R}_3\text{MgM} \quad (6)$$

Reaction of a large excess of lithium metal with a hydrocarbon–ether solution of di-*n*-butylmagnesium resulted in formation of a solution with a lithium:magnesium ratio of 1 and with no loss of total base, as would be expected for the 1:1 complex formation illustrated in eq 4. The lithium:magnesium ratio in the solution was unity within 9 hr of reaction at 25° and remained constant at about this value for at least 22 hr of contact with excess dispersed lithium. However, it did appear to slowly change (increase) so that after 45 hr of reaction a solution containing a 1.5:1 ratio of lithium to magnesium was produced, giving evidence that complexes with more lithium than magnesium content are formed. Better evidence for such complexes was obtained in the lithium metal reduction of di-*sec*-butylmagnesium solution, when a 3:1 ratio of the metals was formed in the solution as in eq 7.

$$5(\textit{sec}\text{-Bu})_2\text{Mg} + 3\text{Li} \longrightarrow 2(\textit{sec}\text{-Bu})_5\text{MgLi}_3 + 3\text{Mg}\downarrow \quad (7)$$

The ratio of lithium:magnesium in the reaction of di-*sec*-butylmagnesium with lithium remained constant at 3 from 20 to 35 hr of reaction, but it also increased gradually after this time. Conceivably, a magnesium alkyl could be reduced all the way to a lithium alkyl with sufficient reaction time, but there can be little doubt that formation of specific intermetallic complexes results in a greatly reduced reactivity of the magnesium reagent and a consequent inhibition of further reduction.

Findings made with the intermetallic complexes between the lithium and magnesium alkyls, namely, that stable solutions of complexes could be produced, were not surprising, considering the known solubility and stability of lithium reagents themselves. Greater interest in initiating this study came from considering whether stable solutions involving potassium and other alkali metal alkyls could be produced, for the organic derivatives of these metals are known to be insoluble and unstable.[9] Thus, it was not unexpected that, in the first experiments involving treatment of cyclohexane solutions of di-*sec*-butylmagnesium with dispersions of potassium metal, all active alkyl disappeared from solution in less than 1 hr at 80°. Reduction did occur, with the typical appearance of black amorphous magnesium precipitate. The evidence suggests that a cyclohexane-insoluble 1:1 complex, tri-*sec*-butylmagnesiumpotassium, was formed according to eq 8. For ex-

$$3\text{R}_2\text{Mg} + 2\text{K} \longrightarrow 2\text{R}_3\text{MgK} + \text{Mg}\downarrow \quad (8)$$

ample, a solution of di-*sec*-butylmagnesium was refluxed with potassium metal for 1 hr, after which essentially all total base had disappeared from solution. After removal of the cyclohexane, benzene was added and the mixture was stirred briefly. The supernatant benzene was then found to contain total base, magnesium, and potassium in the ratio 2.9:1.0:0.9. The conclusion is that the 1:1 complex is precipitated from cyclohexane, but it dissolved in benzene. Solutions of tri-*sec*-butylmagnesiumpotassium in benzene are not stable at room temperature for more than a few days. Cold storage (2–4°) inhibits the decomposition process, but even under these conditions the complex slowly decomposes owing to metalation of the solvent.

Observations with reduction of di-*n*-butylmagnesium were somewhat different, primarily owing to the presence of a small amount (approximately 2–3%) of diethyl ether necessary to keep the magnesium alkyl in cyclohexane solution. The diethyl ether tended to hold this complex in the initial cyclohexane solution, so that as reduction occurred, not all of the total base would precipitate. When the solids from one of those products were treated with a solution of benzene–diethyl ether, the resultant supernatant solution was shown to contain total base, magnesium, and potassium in the ratio 1.0:1.0:1.0.

In order to make a trialkylmagnesiumpotassium reagent conveniently available for study, some effort was expended in developing a more direct synthesis of this type of compound, *i.e.*, one that did not involve prior formation of the pure magnesium alkyl. Grignard reagents, or magnesium alkyls still containing some chloride, are simpler to prepare than pure alkyls. In a preliminary experiment, a magnesium reagent solution containing the equivalent of 1 mol of Grignard reagent (*n*-BuMgCl) per mole of magnesium alkyl (*n*-Bu_2Mg), *i.e.*, the equivalent of *n*-$\text{Bu}_3\text{Mg}_2\text{Cl}$, was treated with potassium metal. Reduction did occur as in eq 9, yielding a solution of the tri-*n*-butyl-

$$n\text{-Bu}_3\text{Mg}_2\text{Cl} + 2\text{K} \longrightarrow n\text{-Bu}_3\text{MgK} + \text{Mg}\downarrow + \text{KCl}\downarrow \quad (9)$$

(9) G. E. Coates and K. Wade, "Organometallic Compounds," Vol. 1, 3rd ed, Methuen and Co., London, 1967, p 42.

magnesiumpotassium reagent free of chloride and with a potassium:magnesium ratio of 1.0.

It seemed likely that even magnesium chloride should be reduced by potassium, as represented in eq 10,

$$MgCl_2 + 2K \longrightarrow 2KCl\downarrow + Mg\downarrow \quad (10)$$

so that the final technique evolved for trialkylmagnesiumpotassium preparations was the following "one-pot" synthesis. Starting with *n*-butyl chloride and magnesium in cyclohexane with a limited amount of *N*,*N*,*N'N'*-tetramethylethylenediamine (TMEDA), a mixture of solids and supernatant was obtained containing di-*n*-butylmagnesium and magnesium chloride. Sufficient metallic potassium was then added to this mixture for reaction with both the organometallic product, as in eq 4, and the magnesium chloride, as in eq 10. The overall reaction in the vessel was thus as in eq 11.

$$3RCl + Mg + 4K \longrightarrow R_3MgK + 3KCl \quad (11)$$

Actually, when potassium reduces a mixture of magnesium alkyls and magnesium chloride, it is quite likely that the magnesium chloride is not being reduced directly as in eq 10, but that the following two reactions are occurring in sequence. The sum of eq 12 and 13 is eq 10. After all of the magnesium chloride

$$R_2Mg + 2K \longrightarrow 2RK + Mg \quad (12)$$

$$2RK + MgCl_2 \longrightarrow R_2Mg + 2KCl \quad (13)$$

has been reduced (alkylated), the formation of RK as in eq 12 leads to complex formation as below (eq 14).

$$RK + R_2Mg \longrightarrow R_3MgK \quad (14)$$

Experimental evidence consistent with the above interpretation of the reduction of a mixture of magnesium alkyl and magnesium chloride is the following. This reduction goes to completion in about 2 hr under the conditions developed, *i.e.*, at the end of that time a clear supernatant is formed containing no chloride, a maximum amount of total base, and as many gram-atoms of potassium as of magnesium. However, during the first 1.5 hr of this reduction, no potassium appears in solution, and all chloride disappears from solution. It seems likely that during this first 1.5 hr, only reactions 12 and 13 are occurring; subsequently, only 30 min are required to dissolve the potassium *via* reactions 12 and 14.

Observations with sodium metal reductions of magnesium alkyls were not so straightforward as those with lithium and potassium. With the latter, reduction appeared to go directly and rather rapidly to a 1:1 intermetallic complex and stop, and initially advantage was taken of the fact that precipitation of this complex occurred when di-*sec*-butylmagnesium was reduced in cyclohexane. With sodium the reduction was slower, precipitation did not occur (although phasing of the reduction mixtures sometimes did), and an intermediate 1:2 complex apparently formed, as in eq 15.

$$5R_2Mg + 2Na \longrightarrow 2R_5Mg_2Na + Mg\downarrow \quad (15)$$

During the study of the reaction of sodium with di-*sec*-butylmagnesium in cyclohexane, a phasing of the reaction product was noted; two liquid layers formed. This peculiar phasing is not without precedent. A similar phasing was observed in the reactions of ethylsodium with diethylzinc (eq 16), and the products

$$EtNa + Et_2Zn \longrightarrow Et_3ZnNa \quad (16)$$

from the reaction of alkali metals on diethylzinc (eq 17). The mobile upper phase consisted of a dilute

$$2M + 3Et_2Zn \longrightarrow 2Et_3ZnM + Zn \quad (17)$$

solution of the complex in diethylzinc, and the lower viscous layer consisted of a solution of diethylzinc in the complex. The separation into layers was attributed to the formation of two phases of considerably different polarity and dielectric constant.[10]

The phasing observed in the present study can be interpreted similarly. The two phases after centrifuging are initially clear, but gradually each phase becomes hazy. This is probably due to a dissolution process of the complex in the upper layer. From the analyses of the upper, it appears that the di-*sec*-butylmagnesium is slowly dissolving in the lower layer, which consists mainly of *sec*-butylsodium. When sufficient *sec*-butylsodium is present to form the soluble 1:1 complex, phasing is no longer observed.

Observations made on the reduction of the magnesium alkyls with rubidium were similar in many respects to those with potassium. Thus, when a solution of di-*sec*-butylmagnesium in cyclohexane is treated with rubidium metal, virtually all of the active alkyl is removed from solution and the appearance of the precipitated magnesium metal is evident. Removal of the cyclohexane and addition of benzene results in a reappearance of the active alkyl in solution and equal gram-atoms of rubidium and magnesium in the solution. The conclusion is again that a 1:1 complex is formed which is cyclohexane insoluble but benzene soluble. As with the potassium reagent, tri-*sec*-butylmagnesiumrubidium in benzene is not stable to long term storage owing to the facile metalation of solvent. One to one complexes are also observed when di-*n*-butylmagnesium and di-*tert*-butylmagnesium are reduced by rubidium.

Reductions of dialkylmagnesium reagents with cesium occurred, but the intermetallic complexes formed were found to be less stable and more heat sensitive than those of the other alkali metals. Initial attempts at reducing di-*sec*-butylmagnesium in cyclohexane with cesium at reflux and room temperature resulted in extensive decomposition of the active alkyl in the reaction mixture. At lower temperatures the cesium apparently reduced the di-*sec*-butylmagnesium in the usual manner, although less cesium than magnesium went into the product. In the reduction of di-*sec*-butylmagnesium by cesium, phasing was observed in the reaction product similar to that observed in some of the sodium reductions.

In the reaction of di-*tert*-butylmagnesium with cesium, no phasing was observed but reduction did occur. The product, as in the case of the *sec*-butyl analog, precipitated from cyclohexane but dissolved in benzene. The resultant solution contained a cesium:magnesium ratio of about one.

Table I presents a summary of representative preparations of the intermetallic complexes involving magnesium and alkali metal alkyls. Since organic deriva-

(10) Reference 9, pp 44, 45.

TABLE I

PREPARATION OF INTERMETALLIC COMPLEXES BY REDUCTION OF DIALKYLMAGNESIUM COMPOUNDS

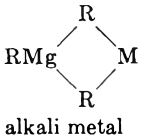
		Reactants		Reaction		Product analysis			
Registry no.	Compd prepared	R_2Mg amount, mol	Alkali metal amount, g-atom	Time, hr	Temp, °C	Total base, N	Mg, M	Alkali metal, M	Alkali metal/Mg
20910-20-7	n-Bu_3MgLi	0.034	0.13	22	25	1.37	0.43	0.45	1.05
39342-44-4	s-Bu_5MgLi_3	0.033	0.13	20	25	0.93	0.16	0.50	3.12[a]
41120-87-0	s-Bu_3MgNa	0.036	0.046	6	80	0.92	0.33	0.26	0.79
41120-88-1	n-Bu_3MgNa	0.022	0.044	2	80	1.12	0.38	0.32	0.84
39342-45-5	n-Bu_6Mg_2Na	0.039	0.052	4	80	1.39	0.58	0.23	0.40[b]
41120-89-2	n-Bu_3MgK[c]	0.021	0.021	7.5	80	0.81	0.27	0.27	1.00
	n-Bu_3MgK[d]	0.035	0.200	2	80		0.20	0.20	1.00
41120-90-5	s-Bu_3MgK	0.040	0.045	1	80	1.09	0.36	0.33	0.92
41120-91-6	n-Bu_3MgRb[c]	0.012	0.012	20	25	0.83	0.28	0.29	1.04
	n-Bu_3MgRb[d]	0.065	0.059	14	25		0.34	0.34	1.00
41120-92-7	s-Bu_3MgRb	0.012	0.012	1.3	0	0.61	0.21	0.19	0.91
41120-93-8	t-Bu_3MgRb	0.006	0.012	2	0	0.19[e]	0.06	0.07	1.17
41120-94-9	s-Bu_3MgCs	0.0075	0.0075	2.5	0	0.30	0.12	0.09	0.73
41120-95-0	t-Bu_3MgCs	0.0055	0.0075	1.5	0	0.27[f]	0.08	0.09	1.13

[a] Ratio was 3.13 after 35 hr of reaction time. [b] Ratio was 0.58 after 18 hr of reaction time. [c] Complex prepared with di-n-butylmagnesium in cyclohexane–diethyl ether (98:2) solution. [d] Complex prepared with di-n-butylmagnesium in cyclohexane–TMEDA solution. [e] After 20 hr of standing at ambient temperature, solution had fallen to 0.01 N in total base. [f] After 20 hr of standing at ambient temperature, solution had fallen to 0.07 N in total base.

tives of the alkali metals (other than lithium) in the past have been observed to be unstable, insoluble species,[9] the significance of the present work is that hydrocarbon-soluble, relatively stable derivatives of these alkali metal reagents have been obtained. In the case of the n-butyl reagents, some of the solutions contained ether and it is even more surprising that this ether did not cause rapid reaction (decomposition) of the potassium reagents.

Besides the analysis of the supernatants for total base, magnesium, and alkali metal, an auxiliary method for monitoring the reactions was to follow the chemical shift of the protons on the carbon α to the metal. As the reaction progressed, the chemical shift (measured from benzene internal standard) of these protons moved to higher field. For example, in one of the "one-pot" syntheses of tri-n-butylmagnesiumpotassium in cyclohexane–TMEDA, the chemical shift of the α-methylene protons moved from τ 10.57 initially to τ 10.74 after reaction was complete. A summary of the chemical shifts of the complexes is presented in Table II.

The species R_3MgM could be represented as salt-like in character, *i.e.*, $M^+[R_3Mg]^-$. However, the observed hydrocarbon solubilities of some of these compounds (R = *sec*-butyl and R = *tert*-butyl) seem inconsistent with this representation. Di-*sec*-butylmagnesium has been shown to exist as a dimer in cyclopentane.[7] With this in mind, a structure is proposed in which a di-*sec*-butylmagnesium molecule is replaced by a *sec*-butylalkali compound in the original dimer of di-*sec*-butylmagnesium. The reluctance of



M = alkali metal
R = *sec*-butyl, *tert*-butyl

cesium to enter into complexes with a cesium:magnesium ratio greater than about 0.7 may have been in part due to the inability of the large cesium atom to move fully into this 1:1 complex.

TABLE II

NMR CHEMICAL SHIFTS IN SOME SELECTED ORGANOMETALLIC SOLUTIONS

Reagent	Solvent system[a]	Chemical shift[b] of α proton(s)
s-Bu_2Mg	Cyclohexane	436
n-Bu_2Mg	Cyclohexane–DEE	449
n-Bu_2Mg	Cyclohexane–THF	446
n-Bu_3MgLi	Cyclohexane–DEE	473
s-Bu_3MgLi	Cyclohexane	447
s-Bu_3MgNa	Cyclohexane	484
n-Bu_3MgNa	Cyclohexane–DEE	477
n-Bu_5Mg_2Na	Cyclohexane–DEE	474
s-Bu_3MgK	Benzene	483
n-Bu_3MgK	Cyclohexane–DEE	474
n-Bu_3MgK	Benzene–DEE	479
n-Bu_3MgK	Cyclohexane–TMEDA	477
s-Bu_3MgRb	Benzene	461
n-Bu_3MgRb	Cyclohexane–TMEDA	480
n-Bu_3MgRb	Cyclohexane–DEE	482
n-Bu_3MgRb	Cyclohexane–THF	483
s-Bu_3MgCs	Benzene	458

[a] Symbols: DEE, diethyl ether; THF, tetrahydrofuran; TMEDA, tetramethylethylenediamine. [b] Cycles per second upfield from benzene internal standard.

Experimental Section

Reagents.—Di-*sec*-butylmagnesium and di-*tert*-butylmagnesium were prepared in hydrocarbon solutions by alkylation of an "activated" magnesium chloride with *sec*-butyllithium and *tert*-butyllithium, respectively, according to the general procedure given by Kamienski and Eastham.[7] Di-n-butylmagnesium was prepared in the following manner. A solution consisting of 0.20 mol of n-butyl chloride, 30 ml of cyclohexane, and 0.025 mol of diethyl ether was added dropwise to a slurry of 0.24 g-atom of magnesium powder in 60 ml of cyclohexane at 80°. The mixture was refluxed for an additional 1 hr, then filtered while hot, and the solids were washed with cyclohexane to give an initially clear solution which gradually became hazy owing to precipitation of n-Bu_2Mg. Another equivalent (0.025 mol) of diethyl ether was added. The resultant clear, colorless solution was analyzed and found to be 1.45 N in total base, 0.75

M in magnesium, and 0.05 M in chloride. The nmr of this solution showed the characteristic triplet of the methylene group at τ 10.15. The yields of n-Bu_2Mg *via* this method ranged from 70 to 80%.[11] *sec*-Butyllithium was obtained from Foote Mineral Co. *tert*-Butyllithium was obtained from Lithium Corporation of America. Lithium powder was obtained from Lithium Corporation of America as a 30 wt % suspension in mineral oil. Rubidium and cesium were obtained in vials from MSA Research Corp. Magnesium powder (200 mesh) was obtained from the Reade Manufacturing Co.

Anhydrous diethyl ether was dried over sodium wire before use. *N,N,N',N'*-tetramethylethylenediamine (TMEDA) was obtained from the Rohm and Haas Co. and was distilled from lithium aluminum hydride and stored over Linde 4A Molecular Sieves. Reagent grade *n*-butyl chloride was distilled and stored over Linde 4A Molecular Sieves. Hydrocarbon solvents were reagent grade and were refluxed overnight over lithium aluminum hydride and then distilled and stored over Linde 4A Molecular Sieves. All reactions and manipulations were carried out under an atmospheric pressure of dry nitrogen.

Instrumentation and Analytical Techniques.—Hydrocarbon solutions of organomagnesium reagents were analyzed by hydrolysis and analysis of the aqueous solutions for total base, chloride, and magnesium and other metal ions. Usually 1 or 2 ml of the initial organometallic solution was sufficient for the analyses. Chloride analyses were carried out using an absorption indicator method (Fajan's procedure) with dichlorofluorescein as indicator. Magnesium analyses were conducted using the standard ethylenediaminetetraacetic acid disodium salt (EDTA) method, with "calmagite" from Matheson Coleman and Bell as indicator. Analyses for total base were conducted by using an excess amount of standard aqueous acid solution in the initial hydrolysis of the organometallic solution and then back-titrating with standard base using phenolphthalein as indicator.

Lithium, sodium, and potassium were determined by flame photometry on a Perkin-Elmer Model 52C flame photometer. Rubidium and cesium were determined by atomic absorption at the laboratories of Lithium Corporation of America, Bessemer City, N. C. Samples for analysis by flame photometry and atomic absorption were prepared in the following manner. An accurately measured sample (usually 1 or 2 ml) of organometallic solution was hydrolyzed in *ca.* 100 ml of distilled water. The resultant hydrolysate was acidified by the addition of concentrated hydrochloric acid, and the hydrocarbon phase was evaporated by gently heating the solution on a hot plate. The aqueous solution was transferred quantitatively to a volumetric flask, diluted to the mark with distilled water, and analyzed for alkali metal. Nuclear magnetic resonance spectra were obtained at ambient temperature with a Varian A-60 nmr spectrometer using benzene as internal standard for measuring chemical shifts.

Preparation of Complexes. A. Reaction of Lithium with Di-*n*-butylmagnesium.—To a 100-ml three-neck round-bottom flask equipped with a reflux condenser and two rubber septum caps was added a vial containing 0.90 g (0.13 g atom) of lithium powder in a mineral oil suspension. The vial was broken under a nitrogen atmosphere in the reaction flask. To this was added 49 ml (0.034 mol) of 0.70 M di-*n*-butylmagnesium in the cyclohexane–diethyl ether (approximately 98:2). After stirring for 3 hr at room temperature an aliquot was removed and centrifuged, and the supernatant was analyzed to show 1.31 N in total base, 0.51 M in magnesium, and 0.30 M in lithium. After a total of 9 hr of stirring, analysis of another centrifuged aliquot showed 1.32 N in total base, 0.43 M in magnesium, and 0.40 M in lithium. After a total of 22 hr of stirring the supernatant was found to be 1.37 N in total base, 0.43 M in magnesium, and 0.45 M in lithium. After a total of 45 hr, the supernatant was found to be 0.35 M magnesium and 0.49 M lithium.

B. Reaction of Sodium with Di-*sec*-butylmagnesium.—To a 200-ml three-neck round-bottom flask equipped with a reflux condenser and two rubber septum caps was added 1.05 g (0.046 g-atom) of lump sodium. Enough methylcyclohexane was added to cover the sodium, which was dispersed by stirring and refluxing the methylcyclohexane overnight. The supernatant hydrocarbon was removed from the sodium with syringe and 75 ml (0.036 mol) of 0.48 M di-*sec*-butylmagnesium was added. This mixture was refluxed with vigorous stirring for 1 hr, after which it was cooled and a sample of the hazy supernatant was removed and centrifuged for analysis. The supernatant separated into an upper mobile phase and a smaller lower viscous phase. These layers were clear immediately after centrifuging, but both gradually became hazy. Further centrifuging caused each layer to become clear again, but the haziness subsequently reappeared. Samples from the upper layer were hydrolyzed for analysis while the layer was clear and found to be 0.80 N in total base, 0.39 M in magnesium, and 0.03 M in sodium. The reaction mixture was heated to reflux for an additional 1 hr and a sample was removed for analysis. Once again phasing was observed, but there was considerably more of the lower layer than after 1 hr of reflux. The upper layer was 0.64 N in total base, 0.30 M in magnesium, and 0.05 M in sodium. After a total of 4 hr of reflux, the supernatant no longer separated into two phases and analysis showed it to be 0.92 N in total base, 0.33 M in magnesium, and 0.26 M in sodium. An nmr spectrum of this solution showed the characteristic multiplet of the methine proton from the *sec*-butyl group at τ 10.68.

C. Reaction of Potassium with Di-*sec*-butylmagnesium.—To a 200-ml three-neck round-bottom flask was added 1.75 g (0.045 g-atom) of potassium. Enough cyclohexane to cover the lumps of potassium was added and the potassium was dispersed. The supernatant hydrocarbon was removed, 84 ml (0.040 mol) of 0.48 M di-*sec*-butylmagnesium was added, and the mixture was refluxed for 1 hr with vigorous stirring. The total base concentration in the supernatant had fallen to 0.01 N. The supernatant was removed by syringe and the solids were washed with two 20-ml portions of cyclohexane. To the solids was added 60 ml of dry benzene and the mixture was stirred for several minutes. The solids were allowed to settle while the reaction flask was immersed in an ice bath. Samples of the supernatant were removed for analysis while cold and the solution was found to be 1.09 N in total base, 0.36 M in magnesium, and 0.33 M in potassium. The yield of complex was approximately 85% based on *sec*-Bu_2Mg. An nmr spectrum of this solution showed the characteristic multiplet from the methine proton of the *sec*-butyl group at τ 10.75.

D. Reaction of Potassium with the Product from Reaction of Magnesium and *n*-Butyl Chloride.—To a 200-ml three-neck round-bottom flask equipped with a reflux condenser, a rubber septum cap, and a 250-ml pressure-equalizing dropping funnel was added a weight of 3.28 g (0.14 g-atom) of magnesium powder, 60 ml of cyclohexane, and 3.87 g (0.034 mol) of TMEDA. A solution of 9.25 g (0.10 mol) of *n*-butyl chloride in 30 ml of cyclohexane was added to the dropping funnel. After about one third of the butyl chloride was introduced to the magnesium slurry, the mixture was heated to reflux. The remainder of the solution was added dropwise to the reaction mixture, which was refluxed 9 hr after addition was complete. A weight of 7.5 g (0.19 g-atom) of potassium was added to the cooled reaction flask and the mixture was heated to reflux again and vigorously stirred. After a 30-min reflux period, the mixture was cooled and an aliquot was removed for analysis. The supernatant was found to be 0.42 M in magnesium, 0.06 M in chloride, and to contain no potassium. After a total of 60 min of reflux, the supernatant was still colorless, contained no chloride or potassium, and was 0.41 M in magnesium. After a total of 90 min of refluxing, the supernatant had assumed a red-orange color and analysis showed it to be chloride-free, 0.25 M in magnesium, and 0.25 M in potassium. Nmr spectral analyses showed that the absorption of the α-methylene protons of the *n*-butyl group had shifted from τ 10.60 after 39 min reflux to τ 10.74 after 90 min reflux. The overall yield of total base in the supernatant solution was 50% based on *n*-butyl chloride.

In two additional runs using this same procedure, except that no intermediate analyses were conducted, the product contained magnesium and potassium in a 1:1 ratio and the overall yields were estimated to be 50–60% based on *n*-butyl chloride.

E. Reaction of Rubidium with Di-*sec*-butylmagnesium.—A weight of 1.0 g (0.012 g-atom) of rubidium in a vial was added to a 100-ml three-neck round-bottom flask equipped with a reflux condenser and two septum caps. Enough cyclohexane was added to cover the vial, which was then broken. The rubidium was subsequently dispersed by stirring vigorously and refluxing the cyclohexane. The cyclohexane was removed by syringe from the dispersed metal. The flask was immersed in an ice bath and 25 ml (0.012 mol) of 0.48 M di-*sec*-butylmagnesium was added. After stirring vigorously for 1 hr at ice-bath temperature the supernatant was 0.01 N in total base and was removed by

(11) Additional details on the preparation of the magnesium alkyls and intermetallic complexes are given in the Doctoral Dissertation of D. B. Malpass, The University of Tennessee, 1970.

syringe. The solids were washed with cold cyclohexane. Benzene (20 ml) was added to the reaction flask and the mixture was stirred for several minutes. An aliquot was removed and centrifuged and analysis of the supernatant showed it to be 0.61 *N* in total base, 0.21 *M* in magnesium, and 0.19 *M* in rubidium.

F. Reaction of Cesium with Di-*sec*-butylmagnesium.—A weight of 1.0 g (0.0075 g-atom) of cesium in a vial was placed in a 100-ml three-neck round-bottom flask equipped with a reflux condenser and two rubber septum caps. The cesium was dispersed under cyclohexane in the usual manner and the dispersing cyclohexane was removed. The reaction flask was immersed in an ice bath, 16 ml (0.0077 mol) of 0.48 *M* di-*sec*-butylmagnesium in cyclohexane was added, and the mixture was stirred vigorously for 3 hr. The supernatant was removed and the solids were washed with two 10-ml portions of cold cyclohexane. To the solids was added 12 ml of dry benzene and the mixture was stirred for several minutes, after which the benzene was removed by syringe and centrifuged. The supernatant separated into an upper, mobile, orange phase and a lower, wine-red, viscous phase. The upper phase was analyzed and found to be 0.30 *N* in total base, 0.13 *M* in magnesium, and 0.09 *M* in cesium. After all of the upper layer was removed, 8 ml of benzene was added to the remaining lower layer. The tube was shaken vigorously for several minutes and centrifuged once again. Phasing was observed again; however, the volume of the lower layer was decreased. Analysis of the upper layer showed it to be 0.24 *N* in total base, 0.10 *M* in magnesium, and 0.07 *M* in cesium. To the remaining two phases in the centrifuge tube was added 8 ml of diethyl ether and the tube was shaken by hand for a few minutes and centrifuged. No phasing was observed and the solution was found to be 0.61 *N* in total base, 0.23 *M* in magnesium, and 0.15 *M* in cesium.

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Registry No.—Di-*sec*-butylmagnesium, 17589-14-9; di-*tert*-butylmagnesium, 14627-81-7; di-*n*-butylmagnesium, 1191-47-5; *n*-butyl chloride, 109-69-3; magnesium, 7439-95-4.

Acid-Catalyzed Reaction of Acetylferrocene with Triethyl Orthoformate

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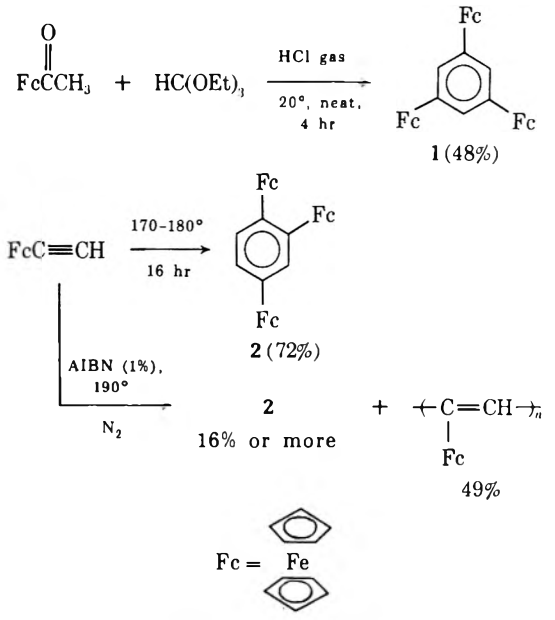
The major product obtained when acetylferrocene was allowed to react with triethyl orthoformate and dry hydrochloric acid was 1,3-diferrocenylbut-2-en-1-one, and only a small amount of the cyclic trimer, 1,3,5-triferrocenylbenzene, was obtained. This result was found using either benzene or methylene chloride as the solvent or upon running the reaction without solvent. The reaction of acetylferrocene with triethyl orthoformate in ethanol, upon catalysis by *p*-toluenesulfonic acid, gave 2-ferrocenylpropene, ethyl ferrocenoate, polyvinylferrocene, a more complex polymer, and small amounts of 1,3,5-triferrocenylbenzene, 1,2,4-triferrocenylbenzene, and 1,3-diferrocenylbut-2-en-1-one. These results are compared with previous studies, and mechanisms are discussed.

Schlogl[1] reported that the reaction of acetylferrocene with a slight excess of triethyl orthoformate (1.2 equiv) in the presence of anhydrous hydrochloric acid at 20° for 4 hr gave a 48% isolated yield of 1,3,5-triferrocenylbenzene (**1**). The unsymmetrical 1,2,4 isomer, **2**, was not formed and other products were



not discussed. The 1,2,4 isomer has been prepared by the thermal cyclotrimerization of ethynylferrocene,[1] and it is also a by-product in the free-radical polymerization of ethynylferrocene.[2,3] Since ketones readily give ketals in the presence of triethyl orthoformate and catalytic amounts of acids,[4] the formation of **1** reported by Schlogl was presumed to proceed *via* an elimination product of the diethyl ketal of acetylferrocene. To our surprise, attempts to generate **1** by Schlogl's method resulted in the isolation of large quantities of 1,3-diferrocenylbut-2-en-1-one (**3**), and only small amounts of the cyclotrimer **1**. Thus, we studied this reaction under several different conditions and found that the use of *p*-toluenesulfonic acid led to a complex mixture of products, including 2-ferrocenylpropene (one carbon addition) and ethylferrocenoate (one carbon removed). Increased yields of cyclotrimer **1** can be obtained at very high gaseous HCl rates of bubbling into the reaction.

Results and Discussion

Acetylferrocene was allowed to react at 20° with triethyl orthoformate and dry HCl gas (1) in dry benzene, (2) in dry methylene chloride, and (3) without solvent (Schlogl's conditions). In each case the major product was dimer **3**, and only small yields of symmetrical cyclotrimer **1** were observed. None of the unsymmetrical trimer **2** was detected. The yields of

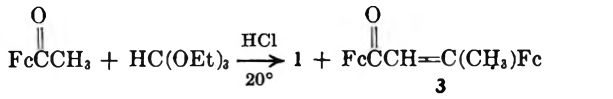
(1) K. Schlogl and H. Soukup, *Monatsh. Chem.*, **99**, 927 (1968).

(2) C. Simionescu, T. Lixandru, J. Mazilu, and L. Tataru, *Makromol. Chem.*, **147**, 69 (1971).

(3) C. U. Pittman, Jr., and Y. Sasaki, unpublished results using AIBN as the initiator.

(4) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 1206.

3 varied from 62 to 81%, while 1 was not obtained in excess of 12.1%. This is only one fourth that previ-



ously reported.[1] Representative results are summarized in Table I. Tlc studies conducted during the

TABLE I

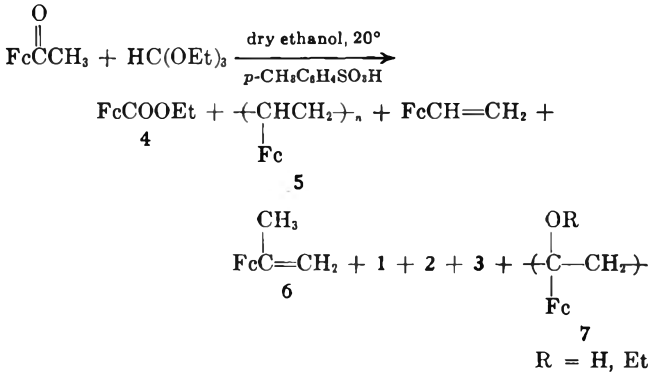
REACTION OF ACETYLFERROCENE AND TRIETHYL ORTHOFORMATE WITH HCl AT 20°

Solvent	Acetylferrocene[a] reacted, mmol	Time, hr	1,3,5-Triferrocenylbenzene[b] Mmol	1,3,5-Triferrocenylbenzene[b] Yield, %	1,3-Diferrocenylbut-2-en-1-one[b] Mmol	1,3-Diferrocenylbut-2-en-1-one[b] Yield, %
C_6H_6	17.5	4	0.477	8.2	7.06	80.5
CH_2Cl_2	16.7	4	0.492	8.8	6.60	79.0
None	18.7	21	0.754	12.1	5.82	62.0
None[c]	18.7	22	1.89	29.9	4.42	47.1

[a] Amount charged to reactor was 21.9 mmol of acetylferrocene and 23.6 mmol of triethyl orthoformate in every case. [b] Yields are based on the amount of acetylferrocene that reacted (some acetylferrocene was recovered in each reaction). [c] In this experiment the HCl was added by bubbling so fast that the reactants were vigorously sprayed throughout the reaction vessel.

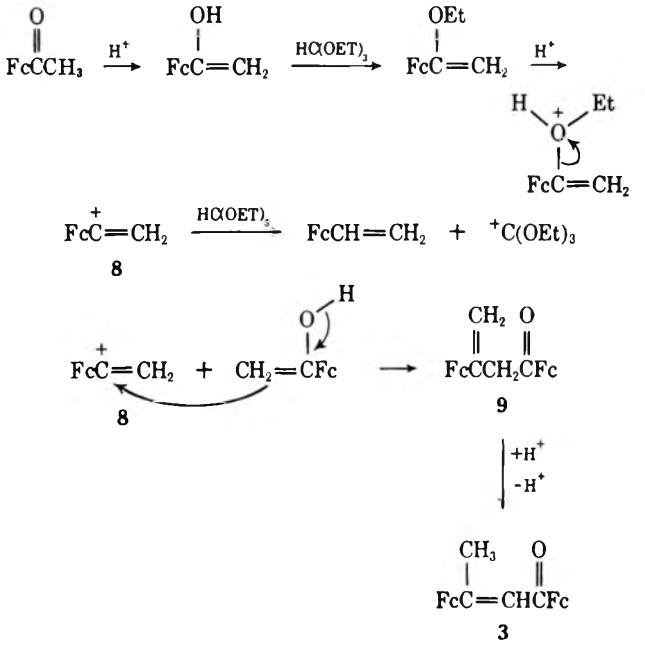
course of the reaction gave no evidence for an intermediate buildup of 1 at reactions times between 1 and 20 hr.

The reaction was far more complicated when catalytic amounts of *p*-toluenesulfonic acid in ethanol were used in place of anhydrous HCl. The major products were ethyl ferrocenoate (**4**, 45%), low molecular weight ($\bar{M}_n$ 1800) polyvinylferrocene (**5**, 15%), and 2-ferrocenylpropene (**6**, 8%). Other products included both cyclotrimers **1** and **2** (4% total), dimeric ketone **3** (5–6%), a polymer, **7**, similar to polyvinylferrocene but

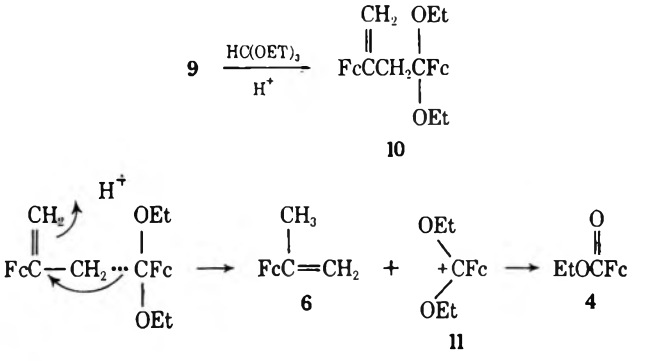


containing many polar groups such as OH moieties (6%), and unreacted acetylferrocene. Traces of vinylferrocene were recovered in some runs. Despite this complexity, the results were reproducible. It is quite likely that the unexpected products (particularly **4** and **6**) result from an intermediate cationic species rendered especially stable by an adjacent ferrocene unit, since analogous products are not found with aliphatic or phenyl ketones.

Two mechanisms are readily envisioned to account for the production of dimer **3** in all the reactions. The first involves an α-ferrocenylvinyl cation intermediate, **8**, which could readily react with the enol form of acetylferrocene to give β,γ-unsaturated ketone **9** which, in turn, would readily isomerize to **3** in the presence of



acid. The involvement of **9** is attractive because the production of both **6** and **4** from its diethyl acetal, **10**, can be explained by the fragmentation of **10** to give **6** and the stable ferrocenyldiethoxy carbonium ion, **11**,



which would hydrolyze to **4**. Fragmentation of **10** would lead, initially, to equal amounts of **6** and **4**, but some incorporation of **6** into the polymeric products could be occurring.

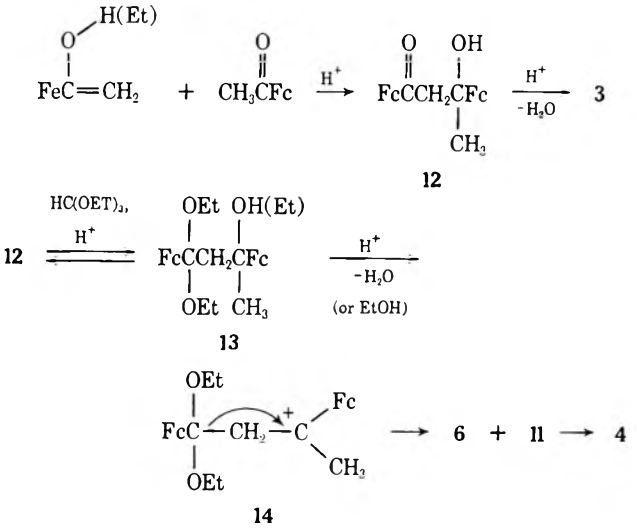
Vinyl cation **8** could also lead to vinylferrocene by hydride transfer from triethyl orthoformate. In the acidic media, polyvinylferrocene would arise by cationic polymerization where proton, $^+C(OEt)_3$, etc., could initiate polymerization. All cationic polymerizations of vinylferrocene previously studied have generated only low molecular weight polymers similar to those found in this study.[5]

Control experiments demonstrated that α,β-unsaturated ketone **3** could not give rise to **4** or **6** under the conditions of the *p*-toluenesulfonic acid reaction. Thus, if **9** (*via* **10**) is the correct route to **4** and **6**, no kinetically important quantity of **9** can be generated in equilibrium from the more stable isomer **3**.

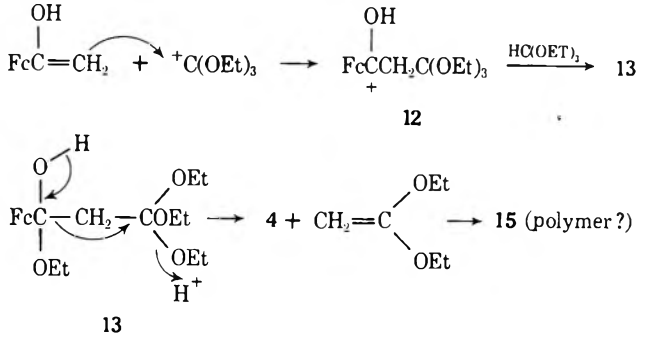
The second mechanism readily envisioned for the production of **3** is the condensation of protonated acetylferrocene with its enol form, followed by dehydration. This route also provides a potential path to **4** and **6** if 1,3-diferrocenyl-3-hydroxybutan-1-one (**12**) can be converted to its diethyl acetal, **13**, in com-

(5) C. Aso, T. Kunitake, and T. Nakashima, *Makromol. Chem.*, **124**, 232 (1969).

petition with dehydration. In acid, **13** could lose H_2O (EtOH) generating cation **14**, which would give **6** and ultimately **4**.



An alternate pathway to **4** involves the addition of the triethoxycarbonium ion to the enol form of acetylferrocene followed by EtO^- transfer to cation **12** and subsequent elimination of ethanol and 1,1-diethoxyethylene from **13**.



The incorporation of 1,1′-diethoxyethylene into a polymeric species is possible and would account for a portion of polar polymer **7**.

A choice between these general routes is not yet possible. However, the general bias against vinyl cations probably cannot be invoked here based on the marked ability of ferrocene to stabilize adjacent cation sites[6-9] and on recent observations showing that many vinyl cations may be far more easily generated than had previously been recognized.[10] It is clear that the cyclotrimerization of acetylferrocene using triethyl orthoformate and acid is a more complex reaction than was previously thought. The ability of ferrocene to stabilize adjacent positive charge plays a major role in this behavior. Finally, if higher yields of cyclotrimer **1** are desired in neat reactions (Schlogl's method[1]), the HCl addition rate should be exceedingly rapid.

Experimental Section

Melting points were not corrected. Infrared spectra were obtained on a Beckman IR-33 spectrometer; nmr spectra were measured on a Hitachi Perkin-Elmer R-20 spectrometer; mass spectra were obtained using a Consolidated Electronics Corp. Model 31-104 mass spectrometer; gel permeation chromatograms were obtained on a Waters Associates GPC Model 301 equipped with 16 ft of styragel columns calibrated *vs.* polystyrene standards. The Universal calibration technique was employed.

Materials.—Acetylferrocene was recrystallized from octane, mp 85–86° (lit.[11] mp 85–86°). Alumina used for column chromatography was alumina F-20 (Alcoa). Tlc studies employed silica gel PF-254 (E. Merck). Anhydrous hydrocloric acid (Matheson Co.) was used directly from the tank. Petroleum ether used in the chromatographic separations was a 30–60° cut.

Reaction of Acetylferrocene with Triethyl Orthoformate in Benzene Catalyzed by Hydrochloric Acid.—Acetylferrocene (5.0 g, 21.9 mmol) and triethyl orthoformate (3.5 g, 23.6 mmol) were dissolved in dry benzene (100 ml). HCl gas was bubbled from a tank into the stirred solution for 3 hr at 20°. The resulting dark green solution was stirred for an additional 1 hr and then benzene (300 ml) was added. The solution was washed with water (500 ml) and aqueous $NaHCO_3$ (5%, 500 ml) and then dried (anhydrous $MgSO_4$). After solvent was removed *in vacuo*, the resulting red oil was chromatographed on 150 g of alumina. The products are listed below in the order of their elution. Elution with 1:1 benzene–petroleum ether afforded 300 mg of 1,3,5-triferrocenylbenzene (**1**), which was recrystallized from cyclohexane–methylene chloride: mp 264–265° (lit.[1] mp 265–266°); nmr (CS_2) δ 3.98 (s, 5 H), 4.25 (m, 2 H), 4.56 (m, 2 H), 7.30 (s, 1 H). Further elution with 2:1 benzene–petroleum ether afforded 3.1 g of α,β-unsaturated ketone **3**, which was recrystallized from hexane: mp 121–122° (lit.[12] mp 118–120°); ir (KBr) 1635 (s), 1585 cm^{-1} (s); nmr (CS_2) δ 2.49 (d, J = 1 Hz, 3 H), 4.09 (s, 10 H), 4.35 (m, 4 H), 4.51 (m, 2 H), 4.67 (m, 2 H), 6.62 (d, J = 1 Hz, 1 H); mass spectrum (70 eV) *m/e* (assignment, rel intensity) 438 (M^+, 7.6), 373 ($M^+ - C_2H_5$, 14), 253 ($M^+ - C_{10}H_9Fe$, 1.9), 219 [$M^+ - C_{10}H_9FeC(CH_3)$=CH–, 4.8], 185 ($C_{10}H_9^+$, 2.7), 56 (Fe^+, 100).

Further elution with benzene afforded 1.0 g of acetylferrocene. The column contained a small quantity of brown residue at the top. This was not further studied.

Reaction of Acetylferrocene with Triethyl Orthoformate in Methylene Chloride Catalyzed by Hydrogen Chloride.—Acetylferrocene (5.0 g, 21.9 mmol) and triethyl orthoformate (3.5 g, 23.6 mmol) were dissolved in dry methylene chloride (100 ml). HCl gas was bubbled into the stirred solution for 3 hr at 20°. The reaction mixture was treated exactly as the product from the benzene reaction mentioned above.

The products obtained were 310 mg of **1**, 2.9 g of **3**, and 1.2 g of unreacted acetylferrocene.

Reaction of Acetylferrocene with Triethyl Orthoformate, without Solvent, Catalyzed by Hydrogen Chloride.—Hydrochloric acid (gas) was bubbled into a mixture of acetylferrocene (5.0 g, 21.9 mmol) and triethyl orthoformate (3.5 g, 23.6 mmol) at 20° for 3 hr. The reaction mixture was stirred for an additional 18 hr, and then worked up exactly as described for the reaction in benzene.

The products obtained were 481 mg of **1**, 2.55 g of **3**, and 700 mg of unreacted acetylferrocene.

Reaction of Acetylferrocene with Triethyl Orthoformate in Ethanol Catalyzed by *p*-Toluenesulfonic Acid.—Acetylferrocene (5.0 g, 21.9 mmol), triethyl orthoformate (4.0 g, 27.0 mmol), and *p*-toluenesulfonic acid monohydrate (200 mg, 1.05 mmol) were dissolved in 50 ml of dry ethanol (distilled from magnesium ethoxide). At room temperature, the stirred reaction mixture turned a deep green color within 15 min. The reaction mixture was refluxed for 4 hr. Then diethyl ether (100 ml) was added to the reaction mixture, and it was filtered. A brownish solid (95 mg) was collected on the filter and this material was not identified.

The remaining product was collected by stripping the solvent to give a brown solid. Tlc (benzene) indicated the presence of at least seven components (R_f values of 0.6, 0.3, 0.25, 0.17, 0.1, 0.08, and 0.0). This reaction mixture was chromatographed on 200 g of alumina. The products obtained are listed in the order of their elution. Elution with 2% benzene in petroleum ether gave 300 mg of 2-ferrocenylpropene (**6**), which was purified by recrystallization from methanol–water: mp 62–63° (lit.[13] mp

(6) E. A. Hill and R. Wiesner, *J. Amer. Chem. Soc.*, **91**, 509 (1969).
(7) T. G. Traylor and T. C. Ware, *J. Amer. Chem. Soc.*, **89**, 2304 (1967).
(8) M. Cais, *Organometal. Chem. Rev.*, **1**, 435 (1966).
(9) C. U. Pittman, Jr., *Tetrahedron Lett.*, **No. 37**, 3619 (1967).
(10) K. Yates, G. H. Schmid, T. W. Regulski, D. G. Garratt, H. W. Leung, and R. McDonald, *J. Amer. Chem. Soc.*, **95**, 160 (1973).
(11) V. Weinmayr, *J. Amer. Chem. Soc.*, **77**, 3009 (1955).
(12) P. L. Pauson and W. E. Watts, *J. Chem. Soc.*, 3880 (1962).
(13) A. F. Ellis, *Diss. Abstr.*, **24**, 510 (1963).

63–65°); ir (KBr) 1628 cm^{-1} (s); nmr (CCl_4) δ 2.01 (s, 3 H), 3.97–4.26 (m, 9 H), 4.53 (s, 1 H), 5.02 (s, 1 H).

Immediately after this fraction, 560 mg of polyvinylferrocene (5) was eluted: mol wt (gpc) ~1800; ir identical with that of an authentic sample obtained by radical polymerization of vinylferrocene.[14,15]

Further elution with 1:3 benzene–petroleum ether afforded 150 mg of a mixture of the two isomers of triferrocenylbenzene, 1 and 2 (roughly in the same amount by nmr analysis).

Continued elution with 1:1 benzene–petroleum ether afforded 1.90 g of ethyl ferrocenoate (4), which was recrystallized from ethanol–water: mp 62–63° (lit. mp 61–62°,[11] 63–64°[16]); ir (KBr) 1700 cm^{-1} (s); mass spectrum (70 eV) *m/e* (assignment and rel intensity) 258 (M^+, 100), 229 ($M^+ - C_2H_5$, 99), 213 ($M^+ - C_2H_5O$, 10), 185 ($C_{10}H_9Fe^+$, 11), 56 (Fe^+, 85); nmr (CCl_4) δ 1.32 (t, 3 H), 4.1–4.35 (m, 9 H), 4.70 (m, 2 H).

Elution with pure benzene afforded 1.01 g of acetylferrocene followed by 200 mg of dimer 3.

Further elution with 1:2 benzene–diethyl ether afforded 200 mg of hydroxyl-bearing polymeric species 7: mol wt (gpc) ~2900; ir (KBr) 3400 (broad), 3070 (s), 2890 (s), 1450 (s), 1370 (s), 1105 (s), 1000 (s), 820 cm^{-1} (s); nmr ($CDCl_3$) δ ~4.2 (very broad, ~9 H), 1.9 (very broad, ~3 H).

Treatment of Dimer 3 with Triethyl Orthoformate in Ethanol in the Presence of a Small Amount of *p*-Toluenesulfonic Acid.—Dimer 3 (1.00 g, 2.28 mmol), triethyl orthoformate (1.3 g, 9 mmol), and *p*-toluenesulfonic acid (50 mg, 0.26 mmol) were dissolved in 10 ml of dry ethanol and stirred well at room temperature. Tlc studies were conducted from time to time. Even after 2 weeks, no reaction occurs to give any of compounds 1–7.

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Registry No.—1, 39324-45-3; 3, 39336-59-9; 4, 1273-91-2; 6, 33362-30-0; acetylferrocene, 1271-55-2; triethyl orthoformate, 122-51-0.

(14) F. S. Arimoto and A. C. Haven, *J. Amer. Chem. Soc.*, **77**, 6295 (1955).

(15) Y. Sasaki, L. L. Walker, E. L. Hurst, and C. U. Pittman, Jr., *J. Polym. Sci.*, **11**, 1213 (1973).

(16) R. F. Schaaf, *J. Org. Chem.*, **27**, 107 (1962).

Fused Organic Salts. VII.[1] The System Tetra-*n*-pentylammonium Nitrate–Silver Nitrate. Melt Stability. The Silver Nitrate–Carbon Tetrachloride Reaction

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Tetra-*n*-pentylammonium nitrate (fp 113.9°)–silver nitrate (fp 210°) is a simple eutectic system with eutectic temperature 41.7° and eutectic composition 42.2 ± 0.5 mol % $AgNO_3$. While pure tetra-*n*-penytlammonium nitrate gives 1-pentyl nitrate and tripentylamine on pyrolysis at 275°, $AgNO_3$–R_4NNO_3 mixtures yield in addition dipentylnitrosamine. This oxidation of tertiary amine by $AgNO_3$ is observable also in protic and aprotic solvents. Ag metal is formed and the tertiary iminium cation and tertiary amide are thought to be intermediates. The $AgNO_3$–CCl_4 reaction, which is very slow in ethanol but very rapid with $AgNO_3$ adsorbed on silicic acid, proves also to be very slow in molten $AgNO_3$–R_4NNO_3. Consequently the difference in reactivity in the first two media cannot be attributed to deactivation by ion solvation, and the high reactivity of $AgNO_3$/silicic acid must be a surface-chemical phenomenon.

Results and Discussion

Phase Diagram.—Tetra-*n*-pentylammonium nitrate–silver nitrate displays a simple eutectic diagram (Figure 1) with a remarkably low eutectic temperature (41.7 ± 0.5°). The eutectic melt contains 42.4 ± 0.5 mol % (25.7 wt %) of silver nitrate. The availability of such melts containing high concentrations of unsolvated silver ion at moderate temperatures suggests a variety of chemical applications. Here we report on stability relationships in these melts and one test of the electrophilic reactivity of Ag^+ in Ag^+, R_4N^+/NO_3^-.

Stability of the Melt.—While pure liquid $R_4N^+NO_3^-$ is more stable than its analogs with more nucleophilic anions, slow decomposition is known to occur at 140°.[2] This reaction could take either of two paths: nucleophilic displacement (eq 1) or elimination (eq 2).[3] Application of the vacuum pyrolysis technique which provided clean-cut results for the halides[1a] produced the result shown in Table I. Only reaction 1 is important.

$$(n\text{-}C_5H_{11})_4N^+NO_3^- \rightarrow CH_3(CH_2)_3CH_2ONO_2 + (n\text{-}C_5H_{11})_3N \quad (1)$$

$$(n\text{-}C_5H_{11})_4N^+NO_3^- \rightarrow CH_3(CH_2)_2CH{=}CH_2 + (n\text{-}C_5H_{11})_3N + HNO_3 \quad (2)$$

The behavior of R_4N^+, Ag^+/NO_3^- mixtures is expected to be similar, with possible secondary reactions of the products of eq 1 with Ag^+. The observations (Table I) are indeed similar, but the yield of tripentylamine is reduced and some dipentylnitrososamine appears. The latter was shown to result from reaction of tripentylamine with $AgNO_3$.

This reaction takes the course shown in Table II and eq 3. Oxidation of tertiary amines by Ag^+ has

$$2AgNO_3 + (C_5H_{11})_3N = 2Ag + (C_5H_{11})_2NN{=}O + HNO_3 + CH_3(CH_2)_3COOH \quad (3)$$

apparently never been reported, though other oxidants (ClO_2, MnO_2, $Hg(OAc)_2$, $KMnO_4$) are known to produce the enamine or its conjugate acid.[4] We in-

(1) (a) Part VI: J. E. Gordon and P. Varughese, *Chem. Commun.*, 1160 (1971). (b) Part V: J. E. Gordon, J. E. Selwyn, and R. L. Thorne, *J. Org. Chem.*, **31**, 1925 (1966). (c) Part IV: J. E. Gordon, *J. Amer. Chem. Soc.*, **87**, 4347 (1965).

(2) J. E. Gordon, *J. Org. Chem.*, **30**, 2760 (1965).

(3) J. E. Gordon in "Techniques and Methods of Organic and Organometallic Chemistry," D. B. Denney, Ed., Marcel Dekker, New York, N. Y., 1969, p 78.

(4) (a) P. A. S. Smith, "Open-Chain Nitrogen Compounds," Vol. I, W. A. Benjamin, New York, N. Y., 1965, p 49; (b) L. A. Hull, *et al.*, *J. Amer. Chem. Soc.*, **89**, 1163 (1967).

TABLE I

PRODUCTS OF VACUUM PYROLYSIS OF MOLTEN NITRATES[a]

Reactants	Temp, °C	Products, % Tripentylamine	Pentyl nitrate	1-Pentene	Dipentylnitrosamine
$(n\text{-}C_5H_{11})_4N^+NO_3^-$	250–280	93	68	3	Trace
$(n\text{-}C_5H_{11})_4N^+NO_3^-$–$AgNO_3$[b]	250–280	80	79	4	3
$(n\text{-}C_5H_{11})_3NH^+NO_3^-$	150[c]	49			13

[a] 0.001 Torr. [b] 35 mol % $AgNO_3$. [c] In sealed ampoule.

TABLE II

PRODUCTS FROM $(C_5H_{11})_3N$ AND $AgNO_3$[a]

Solvent	Temp, °C	Products, % $(C_5H_{11})_3N$	$(C_5H_{11})_2NN{=}O$
Neat	110	2	55
$C_6H_5NO_2$	110	4	68
t-C_4H_9OH	83	21	10
R_4N^+, Ag^+/NO_3^-[b]	110	*c*	54

[a] Reaction time, 24 hr. Metallic silver and valeric acid also observed; see Experimental Section. [b] 35 mol % $AgNO_3$. [c] Not determined.

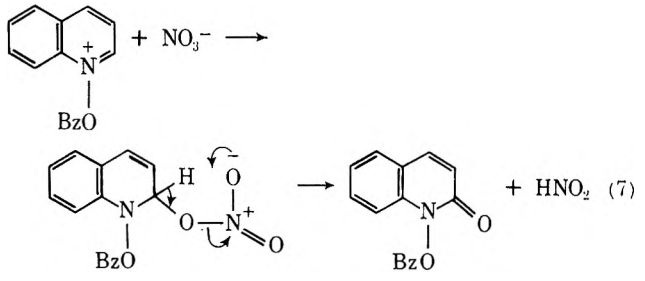
terpret the course of this reaction as eq 4 + eq 5 + eq 6 = eq 3. Nucleophilic addition of nitrate ion to the

$$2Ag^+ + (C_5H_{11})_3N \longrightarrow 2Ag + (C_5H_{11})_2N^+{=}CH(CH_2)_3CH_3 + H^+ \quad (4)$$

$$(C_5H_{11})_2N^+{=}CH(CH_2)_3CH_3 + NO_3^- \longrightarrow (C_5H_{11})_2NCH(CH_2)_3CH_3 \longrightarrow \underset{\displaystyle ONO_2}{\overset{\displaystyle O}{\overset{\|}{(C_5H_{11})_2NC}}}(CH_2)_3CH_3 + HNO_2 \quad (5)$$

$$\underset{\displaystyle O}{\overset{\displaystyle \|}{(C_5H_{11})_2NC}}(CH_2)_3CH_3 + H^+ + HNO_2 \longrightarrow (C_5H_{11})_2N^+CO(CH_2)_3CH_3 + H_2O \longrightarrow \underset{\displaystyle N{=}O}{(C_5H_{11})_2NN{=}O} + HOOC(CH_2)_3CH_3 + H^+ \quad (6)$$

iminium salt, followed by loss of nitrous acid (eq 5), finds a close analogy in the reaction of quinoline *N*-oxide with benzoyl nitrate (eq 7).[5] The nitrosation of



tertiary amides (eq 6) is known[6] to produce the nitrosamine.

The R_3N–$AgNO_3$ reaction was shown to occur in molten R_4NNO_3 medium (Table II) and we consequently attribute the appearance of dipentylnitrosamine in the pyrolysis of Ag^+, R_4N^+/NO_3^- to eq 1 followed by eq 3.

The $AgNO_3$–CCl_4 Reaction in Molten R_4N^+, Ag^+/NO_3^-.—Carbon tetrachloride reacts with $AgNO_3$ slowly in refluxing ethanol, but rapidly with $AgNO_3$ on silicic acid at room temperature.[7] A nitrating agent results, and in the presence of an aromatic substrate processes 8 (interpreted as the sum of eq 10–12 and half of 15) and 9 (interpreted as the sum of eq 10–15) proceed simultaneously.

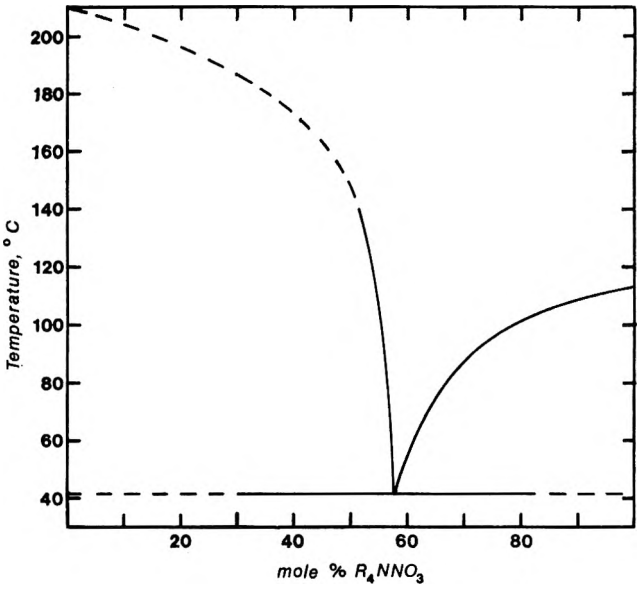


Figure 1.—Phase diagram for the system $AgNO_3$–$(n\text{-}C_5H_{11})_4NNO_3$. The dotted portions are somewhat less certain (liquidus, due to decomposition; solidus, due to difficulty in visual identification of molten eutectic at the composition extremes).

$$CCl_4 + 2AgNO_3 + ArH = 2AgCl + COCl_2 + ArNO_2 + HNO \quad (8)$$

$$CCl_4 + 4AgNO_3 + 2ArH = 4AgCl + 2ArNO_2 + CO_2 + 2HNO_3 \quad (9)$$

$$CCl_4 + AgNO_3 \longrightarrow CCl_3ONO_2 + AgCl \quad (10)$$

$$CCl_3ONO_2 \longrightarrow COCl_2 + NO_2Cl \quad (11)$$

$$NO_2Cl + AgNO_3 \longrightarrow N_2O_5 + AgCl \quad (12)$$

$$COCl_2 + 2AgNO_3 \longrightarrow 2AgCl + CO(ONO_2)_2 \quad (13)$$

$$CO(ONO_2)_2 \longrightarrow CO_2 + N_2O_5 \quad (14)$$

$$2ArH + 2N_2O_5 \longrightarrow 2ArNO_2 + 2HNO_3 \quad (15)$$

In molten R_4N^+, Ag^+/NO_3^- at 110° the reaction of CCl_4 differs considerably from this pattern. No phosgene is detectable, added ArH is not nitrated, and deposition of AgCl is slow. From the very much lower level of reactivity in the melt we conclude that NO_3^- of maximum nucleophilicity[1a] and unsolvated, presumably strongly electrophilic, Ag^+ are insufficient to make the displacement reaction 10 go rapidly. One must therefore look to the surface chemistry of $AgNO_3$/silicic acid for an understanding of the great reactivity with CCl_4.

(5) A. R. Katritzky and J. M. Lagowski, "Chemistry of the Heterocyclic *N*-Oxides," Academic Press, New York, N. Y., 1971, pp 247, 292.

(6) W. Lijinsky, E. Conrad, and R. Van de Bogart, *Nature (London)*, **233**, 165 (1972).

(7) J. E. Gordon, *J. Org. Chem.*, **35**, 2722 (1970).

The principal product from CCl_4–$AgNO_3$ in molten R_4NNO_3 is in fact $R_2NN{=}O$ (Table III), and we attribute its formation to interception of the nitrating agent formed from CCl_4–$AgNO_3$ by the tripentylamine from decomposition of R_4NNO_3. This is summarized by eq 16, which is the sum of eq 10–14, 2 × eq 1 and

TABLE III

PRODUCTS FROM CCl_4 AND $AgNO_3$ IN MOLTEN TETRAPENTYLAMMONIUM NITRATE[a]

Reactants, mmol				Products, mmol	
$AgNO_3$	R_4NNO_3	CCl_4	R_3N	$R_2NN{=}O$	1-Pentene
2.54	4.64	1.53		0.074	
2.52	4.65	1.53	0.171	0.200	
2.52	4.66		0.171	0.093	Trace

[a] 110° for 24 hr.

$$CCl_4 + 4AgNO_3 + 2(C_5H_{11})_4NNO_3 = 4AgCl + CO_2 + 2C_5H_{11}ONO_2 + 2(C_5H_{11})_2NNO + 2C_4H_9CHO + 2HNO_3 \quad (16)$$

2 × eq 17. The nitration of tertiary amines by tetranitromethane is known to give the secondary nitrosamine,[8] and we have confirmed that nitration by HNO_3 does also by studying the pyrolysis of tripentylammonium nitrate (Table I).[9] The reaction can be rationalized by analogy with the nitrosation of tertiary amines[12] and the nitration by $C(NO_2)_4$[13] as eq 18–21,

$$(C_5H_{11})_3N + N_2O_5 \text{ (or } HNO_3 + H^+) \longrightarrow (C_5H_{11})_3N^+NO_2 + NO_3^- \text{ (or } H_2O) \quad (18)$$

$$(C_5H_{11})_3N^+NO_2 \longrightarrow (C_5H_{11})_2N^+{=}CHC_4H_9 + HNO_2 \quad (19)$$

$$(C_5H_{11})_2N^+{=}CHC_4H_9 + H_2O \longrightarrow (C_5H_{11})_2NH + C_4H_9CHO + H^+ \quad (20)$$

$$(C_5H_{11})_2NH + HNO_2 \longrightarrow (C_5H_{11})_2NN{=}O + H_2O \quad (21)$$

whose sum is eq 17. The yield of dipentylnitrosamine, based on $AgNO_3$ according to eq 16, is 12%. In the presence of added tripentylamine the production of nitrosamine rises by 0.126 mmol, a 74% yield based on R_3N. However, up to 0.093 mmol (final entry, Table III) arises from the $AgNO_3$–R_3N reaction (eq 3), and the remainder, $\geq$0.033 mmol, is due to eq 17. This partitioning of added R_3N in comparable amounts through the two pathways to $R_2NN{=}O$ probably also occurs with the R_3N arising from R_4NNO_3.

Experimental Section

General.—Tetra-*n*-pentylammonium nitrate was prepared according to Gordon,[1c] mp 113.5–114° (lit.[1c] 113.9°). 1-Pentyl nitrate, prepared according to Ferris, *et al.*,[14] was distilled at 20 Torr; the material collected at 59–60° was used after verification of identity by ir and nmr. Di-*n*-pentylnitrosamine was prepared by the procedure of Carroll and Wright[15] and distilled through a Vigreux column, bp 83–83.5° (0.45 Torr) [lit.[16] 146° (12 Torr)]. Ir and nmr [δ 0.9 (t, 6 H, J = 5 Hz, CH_3), *ca.* 1.3 (m, 12 H, CCH_2C), 3.58 (t, 2 H, J = 7 Hz, cis CH_2N), and 4.08 (t, 2 H, J = 7 Hz, trans CH_2N)] spectra were consistent with the structure and literature reports.[17,18] The mass spectrum (70 eV) showed *m/e* (rel intensity) 186 (M^+, 3), 169 (11), 129 (5), 128 (19), 113 (15), 100 (10), 98 (37), 84 (13), 71 (18), 58 (22), 57 (10), 44 (38), 43 (100), 42 (25), 41 (47), 39 (19), 30 (15), 29 (26), 27 (26).

Anal. Calcd for $C_{10}H_{22}N_2O$: C, 64.47; H, 11.90; N, 15.04. Found: C, 64.36; H, 11.99; N, 15.25.

Tri-*n*-pentylamine was Distillation Products Industries White Label. Solvents were reagent grade materials, redistilled before use. Silver nitrate was Baker Analyzed reagent grade.

Nmr spectra were obtained using a Varian A-60 instrument; mass spectra used a GEC-AEI MS-12 spectrometer. Melting points were determined by hot-stage microscopy and were corrected. Analyses were performed by Galbraith Laboratories, Inc.

Phase Diagram.—The form of the diagram and the eutectic temperature (41.4 ± 0.5°) were determined by observation of the Kofler contact preparation[19] on a Reichert–Kofler RCH-4065 hot-stage microscope. The liquidus curve was fixed by hot-stage observations of the temperature of last-crystal disappearance on thoroughly ground mixtures of known composition prepared using a microbalance. Visual identification of the excess component after eutectic fusion allowed convergence on the eutectic composition, which was fixed by this method at 42.3 ± 0.5 mol % $AgNO_3$. A second determination of the eutectic composition was made by elemental analysis of the liquid eutectic obtained in the following manner. $AgNO_3$-rich melts were seeded with $AgNO_3$, cooled slowly to *ca.* 42°, and placed in a constant-temperature bath at the eutectic temperature. Liquid samples were withdrawn and analyzed as equilibrium was established over several days, with the results shown in Table IV. The limiting composition obtained from the carbon analyses is in excellent agreement with that obtained by hot-stage microscopy. As expected,[20] the hydrogen determinations were confirmatory but less precise. The liquidus curve is unreliable beyond *ca.* 50 mol % $AgNO_3$ ($\gtrsim$150°) due to evident decomposition on the hot stage. There is evidence of incomplete liquid–liquid miscibility just above the liquidus in the vicinity of 70 mol % $AgNO_3$, but this may be an artifact produced by decomposition.

TABLE IV

COMPOSITION OF THE $(n\text{-}C_5H_{11})_4NNO_3$–$AgNO_3$ EUTECTIC LIQUID

Time, hr	Wt % C	Mol % $AgNO_3$	Wt % H	Mol % $AgNO_3$
45	47.00	46.9	8.74	45.7
65	49.23	42.9	9.13	41.8
90	49.91	41.7	9.43	38.5
115	49.33	42.8	9.47	38.2
		Mean 42.5 ± 0.5[a]		Mean 39.5 ± 1.6[a]

[a] Last three values.

Analytical Procedure.—Vacuum pyrolysates recovered from cold traps were transferred with dioxane and made up to 5.0 or 10.0 ml in volumetric flasks (runs of Table I). Products of reactions conducted in ampoules (runs of Table III) were triturated with dioxane or ethyl ether (in which the quaternary salts are insoluble) and filtered; filtrate and washings were made up to 10.0 ml in volumetric flasks.

These solutions were chromatographed on a 5 ft × 0.25 in. column packed with 10% Carbowax 20M on Chromosorb W, manually programmed between 90 and 190° using a Varian 90-P chromatograph with thermal conductivity detection. Peak areas from duplicate 25-μl samples were planimetrically compared with those from standard solutions chromatographed before and after the unknown. The analytical precision was ±0.3%, the detection limit for dipentylnitrosamine, 3 × 10^{-4} mmol/ml.

(8) E. Schmidt and H. Fischer, *Ber.*, **53**, 1537 (1920).

(9) Nitration of R_3N is also said to form the nitramine, R_2NNO_2;[10] this may result from oxidation of R_2NNO by HNO_3.[11]

(10) Reference 4a, p 33.

(11) F. Reverdin, *Bull. Soc. Chim. Fr.*, [4] **9**, 43 (1911).

(12) P. A. S. Smith and R. N. Loeppky, *J. Amer. Chem. Soc.*, **89**, 1147 (1967).

(13) P. A. S. Smith and H. G. Pars, *J. Org. Chem.*, **24**, 1325 (1959).

(14) A. F. Ferris, K. W. McLean, I. G. Marks, and W. D. Emmons, *J. Amer. Chem. Soc.*, **75**, 4078 (1953).

(15) K. K. Carroll and G. F. Wright, *Can. J. Res. Sect. B*, **26**, 271 (1948).

(16) H. Zimmer, L. F. Audrieth, M. Zimmer, and R. A. Rowe, *J. Amer. Chem. Soc.*, **77**, 790 (1955).

(17) R. N. Haszeldine and B. J. H. Mattinson, *J. Chem. Soc.*, 4172 (1955).

(18) G. J. Karabatsos and R. A. Taller, *J. Amer. Chem. Soc.*, **86**, 4373 (1964).

(19) L. Kofler and A. Kofler, "Thermo-Mikro-Methoden," Verlag-Chemie, Weinheim, 1954.

(20) F. W. Power, *Mikrochemie*, **22**, 263 (1937).

Vacuum Pyrolyses.—Samples (0.1 mmol) weighed into Pyrex boats were placed in a horizontal Pyrex pyrolysis tube whose entrance was then sealed off and whose exit led to a U-tube and thence to a vacuum line, the unit being formed from a single piece of glass. The system was pumped out to 10^{-3} Torr, the U-tube immersed in liquid N_2, and the pyrolysis tube heated in an air bath at 250° for 1 hr followed by 30–45 min at 270–280°. The U-tube trap was then sealed off, removed, warmed to 0°, and opened.

Reaction of $AgNO_3$–R_4NNO_3 with Carbon Tetrachloride.—Silver nitrate and tetrapentylammonium nitrate were weighed into a 5-ml ampoule and the mixture was protected from atmospheric moisture and heated at 100–110° for 24 hr to produce a homogeneous melt. CCl_4 and any other additives were added to the cooled mixture *via* a microliter syringe, and the ampoule was sealed, heated under the conditions specified in the tables, chilled, and opened.

Identification of dipentylnitrosamine in a typical product was accomplished by triturating with ether and filtering off AgCl, $AgNO_3$, and R_4NNO_3. Evaporation of the filtrate left a yellow oil whose gc retention time, nmr and mass spectra were those of authentic dipentylnitrosamine. The ir spectrum was that of dipentylnitrosamine plus bands at 3500–2200, 1720, and 945 cm^{-1} attributable to valeric acid. Gas chromatographic evidence for both valeraldehyde and valeric acid was obtained but irreproducibility prevented quantitation.

Pyrolysis of Tripentylammonium Nitrate.—A solution of 1.001 g (4.41 mmol) of tripentylamine in 40 ml of ethanol was treated with 1.04 ml of 5.03 *N* nitric acid (5.23) mmol), and the solution was evaporated (45–50°, 15 Torr) to a yellow oil, 0.1-mmol samples of which were sealed into ampoules, heated at 150° for 24 hr, and worked up as above.

Reaction of Tripentylamine with Silver Nitrate.—(a) A solution of 425 mg (2.50 mmol) of $AgNO_3$ and 50 μl (0.171 mmol) of tripentylamine in 3 ml of nitrobenzene was heated at 110° for 24 hr. Metallic silver was deposited as a mirror and a powdery precipitate, which was filtered and washed with ether. The filtrate was made up to 10.0 ml with ether and analyzed by the standard gc procedure. (b) A solution of 124 mg (0.726 mmol) of $AgNO_3$ and 100 μl (0.342 mmol) of tripentylamine in 3 ml of *tert*-butyl alcohol was refluxed for 24 hr and worked up as in (a). (c) A mixture of 117 mg (0.687 mmol) of $AgNO_3$ and 100 μl (0.342 mmol) of tripentylamine was heated at 110° for 24 hr and worked up as in (a).

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Registry No.—Di-*n*-pentylnitrosamine, 13256-06-9; silver nitrate, 7761-88-8; carbon tetrachloride, 56-23-5; tetrapentylammonium nitrate, 682-02-0; tripentylammonium nitrate, 41507-71-5; tripentylamine, 621-77-2.

Electron Transfer with Aliphatic Substrates. Oxidation of Cyclohexane with Cobalt(III) Ions Alone and in the Presence of Oxygen

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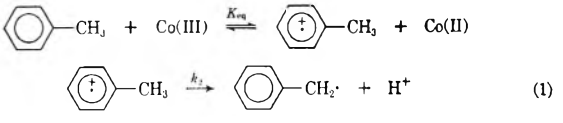
An electron-transfer mechanism is proposed for the oxidation of cyclohexane involving initial interaction of C–H σ bonds with cobalt(III) ions. This mechanism is much broader in scope than the presently accepted radical cation concept limited to alkylbenzenes. In the light of our findings, formation of radical cations with alkylbenzenes is treated as an accompanying phenomenon. In the oxidation of cyclohexane with cobaltic acetate, major products were cyclohexyl acetate, 2-acetoxycyclohexanone, and cyclohexylidene diacetate. Minor products included cyclohexanol, cyclohexanone, and bicyclohexyl. Reactivities of cyclo aliphatic substrates toward cobalt(III) ions investigated followed the sequence *cis*-decalin > *trans*-decalin > *cis*-1,2-dimethylcyclohexane ~ toluene > *trans*-1,2-dimethylcyclohexane > cyclohexane ~ cyclohexane-d_{12} > methylcyclohexane > *trans*-1,4-dimethylcyclohexane, indicating a significant steric effect, just as found with several alkyl aromatics. Oxidation of cyclohexane in the presence of cobaltic acetate and oxygen afforded adipic acid as the major product. Similar reactivities for cyclohexane and also for methylcyclohexane toward cobalt(III) ions alone or with cobalt(III) ions in the presence of oxygen suggest rate-determining electron transfer from the substrate to cobalt(III) ion, both in the presence and absence of oxygen.

A new system for oxidizing alkylbenzenes in the presence of large amounts of cobaltic acetate was described in 1960.[1] Recent papers in this area have dealt mostly with the oxidation of toluene.[2-6] Heiba, *et al.*,[7] in a more recent paper, attempted to finalize the mechanism and suggested the intermediacy of radical cations through isolation of nuclear and side chain substituted products. With several substrates, radical cations were detected by esr spectroscopy.[8] They suggested a mechanism, similar to that proposed by Dewar[9] for the manganic acetate oxidation of *p*-methoxytoluene. This electron-transfer concept offered an explanation for the changed reaction parameters of the new system which required a mechanism different from oxidation by a free radical pathway (eq 1). The rate constant is a product of K_{eq} and k_2, the rate-limiting step.



(1)

In our work, attention has been focused on the aliphatic portion of alkyl aromatic substrates as it is clearly the one undergoing oxidative attack. We compared relative reactivities of primary (methyl), secondary (ethyl), and tertiary (isopropyl) alkyl substituents attached to the aromatic nucleus. In the oxidation of *p*-cymene preferential methyl group oxidation was ob-

(1) W. F. Brill, *Ind. Eng. Chem.*, **52**, 837 (1960).
(2) K. Sakota, Y. Kamiya, and N. Ohta, *Can. J. Chem.*, **47**, 387 (1969).
(3) T. A. Cooper and W. A. Waters, *J. Chem. Soc. B*, 687 (1967).
(4) Y. Ichikawa, G. Yamashita, M. Tokashiki, and T. Yamaji, *Ind. Eng. Chem.*, **62**, 38 (1970).
(5) T. Morimoto and Y. Ogata, *J. Chem. Soc. B*, **62**, 1353 (1967).
(6) Y. Kamiya and M. Kashima, *J. Catal.*, **25**, 326 (1972).
(7) E. I. Heiba, R. M. Dessau, and W. J. Koehl, Jr., *J. Amer. Chem. Soc.*, **91**, 6830 (1969).
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(9) P. J. Andrulis, M. J. S. Dewar, R. Dietz, and R. Hunt, *J. Amer. Chem. Soc.*, **88**, 5473 (1966).

served.[10] Methyl group attack was also prevalent in the oxidation of 1,1-di(*p*-tolyl)ethane and 1,1-di(3,4-dimethylphenyl)ethane.[11] Subsequently, purely aliphatic substrates, such as *n*-butane,[12] *n*-pentane,[12] and cyclohexane, were found to react under identical conditions with formation of carboxylic acids in high selectivity. Oxidation of methylcyclohexane and isobutane proceeded at comparatively lower rates, following a pattern shown in the oxidation of branched chain alkyl aromatics. These observations indicate basically the same mechanism operating in both the oxidation of alkane and alkylbenzenes involving electron transfer from C–H σ bond to Co(III) ion. No reason is seen for a different pathway for alkyl aromatic substrates which appropriately should be considered phenyl-substituted alkanes.

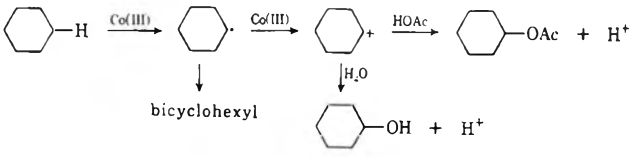
Results and Discussion

Oxidation of Cyclohexane with Cobaltic Acetate.—To elucidate the interaction of cobaltic ion with aliphatic substrates, cyclohexane was treated with cobaltic acetate in acetic acid in the absence of oxygen at 78–80°. The stoichiometry for this reaction was ~7.5 mmol of Co(III)/mmol of cyclohexane reacted at 1.6% hydrocarbon conversion. This ratio is considerably higher than for the oxidation of toluene in the same system, suggesting further oxidation of primary products. The rate of cyclohexane attack by Co(III), however, was slower than for toluene.

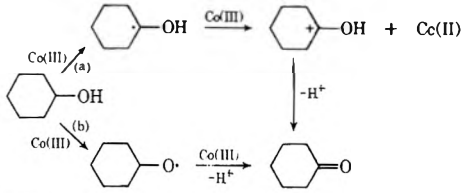
Major products of the reaction were 2-acetoxycyclohexanone (48.8 wt %), cyclohexyl acetate (35.4), and cyclohexylidene diacetate (14.0), identified by vpc by doping with standards and confirmed by mass spectroscopy by their fragmentation patterns. Minor products detected by vpc were cyclohexanone, cyclohexanol, and bicyclohexyl. These products accounted for ~69% of Co(III) ions reduced.

With oxygen excluded from the system, oxygenated derivatives probably arose from interactions involving water of hydration from $Co(OAc)_2 \cdot 4H_2O$[13] or the hydroxyl ligands in $Co(OAc)_3OH$ and $Co(OAc)_4(OH)_2$.[14,15] In agreement with observed stoichiometry, the pathways in Schemes I–III account for the

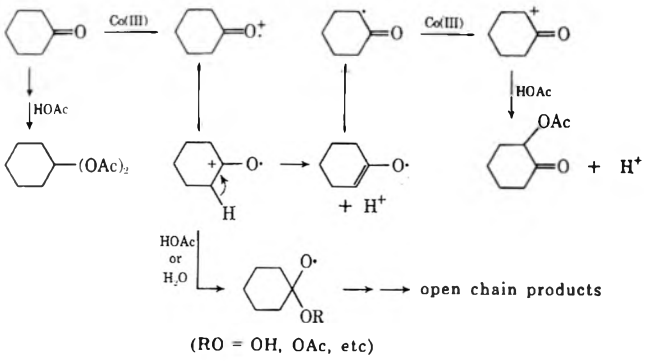
SCHEME I



SCHEME II



SCHEME III



(RO = OH, OAc, etc)

majority of the products. Their nature suggests cyclohexanone as an intermediate, which in turn can be produced from cyclohexanol. Preferential capture of cyclohexyl carbonium ions by the more nucleophilic hydroxyl rather than the acetate ions, explains the observed product distribution. Direct interaction of Co(III) ions with the C–H σ bond is apparent. This is consistent with observations of Waters, *et al.*,[3] who found the oxidation of cyclohexane with Co(III) ions and oxygen to be first order with respect to both cyclohexane and Co(III) in aqueous acetonitrile. Additional evidence is the fact that oxidation of cyclohexane with Co(III) salt in the presence of 0.2 *M* cupric acetate, a common radical terminator *via* electron transfer, proceeded without difficulty. This indicates that the reaction is not dependent on hydrogen abstraction by free radicals. Therefore, C–H σ bonds are the electron donors to the Co(III) ion.

In the presence of oxygen, the mechanism must include interactions between cyclohexyl radicals and oxygen, as well as one or more regenerative steps for Co(II)–Co(III).

Oxidation of Cyclohexane with Co(III) Salt and Oxygen.—Oxidation of cyclohexane with cobaltic acetate and oxygen in acetic acid [95° (1.7 atm)] gave adipic acid as the main product (up to 75% efficiency, 45% conversion) along with smaller amounts of glutaric and succinic acids. Minor products included cyclohexyl acetate, lactones (ir), and unknown materials. Results with cyclohexane (Table I) under conditions identical with those employed in the oxidation of alkyl aromatics with Co(III) ions are surprising. The rate of cyclohexane oxidation again was found to depend on Co(III) ion concentration as in the case of the alkyl aromatic substrates (Table II).

To our knowledge, these experiments are the first examples of alkane oxidation by cobalt acetate. High selectivity and conversion to adipic acid distinguish this reaction from the classical free-radical oxidation of cyclohexane.

Relative Reactivities.—To determine the effect of structure on reactivity, rates of several cycloaliphatic substrates toward Co(III) ions were determined and compared to those observed in typical free-radical reactions (Table III). Relative reactivities for cyclohexane and methylcyclohexane were obtained by competitive oxidation with Co(III) ions alone. Reactivities were also determined for these substrates in the presence of Co(III) ions and oxygen, as well as for several other cycloalkanes. In view of nearly identical reactivities for these substrates in both systems,

(10) A. Onopchenko, J. G. D. Schulz, and R. Seekircher, *J. Org. Chem.*, **37**, 1414 (1972).
(11) A. Onopchenko and J. G. D. Schulz, *J. Org. Chem.*, **37**, 2950 (1972).
(12) J. G. D. Schulz and A. Onopchenko, *J. Org. Chem.*, **38**, 909 (1973).
(13) Cobaltic acetate was prepared from $Co(OAc)_2 \cdot 4H_2O$.[7]
(14) S. S. Lande and J. K. Kochi, *J. Amer. Chem. Soc.*, **90**, 5196 (1968).
(15) A. Tkac, K. Vesely, and L. Omelka, *J. Phys. Chem.*, **75**, 2575 (1971).

TABLE I

OXIDATION OF CYCLOHEXANE[a]

Expt	Reaction time, hr	Cyclohexane reacted, g (%)	Adipic acid, g (% efficiency)	Glutaric acid, g (% efficiency)	Succinic acid, g (% efficiency)	Other products[c]
1	2	35.4 (28.1)	39.1 (63.5)	8.1 (14.6)	2.9 (5.8)	16.0
2	2	32.3 (25.6)	36.1 (64.3)	6.5 (12.8)	2.5 (5.5)	12.2
3	3	45.3 (36.0)	53.9 (68.4)	9.7 (13.6)	3.3 (5.2)	14.0
4	3	44.7 (35.5)	50.4 (64.9)	8.9 (12.7)	3.0 (4.8)	11.0
5	4	55.1 (43.7)	61.6 (64.3)	10.7 (12.3)	3.3 (4.5)	8.5
6	5	56.9 (45.2)	65.4 (66.1)[d]	9.8 (11.0)	3.6 (4.5)	9.2

[a] At 95°, 1.7-atm oxygen pressure. Reactants: 126 g of cyclohexane, 300 g of HOAc, 3.7 g of cyclohexanone,[b] 9.4 g of $Co(OAc)_2 \cdot 4H_2O$. [b] Added as an initial source of peroxy radicals. [c] Weight per cent of total area by vpc. Minor products were cyclohexanone (trace), cyclohexanol (trace), cyclohexyl acetate, lactones (trace), and unknowns. Analysis was by vpc using internal standard procedure. Acids are by isolation. [d] Efficiencies approached 75% in some runs.

TABLE II

EFFECT OF CATALYST CONCENTRATION ON REACTION[a]

Expt	Reaction time, hr	Cyclohexane reacted g (%)	Adipic acid, g (% efficiency)	$Co(OAc)_2 \cdot 4H_2O$, g (wt % of HOAc)	Productivity, g of adipic acid/hr
1	8	66.6 (52.9)	67.1 (57.9)	9.4 (3.1)	8.4
2	8	59.8 (47.5)	59.8 (57.6)	4.7 (1.6)	7.5
3	8	51.7 (41.0)	46.6 (51.9)	3.6 (1.2)	5.8
4	5	26.6 (21.1)	23.1 (50.0)	2.4 (0.8)	4.6

[a] At 75°, 1.7-atm oxygen pressure. Reactants: 126 g of cyclohexane, 300 g of HOAc, 3.7 g of cyclohexanone.

TABLE III

REACTIVITY OF SELECTED HYDROCARBONS TOWARD Co(III) ION AND SOME RADICALS[a]

Hydrocarbon	Registry no.	Co(III), 78°	Co(III) + O_2, 100° (20 atm)	Ph·, 60°,[b] predicted reactivity	*t*-BuO·, 40°,[b] predicted reactivity
cis-Decalin			2.4 (34.7)[c]		
trans-Decalin			1.4 (10.6)[c]		
cis-1,2-Dimethylcyclohexane	2207-01-4		1.1		
Toluene[d]		1.00	1.00 (1.00)[c]	1.00	1.00
trans-1,2-Dimethylcyclohexane	6876-23-9		0.6		
Cyclohexane	110-82-7	0.50	0.47	3.6	6.0
Cyclohexane-d_{12}	1735-17-7	0.42			
Methylcyclohexane	108-87-2	0.19	0.24	4.6	6.6
Cumene	98-82-8	0.3[e]	0.2	2.9	2.3
trans-1,4-Dimethylcyclohexane	2207-04-7		0.1		
Chlorobenzene or *o*-dichlorobenzene[f]					

[a] Relative reactivities per molecule. [b] Calculated from data of Table VI of W. A. Pryor, D. L. Fuller, and J. P. Stanley, *J. Amer. Chem. Soc.*, **94**, 1632 (1972). [c] These are reactivities obtained from autoxidation rates. See F. Jaffe, T. R. Steadman, and R. W. McKinney, *ibid.*, **85**, 351 (1963), ref 8, and G. A. Russell, *ibid.*, **78**, 1047 (1956). [d] Assumed standard. [e] Reference 8, 65°. [f] Internal standard.

interaction of the hydrocarbon with Co(III) ions appears to be the rate-limiting step. This phenomenon was earlier observed with aromatic substrates.

Reactivities in the cobalt system are different from those predicted for typical free-radical abstractions by Ph· and *t*-BuO· radicals. This is particularly evident when compounds with tertiary hydrogen atoms such as methylcyclohexane, dimethylcyclohexanes, and cumene are considered. Lack of reactivity of the tertiary hydrogen appears to be associated with steric effects of both catalyst and substrate. The observed reactivity of toluene toward Co(III) ions is about twice that of cyclohexane. Higher rates with toluene, which on a per hydrogen basis is about eight times as reactive as cyclohexane, are due to the activating effect of a phenyl group on the C–H σ bond.

Finally, rates for oxidation of cyclohexane and perdeuteriocyclohexane by cobaltic ions were compared to each other, showing no isotope effect (Table IV). Earlier investigators have used cobalt compounds in catalytic amounts mostly for initiation.[16–19] Our results, however, are consistent with a mechanism in which metal ions act as chain carriers.

Kinetic Isotope Effect. Identical reactivities of cyclohexane toward Co(III) ions in the presence or absence of oxygen and rate dependence on Co(III) ion concentration suggest initial interaction of metal ions with the substrate. The nature of this interaction is not clear. It was of interest, therefore, to compare the oxidation rate of cyclohexane with that of the deuterated substrate and to observe a possible kinetic isotope effect. Because of the multiplicity of products formed in our system, even at low conversion level and high dilution, reactivities had to be based on the disappearance of the substrates, cyclohexane and cyclo-

(16) P. W. Sherwood, *Petrol. Process.*, **11** (5), 74 (1956).
(17) M. Sittig, *Hydrocarbon Process. Petrol. Refiner*, **41** (6), 181 (1962).
(18) I. V. Berezin, E. T. Denisov, and N. M. Emanuel, "The Oxidation of Cyclohexane," Pergamon Press, New York, N. Y., 1966.
(19) N. M. Emanuel, Ed., "The Oxidation of Hydrocarbons in the Liquid Phase," Pergamon Press, New York, N. Y., 1965.

TABLE IV
COMPETITIVE OXIDATIONS OF C_6H_{12}–C_6D_{12} MIXTURES WITH Co(III) IONS[a]

Expt	Temp range, °C	k_H/k_D[b]
1	78–80	0.85[c]
2	70–72	0.95[d] (0.86)[e]
3	40–42	0.80[f]
	Av	0.86

[a] *Ca.* 0.22 *M* Co(III) in HOAc and 0.1 *M* in C_6H_{12}, C_6H_{12}, and either in C_6H_6 or C_6H_5Cl as internal standard; experiments were 13–16 hr in duration in an inert atmosphere. [b] Analyses were carried out by mass spectrometry. Relative reactivities were calculated from

$$k_H/k_D = \log ([I_A/I_S]_f/[I_A/I_S]_i)/\log ([I_B/I_S]_f/[I_B/I_S]_i)$$

where I = intensity, A = C_6H_{12}, B = C_6D_{12}, and S = internal standard. Subscripts refer to initial and final molar concentrations. [c] In the presence of 1.0 *M* $NaOAc \cdot 3H_2O$. [d] In the presence of 0.3 M $NaOAc \cdot 3H_2O$. [e] Analysis of *n*-C_5 extract. [f] In the presence of 1.2 M LiCl to increase reactivity of Co(III), at the lower temperature.

hexane-d_{12}, a technique earlier used to determine the isotope effect in toluene oxidation.[7]

Reactivities of cyclohexane *vs.* cyclohexane-d_{12} (k_H/k_D) ranged from ~0.80 to 0.95 (average 0.86) in the range of 40–80°. The small inverse deviation of the k_H/k_D ratio from unity is considered to be within the limits of experimental error, although even small values could be explained on the basis of inductive and polarization differences of the C–D bond.[20] With aliphatic substrates, therefore, loss of proton does not occur in the rate-controlling step. In several of our experiments, rates increased with the addition of Co(III) ions and decreased with the addition of Co(II) ions, indicative of an equilibrium situation. Results are consistent with a two-step mechanism (eq 2) where

$$\begin{aligned} RH + Co(III) &\underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} X^+ + Co(II) \\ X^+ &\xrightarrow{k_2} R\cdot + H^+ \end{aligned} \qquad (2)$$

X is an electron-deficient species derived from the substrate by loss of an electron. Assuming a steady-state concentration of X^+, $d[X^+]/dt = 0$, the observed rate constant is given by $k_{obsd} = k_1k_2/k_{-1} + k_2$. When k_2 is small, *i.e.*, $k_2 \ll k_{-1}$, this expression can be approximated by $k_{obsd} = K_{eq}k_2$, as observed with aromatic substrates.[7] When k_2 is large, *i.e.*, $k_2 \gg k_{-1}$, the expression simplifies to $k_{obsd} = k_1$. The kinetic isotope ratio would then be represented by $k_H/k_D = k_{1H}/k_{1D}$. Since breaking or formation of C–H bonds is not involved in the proposed mechanism, the k_H/k_D ratio is expected to be close to unity. Also consistent with this scheme is the observation of an approximately constant k_H/k_D ratio over a wide temperature interval.

We therefore favor a mechanism in which the reaction proceeds over an equilibrium step, in which breaking or formation of C–H bonds is not rate controlling.

Mechanism.—We found that paraffins are oxidized by cobaltic ions and oxygen to carboxylic acids with high selectivity under conditions critical for alkylbenzene oxidation. Oxidations of paraffins and alkylbenzenes in this system appear analogous in the following respects: (1) high rates are observed at low temperature, (2) reactions are limited to Co(III) as the effective oxidant, (3) high selectivities to carboxylic acids are observed, (4) tertiary hydrogen is unreactive, often decreasing the reactivity of the substrate, (5) rates are dependent on Co(III) ion concentration, and (6) reactions are not inhibited by cupric ions. These observations suggest a similar mechanism for alkanes and alkylbenzenes. The π system therefore need not be invoked as a prerequisite for electron transfer to Co(III) ions. Interaction of the C–H σ bonds with Co(III) ions should satisfy oxidation of both hydrocarbon types.

The oxidation of alkanes and alkylbenzenes in this system differ in one respect. A kinetic isotope effect is observed with aromatic substrates (k_H/k_D, 3.7),[7] but not with the alkanes. This can be reconciled with a mechanism in which the rate-controlling step is governed by K_{eq} or k_2, depending on the stability of RH^+ (eq 3). For aromatic substrates K_{eq} is large compared to K_{eq} for the alkanes, where it is rate determining. Stabilization of RH^+ can occur to a varying degree through solvation, or redistribution of charge over several atoms *via* induction, resonance, or hyperconjugation. With initial attack at the σ C–H bond, the proposed mechanism is much broader in scope and not limited to alkylbenzenes, but applicable to other hydrocarbon substrates, including the alkanes. An accompanying phenomenon, formation of nuclearly substituted products in the the reaction of alkylbenzenes with Co(III) salts and added nucleophiles, could be rationalized assuming appropriate resonance structures which, however, need not be invoked for σ electron transfer.

$$\begin{aligned} RH + Co(III) &\underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} RH^+ + Co(II) \\ RH^+ &\xrightarrow{k_2} R\cdot + H^+ \end{aligned} \qquad (3)$$

Elucidation of the structure of the active cobalt species and the effect of changed ligands and added nucleophiles, or of the nature of the solvent system, are beyond the scope of this paper.

Experimental Section

Oxidation of Cyclohexane with Cobalt(III) Acetate and Oxygen.—Oxidations were carried out in a 1-l., 316 stainless steel, magnetically stirred autoclave (Autoclave Engineers, Inc., Erie, Pa.). A typical procedure used for the oxidation of cyclohexane is described in detail for an experiment at 104° and 20 atm of total pressure. A mixture consisting of 20 g of $Co(OAc)_2 \cdot 4H_2O$, 15 g of MEK, and 60 g of cyclohexane in 400 g of glacial acetic acid was charged into the autoclave. The autoclave was brought to the operating temperature and pressure, and held there for 3 hr. The autoclave was cooled and depressured, and the product mixture was removed. The crude product mixture, 545.0 g, was analyzed for water (5.7%), MEK (0.6%), and cyclohexane (0.5%) by vpc using acetone as internal standard. The low boiling components and solvent were removed under reduced pressure in a rotary evaporator, the residue was boiled in 300 ml of water until the solution had turned from dark green to pink, and the mixture was evaporated to dryness. The product was separated from the catalyst by extraction with acetone. Analysis of the isolated product showed 51.8 g (52.0% selectivity) of adipic acid, 7.8 g (8.6) of glutaric acid, and 17.8 g (22.2) of succinic acid to be in a mixture. Conversion of cyclohexane was ~95%. Analyses of experiments in Tables I and II were done by vpc employing 20% Carbowax 20M column and internal standard procedure.

(20) Lars Melander, "Isotope Effects on Reaction Rates," The Ronald Press, New York, N. Y., 1960.

Oxidation of Cyclohexane with Cobalt(III) Acetate.—A total of 23.7 g (285 mmol) of cyclohexane and 130 ml of 0.27 *M* cobalt(III) acetate in acetic acid were stirred under nitrogen atmosphere for 3 days at 70° until Co(III) ions were consumed. The mixture was cooled, diluted with water, saturated with NaCl, and extracted with ethyl ether. The organic layer was washed with water, dried with $MgSO_4$, and concentrated in a rotary evaporator to a volume of ~2 ml. Analysis by vpc identified the following products in order of their appearance on the chromatogram (10 ft × 0.25 in., 10% Carbowax 20M column at 90°): bicyclohexyl (1.8 wt %), cyclohexanone (trace), cyclohexyl acetate (35.4), cyclohexanol (trace), cyclohexylidene diacetate (14.0), and 2-acetoxycyclohexanone (48.8). On the basis of stoichiometry, 4 mol of Co(III) required/mol of cyclohexylidene diacetate, 2 mol/mol of cyclohexyl acetate, and 6 mol/mol of 2-acetoxycyclohexanone, the products accounted for ~69% of the oxidant consumed. The aqueous layer also contained small quantities of cyclohexanone and cyclohexanol which were not determined as well as open-chain products of cyclohexane on the basis of nmr, but their structures have not been established with certainty. Conversion of cyclohexane was ~1.6%. Major products were also identified by their fragmentation patterns (vpc–mass spectrum).

Competitive Rate Study.—Competitive oxidations on mixtures of substrates were done under conditions earlier described.[10] Initial concentration of each substrate was held at a low value (~1.0 *M*) to minimize possible solvent effects. After the initiation period was over, reaction was allowed to proceed for 5 min. Initial charge and the pentane extract of the final mixture were analyzed directly by vpc for the disappearance of starting hydrocarbons. Analyses were carried out by vpc using 20 ft × 1/8 in., 20% Carbowax 20M column (Hewlett-Packard 7620A research chromatograph, TC detector), and chlorobenzene or *o*-dichlorobenzene as internal standard. Peak areas were electronically measured. All reactivities were related to toluene using eq 4

$$\frac{k_a}{k_b} = \frac{\log ([A]_f/[A]_i)}{\log ([B]_f/[B]_i)} \quad (4)$$

where [A] and [B] refer to concentrations of the two substrates before and after the reaction in weight per cent.

Competitive oxidations with cobaltic salts alone were carried out in sealed ampoules under nitrogen atmosphere.

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Registry No.—Cobalt(III) ion, 7440-48-4; cobalt(III) acetate, 917-69-1.

Cleavage of Saturated Fatty Acid Amides by Anhydrous Hydrogen Fluoride–Boron Trifluoride

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N-n-Butylamides of long-chain, unbranched carboxylic acids undergo degradation, isomerization, and (in part) dimerization of the fragments when treated at 0–5° with liquid hydrogen fluoride saturated with boron trifluoride. The compounds studied were the *N-n*-butylamides of undecanoic, myristic, palmitic, and stearic acid. Two major classes of products were obtained: (1) saturated, branched *N-n*-butylamides and (2) saturated, branched *N,N'*-di-*n*-butyldiamides. The ratio of the former to the latter is 2:1. The products from *N-n*-butylundecanamide consist mainly of the following *N-n*-butylamides (relative proportions): 5-methylhexanamide (12.9%), 6-methylheptanamide (25.6%), 5-methylheptanamide (18.5%), 7-methyloctanamide (14.5%), and 6-methyloctanamide (6.5%). The branched diamides are predominantly of chain length C_{12}–C_{15} (acid moiety). Similar results are obtained with *N-n*-butylmyristamide, *N-n*-butylpalmitamide, and *N-n*-butylstearamide when treated under the indicated reaction conditions; however, *N-n*-butylamides of acid moiety chain length shorter than C_{10} (*e.g.*, the *N*-alkyloctanamide) are not affected. The probable mechanism of the reaction is discussed, and it is concluded that the inductive effect of the protonated amide group is important in determining the product distribution.

Acid-catalyzed isomerization and degradation reactions of saturated hydrocarbons have been extensively studied because of their practical importance in the petroleum industry.[2] This work has led to an understanding of certain fundamental aspects of these reactions and has also revealed interesting transformations such as the isomerization of *endo*-trimethylenenorbornane to adamantane.[3] Recently, new reactions in superacid media, such as direct alkylation and nitration of alkanes, have been explained as occurring by the intervention of pentacoordinated carbonium ions,[4,5] a development that has spurred additional interest in this field. However, there have been only scattered studies on the transformations of fatty acid derivatives under strongly acidic conditions.[6–9] The investigation of these reactions is rendered more complex by the presence of the carbonyl group; important questions about the effect of the functional group on the reactivity of C–C and C–H bonds in other parts of the molecule need to be answered. We report here the cleavage reactions of secondary aliphatic amides in the acidic medium hydrofluoric acid–boron trifluoride (HF–BF_3).

Results

In a typical experiment, one of the *N-n*-butylamides **1a–1g** (0.006 mol) was dissolved in 12 ml of liquid HF at 0–5° followed by saturation of the solution with

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(2) H. Pines and N. E. Hoffman in "The Friedel Crafts and Related Reactions," Vol. 2, part 2, George Olah, Ed., Interscience, New York, N. Y., 1964, Chapter 28.

(3) P. v. R. Schleyer and M. M. Donaldson, *J. Amer. Chem. Soc.*, **82**, 4645 (1960).

(4) (a) G. A. Olah, Y. Halpern, J. Shen, and Y. K. Mo, *J. Amer. Chem. Soc.*, **93**, 1251 (1971); (b) G. A. Olah and J. A. Olah, *J. Amer. Chem. Soc.*, **93**, 1257 (1971); (c) G. A. Olah and H. C. Lin, *J. Amer. Chem. Soc.*, **93**, 1259 (1971).

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(6) P. Blanchard, R. Perron, and M. Auffret, *Bull. Soc. Chim. Fr.*, **60**, 1194 (1968).

(7) C. Paquot, R. Perron, and J. Dulieu, *Bull. Soc. Chim. Fr.*, **60**, 1150 (1968).

(8) J. S. Showell, D. Swern, and W. R. Noble, *J. Org. Chem.*, **33**, 2697 (1968).

(9) I. S. Shepherd and J. S. Showell, *J. Amer. Oil Chem. Soc.*, **46**, 479 (1969).

$$R-\underset{\underset{O}{\|}}{C}-NH\text{-}n\text{-}C_4H_9$$

1a, R = n-C_7H_{15}
b, R = n-C_8H_{17}
c, R = n-C_9H_{19}
d, R = n-$C_{10}H_{21}$
e, R = n-$C_{13}H_{27}$
f, R = n-$C_{15}H_{31}$
g, R = n-$C_{17}H_{35}$

anhydrous BF_3. After standing at this temperature for 30 min, the reaction was quenched with water, and the organic products (70–90% by wt) were isolated and identified.

In each case where reaction was observed, the major products were (1) mixtures of saturated branched N-n-butylamides having chain lengths shorter than the starting amide (see Table I) and (2) mixtures of

TABLE I
MONOAMIDE PRODUCTS FROM THE REACTION OF SECONDARY AMIDES WITH HF–BF_3

$$RCNH\text{-}n\text{-}C_4H_9 \xrightarrow{HF\text{-}BF_3} R'CNH\text{-}n\text{-}C_4H_9$$

	Relative yields of monoamide products from starting amides		
Monoamide products, R′	1d, R = n-$C_{10}H_{21}$	1e, R = n-$C_{13}H_{27}$	1f, R = n-$C_{15}H_{31}$
2, $(CH_3)_2CH(CH_2)_3$-	12.9	17.3	9.7
3, $CH_3(CH_2)_5$-	0.4	0.2	0.2
4, $(CH_3)_2CH(CH_2)_4$-	25.6	25.8	22.3
5, $CH_3CH_2C(CH_3)H(CH_2)_3$-	18.5	17.6	14.5
6, $CH_3(CH_2)_6$-	1.3	1.4	0.8
7, $(CH_3)_2CH(CH_2)_5$-	14.5	11.4	12.7
8, $CH_3CH_2C(CH_3)H(CH_2)_4$-	6.5	4.7	5.3
9, $CH_3(CH_2)_7$-	2.3	2.5	2.3
10, $(CH_3)_2CH(CH_2)_6$-	3.6	2.9	6.2
11, $CH_3CH_2C(CH_3)H(CH_2)_5$-	1.9	1.1	2.7
12, $CH_3(CH_2)_8$-	1.9	0.9	1.7
Others	10.7[a]	14.2[b]	21.5[c]

[a] These are comprised of ten branched amides of unknown structure; each component is less than 2.1% of the total monoamides. [b] These are comprised of branched amides, 6.8% of which are unknowns of chain length C_{10} or less, and 7.1% are C_{11} and C_{12} branched amides. [c] These are comprised of branched amides of which 3.6% are unknowns of chain length C_{10} or less, and the remaining 17.9% are C_{11} and C_{12} branched amides.

saturated branched N,N'-di-n-butyldiamides (see Table II). A complex mixture of branched γ-lactones

TABLE II
DIAMIDE PRODUCTS FROM THE REACTION OF SECONDARY AMIDES WITH HF–BF_3

$$RCNHBu \xrightarrow{HF\text{-}BF_3} BuNHC(C_nH_{2n})CNHBu$$

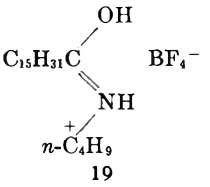
	Yields of diamide products from starting amides		
Saturated diamide products[a,b]	1d, R = n-$C_{10}H_{21}$	1e, R = n-$C_{13}H_{27}$	1f, R = n-$C_{15}H_{31}$
13, n = 9	1.7	3.6	0.8
14, n = 10	9.8	11.0	6.1
15, n = 11	26.2	28.7	21.9
16, n = 12	30.9	31.8	31.8
17, n = 13	16.0	15.1	21.1
18, n = 14	0	0	7.4
Others	15.4	9.8	10.9

[a] Bu = n-C_4H_9. [b] Only branched diamides were observed. The exact branching patterns have not been established.

(2–4%) and hydrocarbon polymers (10–20%) was also isolated.[10,11] The monoamides and diamides were isolated in amounts that accounted for 96–98% of the carbonyl-containing fragments, and the ratio of monoamides to diamides was generally about 2:1. The products were identified by conversion of the monoamides into the corresponding methyl esters **2e–12e** and comparison of their glpc retention times, mass spectra, and ir spectra to those of authentic samples.

The chain length of the starting amide does not greatly affect the production distribution in cases where reaction is observed apart from small proportions of products branched at positions more remote from the functional group. However, there is no reaction under our conditions when the starting amide acid chain contains fewer than ten carbon atoms. Thus, n-butylnonanamide (**1b**) is recovered unchanged and n-butyldecanamide (**1c**) undergoes only partial reaction in 30 min at 0°. Also, no reaction is observed unless trace amounts of unsaturated material are present. For example, olefin-free N-n-butylundecanamide (**1d**) is inert until a little methyl oleate is added as a promoter. We further checked our conclusions regarding the lack of reactivity of the shorter chain length amides by doing runs with mixtures of amides. When N-n-butyloctanamide (**1a**) and N-n-butylundecanamide (**1d**) were mixed and the reaction was completely consumed, while the former remained unchanged.

The results described here[12] may be compared with the isolation of stable amide hydrofluoroborates under similar conditions. The hydrofluoborate **19** can be



19

isolated when N-n-butylpalmitamide, **1f** (0.01 mol), is dissolved in 4 ml of liquid hydrogen fluoride followed by saturation with boron trifluoride.[13] However, if 0.01 mol of **1f** is dissolved in even a larger excess of hydrogen fluoride, and the solution is then saturated with boron trifluoride, the cleavage reaction is observed. Thus, by varying the amount of hydrogen fluoride saturated with BF_3, and therefore the ratio of BF_3 to amide, one of the two results may be selected. We have observed that an amide hydrofluoborate such as **19** also undergoes the cleavage reaction (when subjected to the conditions of our experiments with **1d–1f**) to give product distribution similar to that obtained from free amide starting material. It therefore seems likely that the first step in the reaction is formation of the amide hydrofluoborate.

(10) Yields were determined by assuming an average chain length of C_8 for monoamide products and an average chain length of C_{14} for diamide products. This average is based on the actual product distribution (Tables I and II).

(11) In certain cases (**1f**, **1g**) mixtures of hydrocarbon monomers were also isolated.

(12) Similar results were obtained using N-methyl- and N-*tert*-butylamides. Stearamide and N,N-dimethylstearamide also undergo fragmentation in HF–BF_3.

(13) S. S. Hecht and E. S. Rothman, *J. Org. Chem.*, **38**, 395 (1973).

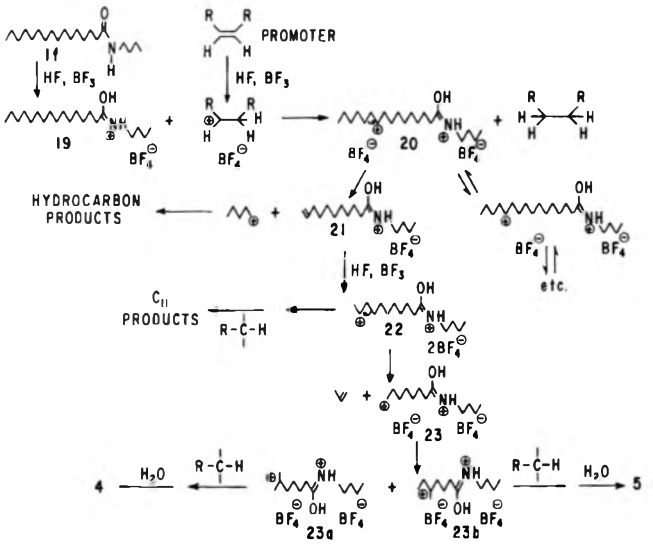
Discussion

In considering a rational explanation for these reactions, it is necessary to account for several facts of special significance. The first of these is the predominance of products having chain lengths (acid moiety) in the range of C_7–C_{10}, regardless of the alkyl chain length of the starting amide. Monoamides shorter than C_7 are not found in the final product mixtures and the C_{11}–C_{12} fractions from **1e** and **1f** are relatively small.

A second important feature is the virtual exclusion of straight-chain products which comprise, on the average, only 5.4% of the monoamide fraction. Unbranched compounds are not present to any significant extent in the diamide mixtures. Also, the selectivity in branching patterns is remarkable, particularly in the case of the C_7 product where *N*-*n*-butylisoheptanamide (**2**) is formed to the complete exclusion of the anteiso-amide. The monoamide product mixtures of longer chain lengths become increasingly complex; the C_{10} amides include three unknowns (4.5% of total monoamides) in addition to the iso-, anteiso-, and straight chain products. The decreased reactivity of short-chain amides is another special feature of the reaction.

A formal scheme accounting for monoamide products from *N*-*n*-butylpalmitamide (**1f**) is presented in Scheme I. The first steps are protonation of **1f** to give amide

SCHEME I



salt **19** and protonation of the trace olefin to give the promoter carbenium ion. Hydride abstraction from **19** by the promoter generates a new carbenium ion **20**. The positive charge on carbon in this intermediate can migrate *via* hydride shifts to other positions along the alkyl chain. There is ample precedent for this equilibration.[8,9,14,15] At positions closer to the carbonyl than C-5, the inductive effect of the strongly electron-attracting amide salt functionality apparently begins to deter carbenium ion formation. More evidence for this is presented later. There are several reaction pathways open to a typical intermediate such as **20**, but the most important one for purposes of this discussion is cleavage to give an amide and a hydrocarbon fragment as indicated.[16] The hydrocarbon fragment gives rise to polymeric material. The unsaturated amide fragment **21** may be protonated to give a new carbenium ion **22** which can undergo either further cleavage to an intermediate formally represented as **23**,[17] or rearrangement and hydride abstraction to give C_{11} products. The unstable ion **23** rearranges to the tertiary carbenium ions **23a** and **23b**, corresponding to the observed products **4** and **5**.[18] This generalized pathway leading to the same results may be written for other typical intermediates related to **20**.

An important aspect of this picture is the apparent lack of stability of intermediates in which the positive charge would be localized at C-4, C-3, or C-2 of the amide salt alkyl chain. Evidence for this is provided by the exclusive formation of *N*-*n*-butylisoheptanamide (**2**) as the C_7 product. By contrast, both the iso and anteiso C_8 amides **4** and **5** are observed in good yield. Rearrangement of a C_7 amide fragment (related to **23**) to *N*-*n*-butylanteisoheptanamide requires location of positive charge at C-4. The absence of this product indicates the probable difficulty of such a process. The isolation of traces of γ-lactones may reflect a certain number of cases in which C-4 carbenium ions were involved.[19] The high yield of the C_8 products **4** and **5** indicates the relative ease of carbenium ion formation at C-5 and C-6.

The predominance of monoamide products having chain length C_7 through C_9 results from the resistance of intermediates such as **23a** and **23b** to further cleavage. These carbenium ions have positive charge localized at the C-6 and C-5 positions. Further cleavage would involve placing a positive charge at the C-3 or C-4 positions, which appears to be energetically unfavorable because of the inductive effect of the amide salt group. By contrast, the intermediate **22** can undergo fragmentation to **23** without experiencing this effect.[20]

The dimeric amides probably result from alkylation of an unsaturated amide with an amide carbenium ion. The predominance of C_{13} and C_{14} diamides may reflect the fact that the C_6 and C_7 carbenium ion fragments have fewer avenues of stabilization available to them.

We have followed the development of products from the reaction of *N*-*n*-butylstearamide (**1g**) with hydrogen fluoride–boron trifluoride. The eventual product distribution for **1g** is similar to those outlined for **1d–f**. In the early stages of the reaction, a random distribution of product monoamides was observed, indicating initial cleavage from a variety of inter-

(14) M. F. Ansell, B. E. Grimwood, and T. M. Kafka, *J. Chem. Soc. C*, 1802 (1967).

(15) M. F. Ansell and G. F. Whitfield, *J. Chem. Soc. C*, 1098 (1971).

(16) Rearrangement of **20a** may precede cleavage, but for simplicity we consider an unrearranged intermediate. Also cleavage to a charged amide fragment and an olefin is possible, but the eventual result is the same.

(17) The actual intermediacy of a primary carbenium ion is an open question. Certain nonclassical ions corresponding to **23** are possible. Also **22** may undergo direct fragmentation to two olefinic molecules.

(18) See D. A. McCaulay, *J. Amer. Chem. Soc.*, **81**, 6437 (1959), for a discussion of the mechanism of isomerization of hydrocarbons under conditions similar to ours.

(19) Only a small fraction of this mixture could have arisen from ring closure of the precursor to *N*-*n*-butylanteisoheptanamide. Ring closure to lactonic products could also proceed through attack on a Δ^4 double bond.

(20) See ref 15 where the same trend is observed in the Friedel–Crafts reactions of alkanoic acids. The pK_a values for $H_3N^+(CH_2)_xCO_2H$ show small increases in acidity over the unsubstituted acids for $x = 4$ and $x = 3$, and much greater effects at $x = 2,1$. The relative contributions of inductive *vs.* field effects in our experiments is not known.

mediates resembling **20**. As the reaction proceeded, the relative amounts of C_7–C_9 amides gradually increased, a result in agreement with the inhibition of further cleavage of species such as **23a** and **23b**. The fact that diamides were observed only after the accumulation of the shorter chain length monoamides indicates that they are probably secondary products.[21]

The lack of reactivity of *n*-butyloctanamide (**1a**) and *n*-butylnonanamide (**1b**) under our conditions probably reflects difficulty in the initial hydride abstraction step. If hydride abstraction were to take place, one might expect at least some isomerization of the starting amide; this is not observed. It seems unlikely that the inductive effect of the amide salt group would play an important role at C-7 or C-8. Other features may be involved in this bimolecular reaction; for example, the approach of the promoter carbenium ion may be hindered by the repulsion of the amide salt positive charge.

From our results, we conclude that the inductive effect of the amide salt functionality is important in determining the eventual product distribution when secondary amides **1d–f** are allowed to undergo the acid-catalyzed cleavage reaction. This conclusion leads to the possibility that reactions of this kind might be controlled to give only prescribed products by judicious placement of suitable electronegative groups.

Experimental Section

Equipment.—Melting points (uncorrected) were determined on a Kofler hot stage. Infrared spectra were measured on a Perkin-Elmer[22] Model 457 grating spectrophotometer. Nmr spectra were recorded on a Jeolco C-60H[15] high-resolution nmr spectrometer. Mass spectra were determined with a Du Pont Model 21-492 mass spectrometer. Combined gas chromatographic–mass spectrometric analyses were obtained using this instrument coupled to a Varian Aerograph gas chromatograph *via* a jet type separator; data were collected with the aid of a Digital Equipment Corporation PDP-12 computer. Routine gas chromatographic runs were conducted with a Hewlett-Packard Model 5750 research chromatograph equipped with a thermal conductivity detector and the following columns: column A (6 ft × 1/4 in. 25% diethylene glycol adipate–3% phosphoric acid on 60–80 Chromosorb A), column B (30 ft × 1/8 in. 15% Carbowax on 45–60 Chrom W), column C (6 ft × 1/4 in. 15% OV-1 on 60–80 W AW DMCS).

Materials.—Commercial grade BF_3 and HF were used directly. The *N*-*n*-butylamides, **1a–e**, were prepared by reaction of *n*-butylamine with the appropriate acid chloride. The amides, **1f–g**, were prepared *via* the method of Jordan and Port.[23] The amides **1a**, **1c**, and **1g** had physical properties in agreement with the reported values.[23–25] Amides **1b**, **1d**, **1e**, and **1f** which have not been reported previously, gave the expected ir and nmr spectral properties and elemental analyses were in accord with expected values. Boiling or melting points are as follows: **1b** (R = *n*-C_8H_{17}), bp 115° (0.2 mm); **1d** (R = *n*-$C_{10}H_{21}$), mp 47–47.2°; **1e** (R = *n*-$C_{13}H_{27}$), mp 66–67°; **1f** (R = *n*-$C_{15}H_{31}$), mp 75–76°.

Reaction of *N*-*n*-Butylamides 1a–g with HF–BF_3.—All HF reactions were performed in a graduated polyethylene bottle with an inlet tube for attachment to HF and BF_3 cylinders and an exit tube protected by calcium sulfate. The usual precautions to maintain dryness were taken. Appropriate safety precautions should be taken to avoid toxicity and severe burns in the handling of HF.

The procedure described here for *n*-butylpalmitamide (**1f**) is identical with that used for all other amides. The amide, **1f** (1.83 g, 0.006 mol), and 1 drop of methyl oleate were dissolved in liquid HF (12 ml) at 0–5°, and BF_3 was bubbled in for 6 min at a moderate rate, or until excess BF_3 was visible in the exit tube. The resulting solution was allowed to stand at 0–5° for 30 min. During this time, a small upper layer appeared.[26] The reaction was terminated by cautious dropwise addition of H_2O (15 ml). Extraction (CH_2Cl_2), combination of organic layers, drying (Na_2SO_4), and evaporation of solvent gave an oil, 1.34 g.

Analysis of Products from 1f.—The oil obtained from the reaction of **1f** with HF–BF_3 was chromatographed on a column of dry Florisil (45 × 4 cm) with sequential elution by CH_2Cl_2, Et_2O, and MeOH to give the following fractions: fraction A (30 mg), fraction B (40 mg), fraction C (610 mg), fraction D (380 mg). These fractions were each examined and had the following spectral and chromatographic properties.

Fraction A (polymeric hydrocarbons; elution with CH_2Cl_2): ir (film) 3000–2800, 1450, 1380 cm^{-1}; nmr ($CDCl_3$) δ 2.5–0.5 (m); glpc (column C, 70–300°, programmed temperature rise 2°/min), no peaks other than solvent.

Fraction B (γ-lactones, elution with CH_2Cl_2): ir ($CHCl_3$) 3000–2850, 1760 (lactone carbonyl), 1460 cm^{-1}; nmr ($CDCl_3$) δ 2.56 (m, $-CH_2C(O)=O-$), 2.1–0.6 ppm (m); mass spectrum *m/e* a series of peaks 99 (4-methyl γ-butyrolactone fragment), 113, 127, 141, 155, 169, etc.; glpc (column C, 50–300°, 4°/min), a complex mixture of at least 20 components eluting between 135–210°.

Fraction C (monoamides, elution with Et_2O): ir ($CHCl_3$) 3455, 3000–2850, 1660, 1460 cm^{-1}; nmr ($CDCl_3$) δ 6.02 (1 H, broad s, –NH), δ 3.30 (2 H, q, $-C(=O)NHCH_2CH_2-$), 2.21 (2 H, t, $CH_2CH_2C(=O)N-$), 1.80–0.7 (22 H, m); glpc (column A, 200°), peak 1 (rel retention time 1.00), peak 2 (1.44), peak 3 (2.02), peak 4 (2.76), peak 5 (3.84); mass spectrum *m/e* (rel intensity of peak 1, 185 (10), molecular ion, 170 (15), 142 (20), 128 (18), 115 (100), peak 2, 199 (15), mol ion, 184 (20), 128 (50), 115 (100); peak 3, 213 (5), molecular ion, 128 (25), 115 (100); peak 4, 227 (5), molecular ion, 128 (30), 115 (100). These spectra are characteristic of saturated *n*-butylamides corresponding to the C_7–C_{10} acids, respectively (peak 5-C_{11}). However, comparison of retention times with those of straight-chain *n*-butylamides indicates branching; *e.g.*, relative retention time of *n*-butyloctanamide on column A at 200° = 1.72.

Fraction D (diamides, elution with MeOH): ir ($CHCl_3$) 3455, 3000–2850, 1660, 1460 cm^{-1}; nmr ($CDCl_3$) δ 5.95 (2 H, broad s, $-C(=O)NH-$), 3.30 (4 H, q, $-C(=O)NHCH_2CH_2-$), 2.20 (4 H, t, $-CH_2CH_2C(=O)NH-$), 1.9–0.8 (34 H, m); glpc (column A, 200°), no peaks visible.

Hydrolysis of Monoamides (Fraction C) and Identification of Products.—The monoamide mixture (610 mg) was added to ethylene glycol (14 ml) and 4 *M* aqueous KOH (2 ml). The mixture was stirred and allowed to reflux for 48 hr. After cooling, it was poured into H_2O (50 ml) and extracted (Et_2O) to give a neutral fraction which contained no extractable material. The aqueous phase was acidified (aqueous HCl) and extracted (Et_2O). The ethereal layers were dried (Na_2SO_4) and concentrated giving 440 mg of acids (100%). The acids were converted into methyl esters with CH_2N_2 and analyzed by glpc (column B, 70–150°, 2°/min) and by combined glpc–ms techniques (same column) giving the following results in peak number (rel retention time, percentage, molecular ion, compound no.): 1 (1.00, 9.7, 144, 2e), 2 (1.12, 0.2, 144, 3e), 3 (1.43, 22.3, 158, 4e), 4 (1.47, 14.5, 158, 5e), 5 (1.54, 1.6, 172, unknown), 6 (1.57, 0.8, 158, 6e), 7 (1.73, 12.7, 172, 7e), 8 (1.76, 5.3, 172, 8e), 9 (1.82, 1.6, 186, unknown), 10 (1.86, 2.3, 172, 9e), 11 (1.99, 2.0, 186, unknown), 12 (2.04, 6.2, 186, 10e), 13 (2.06, 2.7, 186, 11e), 14 (2.13, 4.1, 200, unknown), 15 (2.19, 1.7, 186, 12e), 16 (2.33, 9.0, 200, unknown), 17 (2.38, 3.1, 200, unknown). Each component gave rise to characteristic mass spectral peaks for methyl esters of saturated acids (base peak, *m/e* 74). In each case where identifications have been made, the mass spectra and ir spectra (obtained by trapping) were identical with those of authentic samples. The un-

(21) See ref 6 and 18 in which dimers are thought to be the precursors of monomeric cleavage products.

(22) Reference to brand or firm name does not constitute endorsement by the U. S. Department of Agriculture over others of a similar nature not mentioned.

(23) E. F. Jordan, Jr., and W. S. Port, *J. Amer. Oil Chem. Soc.*, **38**, 600 (1961).

(24) R. F. Moore, *Polymer*, **4**, 493 (1963).

(25) R. R. Mod, E. L. Skau, S. P. Fore, F. C. Magne, A. F. Novak, H. P. Dupuy, J. R. Ortego, and M. J. Fisher, U. S. Patent 3,285,809; *Chem. Abstr.* **66**, 28787*y* (1967).

(26) This additional layer was observed with **1f** and **1g** but not with the other amides. In one case, this material was isolated by transfer to a separatory funnel and recovery of 20 mg of an extremely complex mixture of saturated and unsaturated hydrocarbons.

known components from reactions of amides other than **1f** were the same ones as listed above, with slight variations in percentages. Analysis by glpc was also performed using column C (50–300°, 2°/min) and no additional components were observed.

Hydrolysis of Diamides (Fraction D).—The diamides (380 mg) were hydrolyzed to the corresponding diacids by exactly the same procedure used for hydrolysis of fraction C. This gave diacids (230 mg, 92%) which were esterified with CH_2N_2 and analyzed by glpc (column C, 150–300°; 2°/min) and by combined glpc–mass spectrometry giving the following results in peak number (rel retention time, percentage, number of corresponding diamide in text): 1 (1.00, 0.8, **13**), 2 (1.26, 6.1, **14**), 3 (1.51, 21.9, **15**), 4 (1.61, 6.6, **16**), 5 (1.77, 25.2, **16**), 6 (1.85, 8.7, **17**), 7 (2.00, 12.4, **17**), 8 (2.09, 7.4, **18**), 9 (2.24, 4.9), 10 (2.32, 3.0), 11 (2.55, 1.2). Typical of the mass spectra obtained in this series and characteristic of diesters is that observed from peak 3: *m/e* (rel intensity) 241 (10) (M − 31), 199 (25); 167 (25), 126 (40), 112 (84), 98 (84), 74 (82), 55 (100). The other peaks simply gave rise to homologous spectra. Branching was firmly established by comparison of retention times to those of authentic straight-chain diesters, for example, dimethyl tridecanedioate, rel retention time 1.66, compared to 1.51 for **15**.

Acknowledgment.—The authors express their gratitude to S. F. Osman and C. J. Dooley for combined glpc–mass spectral determinations.

Registry No.—**1b**, 24928-30-1; **1d**, 41328-62-5; **1e**, 41328-72-7; **1f**, 41328-73-8; **1g**, 4219-50-5; HF–BF_3, 16872-11-0.

Conversion of a Saturated to an Unsaturated Acid by Pyridine *N*-Oxide[1a–c]

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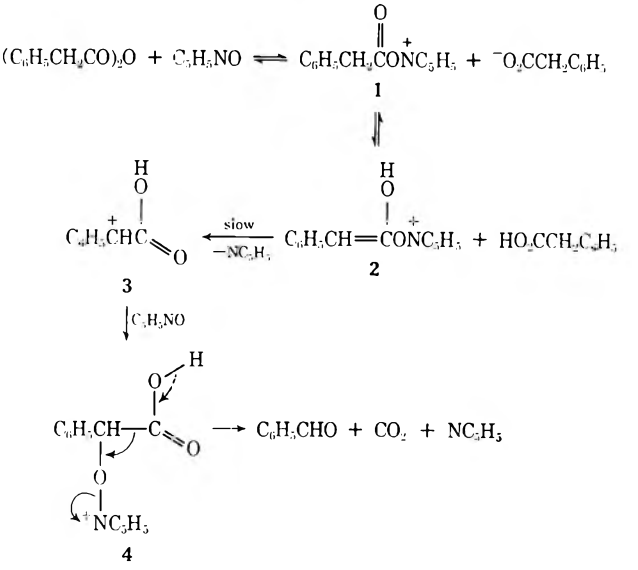
Oxidation of 2,3-diphenylpropanoic acid by pyridine *N*-oxide in the presence of acetic anhydride yields the normal decarboxylative oxidation product deoxybenzoin (**7**, 25%) in addition to the cis and trans isomers of 2,3-diphenylpropenoic acid (**8**, 20%) and 2-acetoxy-2,3-diphenylpropanoic acid (**9**, 43%). The production of **8** and **9** is taken as further evidence that a key intermediate bearing a cationic site α to a carboxyl function (in this case **6**) is involved in such reactions. The mass spectral fragmentation pattern of methyl 2,3-diphenylpropenoate is discussed in terms of a 1,3-methoxyl migration in the parent radical cation.

Certain carboxylic acid anhydrides which possess an acidic α hydrogen atom may be oxidatively decarboxylated by aromatic amine oxides.[2–5] For example, the oxidation of phenylacetic anhydride by pyridine *N*-oxide produces benzaldehyde and proceeds according to the following stoichiometry.

$$(C_6H_5CH_2CO)_2O + 2C_5H_5NO \longrightarrow C_6H_5CHO + 2C_5H_5N + CO_2 + C_6H_5CH_2CO_2H$$

In the presence of acetic anhydride, the corresponding carboxylic acid is readily oxidized in a similar manner.[2b,5] The first step in the reaction is thought[2–5] to involve reversible acylation of the *N*-oxide to give cation **1**. Deuterium isotope effect studies[6] and the requirement for an α hydrogen atom[2b,3c,5] suggest the reversible formation of an enol species **2** prior to the rate-determining step in which **2** is attacked in an SN1′ manner[7] by a second *N*-oxide molecule to yield the *N*-(α-carboxybenzyloxy)pyridinium ion **4**. In the latter step, the reactive electrophilic species **3** would be an intermediate.[8] Decarboxylative fragmentation of **4** with loss of pyridine would then lead to the major observed products. The scheme is consistent with the kinetics observed by Koenig.[4] Some such electrophilic intermediate has been trapped by acetic acid and by pyridine, each utilized as a solvent.[5] In the present paper, we present additional evidence for a cationic intermediate of type **3** in the oxidation of carboxylic acids by pyridine *N*-oxide.



Although one of the most characteristic reactions of carbocations is the loss of an adjacent proton to yield

(1) (a) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. (b) Partial support was provided by Grant GU-3184 from the National Science Foundation. (c) Taken, in part, from the Ph.D. thesis of J. A. Jenkins, University of Pittsburgh, Pittsburgh, Pa., 1970. (d) NASA Predoctoral Fellow.

(2) (a) T. Cohen and J. H. Fager, Abstracts, 146th National Meeting of the American Chemical Society, Denver, Colo., Jan 1964, p 36c; (b) T. Cohen, I. H. Song, and J. H. Fager, *Tetrahedron Lett.*, 237 (1965).

(3) (a) C. Rüchardt, S. Eichler, and O. Krätz, *Tetrahedron Lett.*, 233 (1965); (b) C. Rüchardt and O. Krätz, *ibid.*, 5915 (1966); (c) C. Rüchardt, O. Krätz, and S. Eichler, *Chem. Ber.*, **102**, 3922 (1969).

(4) (a) T. Koenig, *Tetrahedron Lett.*, 3127 (1965); (b) T. Koenig, *ibid.*, 2751 (1967).

(5) T. Cohen, I. H. Song, J. H. Fager, and G. L. Deets, *J. Amer. Chem. Soc.*, **89**, 4968 (1967).

(6) J. A. Jenkins and T. Cohen, Abstracts, 160th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1970, ORGN 172.

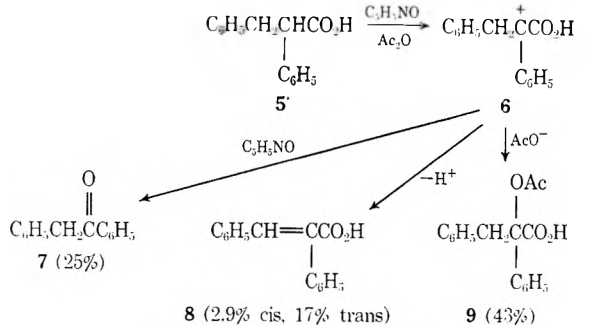
(7) T. Cohen, G. L. Deets, and J. A. Jenkins, *J. Org. Chem.*, **34**, 2550 (1969).

(8) The conjugate base of **3**, which is the open form of an α-lactone,[9] appeared as a reasonable intermediate at one time,[5] but Rüchardt[3c] has reported experiments, which have been confirmed by Koenig,[10] indicating that the behavior of a related α-lactone is unaffected by the presence of pyridine *N*-oxide.

(9) O. L. Chapman, P. W. Wojtkowski, W. Adam, O. Rodriquez, and R. Rucktäschel, *J. Amer. Chem. Soc.*, **94**, 1365 (1972).

(10) T. Koenig and T. Barklow, *Tetrahedron*, **25**, 4875 (1969).

an olefin, there are no reported cases of the production of an α,β-unsaturated carboxylic acid from the saturated acid by means of pyridine *N*-oxide. Such a process might be expected to be quite favorable for the cation **6**, which, after proton loss, would yield the extensively conjugated 2,3-diphenylpropenoic acid (**8**). The electrophilic species **6** would presumably be an intermediate in the oxidative decarboxylation of 2,3-diphenylpropanoic acid (**5**) by pyridine *N*-oxide. Alternatively, attack by the *N*-oxide on **6** would lead to deoxybenzoin (**7**), the expected redox product.



When a benzene solution of pyridine *N*-oxide was slowly added dropwise to a refluxing solution of 2,3-diphenylpropanoic acid (**5**) and excess acetic anhydride in benzene, under nitrogen, the expected products (**7**, **8**, and **9**) were formed in the indicated yields, based on 2,3-diphenylpropanoic acid consumed. A 3.2% yield of benzoin was also obtained. The *cis*- and *trans*-2,3-diphenylpropenoic acids (**8**) were identified by comparison of the glpc retention times and mass spectra of their methyl esters with those of authentic samples. The benzoin and deoxybenzoin had the same retention times as authentic samples. The ester **9** was identified by comparison of the spectral data of an isolated sample with those of an authentic specimen and by hydrolysis to the known 2,3-diphenylglycolic acid, which was identical with an authentic sample.

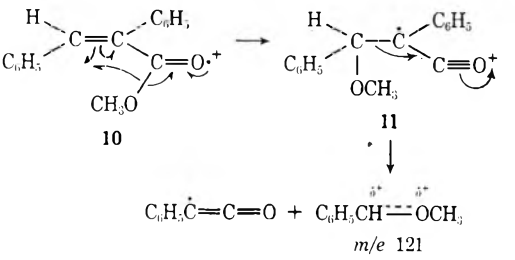
The benzoin may very well arise by oxidation of the deoxybenzoin by traces of air in the nitrogen that flowed through the system throughout the reaction. A control test indicated that air oxidation occurs in the presence of pyridine, but not in its absence, even when pyridine *N*-oxide is present. Benzoin is also not produced by the reaction of deoxybenzoin (**7**) with pyridine *N*-oxide in the presence of acetic anhydride.

The production of acetylmandelic acid from the reaction of phenylacetic acid with pyridine *N*-oxide in the presence of acetic anhydride has been noted previously, the highest yield (10.5%) being obtained in acetic acid as solvent.[5] The much higher yield in the present case may be due, in part, to the deficiency of pyridine *N*-oxide as maintained by its slow addition.

It is very difficult to rationalize the production of the unsaturated acids **8** and the ester **9** without invoking an intermediate with an electrophilic site at the α position. In view of the previous evidence for such an intermediate in the production of the aldehydes and ketones as well, it is satisfying to consider the same species (**6**) as the precursor of all three major products.

An interesting anomaly was observed in the mass spectral fragmentation pattern of the methyl ester (**10**) of 2,3-diphenylpropenoic acid. The base peak for the ester was *m/e* 121, corresponding to a P − 117 fragment or loss of C_6H_5CCO. Such an abundant ion could arise by a 1,3-methoxyl shift and subsequent bond cleavage.

The ion also occurs, but in low abundance (2%),[11] in the mass spectrum of the related ester methyl 3-phenylpropenoate (methyl cinnamate). The most abundant ion (P − 31) of the latter compound is due to the loss of the methoxyl radical. It is likely that the benzene ring lowers the energy of activation for the rearrangement of **10** to **11** by stabilizing the developing radical so that this process becomes faster than loss of a methoxyl radical.



Experimental Section[12]

2,3-Diphenylpropanoic Acid (5).—This compound was prepared[13] by the hydrolysis of 2,3-diphenylpropionitrile, which was itself prepared[13] by benzylation of the sodium salt of phenylacetonitrile. The acid had mp 88–89°; it was long ago reported[14] that this material exists in three modifications with mp 82, 88–89, and 95–96°, and all three melting points have been reported in subsequent work.[13,15] The acid had an nmr (CCl_4) singlet at τ − 1.55 (1 H, acid H), multiplet at 2.70–3.15 (10 H, aryl H), and multiplet at 6.10–7.28 ppm (3 H, α and β H).

Reaction of 2,3-Diphenylpropanoic Acid (5) with Pyridine *N*-Oxide.—A solution of 1.6 g (17 mmol) of pyridine *N*-oxide in 20 ml of benzene was added dropwise over a period of 2 hr to a refluxing solution of 1.9 g (8.4 mmol) of 2,3-diphenylpropanoic acid and 3.5 g (34 mmol) of acetic anhydride in 20 ml of benzene under a nitrogen atmosphere. After the solution had been heated at reflux for 18 hr, another 1.6 g of pyridine *N*-oxide in 15 ml of benzene was added in one portion. This process was repeated two additional times at 12-hr intervals and the mixture was maintained at reflux for 12 hr after the last addition of the *N*-oxide. The cooled reaction mixture was divided into two parts.

The major part (81% by weight) was thoroughly washed with saturated sodium bicarbonate (125 ml). The alkaline aqueous solution was washed once with ether and the ether wash was combined with the organic layer. The aqueous solution was made strongly acidic with dilute HCl and extracted with ether. Evaporation of the dried ($MgSO_4$) ether extract gave 0.53 g of acidic material, which was treated with ethereal diazomethane to give the following four methyl esters in order of glpc retention

(11) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco, Calif., 1967, p 202.

(12) Melting points were determined on a Thomas-Kofler micro hot stage utilizing a stage-calibrated thermometer and are thus corrected. Boiling points are uncorrected. Reactions were performed under a continuous stream of nitrogen. Infrared spectra were determined on a Beckman IR-8 spectrophotometer. Proton magnetic resonance spectra were determined on a Varian A-60 instrument; chemical shifts are reported on the τ scale, relative to internal tetramethylsilane. Analytical gas chromatography was performed on a Varian 1860-3 instrument equipped with a flame ionization detector and a Disc integrator. For determining yields, the flame responses of authentic samples were calibrated against those of various standards. Isomers were assumed to have identical flame responses. Mass spectra were determined at 70 eV on an LKB-9000 combined gas chromatograph–mass spectrometer.

(13) N. Campbell and E. Ciganek, *J. Chem. Soc.*, 3834 (1956).

(14) W. Miller and G. Rhode, *Chem. Ber.*, **25**, 2017 (1892).

(15) R. B. Meyer and C. H. Hauser, *J. Org. Chem.*, **26**, 3696 (1961); H. Normant and B. Angelo, *Bull. Soc. Chim. Fr.*, 810 (1962); D. Y. Curtin, J. A. Kampmeier, and M. L. Farmer, *J. Amer. Chem. Soc.*, **87**, 874 (1965).

time: methyl 2,3-diphenylpropanoate, methyl *cis*-2,3-diphenylpropenoate, methyl *trans*-2,3-diphenylpropenoate, and methyl 2-acetoxy-2,3-diphenylpropanoate. The first three esters were identified by comparison of retention times and mass spectra (glpc–mass spectra) with those of authentic samples prepared by similar methylation of the saturated acid **5** and the two unsaturated acids **8** (Frinton Laboratories). The mass spectra of the two unsaturated esters were nearly identical: *m/e* (rel intensity, assignment) 238 (71, P^+), 207 (36, $P^+ - OMe$), 179 (79, $P^+ - CO_2Me$), 178 (64, $C_6H_5C{\equiv}CC_6H_5^+$), 165 (14), 152 (21), 121 (base, $P^+ - C_6H_5C{=}C{=}O$, see text), 102 (14), 89 (29), 77 (29, $C_6H_5^+$), and 51 (29).

The last component was isolated in the following way. The above mixture of methyl esters was dissolved in 5 ml of methanol and injected by syringe into a flask containing 25 mg of prereduced Adams catalyst in 2 ml of methanol. The mixture was stirred under a positive pressure of hydrogen for 6 hr, and the catalyst was separated by filtration. By glpc, the methanol was shown to contain only methyl 2,3-diphenylpropanoate and methyl 2-acetoxy-2,3-diphenylpropanoate. The mixture was separated into its components by chromatography on a silica gel column (10 g, Baker) using *n*-pentane and benzene as eluents. The acetoxy ester, which eluted last, was subject to flash distillation (260° bath temperature, 2 mm) to afford 76 mg of pure material. No decomposition to the α,β-unsaturated esters of **8** occurred upon gas chromatographic analysis of this ester. The infrared, nmr, and mass spectra of the acetoxy compound were identical with those of an authentic sample: ir (neat) 1740 (C=O), 1250 (COC), 753, 730, 705 cm^{-1}; nmr ($CDCl_3$) τ 2.6–3.7 (m, 10 H, aromatic), 6.3 (center of AB quartet, 2 H, benzylic protons), 6.43 (s, 3 H, OCH_3), and 7.95 (s, 3 H, CH_3CO); mass spectrum *m/e* 238 ($P^+ - HOAc$), 207 ($P^+ - HOAc - OCH_3$ or $P^+ - C_6H_5CH_2$), 165 ($P^+ - C_6H_5CH_2 - CH_2CO$), 105, 77 ($C_6H_5^+$), 51, 43.

The benzene solution of the nonacidic fraction was dried and analyzed by glpc. It consisted of benzoin and deoxybenzoin, identified by coinjection with authentic samples.

The minor portion (19%) of the original reaction mixture was treated with an ethereal solution of diazomethane, a weighed quantity of benzophenone was added as an internal standard, and quantitative glpc analysis was performed on an OV-17 column, with temperature programmed at 6°/min from 170 to 190°. The yields of the five products are indicated in the text.

It was shown that *cis*-2,3-diphenylpropenoic acid did not isomerize to the trans isomer when its benzene solution containing acetic anhydride and pyridine *N*-oxide was maintained at reflux for 36 hr.

Hydrolysis of Methyl 2-Acetoxy-2,3-diphenylpropanoate.—A solution of the acetoxy ester (71 mg), isolated as above, in 1 ml of ethanol was treated with 1 ml of 1 *N* potassium hydroxide in 1 ml of 95% ethanol. The homogeneous solution was stirred at room temperature for 18 hr under nitrogen. It was acidified with dilute hydrochloric acid and extracted with ether. The ether extract was dried ($MgSO_4$) and evaporated to give 44 mg (76% crude yield) of yellowish solid, mp 125–140°. Recrystallization from benzene gave a colorless solid, mp 164–165° (lit.[16] mp 168.0–168.5°); mixture melting point with an authentic sample (mp 166.0–166.5°) of 2,3-diphenylglycolic acid was 165–167°. The ir and nmr spectra of this material were identical with those of the authentic sample.

2,3-Diphenylglycolic Acid.—A solution prepared by mixing 10 g of chalcone oxide[17] and 13 ml of 30% sodium hydroxide with 50 ml of 95% ethanol was heated at reflux for 90 min, poured into 500 ml of water, and acidified with 4 *N* hydrochloric acid (20 ml). The yellow precipitate (7.5 g, mp 161–164°) was recrystallized from benzene to give a white solid, mp 166.0–166.5° (lit.[16] mp 168.0–168.5°). Its nmr spectrum (acetone-d_6) corresponded with that in the literature.[16]

Methyl 2-Acetoxy-2,3-diphenylpropanoate.—A solution of 2.0 g of 2,3-diphenylglycolic acid in 10 ml of anhydrous ether was cooled in an ice bath and treated with excess diazomethane in ether to give 2.1 g of the methyl ester, mp 88–89° (lit.[18] mp 88–89°); its nmr and ir spectra were consistent with the assigned structure. A mixture of 1.34 g (52.3 mmol) of this methyl ester, 10 ml of acetyl chloride, and 10 ml of *N,N*-dimethylaniline in 30 ml of chloroform was heated at reflux (62°) for 36 hr, cooled in an ice bath, and thoroughly mixed with 100 ml of ice water. The deep blue organic layer was washed extensively with water and saturated sodium bicarbonate solution. Evaporation of the dried (magnesium sulfate) organic layer yielded a deep brown oil which was chromatographed on 25 g of silicic acid gel (Baker) using benzene as the mobile phase. The resulting 1.75 g of clear, colorless liquid was distilled to give a glassy liquid (1.22 g, 78.5% yield), bp 139–140° (0.2 mm). Its spectral properties are given above.

Anal. Calcd for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08. Found: C, 72.58; H, 6.15.

Oxidation of Deoxybenzoin (7) to Benzoin.—A solution of 1.65 g of deoxybenzoin and 2 ml of pyridine in 20 ml of benzene was allowed to remain at room temperature under slow air ebullition for 24 hr. Analysis by glpc indicated that about 3% of benzoin was produced. None of the latter was produced in the absence of pyridine, even when pyridine *N*-oxide was present. Neither was benzoin produced when a benzene solution of deoxybenzoin containing acetic anhydride and pyridine *N*-oxide was maintained at reflux for 2.5 days.

Acknowledgment.—We wish to thank Mr. John Wood and Mr. Glen Herman for technical help and the former for a useful discussion.

Registry No.—**5**, 3333-15-1; *cis*-**8** methyl ester, 41366-87-41; *trans*-**8** methyl ester, 36854-27-0; **9** methyl ester, 41366-89-6; pyridine *N*-oxide, 694-59-7; 2,3-diphenylglycolic acid, 76-93-7; chalcone oxide, 5411-12-1.

(16) E. K. Raunio and W. A. Bonner, *J. Org. Chem.*, **31**, 396 (1966).

(17) E. Rohrmann, R. G. Jones, and H. A. Shonle, *J. Amer. Chem. Soc.*, **66**, 1856 (1944).

(18) M. Avramoff and Y. Sprinzak, *J. Amer. Chem. Soc.*, **85**, 1655 (1963).

A Mild Conversion of Halopyridines and Quinolines to the Corresponding Pyridone or Quinolone

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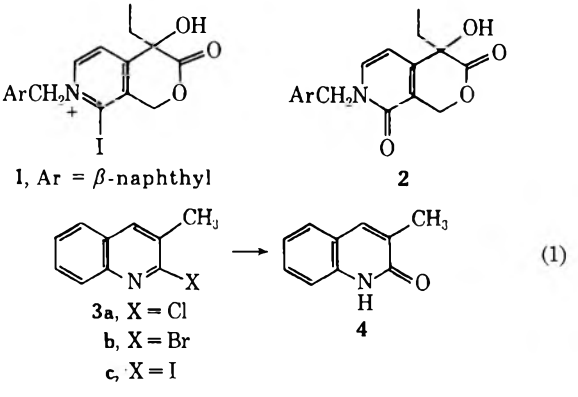
The conversion of halopyridinium salts to pyridones in good yields occurs by reaction with dimethyl sulfoxide at 100°. The reaction of 2-iodoquinolines to quinolones requires an acid catalyst but not quaternary salt formation. The 2-chloro- and 2-bromoquinolines can be converted by adding sodium iodide to form the iodo derivative. The reaction seems to be an oxidation–reduction rather than a simple hydrolysis.

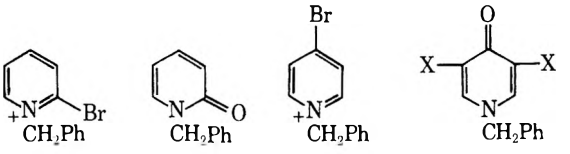
A general method for the preparation of 2- or 4-oxo derivatives of nitrogen aromatic heterocycles involves the hydrolysis of the corresponding halogen derivative. The conversion can be accomplished in either acidic or basic medium; however, the reaction conditions are often extreme, limiting the kinds of substituents that can be present.[1] This conversion presented a particular problem in the preparation of analogs of camptothecin, which contains a pyridone ring.[2] The change in nmr spectrum of the iodopyridinium salt (**1**) which occurred when a dimethyl sulfoxide (DMSO) solution was allowed to stand led to the discovery of a novel method for causing this conversion. The nmr spectrum of a solution of **1** in DMSO after several days gave a doublet at 6.45 ppm which was characteristic of the 5 proton of a pyridone such as **2**. The formation of **2** was confirmed by isolation and characterization of the compound formed from the DMSO reaction.

To determine the generality of the reaction, 2-iodo-3-methylquinoline (**3c**) was treated with DMSO. No reaction was observed unless an acid was added. With 2-chloro- (**3a**) and 2-bromo-3-methylquinoline (**3b**) no reaction occurred unless sodium iodide was added to convert the halide to the 2-iodo derivative **3c**. These reactions were converted to a convenient synthetic procedure by mixing the haloquinoline, concentrated hydrochloric acid, and sodium iodide in DMSO to give high yields of the quinolone **4** (eq 1).



(1)

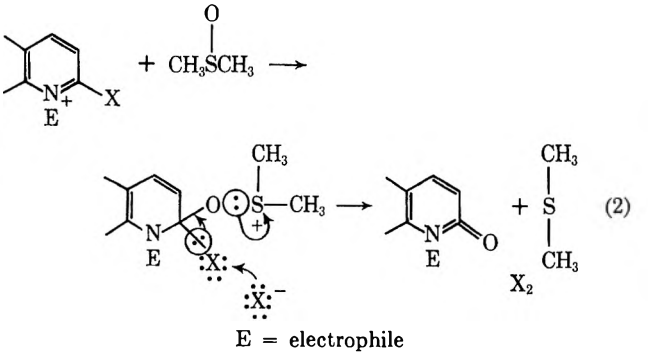
The corresponding condition which worked well with the quinoline series gave no reaction with 2-bromopyridine, although, the 2-iodopyridine could be obtained. The reaction of the quaternary salt, 1-benzyl-2-bromopyridinium bromide (**5**), with DMSO gave the 1-benzyl-2-pyridone (**6**) at 100° in <2 hr. The 1-benzyl-4-bromopyridinium bromide (**7**) was converted to the pyridone (**8**); however, **8** underwent bromination to give 1-benzyl-3,5-dibromo-4-pyridone (**9**) as



the isolated product. Some unsubstituted pyridone **8** could be detected in the aqueous medium of the isolation.

During the course of this investigation the conversion of 4-chloroquinolines to 4-quinolones was reported to occur by treatment with DMSO.[3] The conversion occurred only with this heterocyclic ring system when a 3-alkoxycarbonyl substituent was present.

The results of Harris as well as those reported herein could be explained by hydrolysis of the halo heterocycle promoted by the highly polar solvent DMSO. The order of reactivity of the 2-haloquinolines (I > Br or Cl) and the *in situ* bromination of the 1-benzyl-4-pyridone (**8**) to form **9** are not readily explained by this mechanism, however. The reaction products and properties are consistent with a mechanism of nucleophilic addition of DMSO followed by an oxidation–reduction mechanism (eq 2) also implied by Harris.[3]



(2)

E = electrophile

It is evident that a ring system which can stabilize the product of nucleophilic addition is required. An electrophilic aromatic π system is required; so salts of the heterocyclic nitrogen or electron-withdrawing substituents must be present to cause a successful

(1) T. Kametani, *Tetrahedron*, **26**, 5753 (1970).

(2) R. E. Lyle, J. A. Bristol, M. J. Kane, and D. E. Portlock, *J. Org. Chem.*, **38**, 3268 (1973).

(3) N. D. Harris, *Synthesis*, 625 (1972).

reaction. Quinoline is more reactive than pyridine, for the dihydroquinolines are more stable than the dihydropyridines. A quaternary salt rather than a proton salt is required to form the intermediate in the later case. The failure of the 2-chloro- and 2-bromoquinolines to give a reaction probably reflects the higher oxidation potential of these substituents.

The formation of iodine and dimethyl sulfide in these reactions could readily be demonstrated; however, this is not conclusive since iodide ion is converted to iodine by DMSO in acidic medium.[4] The formation of 3,5-dibromo-4-pyridone (**9**) is clear proof for the presence of bromine as a reaction product from **7** with DMSO and strongly supports eq 2 as the reaction pathway. There are numerous examples of the oxidative replacement of halides from alkyl halides in which the removal of a proton initiates the oxidation–reduction reaction,[5] but these reactions of DMSO are the first examples of oxidation–reduction of a sulfoxonium salt initiated by loss of positive halogen.

On the basis of the probable mechanism it seems possible that oxidation of pyridinium salts to pyridones could be achieved with DMSO by addition–elimination. The pyridinium salts with 3 substituents which are electron withdrawing usually most readily add nucleophiles. Thus the reaction of 1-methyl-3-benzoylpyridinium iodide with DMSO was attempted but no oxidation occurred.

Experimental Section

Preparation of 3-Methyl-2-quinolone (4).—To 221 mg (0.0818 mmol) of 2-iodo-3-methylquinoline (**3a**) were added 3 ml of dry DMSO and 5 drops of concentrated hydrochloric acid. The mixture was heated at 100° for 24 hr, cooled, and diluted with water, and the mixture was filtered. The insoluble solid was 30 mg of 3-methyl-2-quinolone (**4**). The filtrate was extracted with ether and the ether extracts were washed with aqueous $NaHSO_3$, dried (K_2CO_3), and concentrated to give 70 mg of 3-methyl-2-quinolone (**4**) as a white solid, mp 237–240° (lit.[6] mp 237–239°). A mixture melting point showed no depression. The total yield was 91%.

The reactions of **3b** and **3c** were run as above; however, 0.3 g of sodium iodide was added. The reactions gave **4** in 92 and 82% yields, respectively.

Preparation of *N*-Benzyl-2-pyridone (6).—To 3.6 g (0.011 mol) of *N*-benzyl-2-bromopyridinium bromide (**5**) was added NaI and 20 ml of DMSO. The mixture was heated at 100° for 1.5 hr. During the reaction the mixture was monitored by uv absorption. After cooling, water, ether, and solid $NaHSO_3$ were added. The aqueous layer was extracted several times with ether, and the combined ether extracts were dried (K_2CO_3) and concentrated under reduced pressure to give 2.03 g (100%) of *N*-benzyl-2-pyridone (**6**) as a crude oil. Column chromatography on silica gel of the oil gave 1.32 g (65%) of *N*-benzyl-2-pyridone (**6**) as white crystals, mp 60–68°. Recrystallization of the solid from ether–hexane gave *N*-benzyl-2-pyridone (**6**) as white needles, mp 63–65° (lit.[7] mp 71.8–72.8°), picrate mp 130–131.5° (lit.[7] mp 129.5–130.5°).

Preparation of *N*-Benzyl-3,5-dibromo-4-pyridone (9).—To 2.0 g (0.006 mol) of 4-bromo-*N*-benzylpyridinium bromide (**7**) was added 10 ml of DMSO. This mixture was heated for 2.25 hr at 100° in an oil bath. The reaction was monitored by uv absorption. Water was added causing the loss of the yellow color of the solution, and a white solid precipitated from the solution.[8] The solid was collected by filtration to give 0.4 g (20%) of *N*-benzyl-3,5-dibromo-4-pyridone (**9**), mp 173–178°. Recrystallization of the solid from $HOAc \cdot H_2O$–ethanol (1:1) gave *N*-benzyl-3,5-dibromo-4-pyridone (**9**) as white needles, mp 196–199° (lit.[6] mp 184–186°). Another 0.24 g (12%) was obtained from the filtrate by extraction with ether to give a white solid, mp 188–193°; the total yield of *N*-benzyl-3,5-dibromo-4-pyridone (**9**) was 0.65 g (32%).

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Registry No.—**3a**, 35820-73-6; **4**, 2721-59-7; **5**, 14532-01-5; **6**, 1753-62-4; **7**, 2589-30-2; **9**, 41366-77-2; DMSO, 67-68-5.

(4) G. Modena, G. Scorrano, D. Landini, and F. Montanari, *Tetrahedron Lett.*, No. **28**, 3309 (1966).

(5) N. Kornblum, *J. Amer. Chem. Soc.*, **79**, 6562 (1957).

(6) G. Ornstein, *Chem. Ber.*, **40**, 1088 (1907).

(7) F. Krochnke and H. Schaefer, *Chem. Ber.*, **95**, 1104 (1962).

(8) The uv absorption spectrum of this layer indicated the presence of 1-benzyl-4-pyridone (**8**).

Azole Chemistry. VIII.[1] Ring–Chain Tautomerism of Some 2-Mercaptoperimidine Derivatives

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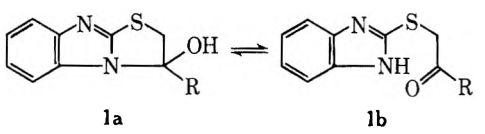
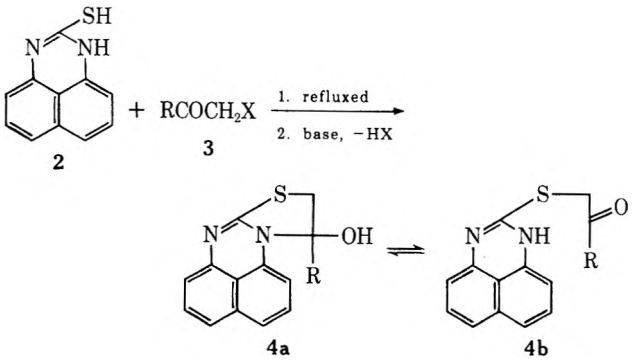
Reaction of α-halo ketones with 2-mercaptoperimidine affords carbinolamines and/or the tautomeric amino ketones. Inductive, conjugative, and steric effects on the ring–chain tautomeric equilibrium are discussed. The influence of basicity on ring–chain tautomerism is noted.

A recent investigation of the amino ketone carbinolamine ring–chain tautomerism for the products (**1a** ⇌ **1b**) obtained from the reaction of 2-mercaptobenzimidazole with α-halo ketones indicated the importance of inductive effects on the tautomeric process. Except for bulky (*e.g.*, **1**, R = diphenylmethyl) or conjugative (*e.g.*, **1**, R = aryl) groups, the tautomeric equilibrium is governed by the inductive effect of R.[2] We now report a study of ring–chain tautomerism of some 2-mercaptoperimidine derivatives. Although the latter heterocyclic system has a six-membered rather than a five-membered nitrogen-containing ring as in **1**, perimidines possess many of the properties characteristic of azoles.[3] Since the basicity of perimidine (pK_a = 6.39)[4] is different from that of benzimidazole (pK_a = 5.53),[5] it was also of interest to learn what effect basicity has on the ring–chain process.



1a **1b**

Treatment of 2-mercaptoperimidine (**2**) with a series of α-halo ketones (**3**) in either tetrahydrofuran or 2-butanone gave the hydrohalide salt of **4** in good yields



2 **3** **4a** **4b**

(see Table I for yields, melting points, and analytical data). The free base was obtained by exposure of the hydrohalide salt to triethylamine. Condensation of **2** with various α-halo acids has been shown to occur at the mercapto group.[6]

Solid-state spectra for **4** are those of the ring or chain forms, but not both, as ring–chain tautomerism does not occur in the solid state. Characteristic bands for **4a** appear in the region of 3600–2500 cm^{-1} and at 1125–1050 cm^{-1}, and are due to the hydrogen-bonded hydroxyl group stretch and to the carbon–oxygen stretching vibrations, respectively. A broad absorption (3600–2500 cm^{-1}) was also observed in the solid-state spectra of the β-keto sulfide **4b**, owing to the hydrogen-bonded NH stretch (free NH stretching at 3300–3270 cm^{-1} was noted in several instances). The carbonyl stretching absorption occurred at 1760–1660 cm^{-1}. Solution spectra showed similar bands for **4a** and/or **4b**.

The nuclear magnetic resonance (nmr) spectra were recorded in dimethyl sulfoxide-d_6 (Table I). Except for **4**, R = H, $COOC_2H_5$, the nmr spectra of **4a** ⇌ **4b** displayed a singlet signal for the methylene protons of **4b** and an AB quartet for the corresponding protons of **4a**. Where both ring and chain tautomers were present, the per cent of each tautomer was determined by repeated integration of the signals for the methylene protons. For **4b**, R = $COOC_2H_5$, a quartet (J = 14 Hz) was observed for the methylene protons of the SCH_2 group, and is due to possible restricted rotation. The carbonyl stretching frequency ($CHCl_3$) of **4b**, R = $COOC_2H_5$, was at an identical position with that of **1b**, R = $COOC_2H_5$ (1745 cm^{-1}). The carbonyl stretching absorption of **4a** would be expected to occur at a lower wavenumber than that of **4b**. For **4a**, R = H, the quartet for the methylene group is further split by the methine proton attached to the adjacent carbon.

The amount of chain tautomer increases with increasing electron-releasing ability of the R group for the series R = CH_3, C_2H_5, $CH(CH_3)_2$, and $C(CH_3)_3$. This trend is in agreement with results obtained for **1a** ⇌ **1b**, which demonstrated the control of the tautomeric equilibrium by the inductive effect of R for all but conjugative or very bulky substituents (*e.g.*, 1-adamantyl). Steric considerations can also account for the observed trend for these alkyl groups.

It was hoped that the study could be extended to **4**, R = CF_3, but basification of the hydrogen bromide adduct resulted in formation of 2,3-dihydro-1*H*-perimidin-2-one (**5**), an unusual example of a sulfur–carbon cleavage reaction. The mechanism for formation of **5** is unknown but it may occur *via* the chain tautomer (**4b** HBr) of the hydrohalide salt. Solid-state and solution infrared spectra, as well as nmr spectra for the hydrobromide salt of **4**, R = CF_3, clearly show the presence of only the ring tautomer, again in agreement with the results obtained for **1**, R = CF_3. If steric effects were important, there should be a considerable

(1) Azole Chemistry. VII: H. Alper, L. S. Dinkes, and P. J. Lennon, *J. Organometal. Chem.*, in press.

(2) H. Alper, E. C. H. Keung, and (in part) R. A. Partis, *J. Org. Chem.*, **36**, 1352 (1971).

(3) E. J. Browne, *Aust. J. Chem.*, **26**, 449 (1973), and references cited therein.

(4) A. Albert in "Physical Methods in Heterocyclic Chemistry," Vol. III, A. R. Katrizky, Ed., Academic Press, New York, N. Y., 1971, p 1.

(5) D. J. Brown, *J. Chem. Soc.*, 1974 (1958).

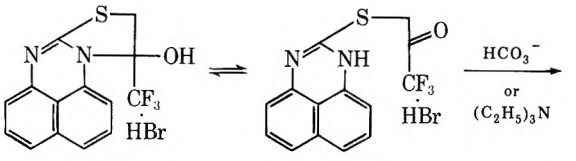
(6) H. S. Chaudhary and H. K. Pujari, *Indian J. Chem.*, **7**, 767 (1969).

TABLE I

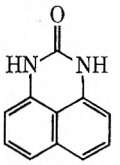
YIELDS, MELTING POINTS, NMR DATA, AND RING–CHAIN TAUTOMERIC RATIOS FOR 4a ⇌ 4b

R	Formula[a]	Yield,[b] %	Mp, °C	Time, hr	Nmr[d] Chain SCH_2 (J)	Nmr[d] Ring SCH_2 (J)[e]	% chain[f]
H	$C_{13}H_{10}N_2OS$	86	155 dec	12[c]		3.74[g] (6) 3.18[h] (12)	0
CH_3	$C_{14}H_{12}N_2OS$	76	124.5–126.5	37	4.07	3.46	33
C_2H_5	$C_{15}H_{14}N_2OS$	82	113–115	2.5	4.04	3.48 (11)	40
$CH(CH_3)_2$	$C_{16}H_{16}N_2OS$	73	188.5 dec	2.5	3.97	3.56	65
$C(CH_3)_3$	$C_{17}H_{18}N_2OS$	72	151 dec	15	4.33		100
$CO_2C_2H_5$	$C_{16}H_{14}N_2O_3S$	97	138.5 dec	0.25	3.65 (14)		100
1-Adamantyl	$C_{23}H_{24}N_2OS$	87	163 dec	12	4.27		100
C_6H_5	$C_{19}H_{14}N_2OS$	80	153 dec	12	4.71		100
p-$CH_3OC_6H_4$	$C_{20}H_{16}N_2OS$	89	155 dec	11.5	4.65		100
p-BrC_6H_4	$C_{19}H_{13}N_2OS$	86	167 dec	0.33	4.69		100

[a] All compounds except 4, R = CH_3 (Calcd: N, 10.93. Found: N, 10.47.) and 4, = R = H (Calcd: N, 11.56. Found: N, 10.93.) gave C, H, and N analysis within 0.4 of the calculated values and the analytical data were made available to the editors and referees. [b] Based on hydrohalide adduct. [c] Reaction was run at room temperature. [d] Chemical shifts in parts per million based on tetramethylsilane. Dimethyl sulfoxide-d_6 was used as the solvent. [e] Coupling constants in cycles per second. [f] Accurate to within 3%. [g] Proton of methylene group cis to OH. [h] Proton of methylene group trans to OH.



4a HBr ⇌ 4b HBr



5

amount of chain tautomer for 4, R = CF_3, since the steric effect of the trifluoromethyl group is between that of the isopropyl and *tert*-butyl groups.[7] The trifluoromethyl group of 4, R = CF_3, makes the carbonyl carbon of **4b** more positive and therefore more susceptible to cyclization to **4a** by reaction with the amino group. The greater the electron-donating ability of R, for 4, R = CH_3, C_2H_5, $CH(CH_3)_2$, and $C(CH_3)_3$, the less positive the carbonyl carbon of **4b**, and therefore the less the amount of ring tautomer.

The parent system 4, R = H, is exceptional, since an aldehyde function (**4b**, R = H) would be expected to undergo cyclization more readily than a ketone carbonyl. A second exception occurs when a 1-adamantyl substituent is present (4, R = 1-adamantyl). Although the inductive effect of the 1-adamantyl group is estimated to be similar to that of a methyl group,[8] the steric effect of the 1-adamantyl group is expected to be substantial, and consequently only the chain tautomer **4b** is present in chloroform or dimethyl sulfoxide-d_6 solutions of 4, R = 1-adamantyl.

Only the chain tautomer was observed for 4, R = C_6H_5, p-$CH_3OC_6H_4$, p-BrC_6H_4, and $COOC_2H_5$. Inductive effects are not important in these cases, as conjugation of the carbonyl group of the amino ketone with a benzene ring or with the carboethoxy group in **4b** would be destroyed on cyclization to **4a**.

Returning to the discussion of the results for 4, R = CH_3, C_2H_5, and $CH(CH_3)_2$, it is true that, although the trends in the proportion of chain tautomer for these compounds and the same series for 1 are the same, the actual percentages are significantly different (Table II).

TABLE II

COMPARISON OF SOME OF THE DATA FOR 1 AND 4

1 or 4, R	% chain 1	% chain 4
CH_3	65	33
C_2H_5	71	40
$CH(CH_3)_2$	90	65

The difference in per cent chain isomer for 4, R = CH_3, as compared to 1, R = CH_3, may be due, at least in part, to the difference in basicity of the heterocyclic ring systems. Perimidine (pK_a = 6.39)[4] is a stronger base than benzimidazole (pK_a = 5.53).[5] Therefore, the tendency for the amino ketone **4b**, R = CH_3, to cyclize to **4a**, R = CH_3, would be enhanced relative to ring closure of **1b**, R = CH_3, to **1a**, R = CH_3. Consequently, the per cent chain of 4, R = CH_3, is less than that for 1, R = CH_3. The same rationale can be used to account for the results in the ethyl- and isopropyl-substituted derivatives of 1 and 4. These studies indicate the importance of basicity in ring–chain tautomerism.

Experimental Section

α-Halo Ketones.—Ethyl bromopyruvate, 1-adamantyl bromomethyl ketone, chloro-2-propanone, 1-bromo-3,3,3-trifluoro-2-propanone, chloroethanal, 2-bromoacetophenone, and 2-bromo-4′-methoxyacetophenone were commercially available.

Bromination of pinacolone gave 1-bromo-3,3-dimethyl-2-butanone.[9] 1-Chloro-3-methyl-2-butanone[10] was prepared by reaction of dioxane dibromide with 3-methyl-2-butanone at room temperature. Bromination of 2-butanone in aqueous solution in the presence of potassium chlorate[11] gave 1-bromo-2-butanone.

General Procedure for the Reaction of 2-Mercaptoperimidine with α-Halo Ketones.—An equimolar amount of the heterocycle (recrystallized first from THF and pentane, and then from 2-butanone and pentane) and α-halo ketone (5–10 mmol) in tetrahydrofuran (THF) or 2-butanone (100–150 ml) was refluxed with

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(9) M. Charpentier-Morize, *Bull. Soc. Chim. Fr.*, 920 (1962).

(10) N. A. Oshueva and T. Temnikova, *J. Gen. Chem. USSR*, **29**, 3686 (1959).

(11) J. R. Catch, D. F. Elliot, D. H. Hey, and E. R. H. Jones, *J. Chem. Soc.*, 272 (1948).

mechanical stirring. The reaction mixture was cooled to room temperature, the hydrohalide salt generally having precipitated out of solution. Soluble hydrohalide salts were precipitated by addition of pentane. The salt was filtered and dried. Conversion to the free base was accomplished by dissolving the salt in hot ethanol (95 or 100%), adding triethylamine until the solution was basic (pH usually 8–10), and, finally, pouring the solution into 1–4 volumes of ice water. This resultant mixture was allowed to stand undisturbed for 0.5–2 hr. Work-up was effected as follows in the individual cases.

A. **R** = C_6H_5.—The crystals were filtered and dissolved in hot benzene and Nuchar was added to effect partial decolorization. After filtration, the benzene filtrate was flash evaporated and petroleum ether (bp 30–60°) was then added to the residue. Slow crystallization occurred when the solution was kept in the refrigerator. The isolated solid was dissolved in the minimum amount of chloroform and chromatographed on Florisil. Elution with chloroform gave pure **4**, R = C_6H_5.

B. **R** = CH_3.—The product was extracted from the aqueous solution with methylene chloride, and the organic extract was dried over $MgSO_4$ and flash evaporated to an oil. The latter was covered with pentane (~125 ml) and kept overnight in the refrigerator. Pentane was decanted and the residue was treated with hot isooctane and filtered. The isooctane treatment was repeated until the filtrate was faint green in color. The product was then isolated by flash evaporation.

C. **R** = *p*-$CH_3OC_6H_4$.—The product was extracted from the aqueous solution with methylene chloride, and the organic extract was dried and flash evaporated. The residue was dissolved in the minimum amount of benzene and chromatographed on Florisil. Elution with chloroform gave pure β-keto sulfide.

D. **R** = 1-Adamantyl.—The crystals were filtered and dissolved in hot acetonitrile, and Nuchar was added to effect partial decolorization. The solution was filtered, the filtrate was evaporated, and acetone was then added to the residue to afford pure **4**, R = 1-adamantyl.

E. **R** = $CO_2C_2H_5$.—The aqueous solution was treated with methylene chloride, the layers were separated, and Nuchar was added to the organic extract. The solution was heated to boiling and filtered hot, and the filtrate was then flash evaporated. The residual oil was dissolved in chloroform and chromatographed on Florisil. Elution with chloroform gave a yellow oil. The latter was treated with a few milliliters of tetrahydrofuran, and addition of excess pentane resulted in crystallization.

F. **R** = H.—The crystals were filtered and dissolved in hot chloroform (Nuchar added), and the solution was filtered. Recrystallization from chloroform–pentane gave pure **4**, R = H.

G. **R** = $C(CH_3)_3$.—The crystals were treated with hot tetrahydrofuran (Nuchar added) and filtered, and the filtrate was concentrated to a few milliliters. Addition of pentane resulted in precipitation of impurities, which were removed by filtration. Evaporation of the filtrate gave the product. Analytically pure **4**, R = $C(CH_3)_3$, was obtained by repetition of this work-up procedure.

H. **R** = C_2H_5 or $CH(CH_3)_2$.—The aqueous solution was extracted with chloroform, the chloroform extract was flash evaporated, and the residue was chromatographed on Florisil. Elution with chloroform gave a new oil which, in the case of R = C_2H_5, was rechromatographed on alumina (neutral, Woelm activity grade I), whereby another oil was obtained on elution with chloroform. A few milliliters of tetrahydrofuran was added, and the product was crystallized on subsequent addition of pentane. Analytically pure material was obtained by recrystallization from tetrahydrofuran–pentane.

I. **R** = CF_3.—The crystals were filtered, treated with hot absolute methanol (Nuchar added), and filtered. The filtrate was flash evaporated until a green solid precipitated out of solution. The solution was filtered, and evaporation of the filtrate gave 2,3-dihydro-1*H*-perimidin-2-one: mp 301.5–303.0° after recrystallization from glacial acetic acid (lit.[12] mp 304–305°); nmr (DMSO-d_6) δ 6.50 (m, 2 H, ortho protons to nitrogen-bearing carbons), 7.20 (m, 4 H, meta and para protons), 10.1 (s, 2 H, NH); mass spectrum *m/e* 184, 166, 139, 128, 112, 92.

Anal. Calcd for $C_{11}H_8N_2O$: C, 71.73; H, 4.38; N, 15.21. Found: C, 71.29; H, 4.31; N, 14.94.

J. **R** = *p*-BrC_6H_4.—The crystals were filtered, dissolved in chloroform, and chromatographed on Florisil. Elution with chloroform gave **4**, R = *p*-BrC_6H_4.

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Registry No.—**2**, 30837-62-8; **3** (R = H, X = Cl), 107-20-0; **3** (R = CH_3, X = Cl), 78-95-5; **3** (R = CH_3CH_2, X = Br), 816-40-0; **3** (R = $CH(CH_3)_2$, X = Cl), 17687-63-7; **3** (R = $C(CH_3)_3$, X = Br), 5469-26-1; **3** (R = $CO_2C_2H_5$, X = Br), 70-23-5; **3** (R = 1-adamantyl, X = Br), 5122-82-7; **3** (R = Ph, X = Br), 70-11-1; **3** (R = *p*-$CH_3OC_6H_4$, X = Br), 2632-13-5; **3** (R = *p*-BrC_6H_4, X = Br), 99-73-0; **3** (R = CF_3, X = Br), 431-35-6; **4a** (R = H), 41367-08-2; **4a** (R = CH_3), 41367-09-3; **4b** (R = CH_3), 41367-10-6; **4a** (R = C_2H_5), 41367-11-7; **4b** (R = C_2H_5), 41367-12-8; **4a** (R = $CH(CH_3)_2$), 41367-13-9; **4b** (R = $CH(CH_3)_2$), 41367-14-0; **4b** (R = $C(CH_3)_3$), 41367-15-1; **4b** (R = $CO_2C_2H_5$), 41367-16-2; **4b** (R = 1-adamantyl), 41367-17-3; **4b** (R = C_6H_5), 41367-18-4; **4b** (R = *p*-$CH_3OC_6H_4$), 41367-19-5; **4b** (R = *p*-BrC_6H_4), 31797-11-2; **5**, 5157-11-9.

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Conformational Analysis about the Nitrogen–Nitrogen′ Bond by Nuclear Magnetic Resonance Spectroscopy. *N′*-Sulfonyl Derivatives of *N*-Aminocamphorimide

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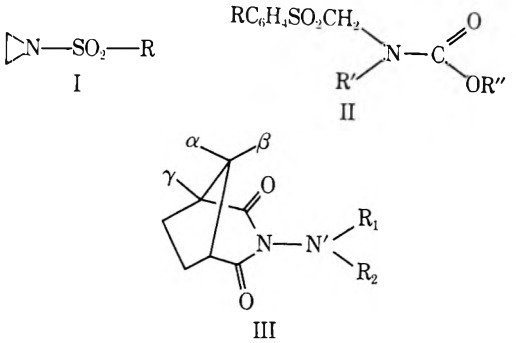
The effect of the sulfonyl groups directly bonded to the exocyclic nitrogen in disubstituted *N*-aminocamphorimides on the conformational process about the N–N′ bond has been investigated by nmr spectroscopy. A number of *N′*-sulfonyl derivatives have been synthesized and their nmr spectra compared with those of the *N′*-acyl analogs. Shielding constants of the β-methyl group of the nonplanar cage structure, *i.e.*, the bicyclic camphorimidyl system, have been used for the conformational study. Temperature-dependent spectral changes have been related to the conformational changes about the N–N′ bond. The free energies of activation, $\Delta G^{\ddagger}$, for rotation about the N–N′ bond in these compounds are of similar order as those for the *N′*,*N′*-diacyl derivatives. Nmr spectra indicate that there is a free rotation about the N′–SO_2 bond in *N′*-mesyl derivatives whereas the tosyl substituents prefer a fixed conformation about the N′–SO_2 bond.

Hindered nitrogen inversion[1,2] and rotation about the N–N bond in cyclic[3] and acyclic[4-6] systems studied by nmr spectroscopy have been reviewed.[7] The large barriers, observed for the nitrogen inversion in *N*-sulfonyl derivatives of dihydroquinolones[1] were attributed to the steric hindrance of the sulfonyl group, whereas the increased rates of N inversion in *N*-sulfonylaziridines[8] (I) were assigned to the delocalization of



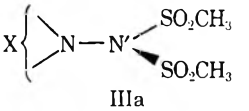
I II III

nitrogen lone-pair electrons on to the sulfonyl group. Hindered rotation about methoxy–carbonyl bond in the compound of the type II was attributed to the presence of the aryl sulfonyl group in the β position to the nitrogen atom.[9]

Recently, we reported[10] the preferred conformations about the N–N′ and N′–CO bonds in a series of *N′*-acyl derivatives of *N*-aminocamphorimide (III) by making use of the shielding constants of the β-methyl group of the nonplanar cage structure. It was of considerable interest to examine the effects of a sulfonyl substituent at the exocyclic nitrogen atom on the conformational processes about the N–N′ and N′–SO_2 bonds. The present communication deals with the syntheses and the nmr studies of some *N′*-sulfonyl-*N*-aminocamphorimides (IIIa–IIIs). The conformations and anisotropic effect of mesyl and tosyl groups were investigated by a comparative study of the shielding constants of the cage β-methyl group. The free energies of activation ($\Delta G^{\ddagger}$) to the rotation about the N–N′ bond were estimated from the variable temperature nmr spectral parameters using Eyring's rate equation[11] (Table I).

The variable temperature nmr spectra of the compounds were studied in nitrobenzene. The general spectral pattern observed in nitrobenzene was similar to that observed in $CDCl_3$. The rate constants (k_t) at $t°$, below the coalescence temperature involved in the Eyring's rate equation, were extracted from the equation $k_t = (\pi/2^{1/2})(\Delta\nu_0^2 - \Delta\nu_t^2)^{1/2}$ where $\Delta\nu_0$ and $\Delta\nu_t$ are the internal chemical shifts (in hertz) of the temperature-dependent signals at 44.5 and $t°$, respectively. This expression for rate constants is actually applicable to the exchanges between two different uncoupled sites of equal populations, and therefore the accuracy of the obtained $\Delta G^{\ddagger}$ values is limited as the rate processes, observed in some cases, involve exchange between sites of unequal populations. However, these values were taken to be sufficiently accurate for comparison purpose.[3,12]

***N′*,*N′*-Dimesyl-*N*-aminocamphorimide (IIIa).**—The nmr spectrum of IIIa in $CDCl_3$ shows two sharp singlets for the mesyl groups. The spectrum is temperature dependent and the two signals of the mesyl protons move closer as the temperature is raised ($\Delta\nu$ being 5.7 and 5.05 Hz at 44.5 and 150°, respectively, in nitrobenzene). This behavior provides evidence for some slow conformational change in the molecule in solution.



IIIa

(X represents the bicyclic camphorimidyl cage moiety)

The structure of the exocyclic trivalent nitrogen atom is assumed to be nearly planar since the sulfonyl group

(1) W. N. Speckamp, U. K. Pandit, and H. O. Huisman, *Tetrahedron Lett.*, 3279 (1964); W. N. Speckamp, U. K. Pandit, P. K. Korver, P. J. Van der Haak, and H. O. Huisman, *Tetrahedron*, **22**, 2413 (1966).

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TABLE I

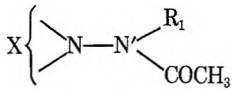
VARIABLE TEMPERATURE SPECTRAL DATA AND THE ESTIMATED FREE ENERGIES OF ACTIVATION ($\Delta G^{\ddagger}$) TO THE ROTATION ABOUT THE N–N′ BOND IN NITROBENZENE BELOW THE COALESCENCE TEMPERATURE

Compound	Spectral change studied	$\Delta\nu$ at 44.5°	$\Delta\nu$ at t°	$\Delta G^{\ddagger}$ at t°, kcal/mol
IIIa	Decrease in $\Delta\nu$ of the mesyl signals	5.70	5.05 (150)	23.7
IIIb	Decrease in $\Delta\nu$ of the acetyl signals	7.90	5.80 (100)	20.3
IIIc	Decrease in $\Delta\nu$ of the acetyl signals	9.75	7.25 (120)	21.3
IIId	Decrease in $\Delta\nu$ of the β-methyl signals	78.50	63.75 (120)	19.7
IIIe	Decrease in $\Delta\nu$ of the β-methyl signals	75.50	61.50 (120)	19.8
IIIf	Decrease in $\Delta\nu$ of the β-methyl signals	71.80	60.40 (120)	19.9
IIIh	Decrease in $\Delta\nu$ of the β-methyl signals	74.00	63.50 (120)	19.9
IIIj	Decrease in $\Delta\nu$ of the β-methyl signals	71.00	60.00 (120)	19.9
IIIk	Decrease in $\Delta\nu$ of the β-methyl signals	67.50	56.50 (120)	19.9
IIIl	Decrease in $\Delta\nu$ of the β-methyl signals	40.75	39.50 (100)	19.8
IIIn	Decrease in $\Delta\nu$ of the β-methyl signals	39.50	39.00 (100)	20.2
IIIo	Decrease in $\Delta\nu$ of the β-methyl signals	46.00	39.50 (120)	20.3

is as efficient as a carbonyl group for the delocalization of the nitrogen lone-pair electrons.[13] The possibility of slow rotation about the N′–SO_2 bonds is discarded since the free rotation about this bond is possible even with effective $p\pi$–$d\pi$ delocalization.[13,14] The β-methyl signal of IIIa (Figure 1)[15] appearing at δ 1.16 seems to be only slightly deshielded as compared to that of camphorimide[10] (δ 1.05) which also suggests that there is a free rotation about the N′–SO_2 bonds. Hence a slow rotation about the N–N′ bond could be the only possibility for the observed multiplicity in the spectrum.

Noncoplanar structures, similar to those proposed for tetraacylhydrazine[4,16] and certain acyclic diacylhydrazine derivatives, would obviously explain the observed multiplicity for the mesyl groups. One of the two mesyl groups lies above and the other below the common plane of the imide bridge as shown in Figure 1; thus the two groups experience two different magnetic environments due to the cage moiety. $\Delta G^{\ddagger}$ to the rotation about the N–N′ bond was found to be in excess of 23.7 kcal/mol at 150°. This value is comparable with that of the corresponding *N′,N′*-diacetyl-*N*-aminocamphorimide[10] ($\Delta G^{\ddagger}$, 22.4 kcal/mol at 150°, below the coalescence temperature).

***N′*-Sulfonyl-*N′*-acetyl-*N*-aminocamphorimides (IIIb and IIIc).**—The spectra of IIIb and IIIc in $CDCl_3$ are very similar; both show two singlets for the acetyl protons. Compound IIIb shows two singlets for its

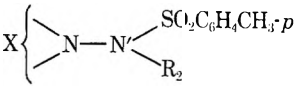


IIIb, $R_1 = SO_2CH_3$
c, $R_1 = SO_2C_6H_4CH_3$-*p*

mesyl methyl protons at δ 3.50 and 3.58, whereas the compound IIIc shows a slightly broad singlet at δ 2.5 (Figure 2)[15] for the tosyl methyl protons. The spectra indicate the possibility of two preferred conformations arising due to restricted rotation about the N–N′ bond as has been observed in *N′,N′*-dimesyl- (IIIa) and *N′,N′*-diacetyl-*N*-aminocamphorimides.[10] A singlet observed for tosyl methyl group suggests that in both the conformations this lies out of the effective zone of the cage moiety, but the tosyl aromatic protons, however, observe the asymmetry in the cage and thus differently shielded in the two conformations. The downfielded doublet of the protons adjacent to sulfonyl group (in AB quartet of aromatic protons) appear as a pair of doublets due to the two conformations.

The tosyl group in IIIc does not have any shielding effect on the β-methyl protons which further supports a fixed conformation about the N′–SO_2 bond where the aryl part of the tosyl group is projected away from the cage moiety. Shielding of a methyl and a *tert*-butyl group has been reported in 2-tosyldiazabicyclo[3.2.0]-heptanone[17] and 2,5-*tert*-butylcyclohexyl tosylate,[18] respectively.

***N′*-Tosyl-*N′*-aroyl-*N*-aminocamphorimides (IIId–IIIg).**—A representative spectrum of this series is shown



IIId, $R_2 = COC_6H_5$
e, $R_2 = COC_6H_4CH_3$-*p*
f, $R_2 = COC_6H_4CH_3$-*m*
g, $R_2 = COC_6H_4CH_3$-*o*

in Figure 3[15] for the compound IIIf. The nmr spectra of all *N′*-tosyl-*N′*-aroyl compounds (IIId–IIIg) in $CDCl_3$ are quite characteristic showing four signals for the three methyls of the cage moiety. The ring methylenes are shielded and appear over a wide range (δ 0.5–2.40). The toluoyl methyl protons appear as a pair of singlets and the tosyl methyl protons appear as a slightly broad singlet.

Two different conformations which could arise due to the hindered rotation about the N–N′ bond may be represented as IV and V. The shielding of β-methyl (δ 0.23) in IV is essentially due to the aromatic ring

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(15) See paragraph at end of paper regarding supplementary material.
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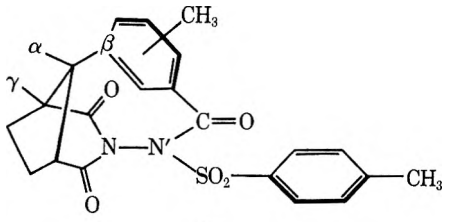
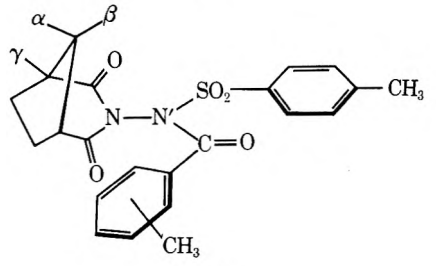


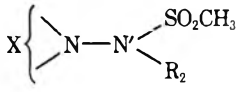
IV



V

of the toluoyl group as no shielding of any of the cage methyls is observed in the spectrum of *N′*-tosyl-*N′*-acetyl compound IIIc (Figure 2).[15] Moreover, the tosyl methyl group appears as a singlet (δ 2.5) suggesting that its aromatic part is projected away from the cage. Thus, the abnormal shielding of the β-methyl as well as that of the ring methylenes could only be due to the *N′*-aroyl group which may be assumed to have a preferred conformation about N′–CO bond as shown in IV and V.

***N′*-Mesyl-*N′*-aroyl-*N*-aminocamphorimides (IIIh–IIIk).**—The nmr spectrum of compound IIIj in $CDCl_3$

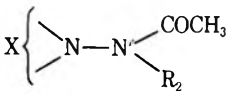


IIIh, R_2 = COC_6H_5
i, R_2 = $COC_6H_4CH_3$-*p*
j, R_2 = $COC_6H_4CH_3$-*m*
k, R_2 = $COC_6H_4CH_3$-*o*

(Figure 4)[15] shows two signals for the mesyl methyl protons, two signals for the *m*-toluoyl methyl protons, and the ring methylene protons shielded over a wide range. Two signals of the β-methyl are also observed (δ 0.08 and 1.19), the downfielded signal of which accidentally overlaps on that of the γ-methyl. (This accidental overlap was, however, removed by the "solvent shift" while studying the high temperature spectra in nitrobenzene.) Slight splittings are also observed in the α- and γ-methyl signals (Figure 4).[15] All the compounds of this series (IIIh–IIIk) show a similar nmr pattern.

Two preferred conformations about the N–N′ bond similar to IV and V would explain the observed multiplicities. The abnormal shielding observed for the β-methyl group as well as that of the ring methylenes in *N′*-mesyl-*N′*-aroyl compounds (IIIh–IIIk) could only be due to the *N′*-aroyl group, oriented towards the cage moiety about the N′–CO bond. The nmr spectral pattern of these compounds (IIIh–IIIk) is very similar to that of the *N′*-tosyl-*N′*-aroyl compounds (IIId–IIIg) supporting the conformations IV and V, where shielding of the β-methyl and the ring methylenes has been shown to be due to the *N′*-aroyl group and not due to the *N′*-tosyl group.

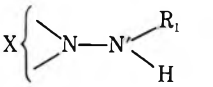
***N′*-Acetyl-*N′*-aroyl-*N*-aminocamphorimides (IIIl–IIIo).**—The spectra of IIIl–IIIo, which constitute a



IIIl, R_2 = COC_6H_5
m, R_2 = $COC_6H_4CH_3$-*p*
n, R_2 = $COC_6H_4CH_3$-*m*
o, R_2 = $COC_6H_4CH_3$-*o*

class of tetraacylhydrazine compounds, are very similar to those of their *N′*-sulfonyl analogs (IIId–IIIk). The nmr spectrum of the compound IIIn in $CDCl_3$ (Figure 5)[15] shows two signals for the acetyl methyl protons, two signals for the β-methyl protons and a slightly broad singlet for the *m*-toluoyl methyl protons (δ 2.41). The ring methylene protons are shielded and appear in the range of δ 0.6–2.30. A similar resonance pattern is observed for other *N′*-acetyl-*N′*-aroyl derivatives (IIIl–IIIo, Table I), where *N′*-aroyl group has strong shielding effect on β-methyl and the ring methylene protons.

***N′*-Monosubstituted *N*-Aminocamphorimides (IIIp–IIIs).**—*N′*-Monoacyl derivatives[10] have been shown



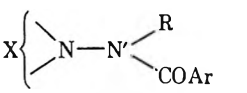
IIIp, R_1 = $COC_6H_4CH_3$-*p*
q, R_1 = $COC_6H_4CH_3$-*o*
r, R_1 = SO_2CH_3
s, R_1 = $SO_2C_6H_4CH_3$-*p*

to have a restricted rotation about N′–CO bond, and consequently the β-methyl signal of the cage is distributed accidentally among the α- and γ-methyl resonances giving rise to only two peaks of 4.5-H intensity for the three methyl groups. Two similar derivatives, IIIp and IIIq, also show this characteristic behavior.

N′-Monosulfonyl derivatives IIIr and IIIs show normal spectra (three singlets for the three methyls) and indicate a free rotation about N′–SO_2 and N–N′ bonds.

Discussion

The nature of the spectra of the three analogous series (A, B, and C) described earlier are typical and reveal

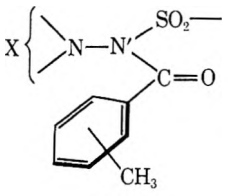


series A, R = tosyl (IIId–IIIg)
B, R = mesyl (IIIh–IIIk)
C, R = acetyl (IIIl–IIIo)

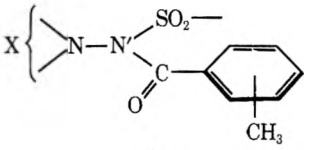
some interesting results regarding the orientation of the substituents at the exocyclic nitrogen atom.

(i) The toluoyl methyl protons show a singlet in *N′*-acetyl-*N′*-aroyl compounds (series C), whereas they are observed as pair of singlets when the acetyl group is replaced by a sulfonyl group (series A and B). This remarkable effect of the sulfonyl group can be

explained by assuming, along with slow rotation about the N–N′ bond, a preferred conformation, VI, about



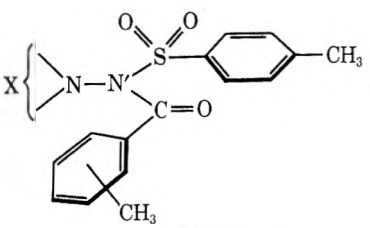
VI



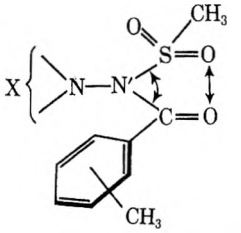
VII

the N′–CO bond. The toluoyl methyl protons, being oriented nearer to the cage moiety, about the N′–CO bond in VI, effectively experience the changes in the magnetic environments due to the conformational changes about the N–N′ bond and therefore appear as two signals corresponding to the two conformations. The other conformation VII about the N′–CO bond is not stable probably because of the large steric hindrance between the *N*′-sulfonyl group and the aryl part of the *N*′-aroyl groups. In case of the corresponding acetyl compounds (series C), the toluoyl group can take either of the two conformations about the N′–CO bond with more or less equal probability because of less hindrance of the acetyl group; thus the toluoyl methyl protons, being less sensitive towards the cage moiety magnetic environments, appear as a singlet only. It is also supported by the observation of the shielding effect of the *N*′-aroyl group on the β-methyl to be more in the *N*′-sulfonyl-*N*′-aroyl compounds (series A and B) than in the *N*′-acetyl-*N*′-aroyl compounds (series C).

(ii) It is further seen that, in *N*′-mesyl-*N*′-aroyl compounds (series B), the upfield β-methyl signal is more shielded and at the same time the downfielded β-methyl signal is less deshielded (overlapping on the γ-methyl signal) as compared to the corresponding signals in the *N*′-tosyl-*N*′-aroyl compounds (series A). As discussed earlier, the tosyl group assumes a fixed conformation about the N′–SO_2 bond as shown in VIII



VIII



IX

and thus has a strong deshielding effect on β-methyl. Further, a free rotation about the N′–SO_2 bond has been established (in compounds IIIa and IIIb). The reduced deshielding of the β-methyl signal in series B is in accordance with the free rotation about N′–SO_2 bond.

The strong shielding of the β-methyl group in *N*′-mesyl-*N*′-aroyl compounds (series B) suggests that the *N*′-aroyl group sits very close over the β-methyl group; *i.e.*, the S–N′–C bond angle in the compounds of series B is larger than that in the compounds of series A. The increased S–N′–C bond angle in series B (IX) may be the result of large stereoelectronic interactions between the sulfonyl and carbonyl oxygens, which are absent in *N*′-tosyl-*N*′-aroyl compounds (A) due to the fixed conformations of the substituents.

Conclusion

From the foregoing account, it is evident that the *N*′,*N*′-disulfonyl and the *N*′-sulfonyl-*N*′-acyl derivatives prefer a noneclipsed conformations about the N–N′ bond. High torsional barriers due to the stereoelectronic repulsive interactions between the carbonyl and sulfonyl groups at the two nitrogens are of the same order of those in the *N*,*N*′-diacyl compounds (Table I). It is interesting to note that, in the *N*′-sulfonyl-*N*′-acyl derivatives (with hindered rotation about the N–N bond), the mesyl derivatives show a free rotation about the N′–SO_2 bond and the tosyl derivatives have a fixed conformation about the N′–SO_2 bond. The orientation of the tosyl group is such that its aromatic ring does not have any shielding effect on the cage moiety protons.

Experimental Section

Nmr spectra were recorded on a Varian A-60D nmr spectrometer, equipped with a variable temperature controller (Model No. V-6040) at 44.5° in $CDCl_3$ using TMS as internal reference standard. The nmr data of the compounds are recorded in Table II.[15] The variable temperature spectral parameters are given in Table I. Ir spectra were recorded in Nujol medium on a Perkin-Elmer 257 spectrophotometer. The melting points of the compounds are fairly sharp and melt within the range of ±1° and are recorded in Table III,[15] along with the analytical data and characteristic ir peaks.

Preparation of Compounds. ***N*′-Mesyl Compounds (IIIa, IIIb, IIIh–IIIk, and IIIr).**—*N*′,*N*′-Dimesyl-*N*-aminocamphorimide (IIIa) was prepared by heating 1 mol of *N*-aminocamphorimide[10] with 2 mol of methanesulfonyl chloride in presence of pyridine at ~120° for 2 hr. It was recrystallized from ethanol.

N′-Monomesyl compound (IIIr) was prepared by heating on water bath the *N*-aminocamphorimide with equimolar quantities of methanesulfonyl chloride and pyridine. The product obtained had a gummy consistency, and the ir and nmr spectra were found to be quite satisfactory (Tables II and III).[15] The *N*′-mesyl-*N*′-acetyl derivative IIIb was obtained by acetylation of compound IIIr with excess of acetic anhydride. All the aroyl derivatives (IIIh–IIIk) were obtained by refluxing compound IIIr in dry benzene with corresponding aroyl chloride in presence of pyridine and were recrystallized from ethanol.

***N*′-Tosyl Compounds (IIIc–IIIg and IIIs).**—The *N*′-monotosyl compound (IIIs) was prepared by heating the *N*-aminocamphorimide with equimolar quantities of *p*-toluenesulfonyl chloride and pyridine at about 120° for 2 hr. It was recrystallized from ethanol. *N*′-Tosyl-*N*′-acetyl compound IIIc was prepared by acetylation of compound IIIs with excess of acetic anhydride in presence of pyridine at water bath. All the aroyl derivatives (IIId–IIIg) were obtained by refluxing compound IIIs in dry benzene with equimolar quantities of the corresponding aroyl chloride and pyridine. These compounds were recrystallized from ethanol.

***N*′-Acyl Compounds (IIIl–IIIq).**—*N*′-Monoaroyl compounds IIIp and IIIq were prepared by refluxing the *N*-aminocamphorimide in dry benzene with equimolar quantities of the corresponding aroyl chloride and pyridine. IIIp, IIIq, and *N*′-monoaroyl-*N*-aminocamphorimides[10] on acetylation with excess of acetic anhydride in presence of pyridine yielded the compounds IIIl–IIIo. These compounds were recrystallized from ethanol.

Acknowledgments.—The authors gratefully acknowledge the research grant from the Council of Scientific and Industrial Research, India. Thanks are also due to Professor G. B. Singh for his keen interest and to Mr. R. C. P. Bipin for recording the nmr spectra.

Registry No.—IIIa, 41262-98-0; IIIb, 41262-99-1; IIIc, 41263-00-7; IIId, 41263-01-8; IIIe, 41263-02-9; IIIf, 41263-03-0; IIIg, 41263-04-1; IIIh, 41263-05-2; IIIi, 41263-06-3; IIIj, 41312-33-8; IIIk, 41263-07-4; IIIl, 41263-08-5; IIIm,

41263-09-6; IIIn, 41263-10-9; IIIo, 41263-11-0; IIIp, 41263-12-1; IIIq, 41263-13-2; IIIr, 41263-14-3; IIIs, 41263-15-4; *N*-aminocamphorimide, 37710-30-8; methanesulfonyl chloride, 124-63-0; acetic anhydride, 108-24-7; *p*-toluenesulfonyl chloride, 98-59-9; benzoyl chloride, 98-88-4; *p*-toluoyl chloride, 933-88-0; *m*-toluoyl chloride, 1711-06-4; *o*-toluoyl chloride, 933-88-0.

Supplementary Material Available.—Tables of nmr, analytical, and ir data and figures showing the nmr of IIIa, IIIc, IIIf, IIIj, and IIIn will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 20 × reduction, negatives) containing all the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-73-3745.

O-(1-Alkyl- or -arylthioalkyl)hydroxylamines. A New Class of Oxime Reagents, Their Preparation and Synthetic Utility

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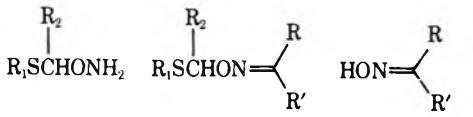
O-(1-Methyl-, -benzyl-, and phenylthioalkyl)hydroxylamines **1a–e** were synthesized by solvolysis of the corresponding *N*-(1-methyl-, benzyl-, and -phenylthioalkoxy)phthalimides **5a–e**. The (1-methyl-, -benzyl-, and -phenylthioalkoxy) oximes, **7a–e**, of the cyclopentanone were prepared, and their stability in acidic, basic, reductive, and oxidative media was determined. The mercury(II)-promoted hydrolysis of **7a–e** to the corresponding hydroxy ketoxime **10** is described.

In connection with the synthesis and chemical transformations of the E prostaglandins, the masking and unmasking of the reactive β-ketol moiety in the cyclopentane ring has been a challenging problem for the organic chemist. Oxime reagents have already been used to stabilize the β-ketol functionality;[1-3] however, the regeneration of prostaglandins from them, in good yield, has so far only been achieved in the case of the *O*-unsubstituted ketoxime derivative.[3] However, the sensitivity of the labile hydroxy ketoximes to acidic and oxidative media[4] substantially limits their role as synthetic intermediates.

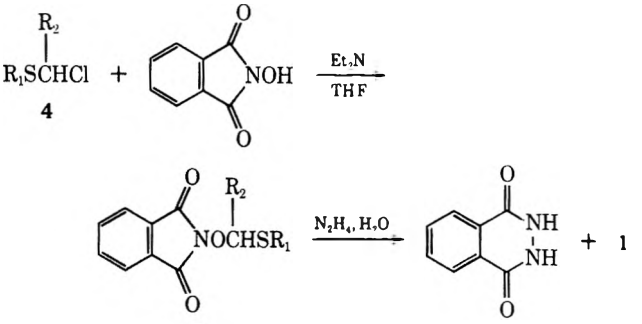
In this paper we wish to report on the development of a new class of oxime reagents, namely the *O*-(1-alkyl- and -phenylthioalkyl)hydroxylamines **1**, to demonstrate the synthetic versatility of such ketoxime derivatives **2**[5] and describe the hydrolysis of **2**, under mild conditions, to the corresponding free oxime derivatives **3**.



1 **2** **3**

The synthesis of the hydroxylamine derivatives **1a–e** was accomplished as outlined in Scheme I. The chloroalkylthio ethers, **4a–e**, were prepared by the method of Bohme, *et al.*[6] The crude reaction products of **4c** and **4e** were unstable to fractional distillation[7] and were used without further purification. Reaction of *N*-hydroxyphthalimide and triethylamine with **4a–e** in refluxing tetrahydrofuran gave the crystalline

SCHEME I



5

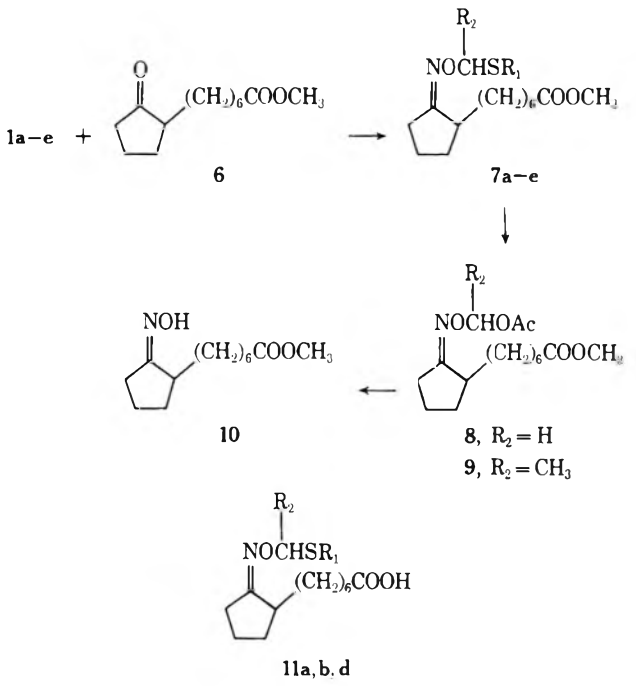
a, $R_1 = CH_3$; $R_2 = H$
b, $R_1 = C_6H_5CH_2$; $R_2 = H$
c, $R_1 = C_6H_5CH_2$; $R_2 = CH_3$
d, $R_1 = C_6H_5$; $R_2 = H$
e, $R_1 = C_6H_5$; $R_2 = CH_3$

phthalimide derivatives **5a–e**[8] in good yield. Solvolysis of **5a–e** with hydrazine hydrate in refluxing ethanol produced the hydroxylamine derivatives **1a–e** as stable distillable liquids. Although the free bases could be stored indefinitely at 0°, their addition salts (*e.g.*, hydrochlorides) slowly decomposed on standing at room temperature.

The hydroxylamine derivatives **1a–e** were treated with the model cyclopentanone **6**[9] in pyridine, in the presence of equivalent amounts of pyridine hydrochloride at room temperature, to give the oximes **7a–e** quantitatively (Scheme II). A variety of conditions were employed in the mercury(II)-promoted hydrolysis of the oximes **7a–e**. By far the best results were obtained when **7a–e** were treated in glacial acetic acid with excess of mercuric chloride and sodium acetate as buffer. Under these conditions acidolysis of **7a–e** resulted in the formation of the stable *O*-acetoxyme-

(1) K. Green, *Chem. Phys. Lipids*, **3**, 254 (1969).
(2) N. Finch and J. J. Fitt, *Tetrahedron Lett.*, 5649 (1969).
(3) J. E. Pike, F. H. Lincoln, and W. P. Schneider, *J. Org. Chem.*, **34**, 3552 (1969).
(4) The authors' unpublished observations.
(5) Acid-catalyzed reactions of *o*-(methylthiomethyl)benzophenone oxime have been reported by J. W. Jones, D. A. Kerr, and D. A. Wilson, *J. Chem. Soc. C*, 2591 (1971).
(6) H. Bohme, H. Fisher, and R. Frank, *Justus Liebigs Ann. Chem.*, **563**, 54 (1949).
(7) An alternative synthesis of **4e** has been described by D. L. Tuleen and T. B. Stephens, *Chem. Ind. (London)*, 1555 (1966).
(8) Compound **5a** was reported during the course of this work by V. Lerch and J. G. Moffat, *J. Org. Chem.*, **36**, 3391 (1971).
(9) (a) J. F. Bagli, T. Bogri, R. Deghenghi, and K. Weisner, *Tetrahedron Lett.*, 465 (1966); (b) N. Finch, J. J. Fitt, and I. H. C. Hau, *J. Org. Chem.*, **36**, 3191 (1971).

SCHEME II



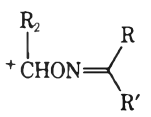
thoxy oximes **8** or **9**, in good yields. The reaction conditions are given in Table I.

TABLE I

MERCURY(II)-PROMOTED ACIDOLYSIS OF *O*-ALKYL- OR -ARYLTHIOALKYL OXIMES IN ACETIC ACID

Compd	Mole ratio $HgCl_2/HgO$	Reaction temp, °C	Reaction time, hr	Product
7a	5:0	50	48	**8**
7b	5:0	50	48	**8**
7c	5:0	25	1	**9**
7d	5:0	50	48	**8**
7e	5:0	25	1	**9**
7d	5:2	25	0.5	**8**

From these data it is apparent that the methyl, benzyl, or phenyl substituent (R_1) in **7a**, **7b**, and **7d**, respectively, had virtually no effect on the rate of solvolysis. On the other hand, the methyl substituent (R_2) in **7c** and **7d** markedly increased the cleavage rate as would be expected considering the intermediacy of the carbonium ion **12**. In an effort to optimize



12

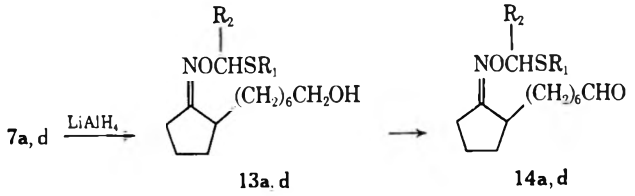
further the conditions for the acidolysis of **7a–e**, it was found that the presence of mercuric oxide dramatically increased the rate of solvolysis,[10] as is indicated in the case of the oxime **7d**.

Finally, mild treatment of **8** or **9** with aqueous potassium carbonate in methanol at room temperature for 5 min gave the oxime **10** quantitatively.

The keto protecting groups in **7a**, **7b**, and **7d** were found to be stable in dilute aqueous hydrochloric acid, while those in **7c** and **7e** were found to hydrolyze slowly to the oxime **10**. Hydrolysis of **7a**, **7b**, and **7d** with aqueous potassium carbonate to the acids **11a**, **11b**, and **11d** and reesterification of the latter to **7a**, **7b** and **7d** in refluxing methanol and *p*-toluenesulfonic acid further demonstrated the stability of the corresponding keto protecting groups to basic or acidic media.

In order to determine the stability of the most promising keto protecting groups in **7a** or **7d** toward reductive or oxidative media, the esters **7a** and **7d** were reduced at room temperature with lithium aluminum hydride in ether to alcohols **13a** and **13d** in good yield (Scheme III). By subjecting **13a** to a modified Moffat oxida-

SCHEME III



tion,[11] the substrate was overoxidized, presumably at the S atom, and only small amounts (5–10%) of a substance tentatively identified as the aldehyde **14a** (on the basis of its ir spectrum) were recovered from the reaction mixture. Similar results were obtained by subjecting **13a** to a Collins oxidation reaction.[12] However the phenyl group in the oxime **13d** markedly decreased the tendency of the S atom to be oxidized, and this substance could now be oxidized to the aldehyde **14d** in good yield, by employing the conditions of the Collins oxidation reaction.[12a]

The *O*-(phenylthiomethyl)hydroxylamine **1d** was thus found to be a versatile oxime reagent for the protection of carbonyl groups. Oximes derived thereof, which are stable against a broad spectrum of hydrolytic reductive, and oxidative reagents, can be hydrolyzed *via* the corresponding hydroxy oximes to ketones in good yields and under mild conditions. The synthetic utility of this keto protecting group was further demonstrated by its use in our total synthesis of prostaglandin E_1.[13]

Experimental Section[14]

N-Methylthiomethoxyphthalimide (**5a**).—To a stirred mixture of chloromethyl methyl sulfide (31.7 g, 0.33 mol) and *N*-hydroxyphthalimide (45.1 g, 0.28 mol) in tetrahydrofuran (500 ml) was added over a 10-min period a solution of triethylamine (46 ml) in tetrahydrofuran (500 ml). The deep red solution was refluxed under nitrogen for 48 hr. The triethylamine hydrochloride was filtered and the solvent was removed under reduced pressure. The residue was dissolved in methylene chloride, the solution was washed four times with aqueous potassium bicarbonate, once with water, dried ($MgSO_4$), and evaporated under reduced pressure. Recrystallization of the residual solid from methylene chloride–ether gave 57.9 g of the phthalimide **5a** as white crystals, mp 95–97° (lit.[8] mp 102–103°).

N-Benzylthiomethoxyphthalimide (**5b**) was synthesized in an

(10) For a recent discussion on related mercury(II)-promoted hydrolysis of 1,3-dithiane derivatives, see E. J. Corey and B. W. Erickson, *J. Org. Chem.*, **36**, 3553 (1971).

(11) K. E. Pfitzner and J. G. Moffat, *J. Amer. Chem. Soc.*, **87**, 5661, 5670 (1965).

(12) (a) J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett.*, 3363 (1968). (b) A mild oxidation method which might be suitable for the oxidation of **13** has been recently reported by E. J. Corey and C. V. Kim, *J. Amer. Chem. Soc.*, **94**, 7586 (1972).

(13) N. Finch, L. DellaVecchia, J. J. Fitt, R. Stephani, and I. Vlattas, submitted for publication in *J. Org. Chem.*

(14) Melting points were obtained in a Thomas-Hoover melting point apparatus and are uncorrected. Nmr were obtained on a Varian A-60 instrument as $CDCl_3$ solutions.

analogous manner described in the preparation of **5a**. Crystallization from methylene chloride–ether gave an analytical sample: mp 102–104°; ir (KBr) 1784, 1724 cm^{-1}; nmr δ 7.81 (s, 4, Ar), 7.35 (s, 5, Ar), 5.17 (s, 2, SCH_2O), 4.07 (s, 2, SCH_2 Ph).

Anal. Calcd for $C_{16}H_{13}NO_3S$: C, 64.21; H, 4.38; N, 4.68. Found: C, 64.39; H, 4.31; N, 4.67.

***N*-Phenylthiomethoxyphthalimide (5d)** was synthesized from chloromethyl phenyl sulfide and *N*-hydroxyphthalimide following the procedure described for the preparation of **5a**. Crystallization from methylene chloride–ether gave an analytical sample: mp 88–89.5°; ir (KBr) 1785, 1725 cm^{-1}; nmr δ 7.9–7.1 (m, 9, Ar), 4.48 (s, 2, SCH_2O).

Anal. Calcd for $C_{15}H_{11}NO_3S$: C, 63.16; H, 3.89; N, 4.91. Found: C, 62.90; H, 3.91; N, 4.86.

Benzyl 1-Chloroethyl Sulfide (4c).—Benzyl mercaptan (61.37 g, 0.44 mol) was cooled to 0° and mixed with acetaldehyde (39.17 g, 0.89 mol). The mixture was stirred at 0° for 15 min and cooled to −15°; dry hydrogen chloride was bubbled through at such a rate so that the temperature remained at 0° for 1 hr. After hydrogen chloride was bubbled through at room temperature for 3 hr, calcium chloride (15 g) was added and dry nitrogen was bubbled through the mixture for 15 hr. The solids were filtered and the yellowish oily filtrate was used in the next step without further purification since attempts to vacuum distil this material led to extensive decomposition: nmr δ 7.28 (s, 5, Ar), 4.95 (q, 1, J = 7 Hz, SCHCl), 3.9 (q, 2, $PhCH_2S$), 1.73 (d, 3, J = 7 Hz, CH_3).

***N*-(1-Benzylthioethoxy)phthalimide (5c).**—To a mixture of the crude chloroethyl thioether **4c** (86 g, 0.46 mol) and *N*-hydroxyphthalimide (91 g, 0.56 mol) in tetrahydrofuran (1000 ml) was added dropwise triethylamine until a faint yellow coloration persisted in the reaction mixture. Additional triethylamine (54 g, 0.53 mol) was then added at once and the mixture was refluxed for 15 hr. The reaction mixture was cooled to room temperature, the solids were filtered, and the filtrates were evaporated under vacuum. The residue was dissolved in methylene chloride and the solution was washed several times with 10% potassium bicarbonate, dried ($MgSO_4$), decolorized with charcoal, and evaporated. The residue was crystallized from methylene chloride–ether to give 56 g of **5c** as white crystals: mp 74–76°; ir (KBr) 1785, 1725 cm^{-1}; nmr δ 7.9–7 (m, 9, Ar), 5.6 (q, 1, J = 7 Hz, OCHS), 4.05 (q, 2, SCH_2Ph), 1.65 (d, 3, J = 7 Hz, CH_3).

Anal. Calcd for $C_{17}H_{15}NO_3S$: C, 65.17; H, 4.82; N, 4.47. Found: C, 65.52; H, 4.92; N, 4.46.

1-Chloroethyl phenyl sulfide (4e) was prepared according to the procedure employed for the preparation of **4c**. As in the case of **4c**, the crude reaction product **4e** was unstable to vacuum distillation [lit.[7] bp 75–78° (0.4 mm)] and was used in the next step without purification: nmr δ 7.7–7.1 (m, 5, Ar), 5.35 (q, 1, J = 7 Hz, SCHCl), 1.75 (d, 3, J = 7 Hz, CH_3).

***N*-(1-Phenylthioethoxy)phthalimide (5e)** was synthesized from the crude chloroethyl sulfide **4e** and *N*-hydroxyphthalimide according to the procedure employed for the preparation of **5c**. Crystallization from methylene chloride–ether gave an analytical sample: mp 65–67.5°; ir (KBr) 1785, 1725 cm^{-1}; nmr δ 7.7–7.0 (m, 9, Ar), 5.9 (q, 1, J = 7 Hz, SCHO), 1.65 (d, 2, J = 7 Hz, CH_3).

Anal. Calcd for $C_{16}H_{13}NO_3S$: C, 64.4; H, 4.38; N, 4.68. Found: C, 64.81; H, 4.64; N, 4.83.

***O*-(Methylthiomethyl)hydroxylamine (1a).**—A mixture of *N*-methylthiomethoxyphthalimide (**5a**, 40 g), hydrazine hydrate (9.42 g), 95% ethanol (350 ml), and water (9.2 ml) was refluxed for 2.5 hr. The reaction mixture was cooled to room temperature, the solids were filtered, and the filtrates were evaporated under aspirator pressure at 40° to a small volume. More solids were formed and were filtered. The filtrate was distilled under aspirator pressure to give 10 g of the amine **1a** as a colorless oil: bp 54–55° (15 mm); nmr δ 5.5 (broad s, 2, NH_2), 4.79 (s, 2, SCH_2O), 2.15 (s, 3, CH_3). The amine **1a** gave a crystalline hydrochloride on treatment with methanolic hydrochloric acid in methanol and subsequent dilution with ether, mp 135° dec.

Anal. Calcd for C_2H_8ClNOS: C, 18.53; H, 6.22; N, 10.81. Found: C, 18.44; H, 6.41; N, 10.52.

By a similar procedure to that described for the preparation of **1a**, the amines **1b–e** were prepared[15] from the corresponding phthalimides **5b–e**.

(15) During fractional distillation of the crude reaction products **1b–e**, overheating should be avoided or decomposition of these compounds might occur.

***O*-(Benzylthiomethyl)hydroxylamine (1b)**: bp 87–89° (0.1 mm); nmr δ 7.33 (s, 5, Ar), 5.43 (broad s, 2, NH_2), 4.7 (s, 2, SCH_2O), 3.8 (s, 2, $PhCH_2S$). *Anal.* Calcd for $C_8H_{11}NOS$: C, 56.79; H, 6.55; N, 8.28. Found: C, 57.19; H, 6.69; N, 8.12.

***O*-(1-Benzylthioethyl)hydroxylamine (1c)**: bp 100–107° (0.1 mm); nmr δ 7.21 (s, 5, Ar), 5.2 (s, 2, NH_2), 4.75 (q, 1, J = 7 Hz, SCHO), 3.75 (s, 2, $PhCH_2S$), 1.37 (d, 2, J = 7 Hz, CH_3). The amine **1c** was further analyzed as the corresponding oxalate, mp 115–116°. *Anal.* Calcd for $C_{10}H_{14}NO_3S$: C, 52.62; H, 6.19; N, 6.14. Found: C, 52.99; H, 6.28; N, 5.97.

***O*-(Phenylthiomethyl)hydroxylamine (1d)**: bp 84–87° (0.1 mm); nmr δ 7.6–7.1 (m, 5, Ar), 5.56 (s, 2, NH_2), 5.05 (s, 2, SCH_2O). *Anal.* Calcd for C_7H_9NOS: C, 54.19; H, 5.85; N, 9.03. Found: C, 54.40; H, 5.99; N, 9.16.

***O*-(Phenylthiomethyl)hydroxylamine hydrochloride** was prepared by treatment of **1d** in ether with ethereal hydrogen chloride: mp 110–112° dec. *Anal.* Calcd for $C_7H_{10}ClNOS$: C, 43.86; H, 5.26; N, 7.31. Found: C, 43.93; H, 5.39; N, 7.41.

***O*-(1-Phenylthioethyl)hydroxylamine (1e)**: bp 73–74° (0.1 mm); nmr δ 7.7–7 (m, 5, Ar), 5.43 (s, 2, NH_2), 5.05 (q, 1, J = 7 Hz, SCH_2O), 1.38 (d, 3, J = 7 Hz, CH_3). *Anal.* Calcd for $C_8H_{11}NOS$: C, 54.19; H, 5.88; N, 9.03. Found: C, 54.40; H, 5.99; N, 9.16.

General Procedures.—The preparation of the oximes **7a–e** from methyl 2-oxocyclopentaneheptanoate **6** and the corresponding amines **1a–e** were carried out using one of the following procedures.

A.—A mixture of cyclopentanone **6** (1 mmol) the amine **1** (1.5 mmol), pyridine (2 ml), and anhydrous pyridine hydrochloride (1.5 mmol) was stirred at room temperature for 15 hr. The pyridine was removed under vacuum; the residue was extracted with ether, washed with water, dried ($MgSO_4$), and evaporated. The residue was purified by preparative tlc on silica gel, followed by bulb-to-bulb distillation.

B.—Same as in A, except that freshly prepared amine hydrochlorides were used in the place of free amine **1** and pyridine hydrochloride.

Methyl 2-(methylthiomethoxyimino)cyclopentaneheptanoate (7a): bp 145–155° (0.1 mm); ir ($CHCl_3$) 1735 cm^{-1}; nmr δ 5.1 (s, 2, OCH_2S), 3.65 (s, 3, OCH_3), 2.35 (m, 5), 2.23 (s, 3, SCH_3), 2.1–1 (m, 14). *Anal.* Calcd for $C_{15}H_{27}NO_3S$: C, 59.78; H, 9.03; N, 4.65. Found: C, 60.1; H, 9.21; N, 4.35.

Methyl 2-(benzylthiomethoxyimino)cyclopentaneheptanoate (7b): bp 195–205° (0.1 mm); ir ($CHCl_3$) 1735 cm^{-1}; nmr δ 7.36 (s, 5, Ar), 5.05 (s, 2, OCH_2S), 3.87 (s, 2, CH_2Ph), 3.63 (s, 3, OCH_3), 2.3 (m, 5), 2.1–1 (m, 14). *Anal.* Calcd for $C_{21}H_{31}NO_3S$: C, 66.82; H, 8.28; N, 3.71. Found: C, 66.94; H, 8.49; N, 3.57.

Methyl 2-(1-benzylthioethoxyimino)cyclopentaneheptanoate (7c): ir ($CHCl_3$) 1735 cm^{-1}; nmr δ 7.3 (m, 5, Ar), 5.3 (q, 1, OCHS), 3.9 (q, 2, $PhCH_2$), 3.64 (s, 3, OCH_3), 2.26 (m, 5), 2.1 (m, 17). *Anal.* Calcd for $C_{22}H_{33}NO_3S$: C, 67.49; H, 8.50; N, 3.58. Found: C, 67.52; H, 8.34; N, 3.22.

Methyl 2-(phenylthiomethoxyimino)cyclopentaneheptanoate (7d): ir ($CHCl_3$) 1735 cm^{-1}; nmr δ 7.6–7 (m, 5, Ar), 5.45 (s, 2, OCH_2S), 3.6 (s, 3, OCH_3), 2.25 (m, 5), 2–1 (m, 14). *Anal.* Calcd for $C_{20}H_{29}NO_3S$: C, 66.09; H, 8.04; N, 3.85. Found: C, 65.69; H, 8.05; N, 4.03.

Methyl 2-(1-phenylthioethoxyimino)cyclopentaneheptanoate (7e): ir ($CHCl_3$) 1735 cm^{-1}; nmr δ 7.68–7.1 (m, 5, Ar), 5.6 (m, 1, OCHS), 3.65 (s, 3, OCH_3), 2.3 (m, 5), 2.1 (m, 17). *Anal.* Calcd for $C_{21}H_{31}NO_3S$: C, 66.82; H, 8.28; N, 3.71. Found: C, 67.17; H, 7.98; N, 3.70.

Hydrolysis and Reesterification of 7a.—A mixture of the ester **7a** (585 mg), methanol (20 ml), and 10% aqueous potassium carbonate (5 ml) was refluxed for 1 hr. The solvent was removed under vacuum and residue was dissolved in water (20 ml). The aqueous solution was extracted twice with ether and the extracts were discarded. The aqueous layer was acidified with 2 *N* hydrochloric acid and extracted twice with ether. The ether extracts were washed with water, dried ($MgSO_4$), and evaporated. The residue was dissolved in absolute methanol (30 ml), *p*-toluenesulfonic acid (30 mg) was added, and the mixture was refluxed for 24 hr. The methanol was evaporated under vacuum, the residue was dissolved in ether and the ether solution was washed with 10% aqueous potassium bicarbonate and water, dried ($MgSO_4$), and evaporated to give 510 mg of the original ester **7a**.

Lithium Aluminum Hydride Reduction of 7a.—To a suspension of lithium aluminum hydride (100 mg) in ether (25 ml) was added a solution of the ester **7a** (750 mg) in ether (15 ml) with stirring and ice–water cooling over a period of 15 min. After 1 hr of stirring at room temperature, the excess of the hydride was destroyed with water, the salts were filtered, and the filtrates were evaporated. The residue was extracted with ether washed with water, dried ($MgSO_4$), and evaporated to give 543 mg of 2-(methylthiomethoxyimino)cyclopentaneheptanol **13a** as a viscous oil: nmr δ 5.07 (s, 2, OCH_2S), 3.55 (t, 2, CH_2O), 2.35 (m, 3), 2.17 (s, 3, OCH_3), 2–1 (m, 16).

In a similar manner, lithium aluminum hydride reduction of ester **7d** gave 2-(phenylthiomethoxyimino)cyclopentaneheptanol (**13d**) as a colorless, viscous oil. Bulb-to-bulb distillation of this compound gave an analytical sample: bp 165° (0.1 mm); nmr δ 7.61–7.1 (m, 5, Ar), 5.45 (s, 2, OCH_2S), 3.6 (t, 2, CH_2O), 2.3 (m, 3), 2.1–1 (m, 16).

Anal. Calcd for $C_{19}H_{29}NO_2S$: C, 68.02; H, 8.71; N, 4.15. Found: C, 67.79; H, 8.85; N, 4.04.

Moffat Oxidation[11] of the Alcohol 13a.—A solution of the alcohol **13a** (250 mg) in benzene (5 ml) and dimethyl sulfoxide (5 ml) was cooled to 0°; pyridine (93 μl), trifluoroacetic acid (75 μl), and 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate (0.8 g) were added; and the mixture was stirred at 4° for 48 hr. The mixture was poured into cold water and extracted three times with ether. The ether extracts were washed with water, dried ($MgSO_4$), and evaporated to give 30 mg of an oily substance: ir ($CHCl_3$) 2725 (weak), 1720 cm^{-1}.

Collins Oxidation of the Alcohol 13d.—To a solution of the alcohol **13d** (130 mg) in dry methylene chloride (50 ml) was added chromium trioxide–pyridine complex[12a] (600 mg) at once, and the mixture was stirred at room temperature for 10 min. The mixture was poured into water; the methylene chloride layer was washed once more with water, dried ($MgSO_4$), decolorized with charcoal, and evaporated. The oily residue was subjected to bulb-to-bulb distillation and gave 104 mg of 2-(phenylthiomethoxyimino)cyclopentaneheptanal (**14d**) as a clear viscous oil: bp 145° (0.1 mm); ir ($CHCl_3$) 2725, 1720 cm^{-1}; nmr δ 10.7 (t, 1, CHO), 7.8–7.1 (m, 5, Ar), 5.5 (s, 2, OCH_2S), 2.7–2.2 (m, 5), 2.1–1 (m, 14).

Anal. Calcd for $C_{19}H_{27}NO_2S$: C, 68.44; H, 8.16; N, 4.20. Found: C, 68.15; H, 7.88; N, 4.03.

Mercuric Chloride Promoted Acidolysis of Methylthiomethoxy Oxime 7a.—Mercuric chloride (270 mg) and potassium acetate (250 mg) were added to a solution of the oxime **7a** (230 mg) in acetic acid (11 ml), and the mixture was stirred at 50° for 48 hr. The precipitate was filtered and the filtrate was treated with hydrogen sulfide gas. The black mercuric sulfide was filtered and the filtrates were evaporated to dryness under vacuum. The residue was extracted with ether and the extracts were washed with water, dried ($MgSO_4$), and evaporated to give 180 mg of methyl 2-(acetoxymethoxyimino)cyclopentaneheptanoate (**8**) as a yellowish oil. Further purification by preparative thin layer chromatography (silica gel, methylene chloride–ether 5:95, R_f 0.65) gave an analytical sample: ir (film) 1755 (sh), 1740 cm^{-1}; nmr δ 5.68 (q, 2, OCH_2S), 3.65 (s, 3, OCH_3), 2.3 (m, 5), 2.08 (s, 3, $COCH_3$), 2.0–1.0 (m, 14).

Anal. Calcd for $C_{16}H_{27}NO_5$: C, 61.32; H, 8.68; N, 4.47. Found: C, 61.62; H, 8.68; N, 4.61.

Under similar acidolysis conditions, the phenylthiomethoxyoximes **7b**, and **7d** gave, after 24 hr, the acetate **8** in 75% yield.

Mercuric Chloride Promoted Acidolysis of Phenylthioethoxy Oxime 7e.—Mercuric chloride (136 mg) and potassium acetate (128 mg) were added to a solution of the oxime **7e** (114 mg) in acetic acid (32 ml), and the mixture was stirred at room temperature for 1 hr. The mixture was diluted with acetone (30 ml) and treated with hydrogen sulfide gas; the salts were filtered. The filtrates were evaporated under vacuum, the residue was extracted with ether, and the extracts were washed with water, dried ($MgSO_4$), and evaporated. Preparative thin layer chromatography of the residue (silica gel, methylene chloride–ethyl acetate 95:5, R_f 0.51) gave 98 mg of ethyl 2-(1-acetoxyethoxyimino)cyclopentaneheptanoate (**9**) as a yellowish viscous oil: ir (film) 1740 cm^{-1}; nmr δ 6.35 (q, 1, OCHS), 3.6 (s, 3, OCH_3), 2.3 (m, 5), 2.0 (s, 3, $COCH_3$), 2.0–1.0 (m, 17).

Anal. Calcd for $C_{17}H_{29}NO_5$: C, 62.36; H, 8.93; N, 4.28. Found: C, 62.42; H, 9.23; N, 4.35.

Under similar acidolysis conditions, the benzylthioethoxy oxime **7c** gave the acetate **9** quantitatively.

Mercuric Chloride–Mercuric Oxide Promoted Acidolysis of 7d.—A mixture of mercuric chloride (456 mg, 1.68 mmol), mercuric oxide (120 mg, 0.56 mmol), potassium acetate (412 mg, 4.2 mmol), and acetic acid (10 ml) was added at once to a solution of the oxime **7d** (200 mg, 0.56 mmol) in acetic acid (20 ml); the mixture was stirred at room temperature for 0.5 hr. The mixture was diluted with acetone (30 ml), treated with hydrogen sulfide gas, and filtered. The filtrates were evaporated under vacuum, the residue was extracted with ether, and the extracts were washed with water, dried ($MgSO_4$), and evaporated to give 150 mg of the acetate **8**.

Methyl 2-(hydroxyimino)cyclopentaneheptanoate (10). 1. From the Acetate 8.—To a solution of 150 mg of the acetate **8** in 1 ml of methanol was added 50 μl of 10% aqueous potassium carbonate, and the mixture was stirred at room temperature for 5 min. The mixture was diluted with 50 ml of ether, washed with water, dried ($MgSO_4$), and evaporated to give the title compound **10** quantitatively: bp 133–138° (0.2 mm); ir (film) 3270, 1740 cm^{-1}.

Anal. Calcd for $C_{13}H_{23}NO_3$: C, 64.70; H, 9.61; N, 5.80. Found: C, 64.34; H, 9.45; N, 5.57.

2. From the Acetate 9.—The acetate **9** was hydrolyzed in a similar manner to give the oxime **10** quantitatively.

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Registry No.—**1a**, 41108-16-1; **1a** hydrochloride, 41108-17-2; **1b**, 41108-18-3; **1b** hydrochloride, 41108-19-4; **1c**, 41108-20-7; **1c** hydrochloride, 41108-21-8; **1c** oxalate, 41108-22-9; **1d**, 41108-23-0; **1d** hydrochloride, 41108-24-1; **1e**, 41108-25-2; **1e** hydrochloride, 41108-26-3; **4c**, 41108-27-4; **4e**, 13557-24-9; **5a**, 31280-44-1; **5b**, 41108-30-9; **5c**, 41108-31-0; **5d**, 41108-32-1; **5e**, 41108-33-2; **6**, 37617-17-7; **7a**, 41108-35-4; **7b**, 41108-36-5; **7c**, 41108-37-6; **7d**, 41108-38-7; **7e**, 41108-39-8; **8**, 41108-40-1; **9**, 41108-41-2; **10**, 41108-42-3; **13a**, 41108-43-4; **13d**, 41108-44-5; **14d**, 41108-45-6; chloromethyl methyl sulfide, 2373-51-5; *N*-hydroxyphthalimide, 524-38-9; chloromethyl phenyl sulfide, 7205-91-6; benzyl mercaptan, 108-98-5; acetaldehyde, 75-07-0; potassium acetate, 127-08-2.

The Mannich Reaction. 6-Alkoxytetrahydro-5,5-dimethyl-1,3-oxazines

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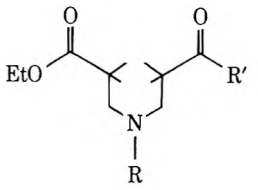
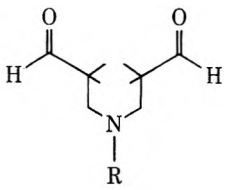
The syntheses of 6-ethoxytetrahydro-3,5,5-trimethyl-2*H*-1,3-oxazine (**6a**) and 6-*tert*-butoxytetrahydrooxazine **6b**, using a modification of the Mannich condensation which involves reaction of 2 equiv of formaldehyde with 1 equiv of methylamine hydrochloride and isobutyraldehyde in the appropriate alcohol solvents, are reported. The importance of this new class of molecules as reaction intermediates is demonstrated by using **6a** to synthesize both ester aldehyde **2b** and dialdehyde **3b** by simple one-step routes. When poorly ionizing solvents or hindered amine salts were used in these reactions, the 2nd equiv of formaldehyde was found not to participate in the reaction and acetals **5a**, **5b**, and **12**, respectively, became the major products. Dialdehyde **3b** could also be obtained in low yield using a double Mannich-type condensation under conditions where all other products were kept in equilibrium.

Recently we reported[1] on the anticancer properties of the hindered *N*-*tert*-butyl-3,3′-imino diester **1**. Our continuing interest in this area has led us to undertake the syntheses of the corresponding hindered ester aldehydes **2a** and **2b**, and dialdehydes **3a** and **3b**.



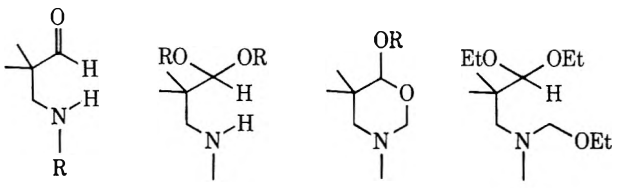
1, R′ = OEt; R = *t*-Bu
2a, R′ = H; R = *t*-Bu
b, R′ = H; R = CH_3



3a, R = *t*-Bu
b, R = CH_3

Our initial attempts to synthesize the less hindered *N*-methyl dialdehyde **3b** by a modification of the Mannich reaction which used 2 equiv of isobutyraldehyde and formaldehyde and 1 equiv of methylamine hydrochloride with ethanol as the solvent did not give dialdehyde **3b**, or its tetraethyl acetal, in appreciable yield, but rather gave a mixture of products, **4a**, **5a**, **6a**, and **7**, as shown in Chart I, the major product being 6-ethoxytetrahydro-3,5,5-trimethyl-2*H*-1,3-oxazine (**6a**).

CHART I

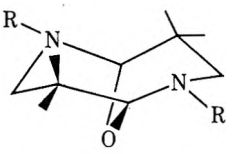


4a, R = CH_3 **5a**, R = Et **6a**, R = Et **7**
b, R = benzyl **b**, R = *n*-Bu **b**, R = *n*-Bu
c, R = *t*-Bu **c**, R = *t*-Bu

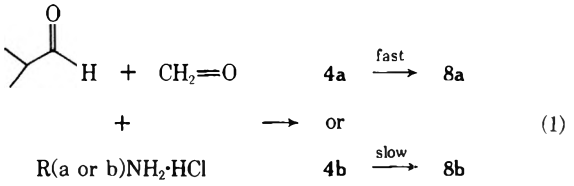
We have now shown that tetrahydrooxazine **6a** can serve as a precursor for the syntheses of both **2b** and **3b**. Because of the apparent use of this new class of molecules as synthetic intermediates[2] and because of the observed physiological properties of **6a**,[3] we have investigated the scope of this type of double Mannich condensation by studying the reactions of isobutyraldehyde with several amine hydrochlorides and formaldehyde in different alcohol solvents and would like to report our results in this area.

Results

The original reactions of isobutyraldehyde with formaldehyde and primary amine hydrochlorides were reported in 1932 by Mannich and Wieder.[4] When they used the hydrochloride salts of small amines, such as methylamine, they found that a novel dimer, **8a**, of the desired secondary β-amino aldehyde, **4a**, was formed in 40% yield. They also noted some formation of amino aldehyde **4a**; however, it was observed to self-condense upon standing at 25°. Later workers[5] noticed that self-condensation of an initially formed β-amino aldehyde, **4b**, occurred less readily when salts of bulkier amines such as benzylamine were employed (eq 1).



8a, R = CH_3
b, R = benzyl



(1)

These results suggested that reaction of the initially formed secondary β-amino aldehyde with a second reactive aldehyde, such as formaldehyde, would be expected to take place unless the nitrogen atom of the amino aldehyde was sterically hindered. This being the case, a double Mannich-type condensation appeared to represent a feasible route leading to the synthesis of **3b**. In fact, when the water formed from the initial condensation of the amine salt and formaldehyde was not removed from the reaction mixture, dialdehyde **3b** could be obtained in 16% yield after acid hydrolysis of the reaction mixture and work-up. The only other major product observed in this reaction was aldehyde **4a** which resulted from the hydrolysis

(1) P. Y. Johnson and I. Jacobs, *Chem. Commun.*, 925 (1972).

(2) For examples of the use of dihydro-1,3-oxazines as reaction intermediates, see A. I. Meyers and E. M. Smith, *J. Org. Chem.*, **37**, 4289 (1972), and references cited therein.

(3) This molecule was shown to cause an average 50% increase in the survival times of mice infected with P388 lymphocytic leukemia at doses ranging from 44 to 200 mg/kg of animal. Testing was kindly performed by CCNSC, National Cancer Institute (NIH).

(4) C. Mannich and H. Wieder, *Ber.*, **65**, 385 (1932).

(5) M. W. Williams, *J. Org. Chem.*, **33**, 3946 (1968).

TABLE I

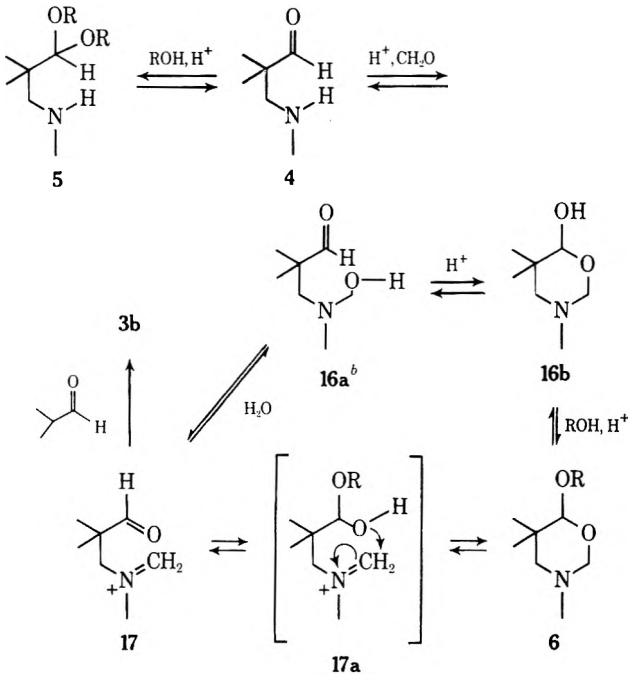
SUMMARY OF GENERAL EXPERIMENTAL PROCEDURE

Runs	RXN solvent for 1-hr reflux (ml)	Bz added after 3-hr reflux, ml	H_2O, ml, removed by azeotrope	(% product yield isolated)
A[a]	EtOH (200)	200	100	**6a** (84[b])
B[a]	*t*-BuOH (200)	200	100	**6c** (25 isolated from mixture)
C[c]	EtOH (100)	100	100	**6a** (25); **8a** (36)
D[c]	EtOH (150), Bz (150)	0	70	**5a** (60)
E[a]	*n*-BuOH (200)	200	100	**5b** (30)
F[d]	EtOH (100)	100	50	**12** (56); **4c** (32)

[a] 0.25-mol scale but 0.50 mol of formaldehyde. [b] Reference 11. [c] 0.25-mol scale for all reagents. [d] *tert*-butylamine salt (0.1 mol; see Experimental Section) was used in this reaction.

of the other potential products. The reaction was run in this manner after early experiments indicated that the yield of **3b** could probably be increased if all other potential products, in particular **6a**, were allowed to remain in equilibrium under hydrolytic conditions so that the only obvious irreversible step in the reaction would be formation of **3b** (Scheme I). This

SCHEME I[a]



[a] Aldehyde species can exist in their hemiacetal or acetal forms; amines can exist as their HCl salts. [b] Structures similar to **16a**, **16b**, and **17** have been postulated to be important in the reactions of β-amino ketones with pyridoxal phosphate in aqueous solvents: M. Skyvova and L. Machelan, *Collect. Czech. Chem. Commun.*, **35**, 2345 (1970).

approach was found to require a 60-hr reaction time to allow for the slow formation of **3b**. After 60 hr other side reactions became important causing a decrease in the already low yield of **3b**.

When the water formed during the reaction was removed from the mixture by azeotrope (Az) in hopes of increasing the concentration of immonium **17** (the procedure employed in our initial studies), the main products were those shown in Chart I. While the product distribution for these reactions was found to be extremely dependent on reaction conditions, the major product, **6a**, could be obtained in as high as 80% yield following the general procedure given in the Experimental Section (see Table I, run A). When less ethanol was used as the solvent in this reaction, there was an over-all decrease in the amount of recovered amine-containing products, but the isolated yield of dimer **8a** was found to increase (Table I, run C). This was probably due to the increased concentration of aldehyde **4a** under these conditions. When larger volumes of ethanol were employed, the amount of acetal **5a** isolated increased as would be expected since ethanol is a reactant in this reaction. When the solvating power of the solvent was decreased by the use of benzene (Bz) as a cosolvent, the amount of acetal **5a** also increased, probably because of a decrease in the concentration of free amine **4a** compared to amine hydrochloride in this poorly ionizing solvent mixture. This would cause a retarding effect on the reaction of **4a** with the 2nd equiv of formaldehyde relative to acetal formation. Using this knowledge we were able to synthesize acetal **5a** in 60% yield (Table I, run D).

Tetrahydrooxazine **6a** was identified by its spectra. Its ir spectra showed no OH, NH, or carbonyl absorptions. The nmr spectrum (100 Mc) showed singlets at δ 0.84 and 0.95 attributable to the nonequivalent methyl groups at C-5. The methylene protons at C-2 and C-4 both gave rise to AB patterns centered at δ 3.72 (J = 8 Hz) and 2.11 (J = 11 Hz), respectively. The methine proton at C-6 appears as a sharp singlet at δ 3.94 showing that it is not coupled to any other protons. Interestingly, while the methyl protons of the ethoxy group give rise to a clean triplet at δ 1.12 (J = 7 Hz), the methylene protons (CH_3CH_2O) appear as two multiplets centered at δ 3.49. Spectra obtained at 60° were identical with those obtained at 25°; however, decoupled spectra obtained by irradiation at δ 1.1 (CH_3CH_2O) showed that the multiplets were converted into clean pairs of doublets (J = 10 Hz) centered at δ 3.26 and 3.62, respectively, indicating that the ethoxy methylene protons are nonequivalent owing to the chiral center at C-6 and not to hindered rotation about the C-6–O or O–Et bonds.

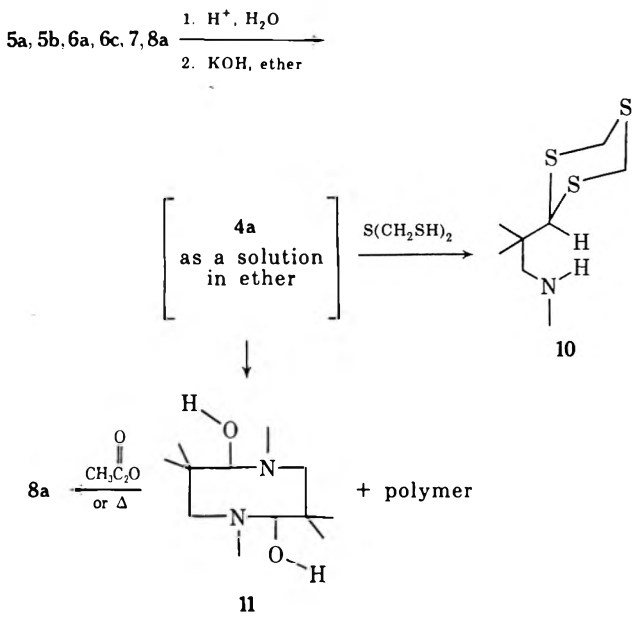
Attempts to make 6-*n*-butoxytetrahydrooxazine **6b** following the general procedure, but using *n*-butyl alcohol as the solvent (Table I, run E), gave instead di-*n*-butyl acetal **5b** as the only major product observed in the crude reaction mixture. Distillation of the crude material gave pure **5b** in 30% yield. The lack of formation of the desired tetrahydrooxazine **6b** is again believed to be due to the low concentration of free secondary amine capable of reacting with the second formaldehyde molecule in this solvent. On the other hand, similar reactions in *tert*-butyl alcohol gave several products from which 6-*tert*-butoxytetrahydrooxazine **6c** could be isolated in 25% yield by careful vacuum distillation of the crude material (Table I, run B). The

other major amine containing product was identified as aldehyde **4a**.

Compounds **5a**, **5b**, **6a**, **6c**, **7**, and **8a** could all be hydrolized in aqueous acid to give, after neutralization and work-up, amino aldehyde **4a** which was stable in solution at 0°.

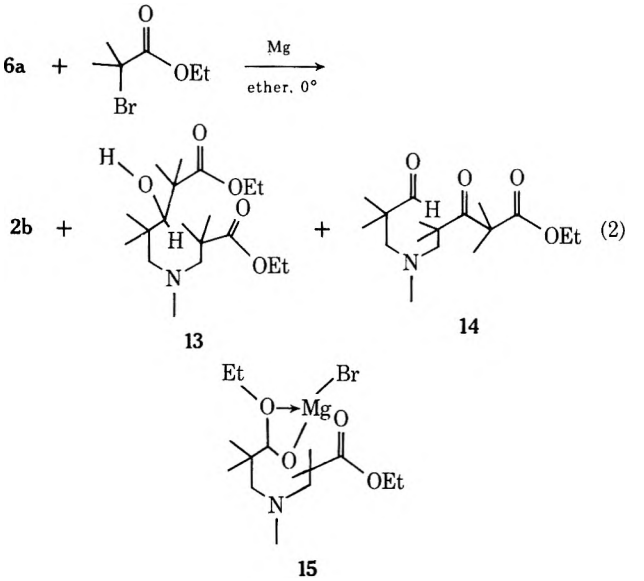
Amino aldehyde **4a** was characterized as its benzenesulfonamide, **9**, and trithiane, **10**, derivatives. While the trithiane was obtained as a white solid (mp 52–54°) using the literature procedure[6] given for the synthesis of these molecules and displayed clean spectra (see Experimental Section) when fresh, it became gummy after standing several days at 25°. When the solvent was allowed to evaporate from an ether solution of aldehyde **4a** over several days, an "oily" solid remained which was shown by nmr not to be dimer **8a**. However, reaction of this solid with acetic anhydride or vacuum distillation of it resulted in low yields of bicyclo ether **8a**. The initial solid has been assigned the amino hemiacetal structure **11**[7] (and related linear polymers of it). These reactions are summarized in Scheme II.

SCHEME II



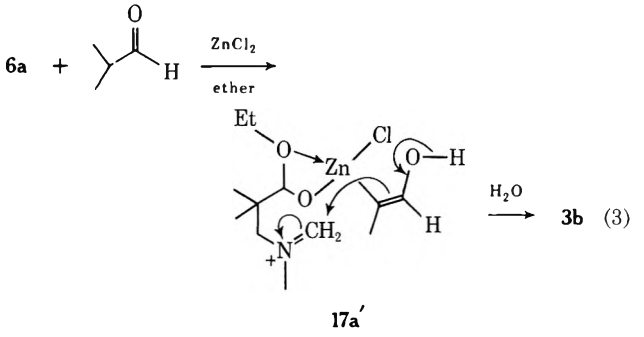
Reaction of the more hindered *tert*-butylamine hydrochloride with isobutyraldehyde and formaldehyde in ethanol gave no tetrahydrooxazine derivatives, but rather gave the diethyl acetal of aldehyde **4c** (**12**) in 56% yield and aldehyde **4c** itself in 32% yield. No products resulting from reaction of the 2nd equiv of formaldehyde were observed in this reaction. Acetal **12** was readily hydrolyzed in aqueous acid to give the stable *tert*-butylamino aldehyde **4c**, in high yield.

Tetrahydrooxazine **6a** was found to be a valuable reaction intermediate. The desired ester aldehyde **2b** could be obtained pure in 40% yield from the reaction of **6a** with a slight excess of the Grignard reagent made from ethyl α-bromoisobutyrate and magnesium at 0° in ether.[8] Two minor amine products, identified as **13** (9%) and **14** (1%), were also isolated from this reaction. Since aldehyde ester **2b** was obtained in high yield relative to **13** in this reaction, it is concluded that the magnesium halide complex of the hemiacetal, **15**, must be formed initially in this reaction preventing, for the most part, free aldehyde formation during the reaction, and that the free aldehyde group results from aqueous work-up of complex **15** (eq 2).



(2)

Dialdehyde **3b** could also be synthesized in good yield from **6a**. Treatment of **6a** and isobutyraldehyde in ether with zinc chloride for 3 hr gave, after work-up and purification, **3b** in 49% yield. The mechanism of this reaction is believed to involve attack of the enol of isobutyraldehyde on the zinc halide hemiacetal complex of immonium ion **17a** (eq 3).[9] A small amount



(3)

of the bicyclic ether dimer **8a** was also isolated from this reaction. We are currently undertaking other studies of this new class of reaction intermediates at this time.

Experimental Section

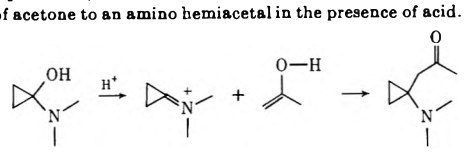
Melting points were taken on a calibrated Mel-Temp apparatus. Ir spectra were taken on a Perkin-Elmer 337 spectrometer; nmr spectra were recorded on Jelco MH-100 and Varian A-60 spectrometers using TMS as an internal standard; and mass spectra were obtained on a Hitachi RMU6D mass spectrometer. Vpc analyses were performed using program temperature con-

(6) See P. Y. Johnson, *Chem. Commun.*, 1083 (1971), for typical procedure.

(7) This type of dimer has been suggested before for secondary amino aldehydes. See E. J. Browne, *Aust. J. Chem.*, **24**, 2389 (1971).

(8) For an example of a similar type of reaction involving an oxazolidine system, see P. Johnson and M. Davis, *Tetrahedron Lett.*, 293 (1973).

(9) This reaction is believed to be analogous to a Mannich-type reaction reported by Deboer, *et al.* [*Tetrahedron Lett.*, 1677 (1972)], which involves addition of acetone to an amino hemiacetal in the presence of acid.



trol on a Hewlett-Packard 5750 gas chromatograph equipped with 8 ft × 0.25 in. 10% Carbowax on Chromosorb P and 8 ft × 0.25 in. 10% SE-30 on Chromosorb P stainless steel columns. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

General Mannich Reaction Procedure.—The general procedure described here for the synthesis of **6a** was used with variations as noted in Table I for the syntheses of **5a**, **5b**, **6c**, **8a**, and **12**.

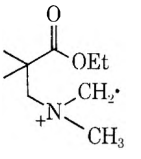
To a dry 1000-ml three-neck flask, under N_2, was added 200 ml of ethanol, 15 drops of concentrated HCl, 16.87 g (0.25 mol) of methylamine hydrochloride, and 15 g (0.5 mol) of formaldehyde (trioxane). The stirred reaction mixture was heated at reflux for 1 hr at which time 18 g (0.25 mol) of isobutyraldehyde was added dropwise to the mixture which was then refluxed an additional 3 hr. After the mixture was allowed to cool, 200 ml of benzene was added to the reaction mixture. A Dean-Stark trap was attached to the reaction flask and 100 ml of solvent was slowly removed as an azeotrope.

After removal of the specified amount of solvent, the reaction mixture was cooled to 0° and 100 ml of ice water was added. The cold acidic layer was separated, after the mixture was shaken well, and washed several times with ether. The acidic aqueous layer was made basic (keep cold) with solid Na_2CO_3 or KOH[10] and the amine products were extracted from the basic layer with four 150-ml portions of cold ether which were dried with $MgSO_4$, filtered, and evaporated. Careful distillation of the crude residue using a 20-cm column gave 36.5 g (84% yield) of **6a**:[11] bp 42–45° (1.5 mm), 28–29° (0.2 mm); ir and nmr (see text); mass spectrum (70 eV) *m/e* (rel intensity) 173 (7, M^+), 128 (10), 102 (15), 100 (54), 99 (20), 72 (30), 59 (25), 58 (60), 45 (100).

Anal.[12] Calcd for $C_9H_{19}NO_2$: C, 62.30; H, 11.02; N, 8.07. Found: C, 61.19; H, 10.78; N, 7.84.

Synthesis of *N*-Methyl-3-imino-2,2-dimethylpropanal Diethyl Acetal (5a).—This reaction was run using the general procedure given above (Table I, run D) affording **5a**: bp 25–26° (0.15 mm), 80–85° (25 mm); ir (CCl_4) 3345 cm^{-1}, no C=O stretch; nmr (CCl_4) δ 0.88 (s, 6), 1.18 (t, 6), 1.42 [s, 1, not present in D_2O (NH)], 2.37 (s, 3), 2.41 (s, 2), 3.65 (m, 4, OCH_2CH_3), 4.21 (s, 1); mass spectrum (70 eV) *m/e* (rel intensity) 189 (1, M^+), 128 (1), 114 (1), 103 (19), 101 (4), 100 (75), 98 (7), 75 (15), 72 (30), 60 (50), 57 (10), 47 (20), 44 (100).

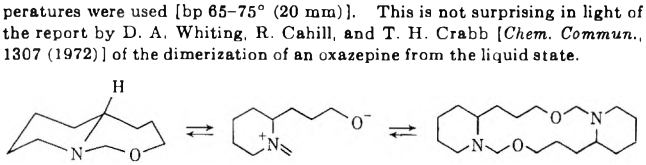
***N*-Ethoxymethyl-*N*-methyl-3-imino-2,2-dimethylpropanal Diethyl Acetal (7).**—Acetal **7** [bp 50–54° (0.1 mm)] was isolated as a minor product from several of these reactions and was identified by its spectra (Table I, runs A, C, and D): ir (CCl_4) no OH, C=O; nmr shows a series of multiplets which are not unambiguously assigned but which are compatible with the proposed structure; mass spectrum shows *m/e* 172 as the highest molecular weight ion (a) (all other major peaks can be accounted for by further breakdown of ion a).



a

(10) Tertiary amines (**6a**, **6c**, **8a**, **2b**, and **3b**) could be extracted from an aqueous Na_2CO_3 solution with ether; however, secondary amines (**4a**, **5a**, and **5b**) could only be extracted from an aqueous hydroxide solution. This observation allowed for a simplified purification of products in many cases; *e.g.*, acetal **5a** could be separated from **6a** by first neutralizing the acidic mixture with Na_2CO_3, washing with ether, and then adding KOH to the aqueous layer and reextracting it with ether, giving **5a** free of **6a** after evaporation of the solvent. **6a** could be recovered from the first ether wash if desired.

(11) This represents the highest yield obtained for **6a**. Average yields were closer to 50–60%. Lower yields were obtained when the mixture was overconcentrated during the azeotrope step or when higher distillation temperatures were used [bp 65–75° (20 mm)]. This is not surprising in light of the report by D. A. Whiting, R. Cahill, and T. H. Crabb [*Chem. Commun.*, 1307 (1972)] of the dimerization of an oxazepine from the liquid state.



(12) We found it difficult to obtain proper analyses for several of these labile molecules; however, hydrolysis and spectra data support structure assignments and purity of fresh samples.

Synthesis of 2,4,4,6,8,8-Hexamethyl-2,6-diaza-9-oxabicyclo[3.2.1]nonane (8a).—This reaction was run using the general procedure given above (Table I, run C) affording **8a**: mp (EtOH) 64.5–65.5° (lit.[4] mp 68°); ir (CCl_4) no OH, C=O stretch; nmr (CCl_4) δ 0.73 (s, 6), 1.21 (s, 6), 2.27 (d, 2, J = 15 Hz), 2.71 (s, 6), 3.27 (d, 2, J = 15 Hz), 3.77 (s, 2); mass spectrum (70 eV) *m/e* (rel intensity) 212 (5, M^+), 197 (1), 169 (10), 156 (1), 155 (3), 154 (2), 141 (4), 127 (1), 115 (2), 113 (3), 99 (5), 98 (100).

Anal. Calcd for $C_{12}H_{24}N_2O$: C, 67.94; H, 11.31; N, 13.20. Found: C, 68.00; H, 11.31; N, 13.06.

Synthesis of 6-*tert*-Butoxytetrahydro-3,5,5-trimethyl-2*H*-1,3-oxazine (6c).—This reaction was run using the general procedure given above (Table I, run B) affording **6c**: bp 49–51° (0.5 mm); ir (CCl_4) no OH, C=O stretch; nmr (CCl_4) δ 0.89 (s, 3), 0.99 (s, 3), 1.22 (s, 9), 2.04 (d, 1, J = 10 Hz), 2.09 (s, 3), 2.38 (d, 1, J = 10 Hz), 3.71 (d, 1, J = 7 Hz), 4.10 (d, 1, J = 7 Hz), 4.32 (s, 1); mass spectrum (70 eV) *m/e* (rel intensity) 201 (7, M^+), 144 (8), 128 (41), 99 (26), 72 (100), 59 (10), 58 (27), 57 (28), 56 (14), 44 (82).

Synthesis of *N*-Methyl-3-imino-2,2-dimethylpropanal Di-*n*-butyl Acetal (5b).—This reaction was run using the general procedure given above (Table I, run E) affording **5b**: bp 64–66° (0.1 mm); ir (CCl_4) 3345 cm^{-1}, no C=O stretch; nmr (CCl_4) δ 0.86 (s, 6), 0.93 (t, 6), 1.1–1.7 (m, 8), 2.36 (s) and 2.38 (s, 5 total), 3.2–3.9 (m, 4), 4.13 (s, 1); mass spectrum (70 eV) *m/e* (rel intensity) 245 (M^+, none), 160 (4), 128 (48), 98 (87), 72 (85), 60 (19), 57 (62), 56 (43), 44 (100), 43 (43), 42 (49), 41 (55).

Hydrolysis of 5a, 5b, 6a, 6c, 7, and 8a.—Amines **5a**, **5b**, **6a**, **6c**, **7**, and **8a** were stirred either separately or as a mixture in H_2O–H_2SO_4 (pH 1) for 24 hr. The acid mixture was extracted several times with ether and then cooled in ice. Fresh ether (the amount depends on the desired concentration of aldehyde **4a**) was added to the cooled acid layer and KOH pellets were added slowly with stirring until the aqueous layer was basic. The ether layer was separated and dried over $MgSO_4$. Aldehyde **4a** was further used in solution where it was stable at 0°: nmr (CCl_4) δ 1.10 (s, 6), 2.44 (s, 3), 2.69 (s, 6), 9.45 (s, 1); mass spectrum (70 eV) *m/e* (rel intensity) 115 (1, M^+), 98 (40), 72 (14), 44 (100), 43 (25), 42 (40), 41 (20).

Synthesis of *N*-Methyl-3-imino-2,2-dimethylpropanal Benzenesulfonamide (9).—A concentrated ether solution of **4a** generated from a known amount of **5a** was shaken with 1.2 equiv of benzenesulfonyl chloride in concentrated NaOH according to the standard procedure[13] giving a good yield (based on **5a**) of **9** which was recrystallized from hexane: mp 54–55°; ir (CCl_4) 2800, 2710, 1735 cm^{-1}; nmr (CCl_4) δ 1.14 (s, 6), 2.68 (s, 3), 3.16 (s, 2), 7.70 (m, 5), 9.79 (s, 1); mass spectrum (70 eV) *m/e* (rel intensity) 255 (none, M^+), 218 (8), 184 (100), 172 (19), 141 (84), 125 (20), 77 (95), with a large metastable peak at 108.0 (141^2/184).

Anal. Calcd for $C_{12}H_{17}NO_3S$: C, 56.49; H, 6.66; N, 5.48. Found: C, 56.20; H, 6.48; N, 5.23.

Synthesis of 2-(2-*N*-Methylamino-1,1-dimethylethyl)-1,3,5-trithiane (10).—Trithiane **10** was synthesized according to the literature procedure for amino aldehydes[6] from an ether solution of amino aldehyde **4a**. Recrystallization of **10** from hexane gave a good yield of a white solid: mp 52–54° dec; nmr ($CDCl_3$) δ 1.09 [s, 6, $>C(CH_3)_2$], 1.22 (br s, 1, NH), 2.46 (s, 3, CH_3N), 2.58 (s, 2, CCH_2N), 4.05 (d, 2, J = 13 Hz, SCH_aHS), 4.48 (s, 1, SCHS), 4.51 (d, 2, J = 13 Hz, $SCHH_eS$). This material turned to a gum after several days.

Direct Synthesis of *N*-Methyl-3,3′-imino-2,2,2′,2′-tetramethyldipropanal (3b) *via* a Double Mannich-Type Reaction.—To a flask was added 16.87 g (0.25 mol) of methylamine hydrochloride, 7.5 g (0.25 mol) of formaldehyde (trioxane), 0.5 ml of H_2SO_4, and 200 ml of ethanol. After this mixture refluxed for 1 hr, 18 g (0.25 mol) of isobutyraldehyde was added to the flask dropwise. Then, after 1-hr intervals, formaldehyde (7.5 g) and isobutyraldehyde (18 g) were added to the mixture which was then allowed to stir at reflux under N_2 for 60 hr. (This reaction time was determined by monitoring hydrolized aliquots.) Aqueous HCl [200 ml (5%)] was added to the reaction mixture which was stirred for an additional 3 hr and cooled to 50°. The ethanol was removed from the mixture under vacuum (20 mm) at 50°. The aqueous amine salts were washed with ether and neutralized with KOH. The basic layer was extracted thoroughly with

(13) R. Shriner, R. Fuson, and D. Curtin, "The Systematic Identification of Organic Compounds," 5th ed, Wiley, New York, N. Y., 1969, p 119.

ether and the ether was washed three times with saturated $NaHSO_3$.

Treatment of the bisulfite layer with KOH followed by extraction with ether gave, after drying the ether with K_2CO_3 and evaporation of solvents, 16 g of crude amino aldehyde containing products. Distillation gave 8 g of aldehyde **4a** and 6 g (16.2%) of dialdehyde **3b**: bp 62–64° (0.01 mm); ir (CCl_4) 2960, 2860, 2770, 2690, 1720 cm^{-1}; nmr (CCl_4) δ 1.03 (s, 12), 2.12 (s, 3), 2.62 (s, 4), 9.65 (s, 2); mass spectrum (70 eV) *m/e* (rel intensity) 197 (1, M^+), 128 (54), 98 (17), 72 (10), 58 (100). Dialdehyde **3b** was characterized as its disemicarbazone derivative, mp (MeOH) 148–149°.

Anal. Calcd for $C_{13}H_{27}N_7O_2$: C, 49.82; H, 8.68; N, 31.29. Found: C, 49.72; H, 8.50; N, 31.08.

Synthesis of Aldehyde 3b *via* Tetrahydrooxazine 6a.—To a dry Morton flask equipped with an overhead stirrer was added 250 ml of dry ether, 10 g (0.062 mol) of anhydrous zinc chloride, and 10 g (0.14 mol) of isobutyraldehyde. While the mixture was stirred at 25° under nitrogen, 10 g (0.058 mol) of **6a** in 50 ml of ether was added dropwise to it over 1 hr. After the mixture was allowed to stir for an additional hour, 50 ml of THF was added and stirring was continued for 1 hr at which time 50 ml of concentrated HCl in 150 ml of water was added to the reaction mixture. The acidic mixture was stirred for 1 hr at 25° and the acidic aqueous layer was separated from the ether. The ether layer was back-washed with fresh aqueous acid and the combined acid layers were washed several times with ether. The acid layer was neutralized with Na_2CO_3 and the basic layer was extracted six times with ether which was dried with $CaCl_2$, filtered, and evaporated to give 10.5 g of a crude oil from which 4 g of a white solid crystallized out after 12 hr. After vacuum filtration of the solid, the resulting oil was distilled to give 5.9 g (49%) of pure dialdehyde **3b**, bp 82–85° (0.5 mm).

The white solid was recrystallized from hexane to give 2.4 g of material which was shown to be **8a**, mp 63–65°.

If necessary, the crude dialdehyde could be further purified by standard bisulfite procedures before distillation.

Synthesis of Ethyl *N*-Methyl-3-imino-2,2-dimethylpropanal-3′-imino-2′,2′-dimethylpropionate (2b).—To a dry Morton flask containing 250 ml of dried ether and 3.0 g (0.125 g-atom) of Mg under N_2 at −10° was added dropwise, over 0.5 hr, 22.0 g (0.11 mol) of ethyl α-bromoisobutyrate. After disappearance of most of the Mg, tetrahydrooxazine **6a** [17.3 g (0.1 mol)] was added dropwise to the mixture over 0.5 hr. The reaction was stirred for 3 hr at 0° and allowed to warm to 25° over 1.5 hr at which time it was quenched with aqueous NH_4Cl. The mixture was made acidic with HCl and the aqueous acid layer was separated and washed with ether. The ether layer was shown to contain ethyl isobutyrate, starting bromo ester, and some ethyl isobutyrisobutyrate. The acid layer was cooled, made basic with K_2CO_3, and extracted with ether which was dried and evaporated to give 15 g of crude amine products. Distillation gave 9.7 g (40%) of pure ester aldehyde **2b** and 4.5 g of higher boiling material which was shown by vpc to contain two products (see below). **2b** had the following properties: bp 82–83° (0.125 mm); ir (CCl_4) 2965, 2785, 2695, 1735, 1395, 1375, 1275, 1195, 1150, 1122, 1049 cm^{-1}; nmr (CCl_4) δ 1.04 (s, 6), 1.14 (s, 6), 1.26 (t, 3), 2.13 (s, 3), 2.60 (s, 2), 2.62 (s, 2), 4.10 (q, 2), 9.85 (s, 1); mass spectrum (70 eV) *m/e* (rel intensity) 243 (1, M^+) 242 (1), 228 (1), 214 (1), 198 (3), 172 (28), 128 (100), 98 (7), 58 (75), 44 (42). Ester aldehyde **2b** was characterized as its 2,4-DNP derivative, mp (EtOH) 75–76°.

Anal. Calcd for $C_{19}H_{29}N_5O_6$: C, 53.89; H, 6.90; N, 16.54. Found: C, 53.84; H, 6.79; N, 16.48.

The higher boiling materials were partitioned between ether and saturated bisulfite. The ether layer was dried over K_2CO_3, filtered, and evaporated and the resulting oil was distilled to give 3.2 g (9%) of a material which was identified as alcohol **13** [bp 122–125° (0.15 mm)] from its spectra: ir ($CHCl_3$) 3210, 2970, 1730, 1475, 1390, 1368, 1260, 1145, 861 cm^{-1}; nmr (CCl_4) δ 0.68 (s, 3), 0.98 (s, 3), 1.10 (s, 3), 1.18 (s, 6 + 3 = 9), 1.22 (t, 3), 1.24 (t, 3), 2.21 (s, 3), 2.30 (AB pattern, 2), 2.62 (br s, 2), 3.74 (s, 1), 4.02 (2 q, 4), 5.6 (br s, 1, OH).

The bisulfite layer gave, after destruction of the bisulfite adduct with KOH, extraction with ether, and distillation, 0.3 g of aldehyde diadduct **14**: bp 118° (0.15 mm); ir ($CHCl_3$) 2980, 2790, 2695, 1745, 1730, 1698, 1470, 1385, 1365, 1250, 1145, 1030 cm^{-1}; nmr (CCl_4) δ 1.01 (s, 6), 1.13 (s, 6), 1.30 (t, 3), 1.32 (s, 6), 2.10 (s, 3), 2.56 (s, 2), 2.62 (s, 2), 4.14 (q, 2), 9.45 (s, 1); mass spectrum (70 eV) *m/e* (rel intensity) 313 (trace, M^+), 268 (4), 242 (10), 128 (100).

Attempted Synthesis of Tetrahydrooxazine 6c.—Reaction of 7.21 g (0.1 mol) of isobutyraldehyde, 6.0 g (0.2 mol of $CH_2{=}O$) of trioxane, and 10.95 g (0.1 mol) of *tert*-butylamine hydrochloride in 100 ml of ethanol according to the general procedure given for the synthesis of **6a** (Table I, run F) gave, after work-up, two amine-containing products. *N-tert*-Butyl-3-imino-2,2-dimethylpropanol (**4c**) was obtained in 32% yield: bp 118–120° (30 mm); ir (CCl_4) 3310, 3170, 2960, 2700, 1390, 1360, 1238, 1218, 1110, 888 cm^{-1}; nmr (CCl_4) δ 1.01 (s, 6), 1.03 (s, 9), 2.60 (s, 2), 9.72 (s, 1); mass spectrum (70 eV) *m/e* (rel intensity) 157 (trace, M^+), 156 (1), 142 (19), 129 (9), 113 (7), 86 (29), 72 (32), 70 (77), 58 (32), 57 (64), 56 (10), 55 (19), 43 (30), 41 (100). The acetal of **4c**, *N-tert*-butyl-3-imino-2,2-dimethylpropanal diethyl acetal (**12**) was obtained in 56% yield: bp 130–135° (30 mm); ir (CCl_4) no C=O stretch; nmr (CCl_4) δ 0.82 (s, 6), 1.04 (s, 9), 1.19 (t, 6), 2.88 (s, 2), 3.3–4.0 (m, 4, OCH_2CH_3), 4.19 (s, 1); mass spectrum (70 eV) *m/e* (rel intensity) 231 (none, M^+), 169 (5), 155 (9), 154 (12), 126 (7), 112 (4), 100 (15), 85 (12), 72 (31), 71 (10), 70 (66), 57 (100), 46 (36), 45 (87), 44 (42), 43 (60), 41 (100).

Acetal **12** was readily hydrolyzed in aqueous HCl to aldehyde **4c**, which was a stable liquid characterizable as its 2,4-DNP hydrogen sulfate salt derivative, mp (EtOH) 205–205.5°.

Anal. Calcd for $C_{15}H_{25}N_5O_8S$: C, 41.56; H, 5.76; N, 16.10. Found: C, 41.48; H, 5.91; N, 16.02.

Acknowledgment. —We wish to thank the National Institutes of Health for support of this work.

Registry No.—**2b**, 41348-48-5; **2b** 2,4-DNPH, 41348-49-6; **3b**, 41348-50-9; **3b** disemicarbazone. 41348-51-0; **4a**, 41348-52-1; **4c**, 41348-53-2; **4c** 2,4-DNPH hydrogen sulfate salt, 41348-54-3; **5a**, 41348-55-4; **5b**, 41348-56-5; **6a**, 41348-57-6; **6c**, 41348-58-7; **7**, 41348-59-8; **8a**, 17288-11-8; **9**, 41348-61-2; **10**, 41348-62-3; **12**, 41348-63-4; **13**, 41348-64-5; **14**, 41348-65-6; methylamine hydrochloride, 593-51-1; formaldehyde, 50-00-0; isobutyraldehyde, 78-84-2; *tert*-butylamine hydrochloride, 10017-37-5; butylamine hydrochloride, 3858-78-4; ethyl α-bromoisobutyrate, 600-00-0.

Diaziridines

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Reaction of benzylideneaniline (1a) or benzylidene-*p*-toluidine (1b) with hydroxylamine-*O*-sulfonic acid in the presence of aniline or *p*-toluidine did not give the expected diaziridines but benzaldehyde phenyl- (2a) or *p*-tolylhydrazone (2b). Under the same conditions, Schiff bases of nonaromatic amines gave diaziridines. The configuration of 1-cyclohexyl-3-(*p*-bromophenyl)diaziridine (7) was established by X-ray crystal structure analysis. The reaction of several 1-cyclohexyl-3-aryldiaziridines with phenyl isocyanate gave 1-cyclohexyl-2-(anilinoformyl)-3-aryldiaziridines. The reaction of these latter compounds with *p*-phenetidine is described.

During the course of a study on the reaction of ethoxycarbonylnitrene with Schiff bases it became desirable to have an authentic sample of a 1,3-diphenyldiaziridine. Attempts to prepare it by the reaction of benzylideneaniline (**1a**) with reagents having electrophilic NH groups failed. This led us to investigate the preparation of diaziridines by known methods. This paper deals with the reaction of Schiff bases with hydroxylamine-*O*-sulfonic acid (HAOSA) and the physical and chemical properties of 1-alkyl-3-aryldiaziridines so obtained.

Diaziridines bearing NH groups have been prepared by the reaction of Schiff bases with reagents having electrophilic NH groups such as HAOSA, chloramine, or oxaziridines.[2] However, the reaction of **1a** either with HAOSA in the presence of 2 molar equiv of aniline or with 3-ethyl-3-methyloxaziridine resulted in the formation of benzaldehyde phenylhydrazone (**2a**). Under the same conditions, benzylidenecyclohexylamine gave 1-cyclohexyl-3-phenyldiaziridine as will be shown later. The reaction of benzylidene-*p*-toluidine (**1b**) with HAOSA and *p*-toluidine gave benzaldehyde *p*-tolylhydrazone (**2b**). However, the product obtained by the reaction of **1a** and HAOSA in the presence of 2 molar equiv of *p*-toluidine was found to be a mixture of **2a** and **2b** as ascertained by nmr spectroscopy. The mechanism of the hydrazone formation was not pursued since there seemed to be many possible ways to give the hydrazones. Recently, an elegant way to prepare 1-(nitroaryl)diaziridines was reported by Heine, *et al.*[3] They stated that 1-(2,4-dinitrophenyl)- and 1-(2,4,6-trinitrophenyl)diaziridines bearing NH groups rearranged to the corresponding 2,4-dinitrophenyl- or 2,4,6-trinitrophenylhydrazones on heating in refluxing toluene.

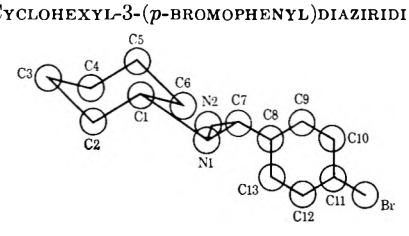
Several 1-alkyldiaziridines (**3**–**7**) were prepared from Schiff bases of nonaromatic amines. Results are summarized in Table I. In the case of **5** and **6**, a pair of isomers of different melting points was obtained after the chromatography of the reaction mixture. The isomers have very similar ir and mass spectra, but differ markedly in their nmr spectra. The lower melting isomers have their δ_{CH} of the methine hydrogen at 3.2–3.4 while the higher melting ones have theirs at 4.2–4.3. The higher melting isomers were found to be thermally unstable and were transformed into the lower melting ones on heating: **5h** and **6h** were completely changed to **5l** and **6l** on heating for 1 hr at 140° (in diphenyl ether) for the former and at 100° (in CCl_4 in a sealed nmr tube) for the latter. Indeed compound **6h** was found to change to **6l** at an appreciable rate when its nmr spectrum was taken at ambient temperatures. The facts suggest that these pairs of compounds are isomers involving cis and trans orientation of the *N*-cyclohexyl and *C*-phenyl group. Detection of isomers of **3** and **4** by silica gel chromatography was impossible since these compounds are very sensitive to silicic acid. The isomer of **7** was not found after a careful chromatography of the reaction mixture.

In oxaziridines and diaziridines,[4] the existence of stereoisomers due to the slow nitrogen inversion (invertomers) has been discussed. In some oxaziridines,[5] the invertomers were actually isolated and the configuration was established by X-ray crystal structure analysis. With respect to diaziridines, there has been a report[4b] referring to the isolation of the invertomers. However, the stereochemistry was not made clear. Thus, the X-ray crystal structure analysis of an invertomer was undertaken. As a representative of the invertomers with smaller δ_{CH}, **7** was chosen to undergo the heavy atom method.

The X-ray structure analysis demonstrated that **7** was a trans isomer with respect to 1-cyclohexyl and 3-(*p*-bromophenyl) groups. Thus, the stereochemistry of the invertomers with smaller δ_{CH} was established to be trans. This result is quite expected from the differences in the thermal stabilities of the pairs of isomers; the more stable isomers, **5l** and **6l**, have the two large groups in trans orientation. It is interesting to note that, in 2-isopropyl-3-(*p*-nitrophenyl)oxaziridine,[5c] the higher melting invertomer has been established to have cis stereochemistry. It is also the case with **5** and **6** in our study. Chart I shows a molecular conformation

CHART I

MOLECULAR CONFORMATION AND NUMBERING OF ATOMS IN 1-CYCLOHEXYL-3-(*p*-BROMOPHENYL)DIAZIRIDINE (**7**)



(1) Tsurumi University, School of Dental Medicine, 2-1-3 Tsurumi, Tsurumi-ku, Yokohama, Japan.

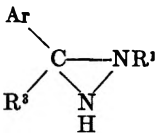
(2) (a) E. Schmitz, *Advan. Heterocycl. Chem.*, **2**, 104 (1963); (b) E. Schmitz, R. Ohme, and S. Schramm, *Chem. Ber.*, **97**, 2521 (1964).

(3) H. W. Heine, P. G. Williard, and T. R. Hoye, *J. Org. Chem.*, **37**, 2980 (1972).

(4) (a) A. Mannschreck, R. Radeglia, E. Gründemann, and R. Ohme, *Chem. Ber.*, **100**, 1778 (1967); (b) A. Mannschreck and W. Seitz, *Angew. Chem., Int. Ed. Engl.*, **8**, 212 (1969).

(5) (a) L. Brehm, K. G. Jensen, and B. Jerslev, *Acta Chem. Scand.*, **20**, 915 (1966); (b) B. Jerslev, *Acta Crystallogr.*, **23**, 645 (1967); (c) J. F. Cannon, J. Daly, and J. V. Silverton, *J. Chem. Soc., Perkin Trans.* **2**, 1137 (1972).

TABLE I
DIAZIRIDINES

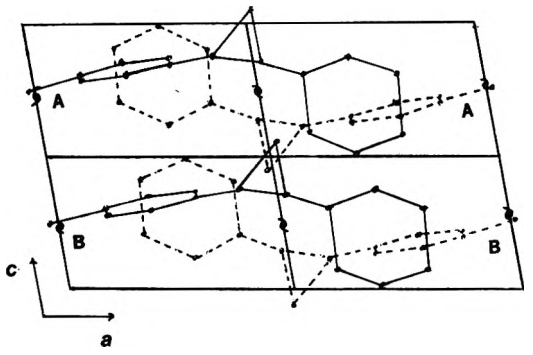


Compd	R¹	Ar	R³	Yield, %	Mp, °C	Nmr data, δ, ppm R³	NH	Solvent	Combustion analytical data: Caled, % C	H	N	Found, % C	H	N
3	Cyclohexyl	Ph	Me	35	96–97	1.75[a]	Not clear	$CDCl_3$	77.73	9.32	12.95	77.91	9.01	13.23
4	$PhCH_2$	Ph	Me	29	60–62	1.68[a]	2.00	CCl_4	80.32	7.19	12.49	80.15	7.06	12.65
5h	Cyclohexyl	Ph	H	2	102–104	4.25[b]	2.30	$CCl_2{=}CCl_2$	77.18	8.97	13.85	77.31	8.72	14.17
5l	Cyclohexyl	Ph	H	23	53–54	3.21[b]	2.00	$CCl_2{=}CCl_2$	77.18	8.97	13.85	77.18	8.62	13.98
6h	$PhCH_2$	Ph	H	2	62–63	4.22[b]	2.54	CCl_4	79.96	6.71	13.32	79.75	6.75	13.49
6l	$PhCH_2$	Ph	H	13	38–40	3.36[b]	1.82	CCl_4	79.96	6.71	13.32	80.14	6.75	13.46
7	Cyclohexyl	p-Br-phenyl	H	26	74–76	3.33[b]	2.05	$CDCl_3$	55.52	6.09	9.96	55.50	6.08	10.11

[a] Chemical shift of C^3 CH_3. [b] Chemical shift of C^3 H.

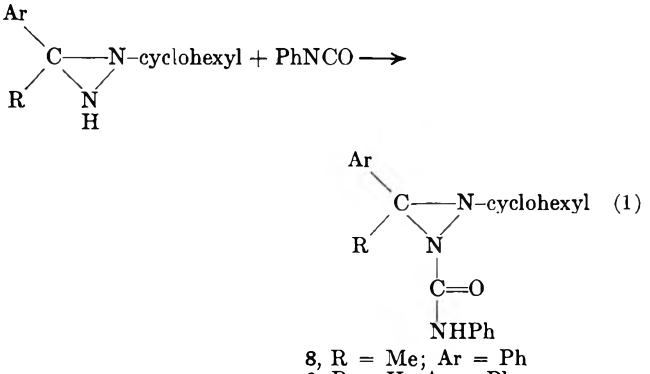
seen from the direction of the *c* axis (hydrogen atoms are excluded). Bond distances and angles are given in Table II with their estimated standard deviations. Chart II is a packing diagram of a unit cell projected

CHART II
PACKING DIAGRAM OF A UNIT CELL PROJECTED DOWN THE *b* AXIS



down the *b* axis. The dotted line represents the two molecules in the lower half and the solid line those in the upper half of the cell. A and B are enantiomers of each other. There are no intermolecular contacts significantly less than 3.4 Å for nonhydrogen atoms.

The reaction of **3** and **5** with phenyl isocyanate was investigated. Compound **3** reacted with phenyl isocyanate slowly in refluxing ether, and gave the adduct **8** (eq 1). The reaction of **5l** with phenyl isocyanate in



(1)

8, R = Me; Ar = Ph
9, R = H; Ar = Ph
10, R = H; Ar = *p*-bromophenyl

ether proceeded at room temperature and a fairly good yield of the adduct **9** was obtained after 3 days. Interestingly, however, **5h** did not react with phenyl isocyanate under the same condition. After several days

TABLE II
BOND LENGTHS AND ANGLES FOR NONHYDROGEN ATOMS WITH ESTIMATED STANDARD DEVIATIONS IN PARENTHESES

A. Lengths

Bond	Å	Bond	Å
Br—C11	1.891 (17)	C7—N1	1.458 (23)
C1—C2	1.496 (21)	C7—N2	1.505 (23)
C1—C6	1.539 (20)	C8—C9	1.415 (19)
C1—N1	1.457 (17)	C8—C13	1.394 (18)
C2—C3	1.532 (25)	C9—C10	1.346 (18)
C3—C4	1.521 (27)	C10—C11	1.391 (22)
C4—C5	1.513 (25)	C11—C12	1.411 (22)
C5—C6	1.493 (23)	C12—C13	1.390 (19)
C7—C8	1.458 (19)	N1—N2	1.506 (17)

B. Angles

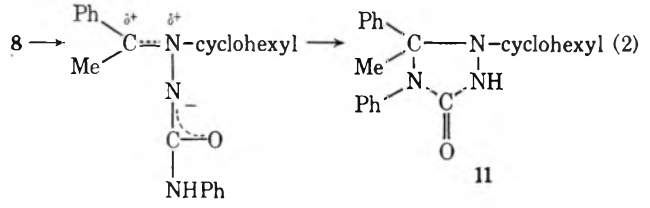
Angle	Degree	Angle	Degree
C2-C1-C6	109.5 (12)	C9-C8-C13	117.9 (12)
C2-C1-N1	110.9 (11)	C8-C9-C10	122.2 (13)
C6-C1-N1	109.3 (11)	C9-C10-C11	119.9 (14)
C1-C2-C3	110.3 (13)	Br-C11-C10	121.4 (12)
C2-C3-C4	112.0 (15)	Br-C11-C12	118.6 (12)
C3-C4-C5	110.1 (15)	C10-C11-C12	120.0 (14)
C4-C5-C6	111.8 (14)	C11-C12-C13	119.3 (13)
C1-C6-C5	112.4 (12)	C8-C13-C12	120.8 (12)
C8-C7-N1	120.5 (15)	C1-N1-C7	114.4 (13)
C8-C7-N2	120.4 (15)	C1-N1-N2	109.8 (10)
N1-C7-N2	61.0 (11)	C7-N1-N2	61.1 (11)
C7-C8-C9	120.4 (12)	C7-N2-N1	58.0 (10)
C7-C8-C13	121.7 (12)		

standing of the ethereal solution of **5h** and phenyl isocyanate, a small amount of **9** separated out of the solution. Inspection of the reaction mixture by tlc showed the existence of an appreciable amount of **5h** remaining. When the reaction mixture was heated, the yield of **9** increased. These facts suggest that there exists a great interference in the reaction of **5h** (cis) with phenyl isocyanate, and that the reaction occurs only after **5h** is isomerized to **5l**. The nature of such an interference is not clear now. Compound **7** gave adduct **10** in a high yield by the reaction with phenyl isocyanate.

That the adducts **8–10** have the diaziridine ring intact is apparent from their physical and chemical properties. In their nmr spectra, the cyclohexyl hydrogens appear as a broad multiplet extending from δ 1 to 2 like they do in the spectra of **3**, **5**, and **7**. This is in contrast to many other cases where the α-CH absorption of the negatively substituted cyclohexyl group appears at a lower field separated from the rest of the

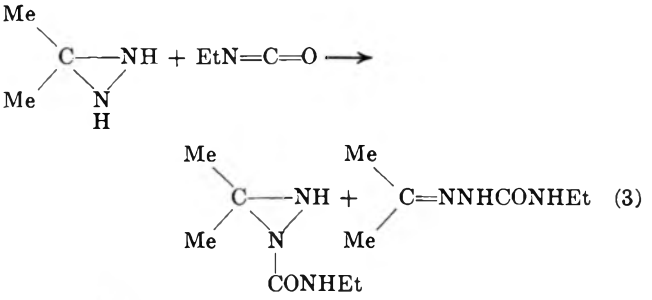
methylene hydrogens of the cyclohexane ring. The nmr spectra of these adducts suggest that only one invertomer has been obtained in each adduct. From the behavior of **5h** and **5l** toward phenyl isocyanate mentioned above, the orientation of 1-cyclohexyl and 3-aryl groups in **9** and **10** are considered to be trans. However, no information has been given concerning the stereochemistry of the 2-anilinoformyl group.

The reaction of **8** and **9** with *p*-phenetidine was carried out at 100° in an atmosphere of nitrogen. The adduct **9** and *p*-phenetidine gave a mixture of 1-cyclohexyl-4-phenylsemicarbazide and benzylidene-*p*-phenetidine along with a small amount of 1-(*p*-ethoxyphenyl)-3-phenylurea. 1-Cyclohexyl-4-phenylsemicarbazide is reported by Schmitz and Habisch.[6] The structure of the semicarbazide was established by the elemental analysis and nmr spectroscopy and by its conversion to the 1-anilinoformyl derivative, 1,2-bis(anilinoformyl)cyclohexylhydrazine.[7] Benzylidene-*p*-phenetidine was confirmed by a comparison with an authentic sample.[8] In the same manner, **8** and *p*-phenetidine gave the same semicarbazide and α-methylbenzylidene-*p*-phenetidine.[9] In this case, however, an appreciable amount of unknown compound, **11**, was obtained at the same time. The same compound was also obtained (in 65% yield) when **8** was heated at 100° for 1 hr. Combustion analysis and mass spectroscopy revealed that compounds **11** and **8** were isomeric. Significant differences are observed in the intensities of peaks at 216 (loss of PhNCO) and 243 (loss of PhNH). Both peaks are more intense in **8** than in **11**, and the difference is more pronounced in those at 243. The nmr spectrum of **11** has the absorption of cyclohexyl α-CH at δ 2.90 separated from the other methylene hydrogens of the cyclohexane ring. These facts strongly suggest that **11** does not hold the diaziridine ring any more. It has an absorption at 1700 cm^{-1} attributable to $\nu_{C=O}$ in the ir.[10] We have tentatively proposed 1-cyclohexyl-4,5-diphenyl-5-methyl-1,2,4-triazolidin-3-one for the structure of **11**, which would be formed finally after the cleavage of the C–N bond of the diaziridine ring in **8**, possibly through the intermediacy of a stabilized 1,3 dipole as depicted in eq 2.[11] No

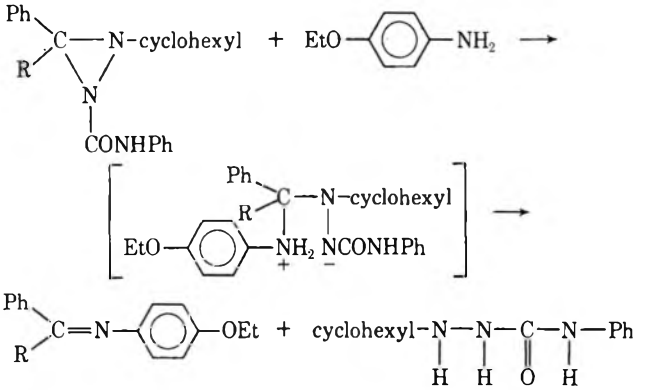


contradictory facts have been found to the proposed structure so far. However, we have not succeeded in the preparation of the corresponding isomer of **9**. Compound **9** seems fairly unstable thermally.

The triazolidinone formation from diaziridines and phenyl isocyanate was once reported by Schmitz and Habisch.[6] According to them, 3,3-dialkyldiaziridines (including 1-cyclohexyl-3,3-dimethyldiaziridine) and phenyl isocyanate gave 1,2,4-triazolidin-3-ones in ether instead of the diaziridine derivatives. The structural assignment was based on the fact that the products did not liberate iodine from acidic KI solution as many diaziridines did. Later,[12] however, they found that some of the diaziridine derivatives failed to oxidize iodide owing to the greater liability of the ring to acidic hydrolysis. After alkaline hydrolysis of the reaction product of 1-cyclohexyl-3,3-dimethyldiaziridine and phenyl isocyanate, they actually obtained the starting diaziridine and thus established the structure of the adduct as 1-cyclohexyl-2-(anilinoformyl)-3,3-dimethyldiaziridine. Thus far, there has been no report which clearly characterizes the reaction product of a diaziridine and phenyl isocyanate or the rearranged product as 1,2,4-triazolidin-3-one. Abendroth[13] reported that the reaction of 3,3-dimethyldiaziridine and ethyl isocyanate gave both the corresponding diaziridine derivative as well as the rearranged hydrazone (eq 3).



The formation of benzylidene-*p*-phenetidines and 1-cyclohexyl-4-phenylsemicarbazide by the reaction of **8** or **9** with *p*-phenetidine may be considered to proceed *via* the ring-opened addition product as shown in eq 4. No appreciable amount of α-methylbenzylidene-*p*-phenetidine was obtained on heating a mixture of *p*-phenetidine and acetophenone at 100° for 2 hr.



Experimental Section[14]

Nmr spectra were obtained on a Hitachi R-20B spectrometer.

Reaction of Benzylideneaniline (1a) with Hydroxylamine-*O*-sulfonic Acid.—Hydroxylamine-*O*-sulfonic acid was prepared, and the purity was determined according to the literature.[15] In a 100-ml, three-necked, round-bottomed flask equipped with

(6) E. Schmitz and D. Habisch, *Rev. Chim. Acad. Rep. Populaire Roumaine*, **7**, 1281 (1962); *Chem. Abstr.*, **61**, 4331 (1964).

(7) M. Busch and K. Linsenmeier, *J. Prakt. Chem.*, [2] **115**, 232 (1927).

(8) Beilstein's "Handbuch der Organischen Chemie," Vol. 13, 1930, p 453.

(9) Beilstein's "Handbuch der Organischen Chemie," Vol. 13, 1930, p 454.

(10) It has been reported recently that 1-*tert*-butyl-2,4,5-triphenyl-1,2,4-triazolidin-3-one has an absorption at 1715 (C=O) and 1,2,4,5-tetraphenyl-1,2,4-triazolidinon-3-one has one at 1710 cm^{-1} in the ir [M. Komatsu, Y. Obshiro, and T. Agawa, *J. Org. Chem.*, **37**, 3192 (1972)].

(11) We thank one of the reviewers for the suggestion.

(12) E. Schmitz, D. Habisch, and C. Grundemann, *Chem. Ber.*, **100**, 142 (1967).

(13) H. J. Abendroth, *Angew. Chem.*, **73**, 67 (1961).

(14) Melting points are uncorrected.

(15) H. J. Matsuguma and L. F. Andrieth, "Inorganic Syntheses," Vol. V, T. Moeller Ed., McGraw-Hill, New York, Toronto, London, 1957.

a stirrer, an addition funnel, and a calcium chloride tube was added 15 ml of dry methanol. After the methanol was cooled with a Dry Ice–acetone bath, 1.25 g of HAOSA (90% purity) was added. To the methanolic suspension was added a solution of 1.81 g (0.01 mol) of **1a** and 2.07 g (0.022 mol) of aniline in 5 ml of methanol dropwise. After the addition was complete, the cooling bath was removed, and the reaction mixture was stirred overnight at room temperature. Ether was added to the mixture to promote the precipitation of aniline sulfate. The sulfate was filtered, and the filtrate was concentrated by rotary evaporation. To the concentrate, ether was added, and the organic solution was washed (H_2O) and dried (Na_2SO_4). Evaporation of ether gave 600 mg (30%) of **2a** melting at 150°. The structure of **2a** was confirmed by a comparison with an authentic sample[16] (lit.[16] mp 152.5°).

The reaction of **1b** with HAOSA and *p*-toluidine and the reaction of **1a** with HAOSA and *p*-toludine were carried out in the same way. The nmr spectrum ($CDCl_3$) of the latter reaction product had a peak at δ 2.25 (CH_3). Comparison of the spectrum with those of authentic **2a** and **2b**[17] indicated that the product was a 1:1 mixture of **2a** and **2b**.

Reaction of 1a with 3-Ethyl-3-methyloxaziridine.—3-Ethyl-3-methyloxaziridine was prepared from ethyl methyl ketone and HAOSA[2b], and was obtained as a mixture with the ketone by distillation under 0.6 mm. The ir (neat) had a characteristic absorption of NH at 3200 cm^{-1}.

The oxaziridine mixture (3.5 g) was dissolved in 200 ml of dry ether. To the solution was added 5 g of **1a** and 0.6 ml of acetic acid. After standing at room temperature overnight, the solution was washed (H_2O), dried (Na_2SO_4), and concentrated. The concentrate was chromatographed (silica gel, benzene) to give 250 mg of **2a** melting at 150°.

1-Cyclohexyl-3-methyl-3-phenyldiaziridine (3).—The procedure for the preparation of **3** and other diaziridines was almost the same as in the reaction of **1a** with HAOSA mentioned above. From 8.0 g (0.04 mol) of α-methylbenzylidenecyclohexylamine, 5.0 g (90% purity) of HAOSA, and 8.8 g (an equivalent amount to HAOSA) of cyclohexylamine, 3.0 g (35%) of almost pure **3** was obtained. Recrystallization from low boiling petroleum ether (bp 35–80°) gave a pure sample of **3** melting at 96–97°. Column chromatography of the reaction mixture (silica gel, benzene) did not give any diaziridine in this case.

Compounds **4** and **7** were obtained in the same manner. Compounds **5** and **6** were not obtained in crystalline form after work-up. The concentrate was chromatographed (silica gel, benzene with increasing amount of chloroform). Lower melting isomers **5l** and **6l** eluted first and then did the higher melting **5h** and **6h**.

All diaziridines obtained above had a characteristic band of NH in the vicinity of 3200 cm^{-1} in the ir (KBr).

X-Ray Crystal Structure Analysis of 1-Cyclohexyl-3-(*p*-bromophenyl)diaziridine (7).—Colorless single crystals of **7** were obtained by recrystallization of purified **7** from *n*-hexane. Weissenberg photographs showed that these crystals belonged to the monoclinic system. The systematic absences, $h0l$, when l is odd, and $0k0$, when k is odd, are consistent with the space group C_{2h}^5-$P2_1/c$.[18] Precision lattice constants were obtained by least-squares refinement using 2θ angles measured with a Rigaku Denki four-circle diffractometer. The crystal data are as follows: $C_{13}H_{17}BrN_2$, mol wt 281.211; a = 12.464 (7), b = 14.715 (8), c = 7.143 (4) Å, and β = 98.99 (1)°; V = 1293.9 (1.2) Å^3. The density of the crystals (d_{obsd}) was found to be 1.4 g cm^{-3} by flotation in potassium iodide solution at room temperature. Assuming that each unit cell contains four formula units of **7**, the calculated density (d_{calcd}) is 1.442 g cm^{-3} which agrees with d_{obsd}.

A crystal with dimensions 0.5 × 0.2 × 0.1 mm was mounted with its c axis parallel with the rotation axis of the goniometer of the diffractometer. X-Ray intensity data were collected in the θ–2θ scanning mode using Mo K_α radiation (λ = 0.7101 Å), and obtained 4056 independent reflections in the range of 2θ > 60°; 1676 reflections with $F_o > 3(\Delta F_o)$ were used for the structure determinations. Lorentz and polarization corrections were made in a usual manner, but the absorption correction was neglected (μ = 33.42 cm^{-1}).

The structure of **7** was solved by the heavy atom method. The bromine atom coordinates were assumed from three-dimensional Patterson functions. Fourier synthesis, with contribution of bromine atoms, found positions of the other atoms except for hydrogens. Further refinement was performed by block-diagonal least squares.[19] First ten cycles using isotropic temperature factors yielded an R value of 0.20. Nine successive cycles of anisotropic refinements gave an R index of 0.16 for 1653 reflections. The minimized quantity was $\Sigma w(|F_o| - k|F_c|)^2$, where weighting the scheme was as follows: w = 0.5 when F_o < 7.90, w = 1.0 when 7.90 ≤ F_o ≤ 29.86, and $w = 29.86/F_o$ when F_o > 29.86.

The positions of the hydrogen atoms were calculated assuming 1.08 Å for both C–H and N–H bond distances, since they were not clearly found from difference Fourier synthesis. A final R value was 0.125 after five cycles of least-squares refinement including all hydrogen atoms using anisotropic temperature factors for nonhydrogen atoms and isotropic temperature factors for hydrogens. A final difference Fourier synthesis seemed free of any significant features. All of the computations were performed on a Hitac 5020E computer at the University of Tokyo. UNICS program system[20] was used for structure refinements. Final atomic parameters are given in Table III, and final structure factors are in Table IV.[21]

Reaction of 3 with Phenyl Isocyanate.—A mixture of 1.08 g (5 mmol) of **3**, 0.60 g (5 mmol) of phenyl isocyanate, and 8 ml of dry ether was refluxed for 20 hr. Concentration of the solution and the subsequent addition of low boiling petroleum ether to the concentrate gave 1.0 g (60%) of the adduct **8** melting at 100–105°. Recrystallization from ether gave a pure sample of **8**: mp 106–106.5°; ν^{KBr} 3350, 1680 cm^{-1}; δ^{CDCl_3} 0.5–2.0 (m, 14, all cyclohexyl protons and CH_3), 6.8–7.7 (m, 10), 8.05 (s, 1).

Anal. Calcd for $C_{21}H_{25}N_3O$: C, 75.19; H, 7.51; N, 12.53. Found: C, 75.13; H, 7.52; N, 12.59.

1-Cyclohexyl-2-(anilinoformyl)-3-phenyldiaziridine (9).—Phenyl isocyanate (60 mg, 0.5 mmol) was dissolved in 2 ml of dry ether. To the solution was added 100 mg (0.5 mmol) of **5l**, and the mixture was left standing at room temperature. White crystals began to separate in a few hours. After 3 days' standing of the mixture, low boiling petroleum ether was added, and the crystals were collected to give 145 mg (90%) of **9** melting at 145–146°. Recrystallization from an ethanol–ether mixture gave a sample for analysis: mp 145–146°; ν^{KBr} 3380, 1700 cm^{-1}; δ^{CDCl_3} 1.0–2.3 (m, 11), 4.15 (s, 1), 6.9–7.6 (m, 10), 7.95 (s, 1).

Anal. Calcd for $C_{20}H_{23}N_3O$: C, 74.74; H, 7.21; N, 13.07. Found: C, 74.36; H, 7.21; N, 13.31.

Reaction of **7** (1.98 g, 7 mmol) with phenyl isocyanate (0.84 g, 7 mmol) was carried out in the same way and gave 2.6 g (93%) of the adduct **10**, mp 144–145°, after 3 days. Recrystallization from ethanol gave white crystals of **10**: mp 145–146°; ν^{KBr} 3350, 1700 cm^{-1}; δ^{CDCl_3} 1.0–2.3 (m, 11), 4.08 (s, 1), 6.8–7.7 (m, 9), 7.87 (s, 1).

Anal. Calcd for $C_{20}H_{22}BrN_3O$: C, 59.98; H, 5.55; N, 10.50. Found: C, 60.07; H, 5.53; N, 10.95.

Reaction of 9 with *p*-Phenetidine.—A mixture of 214 mg (0.67 mmol) of **9** and 88 mg (0.67 mmol) of *p*-phenetidine was heated at 100° for 2 hr in an atmosphere of nitrogen. Low boiling petroleum ether was added to the reaction mixture, and the white crystals were collected on a filter. From the filtrate, 50 mg (33%) of pale yellow crystals of benzylidene-*p*-phenetidine, mp 67–69° (lit.[8] mp 71°), was obtained.

The white crystals on the filter weighed 140 mg and were recrystallized from ethanol. After the removal of a small amount of 1-(*p*-ethoxyphenyl)-3-phenylurea,[22] 1-cyclohexyl-4-phenylsemicarbazide was obtained. The semicarbazide obtained here still seemed to contain some urea from the melting point (130–135°). Careful crystallizations from ethanol gave a pure sample of 1-cyclohexyl-4-phenylsemicarbazide: mp 136–137° (lit.[6] mp 140.5–141°); ν^{KBr} 1665 cm^{-1}; δ^{CDCl_3} 0.9–2.1 (m, 10), 2.65 (br, 1, cyclohexyl α-CH), 3.76 (br, 1, 1-NH), 6.75 (br, 1, 2-NH), 6.8–7.6 (m, 5), 8.25 (s, 1, 4-NH).

Anal. Calcd for $C_{13}H_{19}N_3O$: C, 66.92; H, 8.21; N, 18.01. Found: C, 66.65; H, 8.15; N, 17.96.

(16) (a) E. Fischer, *Chem. Ber.*, **9**, 887 (1876); (b) Beilstein's "Handbuch der Organischen Chemie," Vol 15, 1932, p 134.

(17) O. Schlenk, *J. Prak. Chem.*, [2] **78**, 56 (1908); ref 16b, p 513.

(18) "International Tables for X-Ray Crystallography," Vol I–III, K. Lonsdale, *et al.*, Ed., Kynoch Press, Birmingham, 1969.

(19) Program HBLS written by Dr. T. Ashida.

(20) "Universal Crystallographic Computation Program System," T. Sakurai Ed., Vol. I, II, The Crystallographic Society of Japan, 1967.

(21) See paragraph at the end of the paper regarding supplementary material.

(22) Reference 9, p 481.

On addition of phenyl isocyanate to the ethereal solution of the semicarbazide, 1,2-bis(anilinoformyl)cyclohexylhydrazine was obtained, which was recrystallized from ethanol to give a pure sample: mp 200–202° (lit.[7] mp 202°); ν^{KBr} 1660 cm^{-1}.

Anal. Calcd for $C_{20}H_{24}N_4O_2$: C, 68.16; H, 6.86; N, 15.90. Found: C, 68.10; H, 6.90; N, 15.96.

Reaction of 8 with *p*-Phenetidine.—An equimolar mixture of **8** (224 mg, 0.67 mmol) and *p*-phenetidine (88 mg, 0.67 mmol) was heated at 100° for 2 hr, and the reaction mixture was treated with low boiling petroleum ether as in the preceding example. From the petroleum ether soluble part, 50 mg (31%) of pale yellow crystals of α-methylbenzylidene-*p*-phenetidine was obtained, mp 85–87° (lit.[9] mp 88°).

The product remaining on the filter (130 mg) was a mixture of 1-cyclohexyl-4-phenylsemicarbazide and **11**. Recrystallization of the mixture from ethanol gave 30 mg of **11**, mp 155°. However, a quantitative separation of **11** and the semicarbazide was impossible. Crystallization of crude **11** from ethanol gave a pure sample: mp 156–157°; ν^{KBr} 3200, 1700 cm^{-1}; δ^{CDCl_3} 0.7–2.2 (m, 13), 2.90 (br, 1, cyclohexyl α-CH), 6.30 (s, 1), 6.8–7.2 (m, 10).

Anal. Calcd for $C_{21}H_{25}N_3O$: C, 75.19; H, 7.51; N, 12.53. Found: C, 75.05; H, 7.51; N, 12.60.

Compound **11** was also obtained on heating of **8** (100 mg) at 100° for 1 hr. Treatment of the reaction product with low boiling petroleum ether gave 65 mg of **11** melting at 155°. The tlc of the reaction mixture showed the existence of remaining **8**.

Heating of **9** in the same way resulted in an extensive decomposition as judged from the tlc.

Acknowledgment.—We sincerely wish to thank Professor Yoshio Sasada, Tokyo Institute of Technology, for his kindest guidance in performing the X-ray crystal structure analysis.

Registry No.—**1a**, 538-51-2; **1b**, 2272-45-9; **2a**, 588-64-7; **2b**, 1858-99-7; **3**, 41316-28-3; **4**, 41316-29-4; **5h**, 41316-30-7; **5l**, 41316-31-8; **6h**, 41316-32-9; **6l**, 41316-33-0; **7**, 41316-34-1; **8**, 41316-35-2; **9**, 41316-36-3; **10**, 41316-37-4; **11**, 41316-38-5; α-methylbenzylidine cyclohexylamine, 1562-62-5; α-methylbenzylidenebenzylamine, 14428-98-9; benzylidenecyclohexylamine, 2211-66-7; benzylidenebenzylamine, 780-25-6; *p*-bromobenzylidinecyclohexylamine, 41316-43-2; hydroxylamine-*O*-sulfonic acid, 3400-11-1; 3-ethyl-3-methyloxaziridine, 41316-44-3; phenyl isocyanate, 103-71-9; *p*-phenetidine, 156-43-4; 1-cyclohexyl-4-phenylsemicarbazide, 41316-45-4; 1,2-bis(anilinoformyl)cyclohexylhydrazine, 41316-46-5.

Supplementary Material Available.—Atomic parameter and structure factor tables will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 20× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-73-3758.

Transmission of Substituent Effects in Heterocyclic Systems. Rates of Solvolysis of Substituted 1-(1-Methylimidazolyl)ethyl *p*-Nitrobenzoates[1]

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Reactivities of 1-(1-methyl-2-imidazolyl)ethyl *p*-nitrobenzoate (**2**), 1-(1-methyl-4-imidazolyl)ethyl *p*-nitrobenzoate (**4**), and 1-(1-methyl-5-imidazolyl)ethyl *p*-nitrobenzoate (**5**) are in the order 1:13:15. By comparison with other heteroarylethyl *p*-nitrobenzoates, effective replacement substituent constants, σ^+_{Ar}, are determined as $\sigma^+_{2\text{-Im}} = -0.82$, $\sigma^+_{4\text{-Im}} = -1.01$, and $\sigma^+_{5\text{-Im}} = -1.02$. Substituent effects on the rates of solvolysis of substituted 1-(1-methyl-2-imidazolyl)ethyl *p*-nitrobenzoates were examined, including the following substituents: 5-methyl, 5-chloro, 4-methyl, 4-phenyl, 4-chloro, 4-bromo, and 4,5-dimethyl. Though the rates for 5-substituents were satisfactorily represented by σ_p^+, σ_m^+ failed to account properly for the observed reactivities of 4-substituents. Various methods allowing greater proportions of resonance interaction were explored to seek an explanation for the latter fact and to provide a satisfactory basis for correlation of the observed relative reactivities.

Recent papers from these laboratories have examined the transmission of substituent effects in furan,[2-4] thiophene,[5,6] and thiazole[7] systems. These previous studies have shown that σ_p^+ gives a high quality representation of the influence of substituents when the substituent is located in a position capable of direct conjugation with the reacting side chain. Furthermore, the magnitude of ρ, which is found from the Hammett equation, is directly related to the changes in regional charges associated with the change $ArCH_3 \rightarrow ArCH_2^+$.[5,8] In the present study we examine the heterocyclic nucleus, imidazole.

The reactivity of imidazole in electrophilic substitution has received substantial attention[9] with substitution at the 4(5) position being most facile. 1-Methylimidazole gives substantial amounts of both 1-methyl-4-nitroimidazole and 1-methyl-5-nitroimidazole on nitration. The solvolysis reaction is a useful probe for the susceptibility of an aromatic moiety to electrophilic substitution[2,6,10] and is particularly useful in the present case because of the marked basicity of imidazoles.

The rates of solvolysis of the three isomeric 1-(1-methylimidazolyl)ethyl *p*-nitrobenzoates, **2**, **4**, and **5**, are given in Table I.

The isomeric imidazoles bracket the reactivity of 1-(2-furyl)ethyl *p*-nitrobenzoate; all are somewhat more reactive than the related thiophene. It is of interest that the spread in reactivity of **2**, **4**, and **5** is substantially less than for the analogous set of isomers of

(1) Supported in part by a grant from the National Science Foundation, GP-6133X.

(2) D. S. Noyce and G. V. Kaiser, *J. Org. Chem.*, **34**, 1008 (1969).

(3) D. S. Noyce and H. J. Pavez, *ibid.*, **37**, 2620 (1972).

(4) D. S. Noyce and H. J. Pavez, *ibid.*, **37**, 2623 (1972).

(5) D. S. Noyce, C. A. Lipinski, and R. W. Nichols, *ibid.*, **37**, 2615 (1972).

(6) D. S. Noyce, C. A. Lipinski, and G. M. Loudon, *ibid.*, **35**, 1718 (1970).

(7) D. S. Noyce and S. A. Fike, *ibid.*, **38**, 3316, 3318, 3321, (1970).

(8) D. A. Forsyth and D. S. Noyce, *Tetrahedron Lett.*, 3893 (1972).

(9) J. H. Ridd, *et al.*, *J. Chem. Soc.*, 1051 (1965), and other papers; P. Linda, *Tetrahedron*, **26**, 3297 (1969); M. S. R. Naidu and H. B. Bensusan, *J. Org. Chem.*, **33**, 1307 (1968).

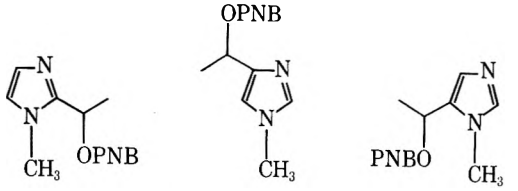
(10) E. A. Hill, M. L. Gross, M. Stasiewicz, and M. Manion, *J. Amer. Chem. Soc.*, **91**, 7381 (1969).

TABLE I

RATE CONSTANTS FOR THE SOLVOLYSIS OF IMIDAZOLYLETHYL *p*-NITROBENZOATES IN 80% ETHANOL

Compound solvolyzed	Temp., °C	10^5k, sec^{-1}	Method[a]	Rel rate	σ^+_{Ar}
2	25	0.313[b]		1	−0.82
	45	3.40 ± 0.04	A		
	45	3.34 ± 0.06	B		
	60	17.2 ± 0.1	A		
	60	16.5 ± 0.3	B		
	75	72.2 ± 1	A		
4	25	4.10[b]		13.1	−1.01
	45	43.0 ± 0.4	A		
	60	209 ± 2	A		
5	25	4.67 ± 0.08	A	15	−1.02
	45	53.0 ± 0.5	A		
	60	242 ± 4.0	A		
1-(2-Furyl)ethyl *p*-nitrobenzoate[c]	25	1.17			−0.93
	45	13.0			
1-(2-Thienyl)ethyl *p*-nitrobenzoate[d]	25	0.227			−0.80[d]
	45	2.61			

[a] A is at constant pH (8.0); B is by titrimetric methods on aliquots. [b] Extrapolated from data at higher temperatures. [c] From ref 2. [d] From ref 6.



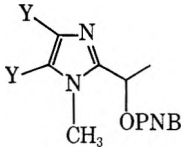
2 4 5

the 1-(thiazolyl)ethyl system studied by Noyce and Fike.[7]

The replacement substituent constants[11] for the aromatic moiety replacing the entire phenyl group in 1-phenylethyl chloride may be easily calculated from the rate data in Table I. The values given in column 6 of Table I were obtained using ρ for the benzene series of −5.8, and starting from the value of $\sigma^+_{2\text{-thienyl}}$ of −0.80 as reported by Noyce, *et al.*[6] If Hill's[10] values are used for thienyl and furyl systems, then the σ^+_{Ar} values for the imidazole moieties are very slightly more negative. The very close similarity of the values derived from **4** and **5** is in gratifying correspondence with the nitration results mentioned above.

Substituent Effects.—We next examined the influence of substituents on the rate of solvolysis of 1-(1-methyl-2-imidazolyl)ethyl *p*-nitrobenzoate. The rates for compounds **8, 10, 12, 14, 17, 20,** and **22** are given in Table II, extrapolated where necessary to 45°. For the three compounds **2, 8,** and **10**, the correlation of the observed rates with σ_p^+[12] is excellent and ρ is −5.6, very similar to that in the benzene series.

However, when the 4-substituted compounds **12, 14, 17,** and **20** are included and using σ_m^+, the quality of the correlation is destroyed. In every instance the 4-substituted compounds solvolyze more rapidly than predicted by the correlation established with the 5-substituted compounds.



8, X = H; Y = CH_3
10, X = H; Y = Cl
12, X = CH_3; Y = H
14, X = C_6H_5; Y = H
17, X = Cl; Y = H
20, X = Br; Y = H
22, X = CH_3; Y = CH_3

TABLE II

RATE CONSTANTS FOR THE SOLVOLYSES OF SUBSTITUTED 1-(1-METHYL-2-IMIDAZOLYL)ETHYL *p*-NITROBENZOATES AT 45.0° IN 80% ETHANOL

Compound solvolyzed	k_1, sec^{-1}	Log k/k_H	σ^+[a]	σ_{calcd}[b]
2	3.38×10^{-5}	(0.00)	(0.00)	
8 (5-Me)	1.67×10^{-3}	1.69	−0.311	
10 (5-Cl)	6.58×10^{-6}	−0.71	0.114	
12 (4-Me)	5.98×10^{-4}	1.25	−0.066	−0.146
14 (4-C_6H_5)	2.13×10^{-4}	0.80	0.109	−0.053
17 (4-Cl)	4.36×10^{-6}	−0.89	0.399	0.200
20 (4-Br)	3.54×10^{-6}	−0.98	0.405	0.214
22 (4,5-Me_2)	2.82×10^{-2}	2.92	−0.377[c]	−0.457[d]

[a] σ_p^+ for 5-substituents; σ_m^+ for 4-substituents. [b] See text, eq 2; $\sigma_{calcd} = \sigma_{m\alpha N}^+$. [c] Additivity assumed. [d] $\sigma_p^+ + \sigma_{calcd}$.

This characteristic behavior has been noted previously with 1-(4-substituted 2-furyl)ethanol derivatives[3] and with 1-(4-substituted 2-thiazolyl)ethanol derivatives.[7]

It was shown, in the consideration of the thiazole results, that a larger proportion of a resonance component in the total influence of the substituent would serve to bring the results into a more satisfactory correlational alignment. For this purpose the observed reactivities of 2-(6-substituted 2-pyridyl)-2-chloropropanes[13] were used as a basis of comparison, with marked improvement in the quality of the correlation (correlation coefficient *vs.* σ_m^+ = 0.76, *vs.* 6-substituted pyridine reactivities = 0.99).

The number of 6-substituted pyridines studied was somewhat limited, and it is therefore desirable to seek means for predicting the expected behavior of additional substituents. Two procedures offer promise in this respect. A new substituent constant may be defined in terms of an inductive parameter and a resonance parameter. The Swain and Lupton approach[14] is excellent in this regard, with the inductive ($\mathcal{F}$) and reso-

(11) D. S. Noyce and R. W. Castenson, *J. Amer. Chem. Soc.*, **95**, 1247 (1973).
(12) H. C. Brown and Y. Okamoto, *ibid.*, **80**, 4979 (1958).
(13) D. S. Noyce and J. A. Virgilio, *J. Org. Chem.*, **38**, 2660 (1973).
(14) C. G. Swain and E. C. Lupton, Jr., *J. Amer. Chem. Soc.*, **90**, 4328 (1968).

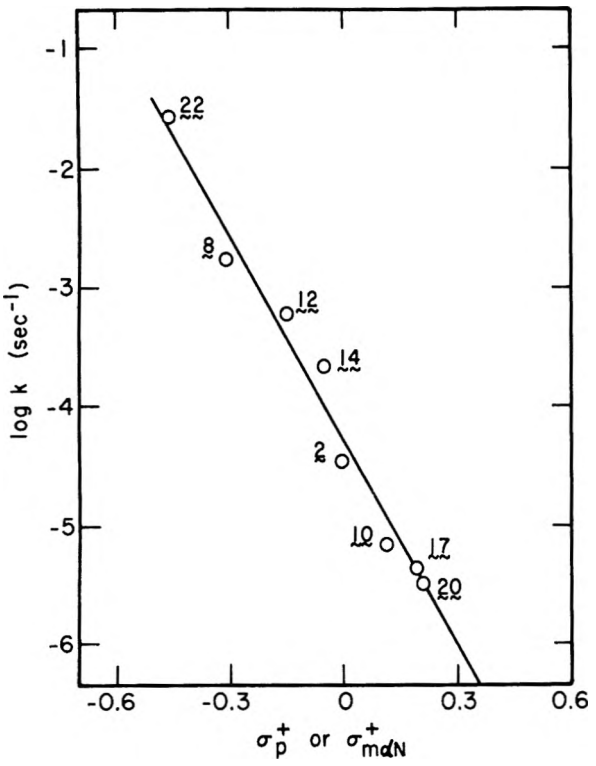


Figure 1.—Correlation of rates of solvolysis of substituted 1-(2-imidazolyl)ethyl *p*-nitrobenzoates with σ_p^+ and $\sigma_{m\alpha N}^+$.

nance parameters (ℜ) being blended to fit the observed reactivities. Alternatively, one may use Taft's σ_I,[15] which Swain and Lupton[14] have shown to be a pure field (ℱ) term within the limits of analysis, and Yukawa's $\Delta\sigma_R^+$ ($\Delta\sigma_R^+ = \sigma_p^+ - \sigma_p$),[16] which can be shown to be ~90% resonance (ℜ) in the Swain and Lupton approach.

Thus, an electrophilic substituent constant applicable to situations where the substituent is located adjacent to a pyridine-type nitrogen and in a "meta" relationship to the reacting side chain may be defined by eq 1 (Swain and Lupton) or eq 2 (using Charton's symbolism).[17]

$$\sigma_{m\alpha N}^+ = f\mathcal{F} + r\mathcal{R} \quad (1)$$

$$\sigma_{m\alpha N}^+ = \lambda\sigma_I + \delta\Delta\sigma_R^+ \quad (2)$$

The measured rates for pyridines[13] give, for eq 2, $\lambda = 0.614$ and $\delta = 0.762$. Using these values of λ and δ and the appropriate values of σ_I and $\Delta\sigma_R^+$, it is then possible to calculate a $\sigma_{m\alpha N}^+$ value for any substituent. Thus, the $\sigma_{m\alpha N}^+$ for bromine was calculated to be 0.214 and that for methylthio to be −0.235. Additivity was assumed in the case of the 4,5-dimethyl substituent. In Table II these values are given in the last column.

Applying $\sigma_{m\alpha N}^+$ to the observed substituent effects for 4-substituted 1-methyl-2-imidazolyl esters greatly improves the situation. The logarithms of the rates for the 4-substituted compounds correlate very nicely with $\sigma_{m\alpha N}^+$ ($\rho = -5.90$, cc = 0.994). In addition, if the rates of the 5-substituents are correlated against σ_p^+ and those of the 4-substituents against $\sigma_{m\alpha N}^+$, the entire set of results gives a satisfactory single correlation line with ρ equal to −5.77 and correlation coefficient (cc) equal to 0.99. This correlation is shown in Figure 1.

On close inspection of the correlation line obtained when the data from the substituted 1-(1-methyl-2-imidazolyl)ethyl esters are plotted against $\sigma_{m\alpha N}^+$ and σ_p^+ (Figure 1), it can be seen that the 4-substituents still tend to fall somewhat above the correlation line. Inasmuch as all the 4-substituents examined were of the π electron donating type, this suggests that there is an even greater degree of resonance stabilization by the substituent for these systems than in the corresponding pyridine cases.

It is of course possible to derive, independently from these results with imidazole, applicable values for δ and λ. When this calculation is carried out, a larger value of δ is obtained, as would be anticipated by the observations noted above. Finally, it is instructive to express the ratio of resonance effects to inductive effects as δ/λ.[17] Some relevant comparisons are given in Table III for various substituent constants and reactivity series.

TABLE III
CORRELATIONS OF VARIOUS SUBSTITUENT CONSTANTS AND REACTIVITY SERIES

Substituent constant	λ	δ	δ/λ	%ℜ[b]
σ_m			0.3–0.5[a]	22
σ_m^+			0.42	33
σ_p			1.00[a]	53
σ_p^+	0.762	1.908	2.50	66
$\sigma_{m\alpha N}^+$	0.614	0.762	1.24	44
$\Delta\sigma_R^+$	0	1.00	∞	~90
Reactivity Series				
6-X-2-Pyridyl[c]			(1.24)	
2-X-4-Thiazolyl[d]			1.26	
4-X-2-Imidazolyl[e]	0.622	1.22	1.96	53

[a] Reference 17. [b] Reference 14. [c] Reference 13; defining series for $\sigma_{m\alpha N}^+$. [d] Reference 7. [e] Present study.

In summary, an enhanced resonance component in the substituent effect is observed when the substituent is α to a pyridine-type nitrogen and is "meta" to the reaction site.

Experimental Section[18]

1-(1-Methyl-2-imidazolyl)ethanol (1).—A solution of 20 g (0.24 mol) of 1-methylimidazole (Aldrich) in 500 ml of anhydrous diethyl ether, under nitrogen, was cooled to Dry Ice–acetone temperature. To this was added dropwise, over a period of 30 min 190 ml of 1.6 *M* *n*-butyllithium in *n*-hexane (Foote Mineral Co.). After the mixture was stirred for 1 hr, 25 ml of acetaldehyde was added in one portion. After 5 hr the reaction mixture was allowed to warm to room temperature and was quenched with water (250 ml). The aqueous phase was separated and continuously extracted with ethyl acetate. Evaporation of the ethyl acetate and distillation of the residue under vacuum yielded 10.6 g (35%) of 1-(1-methyl-2-imidazolyl)ethanol as a yellow oil which crystallized on standing. Crystallization from benzene–hexane yielded colorless prisms: mp 82–83.5°; bp 118–120° (2 mm); nmr ($CDCl_3$) δ 6.70 (s, 2, ring protons), 4.82 (q, 1, J = 7 Hz, $CH(OH)CH_3$), 3.66 (s, 3, NCH_3), and 1.50 (d, 3, J = 7 Hz, $CH(OH)CH_3$).

(15) R. W. Taft, Jr., and I. C. Lewis, *J. Amer. Chem. Soc.*, **80**, 2436 (1958).
(16) Y. Yukawa and Y. Tsuno, *Bull. Chem. Soc. Jap.*, **39**, 2274 (1966).
(17) M. Charton, *J. Amer. Chem. Soc.*, **86**, 2033 (1964).
(18) All melting and boiling points are uncorrected. Routine nmr spectra were determined on a Varian A-60 or a Varian T-60 instrument using tetramethylsilane as an internal standard. The elemental analyses were determined by the Microanalytical Services Laboratory, College of Chemistry, University of California, Berkeley, Calif.

Anal. Calcd for $C_6H_{10}N_2O$: C, 57.12; H, 7.99; N, 22.20. Found: C, 57.22; H, 8.19; N, 21.94.

1-(1-Methyl-2-imidazolyl)ethyl *p*-Nitrobenzoate (2).—To a solution of 5 g of 1-(1-methyl-2-imidazolyl)ethanol and 4.15 g of triethylamine in 50 ml of 1,2-dichloroethane was added dropwise 7.45 g (4.0×10^{-2} mol) of *p*-nitrobenzoyl chloride dissolved in 25 ml of 1,2-dichloroethane. Toward the end of the addition, triethylamine hydrochloride began to precipitate. After 1 hr the precipitated triethylamine hydrochloride was filtered off and the filtrate was washed with water and dried ($MgSO_4$), and the solvent was removed under vacuum. Crystallization from benzene–hexane gave 8.7 g (79%) of 1-(1-methyl-2-imidazolyl)-ethyl *p*-nitrobenzoate as colorless crystals: mp 101–102°; nmr ($CDCl_3$) δ 8.20 (s, 4, $O_2NC_6H_4$–), 7.00 (br s, 1, 4- or 5-H), 6.87 (d, 1, J = 1.1 Hz, 4- or 5-H), 6.28 (q, 1, J = 6.6 Hz, $CH(OH)$-CH_3), 3.74 (s, 3, NCH_3), and 1.87 (d, 3, J = 6.6 Hz, $CH(OH)$-CH_3).

Anal. Calcd for $C_{13}H_{13}N_3O_4$: C, 56.72; H, 4.76; N, 15.26. Found: C, 56.65; H, 4.77; N, 15.09.

1-Methyl-4-imidazolecarboxaldehyde (3) was prepared by the method of Rapoport, *et al.*,[19] from α-amino-β-methylaminopropionic acid *via* **ethyl 1-methyl-2-imidazoline-4-carboxylate** (not purified) and **ethyl 1-methyl-4-imidazolecarboxylate**, mp 56–57°.

Anal. Calcd for $C_7H_{10}N_2O_2$: C, 54.54; H, 6.54; N, 18.17. Found: C, 54.62; H, 6.30; N, 18.04.

Reduction of this ester gave the reported **1-methyl-4-hydroxymethylimidazole**, mp 60–62° (lit.[19] 61–62°), which was oxidized with activated manganese dioxide to **1-methyl-4-imidazolecarboxaldehyde (3)**, mp 65–66° (lit.[19] 65–66.5°).

1-(1-Methyl-4-imidazolyl)ethanol was prepared by the addition of methylmagnesium bromide to **3** in tetrahydrofuran. Isolation in the usual manner, including final exhaustive extraction with chloroform, gave the alcohol, which was not exhaustively purified but was used directly in the preparation of the *p*-nitrobenzoate by the procedure described above for **2**.

Compound **4** was crystallized from benzene–hexane: mp 114–116°; nmr ($CDCl_3$) δ 8.22 (s, 4, $O_2NC_6H_4$–), 7.43 (br s, 1, 2-H), 6.97 (br s, 1, 5-H), 6.19 (q, 1, J = 6.8 Hz, $CH(OH)CH_3$), 3.67 (s, 3, NCH_3), and 1.75 (d, 3, J = 6.8 Hz, $CH(OH)CH_3$).

Anal. Calcd for $C_{13}H_{13}N_3O_4$: C, 56.72; H, 4.76; N, 15.26. Found: C, 56.95; H, 4.59; N, 15.02.

1-Methyl-5-imidazolecarboxaldehyde.—The procedures of Jones and McLaughlin[20,21] were followed for the preparation of **1-methyl-5-hydroxymethylimidazole**. Oxidation with activated manganese dioxide[19] gave the aldehyde, mp 53–55° (lit.[21] 53–54°).

1-(1-Methyl-5-imidazolyl)ethanol.—To a solution of 5.0 g of 1-methyl-5-imidazolecarboxaldehyde in 250 ml of anhydrous diethyl ether was added dropwise 45 ml of methyllithium (1.5 *M* in *n*-hexane, Foote Mineral Co.). During the addition the reaction mixture was maintained under a nitrogen atmosphere and the temperature was maintained below 5°. After stirring for 1 hr at 0°, the mixture was allowed to warm to room temperature, stirred for an additional 0.5 hr, and then quenched with 150 ml of water. The phases were separated and the aqueous phase was continuously extracted with methylene chloride for 16 hr. No product was detected in the ethereal phase. The methylene chloride extracts were concentrated under vacuum and the solid residue was crystallized from benzene to yield 4.5 g (78%) of 1-(1-methyl-5-imidazolyl)ethanol as colorless crystals: mp 126.5–127.5° (lit.[22] mp 128–130°); nmr ($CDCl_3$) δ 7.25 (d, 1, J = 1 Hz, ring proton), 6.75 (br s, 1, ring proton), 4.81 (q, 1, J = 1 Hz, ring proton), 6.75 (br s, 1, ring proton), 4.81 (q, 1, J = 6 Hz, $CH(OH)CH_3$), 3.66 (s, 3, NCH_3), and 1.57 (d, 3, J = 6 Hz, $CH(OH)CH_3$).

1-(1-Methyl-5-imidazolyl)ethyl *p*-nitrobenzoate (5) was prepared in the same fashion as **2**. The crude ester **5** was purified by column chromatography on silica gel eluting with chloroform to yield 3.3 g (50%) of 1-(1-methyl-5-imidazolyl)ethyl *p*-nitrobenzoate (**5**) as a pale yellow solid: mp 99–101°; nmr ($CDCl_3$) δ 8.27 (s, 4, $O_2NC_6H_4$–), 7.50 (s, 1, ring proton), 7.23 (s, 1, ring proton), 6.31 (q, 1, J = 6.8 Hz, $CH(OH)CH_3$), 3.70 (s, 3, NCH_3), and 1.82 (d, 3, J = 6.8 Hz, $CH(OH)CH_3$).

Anal. Calcd for $C_{13}H_{13}N_3O_4$: C, 56.72; H, 4.76; N, 15.26. Found: C, 56.52; H, 4.83; N, 15.28.

1,5-Dimethylimidazole (6).—2-Methylaminopropionaldehyde diethyl acetal[23] was converted to 1,5-dimethyl-2-mercaptoimidazole by treatment with potassium thiocyanate.[24] Oxidative removal of the mercapto group[20,25] gave **6** in 73% yield: bp 110–112° (30 mm); mp 21.5–22.0°; nmr ($CDCl_3$) δ 7.25 (br s, 1, 2-H), 6.63 (m, 1, 4-H), 3.37 (s, 3, NCH_3), and 2.06 (d, 3, J = 1.2 Hz, CH_3).

Anal. Calcd for $C_5H_8N_2$: C, 62.47; H, 8.39; N, 29.25. Found: C, 62.66; H, 8.47; N, 28.92.

1-(1,5-Dimethyl-2-imidazolyl)ethanol (7).—Transmetalation of **6** (20 g) with *n*-butyllithium at −80° was followed by the addition of acetaldehyde (20 ml) at 0°. Work-up in the usual manner gave a crude product which was shown by nmr to be a mixture of **6** and **7**. The mixture was separated by chromatography on silica gel to afford 11.6 g (58%) of recovered **6** and 9.0 g (30%) of 1-(1,5-dimethyl-2-imidazolyl)ethanol (**7**). **7** was purified by crystallization from benzene–hexane: mp 99–100°; nmr ($CDCl_3$) δ 6.48 (br s, 1, 4-H), 4.79 (q, 1, J = 6.7 Hz, CH-$(OH)CH_3$), 3.53 (s, 3, NCH_3), 2.10 (d, 3, J = 0.9 Hz, CH_3), and 1.51 (d, 3, J = 6.7 Hz, $CH(OH)CH_3$).

Anal. Calcd for $C_7H_{12}N_2O$: C, 59.98; H, 8.63; N, 19.98. Found: C, 60.12; H, 8.53; N, 19.78.

1-(1,5-Dimethyl-2-imidazolyl)ethyl *p*-nitrobenzoate (8) was prepared as above for **2**. Crude **8** was crystallized from benzene–hexane to give 1-(1,5-dimethyl-2-imidazolyl)ethyl *p*-nitrobenzoate (**8**) as white crystals: mp 116.5–118°; nmr ($CDCl_3$) δ 8.22 (s, 4, $O_2NC_6H_4$–), 6.78 (br s, 1, 4-H), 6.27 (q, 1, J = 6.6 Hz, $CH(OH)CH_3$), 3.57 (s, 3, NCH_3), 2.20 (d, 3, J = 0.9 Hz, CH_3), and 1.85 (d, 3, J = 6.6 Hz, $CH(OH)CH_3$).

Anal. Calcd for $C_{14}H_{15}N_3O_4$: C, 58.13; H, 5.23; N, 14.52. Found: C, 57.93; H, 5.11; N, 14.55.

1-(1-Methyl-5-chloro-2-imidazolyl)ethanol (9).—A solution of 10 g of 1-methyl-5-chloroimidazole[26] in 250 ml of ether was transmetalated with 1 equiv of *n*-butyllithium in hexane at −80°, and a threefold excess of acetaldehyde was added at room temperature. Work-up in the usual manner afforded crude **9**, which was crystallized from ether to give 8.2 g (64%) of **9** as colorless needles: mp 110–111°; nmr ($CDCl_3$) δ 6.70 (s, 1, 4-H), 4.81 (q, 1, J = 7 Hz, $CH(OH)CH_3$), 3.60 (s, 3, NCH_3), and 1.54 (d, 3, J = 7 Hz, $CH(OH)CH_3$).

1-(1-Methyl-5-chloro-2-imidazolyl)ethyl *p*-Nitrobenzoate (10).—Compound **9** was converted to the *p*-nitrobenzoate (**10**) as above, yielding pale yellow prisms from benzene–hexane: mp 127–128.5°; nmr ($CDCl_3$) δ 8.16 (s, 4, $O_2NC_6H_4$–), 6.90 (s, 1, 4-H), 6.22 (q, 1, J = 7 Hz, $CH(OH)CH_3$), 3.63 (s, 3, NCH_3), and 1.84 (d, 3, J = 7 Hz, $CH(OH)CH_3$).

Anal. Calcd for $C_{13}H_{12}ClN_3O_4$: C, 50.42; H, 3.91; Cl, 11.45; N, 13.57. Found: C, 50.58; H, 3.81; Cl, 11.27; N, 13.32.

1-(1,4-Dimethyl-2-imidazolyl)ethanol (11) was prepared from 1,4-dimethylimidazole[23,25] by transmetalation and treatment with acetaldehyde. A sample purified by chromatography was characterized by nmr: δ ($CDCl_3$) 6.38 (br s, 1, 5-H), 4.78 (q, 1, J = 6.5 Hz, $CH(OH)CH_3$), 3.58 (s, 3, NCH_3), 2.05 (s, 3, CH_3), and 1.47 (d, 3, J = 6.5 Hz, $CH(OH)CH_3$).

1-(1,4-Dimethyl-2-imidazolyl)ethyl *p*-Nitrobenzoate (12).—Conversion of **11** to the ester was accomplished in the usual manner. 1-(1,4-Dimethyl-2-imidazolyl)ethyl *p*-nitrobenzoate **12** crystallized from benzene–hexane as pale yellow crystals: mp 124–125°; nmr ($CDCl_3$) δ 8.20 (s, 4, $O_2NC_6H_4$–), 6.60 (br s, 1, 5-H), 6.25 (q, 1, J = 6.6 Hz, $CH(OH)CH_3$), 3.67 (s, 3, NCH_3), 2.22 (s, 3, CH_3), and 1.86 (d, 3, J = 6.6 Hz, $CH(OH)CH_3$).

Anal. Calcd for $C_{14}H_{15}N_3O_4$: C, 58.13; H, 5.23; N, 14.52. Found: C, 58.31; H, 5.21; N, 14.37.

1-(1-Methyl-4-phenyl-2-imidazolyl)ethanol (13).—Transmetalation of 1-methyl-4-phenylimidazole[27] at −80° with *n*-butyllithium was followed by addition of a threefold excess of acetaldehyde at 0°. Isolation in the usual fashion afforded crude **13**. Crystallization from benzene–hexane gave 62% of 1-(1-methyl-4-phenyl-2-imidazolyl)ethanol as colorless crystals: mp 121–122°; nmr ($CDCl_3$) δ 7.38 (m, 5, phenyl), 6.72 (s, 1, 5-H), 4.90 (q, 1,

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J = 6.4 Hz, $CH(OH)CH_3$), 3.26 (s, 3, NCH_3), and 1.56 (d, 3, J = 6.4 Hz, $CH(OH)CH_3$).

Anal. Calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.03; H, 6.91; N, 14.03.

1-(1-Methyl-4-phenyl-2-imidazolyl)ethyl *p*-nitrobenzoate (14) was prepared in the usual fashion: mp 112–113°; nmr ($CDCl_3$) δ 8.19 (s, 4, $O_2NC_6H_4$–), 7.75 (m, 2, phenyl), 7.32 (m, 3, phenyl), 7.12 (s, 1, 5-H), 6.31 (q, 1, J = 6.6 Hz, $CH(OH)CH_3$), 3.73 (s, 3, NCH_3), and 1.93 (d, 3, J = 6.6 Hz, $CH(OH)CH_3$).

Anal. Calcd for $C_{19}H_{17}N_3O_4$: C, 64.95; H, 4.88; N, 11.96. Found: C, 65.06; H, 4.73; N, 11.82.

1-Methyl-4-chloroimidazole (15).—A solution of 17.8 g (0.153 mol) of 1-methyl-5-chloroimidazole,[28] 57 g (0.4 mol) of methyl iodide, and 150 ml of benzene was refluxed for 1 hr. On cooling, the precipitated 1,3-dimethyl-4(5)-chloroimidazolium iodide was collected by filtration. This was transferred to a round-bottomed flask and heated to 220°. Methyl iodide was evolved. After the majority of the methyl iodide had been removed, the residue was distilled to give 11.1 g (62%) of 1-methyl-4-chloroimidazole and a small amount of the 1,5 isomer, bp 124–125° (20 mm).

1-(1-Methyl-4-chloro-2-imidazolyl)ethyl *p*-Nitrobenzoate (17).—Metalation of **15** was accomplished with *n*-butyllithium, and the resulting 2-lithio derivative was treated with acetaldehyde. The resulting mixture was poured into water, the phases were separated, and the aqueous phase was extracted with chloroform. The combined extracts were dried (Na_2SO_4) and concentrated. The resulting red oil was chromatographed on silica gel, eluting with chloroform to yield 4.6 g (48%) of 1-(1-methyl-4-chloro-2-imidazolyl)ethanol (**16**) contaminated with traces of **9**.

The crude **16** was directly converted to 1-(1-methyl-4-chloro-2-imidazolyl)ethyl *p*-nitrobenzoate (**17**): mp 162–163° (needles from benzene–hexane); nmr ($CDCl_3$) δ 8.27 (s, 4 H, $O_2NC_6H_4$–), 6.82 (s, 1, 5-H), 6.22 (q, 1 H, J = 7 Hz, $CH(OH)CH_3$), 3.75 (s, 3, NCH_3), and 1.84 (d, 3, J = 7 Hz, $CH(OH)CH_3$). There was no indication of the 1,5 isomer by nmr.

Anal. Calcd for $C_{13}H_{12}ClN_3O_4$: C, 50.42; H, 3.91; Cl, 11.45; N, 13.57. Found: C, 50.25; H, 3.81; Cl, 11.42; N, 13.42.

1-(1-Methyl-4-bromo-2-imidazolyl)ethanol (19).—A solution of 8.0 g of 1-methyl-4-bromoimidazole[29] in ether was treated with *n*-butyllithium in hexane at −80°. The resulting 2-lithio derivative was treated with a twofold excess of acetaldehyde at −80°. Isolation in the usual manner and chromatography on silica gel ($CHCl_3$ eluent) afforded 4.7 g of **19** as a viscous pale yellow oil,[30] characterized by nmr and used directly for the preparation of the *p*-nitrobenzoate: nmr ($CDCl_3$) δ 6.73 (s, 1, 5-H), 4.89 (q, 1, J = 6.8 Hz, $CH(OH)CH_3$), 3.68 (s, 3, NCH_3), and 1.52 (d, 3, J = 6.8 Hz, $CH(OH)CH_3$).

1-(1-Methyl-4-bromo-2-imidazolyl)ethyl *p*-Nitrobenzoate (20).—Conversion of **19** to **20** was accomplished in the usual fashion: mp 156–157°; nmr ($CDCl_3$) δ 8.27 (s, 4, $O_2NC_6H_4$–), 6.90 (s, 1, 5-H), 6.22 (q, 1, J = 6.8 Hz, $CH(OH)CH_3$), 3.77 (s, 3, NCH_3), and 1.85 (d, 3, J = 6.8 Hz, $CH(OH)CH_3$).

Anal. Calcd for $C_{13}H_{12}BrN_3O_4$: C, 44.09; H, 3.42; Br, 22.56; N, 11.86. Found: C, 44.30; H, 3.52; Br, 22.74; N, 11.62.

1-(1,4,5-Trimethyl-2-imidazolyl)ethanol (21).—A solution of 11 g of 1,4,5-trimethylimidazole[31] in dry ether was metalated at −80° with *n*-butyllithium. The resulting 2-lithio derivative was treated with a threefold excess of acetaldehyde at 0°. Work-up in the usual manner afforded a modest yield of **21**, which was recrystallized from benzene–hexane to give 3.6 g (24%) of 1-(1,4,5-trimethyl-2-imidazolyl)ethanol (**21**) as colorless needles: mp 126.5–128°; nmr ($CDCl_3$) δ 4.78 (q, 1, J = 7.0 Hz, $CH(OH)CH_3$), 3.58 (s, 3, NCH_3), 2.07 (s, 6, 4-CH_3 + 5-CH_3), and 1.5 (d, 3, J = 7.0 Hz, $CH(OH)CH_3$).

Anal. Calcd for $C_8H_{14}N_2O$: C, 62.31; H, 9.15; N, 18.17. Found: C, 62.10; H, 8.95; N, 17.95.

1-(1,4,5-Trimethyl-2-imidazolyl)ethyl *p*-Nitrobenzoate (22).—Alcohol **21** was converted to the *p*-nitrobenzoate in the usual manner: mp 127.5–128.5° (yellow needles from benzene–hexane); nmr ($CDCl_3$) δ 8.28 (s, 4, phenyl), 6.31 (q, 1, J = 6.8 Hz, $CH(OPNB)CH_3$), 3.57 (s, 3, NCH_3), 2.12 (s, 3, CH_3), 2.11 (s, 3, CH_3), and 1.86 (d, 3, J = 6.8 Hz, $CH(OPNB)CH_3$).

Anal. Calcd for $C_{15}H_{17}N_3O_4$: C, 59.40; H, 5.65; N, 13.85. Found: C, 59.30; H, 5.43; N, 13.62.

Kinetic methods have been described previously.[13] Directly measured rate constants are given in Table IV.

TABLE IV

EXPERIMENTAL RATE CONSTANTS FOR THE SOLVOLYSIS OF SUBSTITUTED IMIDAZOLYLETHYL *p*-NITROBENZOATES IN 80% ETHANOL

Compound solvolyzed	Temp, °C	Method[a]	10^5 k, sec^{-1}
2	45.00	A	3.38 ± 0.05
	60.00	B	16.5 ± 0.3
	60.00	A	17.2 ± 0.2
	75.00	A	72.2 ± 0.8
4	45.00	A	43.0 ± 0.4
	60.00	A	208.0 ± 2.0
5	25.00	A	4.67 ± 0.08
	45.00	A	53.0 ± 0.3
	60.00	A	243.0 ± 4.0
8	25.00	A	18.7 ± 0.3
	45.00	A	167.0 ± 2.0
	60.00	A	712.0 ± 8.0
10	45.00	B	0.658 ± 0.01
	60.00	B	3.85 ± 0.1
	75.00	B	19.4 ± 0.6
12	25.00	A	6.36 ± 0.2
	45.00	A	59.80 ± 0.6
	60.00	A	257.0 ± 5.0
14	25.00	A	1.91 ± 0.04
	45.00	A	21.3 ± 0.3
	45.00	B	22.7 ± 0.4
	60.00	A	106.0 ± 2.0
17	45.00	B	0.436 ± 0.02
	60.00	B	2.82 ± 0.08
	75.00	B	13.2 ± 0.2
20	60.00	B	2.25 ± 0.05
	75.00	B	12.2 ± 0.2
	75.00	A	12.1 ± 0.2
22	0.00	A	13.1 ± 0.2
	8.25	A	41.8 ± 0.8
	25.00	A	317.0 ± 5.0

[a] A is at constant pH (8.0); B is by aliquot.

Registry No.—**1**, 41507-36-2; **2**, 41507-37-3; **3**, 17289-26-8; **4**, 41507-39-5; **5**, 41507-40-8; **6**, 10447-93-5; **7**, 41507-42-0; **8**, 41507-43-1; **9**, 41507-44-2; **10**, 41507-45-3; **11**, 41507-46-4; **12**, 41507-47-5; **13**, 41507-48-6; **14**, 41507-49-7; **15**, 4897-21-6; **17**, 41507-51-1; **19**, 41507-52-2; **20**, 41507-53-3; **21**, 41507-54-4; **22**, 41507-55-5; 1-methylimidazole, 616-47-7; acetaldehyde, 75-07-0; *p*-nitrobenzoyl chloride, 122-04-3; ethyl 1-methyl-4-imidazolecarboxylate, 41507-56-6; methyl bromide, 74-83-9; 1-(1-methyl-5-imidazolyl)ethanol, 23428-92-4; 1-methyl-5-imidazolecarboxaldehyde, 39021-62-0; 2-methylaminopropionaldehyde diethyl acetal, 41507-59-9; 1-methyl-5-chloroimidazole, 872-49-1; 1,4-dimethylimidazole, 6338-45-0; 1-methyl-4-phenylimidazole, 2411-77-0; methyl iodide, 74-88-4; 1-methyl-4-bromoimidazole, 25676-75-9; 1,4,5-trimethylimidazole, 20185-22-2.

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(29) Prepared by methylating 4(5)-bromoimidazole (**18**) with methyl iodide in the presence of excess 10 *N* sodium hydroxide and fractionating the product. Roughly equal quantities of **18** and of 1-methyl-5-bromoimidazole resulted.

(30) Reversing the order of addition or substituting methyllithium for *n*-butyllithium does not change the product obtained. However, when 1-methyl-5-bromoimidazole is subjected to the same sequence, halogen–metal interchange ensues, and the product obtained is 1-(1-methyl-5-imidazolyl)-ethanol.

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Evidence for the Electron Impact Induced Formation of Prominent Cyclic Acetal Ions from Aliphatic Ester Lipids[1]

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Under electron impact complex ester lipids derived from glycerol and other polyhydric alcohols produce ions $[M - X]^+$ and $[M - XH]^+$ in great abundance (X = RCOO, RO, RCH=CHO, HO). High-resolution mass measurements and specific deuterium labeling confirmed that both types of ions formally retain at least one acyl function and the polyol moiety. Simple homolytic cleavage does not suffice to explain the structural requirements of ion formation and the ion intensities from long-chain diesters of a series of α,ω-diols. A detailed study of the mass spectral fragmentation patterns, ions, and ion intensities of representative long-chain cyclic acetals, and especially of a series of α,ω-diol acetals, has now provided strong evidence that ions $[M - X]^+$ and $[M - XH]^+$ from a great variety of aliphatic ester lipids are cyclic in structure. Mechanisms of ion formation are proposed.

Electron-impact induced expulsion of a long-chain acyloxy group X or elimination of a carboxylic acid XH from triglycerides[2-5] is known to lead to prominent ions $[M - X]^+$ and $[M - XH]^+$. Ions $[M - X]^+$ often give rise to the base peak. Other studies in our laboratories have revealed that the same types of fragments are abundantly produced from diesters,[6] alk-1-enyl ether esters[7,8] (X = RCH=CHO), and alkyl ether esters[8] (X = RO) of short-chain diols. Alkyl ether diesters of glycerol,[9] glycerophosphatides,[10] [X = $R_3N(CH_2)_2OPO_3$], and trimethylsilyl derivatives of diglycerides[11] (X = RCOO) also form the ion pair to a significant extent. In the spectra of diglycerides,[12] ions $[M - X]^+$ and $[M - XH]^+$ appear as major contributors to the total ion current (X = HO or RCOO). However, spectra of simple wax esters[13] display the ion pair only in minute intensity. A systematic investigation of the structural parameters required for the formation of these ions, or of the ion structures, has not been undertaken previously.

The present report is based on a detailed study of the mass spectral patterns of a variety of polysubstituted aliphatic ester lipids, including those bearing additional alkoxy and alk-1-enyloxy functions linked to glycerol or to diol backbones. It will be shown that ions $[M - X]^+$ and $[M - XH]^+$, independent of their origin, formally retain the structural elements of at least one acyl grouping and the complete polyol moiety. High-resolution mass measurements and deuterium labeling served to confirm this proposition. Evidence can now be provided for a mechanism that involves *cyclization* of the acyl function with the short-chain backbone leading to resonance-stabilized "cyclic acetal" structures. Scope and limitations of these findings constitute the subject of this report.

Results and Discussion

Under electron impact triglycerides predominantly lose acyloxy groups.[2-5] The intensity of ion $[M - RCOO]^+$ increases with the chain length of the substituent lost, but is largely independent of the location on the glycerol moiety.[4] The intensity is particularly high for monoacid triglycerides, as abstraction of any of the acyloxy functions contributes to the same ion current. Loss of a hexadecanoyloxy group from tripalmitin (**1a**), *e.g.*, gives rise to the base peak at *m/e 551* (6.85%)[14] (Table I). The same ion is produced from the analogous alkoxy lipids in which one of the ester functions of **1a** is replaced by a long-chain alkyl or alk-1-enyl ether grouping. Loss of the alk-1-enyloxy moiety from 1-*O*-hexadec-1′-enyl-2,3-di-*O*-hexadecanoyl-*sn*-glycerol (**1b**)[15] constitutes the major fragmentation pathway leading to ion $[M - RCH{=}CHO]^+$ at *m/e 551* (4.75%). Smaller amounts of $[M - RO]^+$ are formed from 1-*O*-alkyl diglycerides and 1,2-di-*O*-alkyl glycerides **1c** (0.54%) and **1d** (0.58%), respectively.

In context with the structural and mechanistic aspects which are to be considered (*vide infra*), it is significant that the intensities of ions $[M - X]^+$ from diesters, alk-1-enyl ether esters, and alkyl ether esters of ethanediol are similarly dependent upon the substituent lost, as are the ion intensities of the corresponding glycerol derivatives (Table I). $[M - X]^+$ gives rise to the base peak at *m/e 283* in the spectra of di-*O*-hexadecanoylethanediol (**2a**) (12.24%, X = RCOO) and octadec-1-enylhexadecanoylethanediol (**2f**) (28.38%, X = RCH=CHO), whereas expulsion of OR from octadecylhexadecanoylethanediol (**2g**) is

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(14) Abundances of ions are given throughout the manuscript as percentages of total ion current; *m/e* values of base peaks are printed in *italics*.

(15) Alk-1-enyldiacylglycerol (**1b**) was prepared from beef heart plasmalogens and contained approximately 60% C_{18}-enol isomer: W. J. Baumann, H. H. O. Schmid, J. K. G. Kramer, and H. K. Mangold, *Z. Physiol. Chem.*, **349**, 1677 (1968).

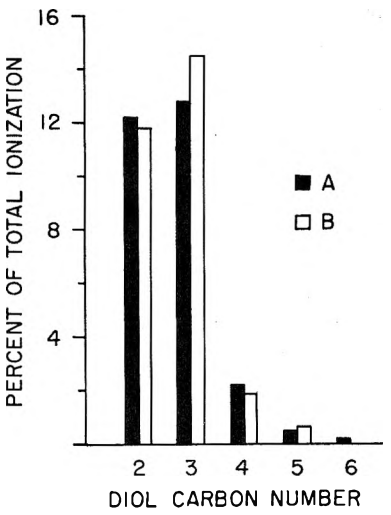


Figure 1.—Cyclic ions from diesters and acetals of α,ω-diols: A, abundances of ions $[M - C_{15}H_{31}COO]^+$ from di-*O*-hexadecanoyldiols (**2a–e**); B, abundances (× 10) of ions $[M - H]^+$ from cyclic acetals of hexadecanal and α,ω-diols (**11a–d**).

TABLE I

ABUNDANCES OF $[M - X]^+$ AND $[M - XH]^+$ FROM LONG-CHAIN ESTERS AND ETHER ESTERS OF POLYHYDRIC ALCOHOLS[a]

Ester lipid	*m/e* (abundance) structure $[M - X]^+$	*m/e* (abundance) structure $[M - XH]^+$
1a	*551* (6.85) **3b**, **4b**[b]	550 (3.74) **6a**, **7a**[b]
1b	*551* (4.75) **3b**, **4b**[c]	550 (0.28) **6a**, **7a**[c]
1c[d]	551 (0.54) **3b**, **4b**[e]	550 (0.23) **6a**, **7a**[e]
	537 (2.84) **3d**, **4d**[b]	536 (1.77) **6b**, **7b**[b]
1d[f]	537 (0.58) **3d**, **4d**[e]	536 (0.25) **6b**, **7b**[e]
2a	*283* (12.24) **5b**[b]	282 (3.55) **8a**[b]
2a-d_4	*287* (11.22) **5b-d_4**[b]	286 (3.55) **8a-d_4**[b]
2b	*297* (12.70) **5d**[b]	296 (4.61) **8b**[b]
2c[g]	311 (2.23) **5f**[b]	310 (1.76) **8c**[b]
2d[h]	325 (0.50) **5h**[b]	324 (0.61) **8d**[b]
2e[i]	339 (0.24) **5j**[b]	338 (0.24) **8e**[b]
2f	*283* (28.38) **5b**[j]	282 (0.54) **8a**[j]
2f-d_4	*287* (33.11) **5b-d_4**[j]	286 (1.66) **8a-d_4**[j]
2g[k]	283 (1.81) **5b**[l]	282 (0.20) **8a**[l]
2g-d_4[m]	287 (2.79) **5b-d_4**[l]	286 (0.35) **8a-d_4**[l]

[a] Abundances in per cent of total ionization; see also ref 14. Molecular and ion structures are given in Schemes I and II. [b] X = $C_{15}H_{31}COO$. [c] X = alk-1-enyloxy, containing approximately 60% of $C_{14}H_{29}CH{=}CHO$; peaks for $[M - RCOO]^+$ and $[M - RCOOH]^+$ are virtually absent. [d] Base peak *m/e* *57* (7.45). [e] X = $C_{16}H_{33}O$. [f] Base peak *m/e* *523* (15.35). [g] Base peak *m/e* *73* (6.58). [h] Base peak *m/e* *69* (7.37). [i] Base peak *m/e* *82* (7.25). [j] X = $C_{16}H_{33}CH{=}CHO$. [k] Base peak *m/e* *57* (8.68). [l] X = $C_{18}H_{37}O$. [m] Base peak *m/e* *57* (6.51).

less likely to occur (1.81%). The abundance of ion $[M - X]^+$ is particularly high for symmetrical diol diesters[6] and also increases with increasing chain length of the acyloxy function lost.[6,8] Moreover, the intensities of $[M - X]^+$ in the spectra of diesters, of α,ω-diols **2a–e** (Table I) are extremely dependent upon the chain length of the constituent diol. Ions $[M - RCOO]^+$ are of maximal abundance for the dihexadecanoates of 1,2-ethanediol (**2a**, 12.24%) and 1,3-propanediol (**2b**, 12.70%); however, their intensities are drastically reduced in magnitude for the diesters of longer chain diols **2c–e** (2.23, 0.50, 0.24%).

In contrast to $[M - X]^+$, ions $[M - XH]^+$ are produced in high abundance only when the elimination involves loss of fatty acid (X = RCOO) from triglyceride (**1a**, 3.74%) or from alkyl diglyceride (**1c**, 1.77%). Elimination of long-chain alk-1-enol from **1b** and **2f**, or of alkanol from **1c**, **1d**, and **2g**, is less likely to occur (0.2–0.5%). In analogy to $[M - X]^+$, ions $[M - XH]^+$ are produced from diesters of the shorter chain diols **2a–c** in significant abundances (4.6–1.8%) and in smaller amounts from the longer chain homologs **2d** and **2e** (0.6, 0.2%).

The elemental compositions of ions $[M - X]^+$ and $[M - XH]^+$ were confirmed by high-resolution mass spectrometry of representative compounds.[16] The compositions of both types of ions were also compatible with the results of deuteration studies. Spectra of triacyl derivatives of perdeuterated glycerol display both ions shifted by 5 amu.[17] Similarly, the spectra of the three classes of hexadecanoates of 1,1,2,2-tetradeuterioethanediol[8] (**2a-d_4**, **2f-d_4**, **2g-d_4**) exhibit $[M - X]^+$ and $[M - XH]^+$ at *m/e* 287 and 286, respectively, with intensities very similar to those at *m/e* 283 and 282 in the spectra of the corresponding nondeuterated diol lipids (Table I). The mass shift observed is consistent with the concept that $[M - X]^+$ as well as $[M - XH]^+$ retain the intact alcoholic moiety.

Favored formation of the ion pair $[M - X]^+$ and $[M - XH]^+$ from polysubstituted ester lipids is indicative of a low-energy pathway leading to highly stable ion structures. Therefore, we have previously postulated formation of cyclic ions from triglycerides[4] and from a number of ethanediol-derived lipids,[7,8] as have other investigators,[10,12] without being able to substantiate such structures. On the basis of the present study, it is clear that a mechanism involving merely simply homolytic single bond cleavage at an acyloxy, alk-1-enyloxy, or alkoxy function with charge retention on the polyol-containing fragment does not suffice to explain the intensity of $[M - X]^+$ in the spectra of a large number of glycerol- and diol-derived ester lipids (Table I) and, for example, the virtual absence of the ion in the spectra of wax esters.[13] Figure 1 (bars A) depicts the high intensities of ions $[M - X]^+$ derived from the diesters of C_2 and C_3 α,ω-diols (**2a**, **2b**) and the abrupt intensity decline for these ions originating from diesters of longer chain diols (**2c–e**). This phenomenon can satisfactorily be explained by the formation of cyclic ions which would be most favored, of course, for the five- and six-membered ring structures derived from the C_2 and C_3 diol diesters, respectively.

In the series of diol diesters **2a–e** ions $[M - XH]^+$ display an intensity pattern similar to that of $[M - X]^+$ (Table I), indicating cyclic ion formation as well. However, elimination of a fatty acid from diol diesters is not so drastically dependent upon the diol carbon number as is the extrusion of the acyloxy function.

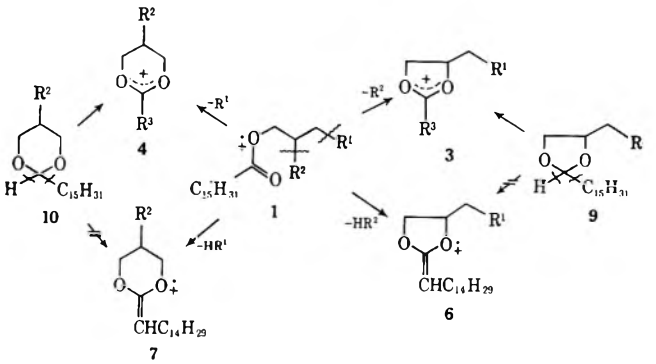
In summary, a great number of glycerol-derived (**1**) and diol-derived (**2**) ester lipids, varying in several structural parameters, produce under electron impact ions $[M - X]^+$ (**3–5**) and $[M - XH]^+$ (**6–8**). We propose that both types of ions possess resonance-

(16) 1,3-Di-*O*-hexadecanoylpropanediol (**2b**): ion **5d**, $C_{19}H_{37}O_2$ (calcd for *m/e*, 297.2794; found, 297.2798); ion **8b**, $C_{19}H_{36}O_2$ (calcd for *m/e*, 296.2715; found, 296.2739). 1,5-Di-*O*-hexadecanoylpentanediol (**2d**): ion **5h**, $C_{21}H_{41}O_3$ (calcd for *m/e*, 325.3106; found, 325.3090); ion **8d**, $C_{21}H_{40}O_2$ (calcd for *m/e*, 324.3028; found, 324.2998). 1,3-Di-*O*-octadecanoylglycerol:[12] ion $[M - RCOO]^+$, $C_{21}H_{41}O_3$ (calcd for *m/e*, 341.3056; found, 341.3055).

(17) Trioctadecanoylglycerol produced $[M - RCOO]^+$ at *m/e* 607 (2.29), $[M - RCOOH]^+$ at *m/e* 606 (2.04). Perdeuteration in the glycerol moiety shifted the ion pair to *m/e* 612 (2.37) and 611 (1.86); *m/e* 610 (0.37).[5]

stabilized cyclic structures such as those depicted in Schemes I and II.

SCHEME I



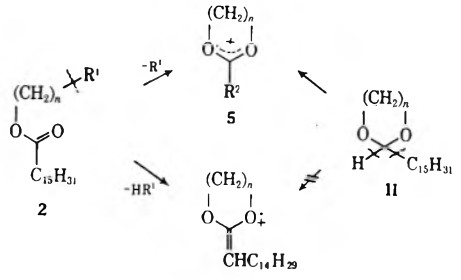
1a, $R^1 = R^2 = C_{15}H_{31}COO$ (*m/e* 806)
b, $R^1 = C_{14}H_{29}CH{=}CHO$; $R^2 = C_{15}H_{31}COO$ (*m/e* 790)
c, $R^1 = C_{16}H_{33}O$; $R^2 = C_{15}H_{31}COO$ (*m/e* 792)
d, $R^1 = R^2 = C_{16}H_{33}O$ (*m/e* 778)
e, $R^1 = H_3N(CH_2)_2OPO_3$; $R^2 = C_{15}H_{31}COO$
f, $R^1 = (CH_3)_3N(CH_2)_2OPO_3$; $R^2 = C_{15}H_{31}COO$

3a, 4a, $R^1 = R^2 = C_{15}H_{31}COO$; $R^3 = H$ (*m/e* 341)
3b, 4b, $R^1 = R^2 = C_{15}H_{31}COO$; $R^3 = C_{15}H_{31}$ (*m/e* 551)
3c, 4c, $R^1 = R^2 = C_{16}H_{33}O$; $R^3 = H$ (*m/e* 327)
3d, 4d, $R^1 = R^2 = C_{16}H_{33}O$; $R^3 = C_{15}H_{31}$ (*m/e* 537)
3e, 4e, $R^1 = R^2 = CH_3COO$; $R^3 = H$ (*m/e* 145)
3f, 4f, $R^1 = R^2 = CH_3COO$; $R^3 = C_{15}H_{31}$ (*m/e* 355)

6a, 7a, $R^1 = R^2 = C_{15}H_{31}COO$ (*m/e* 550)
6b, 7b, $R^1 = R^2 = C_{16}H_{33}O$ (*m/e* 536)

9a, 10a, $R^1 = R^2 = C_{15}H_{31}COO$ (*m/e* 552)
9b, 10b, $R^1 = R^2 = C_{16}H_{33}O$ (*m/e* 538)
9c, 10c, $R^1 = R^2 = CH_3COO$ (*m/e* 356)

SCHEME II



2a, $R^1 = C_{15}H_{31}COO$; $n = 2$ (*m/e* 538)
b, $R^1 = C_{15}H_{31}COO$; $n = 3$ (*m/e* 552)
c, $R^1 = C_{15}H_{31}COO$; $n = 4$ (*m/e* 566)
d, $R^1 = C_{15}H_{31}COO$; $n = 5$ (*m/e* 580)
e, $R^1 = C_{15}H_{31}COO$; $n = 6$ (*m/e* 594)
f, $R^1 = C_{16}H_{33}CH{=}CHO$; $n = 2$ (*m/e* 550)
g, $R^1 = C_{18}H_{31}O$; $n = 2$ (*m/e* 552)

5a, $R^2 = H$; $n = 2$ (*m/e* 73)
b, $R^2 = C_{15}H_{31}$; $n = 2$ (*m/e* 283)
c, $R^2 = H$; $n = 3$ (*m/e* 87)
d, $R^2 = C_{15}H_{31}$; $n = 3$ (*m/e* 297)
e, $R^2 = H$; $n = 4$ (*m/e* 101)
f, $R^2 = C_{15}H_{31}$; $n = 4$ (*m/e* 311)
g, $R^2 = H$; $n = 5$ (*m/e* 115)
h, $R^2 = C_{15}H_{31}$; $n = 5$ (*m/e* 325)
i, $R^2 = H$; $n = 6$ (*m/e* 129)
j, $R^2 = C_{15}H_{31}$; $n = 6$ (*m/e* 339)

8a, $n = 2$ (*m/e* 282)
b, $n = 3$ (*m/e* 296)
c, $n = 4$ (*m/e* 310)
d, $n = 5$ (*m/e* 324)
e, $n = 6$ (*m/e* 338)

11a, $n = 2$ (*m/e* 284)
b, $n = 3$ (*m/e* 298)
c, $n = 4$ (*m/e* 312)
d, $n = 5$ (*m/e* 326)

Cyclic ions of comparable structures must be expected from cyclic acetals, similar to those previously postulated for the fragments from aliphatic[18] and steroidal[19] ketals and acetals. Therefore, we synthesized model compounds and studied the fragmentation patterns and ions produced from these representative long-chain cyclic acetals.

Acetals **9–11** (Table II) show the expected parent ion peaks. The spectra display fewer ions, reflecting the exceptional stability afforded by $[M - C_{15}H_{31}]^+$ and $[M - H]^+$ (**3–5**). It appears reasonable to assume that formation of fragments **3–5** merely involves single-bond fission with charge retention in the ring system, leading to resonance-stabilized cyclic ion structures (Schemes I and II). Favored formation of such ions is indicative of the stability of such structures in general.

TABLE II

PROMINENT IONS IN THE MASS SPECTRA OF CYCLIC ACETALS DERIVED FROM HEXADECANAL[a]

	m/e (abundance) structure		
Cyclic acetal	M^+	$[M - H]^+$	$[M - C_{15}H_{31}]^+$
9a	552 (0.13)	551 (0.29) **3b**	*341* (33.26) **3a**
cis-**10a**	552 (0.21)	551 (0.48) **4b**	*341* (22.34) **4a**
trans-**10a**	552 (0.19)	551 (0.39) **4b**	*341* (22.27) **4a**
9b	538 (0.10)	537 (0.17) **3d**	*327* (18.56) **3c**
cis-**10b**	538 (0.15)	537 (0.26) **4d**	*327* (15.09) **4c**
trans-**10b**	538 (0.06)	537 (0.24) **4d**	*327* (14.61) **4c**
cis-**9c**	356 (0.07)	355 (0.25) **3f**	*145* (33.95) **3e**
trans-**9c**	356 (0.07)	355 (0.22) **3f**	*145* (38.36) **3e**
9c-d_1	357 (0.03)	355 (0.20) **3f**	*146* (47.36) **3e-d_1**
cis-**10c**	356 (0.12)	355 (0.44) **4f**	*145* (23.30) **4e**
cis-**10c-d_1**	357 (0.05)	355 (0.22) **4f**	*146* (19.96) **4e-d_1**
trans-**10c**	356 (0.09)	355 (0.29) **4f**	*145* (20.89) **4e**
trans-**10c-d_1**	357 (0.07)	355 (0.32) **4f**	*146* (28.16) **4e-d_1**
11a	284 (0.28)	283 (1.18) **5b**	*73* (65.00) **5a**
11a-d_1	285 (0.08)	283 (0.29) **5b**	*74* (57.79) **5a-d_1**
11a-d_4	288 (0.08)	287 (0.19) **5b-d_4**	*77* (30.37) **5a-d_4**
11b	298 (0.42)	297 (1.45) **5d**	*87* (45.29) **5c**
11b-d_1	299 (0.05)	297 (0.13) **5d**	*88* (20.15) **5c-d_1**
11c	312 (0.09)	311 (0.18) **5f**	*101* (39.20) **5e**
11c-d_1	313 (0.01)	311 (0.01) **5f**	102 (7.87) **5e-d_1**[b]
11d	326 (0.04)	325 (0.06) **5h**	*115* (16.22) **5g**

[a] Abundances in per cent of total ionization; see also ref 14. Molecular and ion structures are given in Schemes I and II. [b] Base peak *m/e 41* (10.37).

Prominent ions $[M - C_{15}H_{31}]^+$ from 2-pentadecyl-substituted cyclic acetals (**9–11**) give rise to the base peak in the spectra of the isomeric acyl- (**9a**, **10a**), alkyl- (**9b**, **10b**), and acetyl-substituted (**9c**, **10c**) glycerol acetals producing *m/e 341*, *327*, and *145*, respectively (Table II). For all three lipid classes formation of $[M - C_{15}H_{31}]^+$ bearing 1,3-dioxolane structures (**3a**, **3c**, **3e**) is favored over those having the 1,3-dioxane skeleton (**4a**, **4c**, **4e**). Cis dioxanes produce the ion in slightly greater abundance than do trans isomers, while for the isomeric dioxolanes the situation is reversed. The long-chain cyclic acetals of α,ω-diols (**11a–d**) display $[M - C_{15}H_{31}]^+$ (**5a**, **5c**, **5e**, **5g**) with significantly decreasing intensities as the ring

(18) R. A. Friedel and A. G. Sharkey, Jr., *Anal. Chem.*, **28**, 940 (1956); H. Audier, M. Fétizon, J.-C. Gramain, J. Schalbar, and B. Waegel, *Bull. Soc. Chim. Fr.*, 1880 (1964); R. E. Wolff, G. Wolff, and J. A. McCloskey, *Tetrahedron*, **22**, 3093 (1966); J. T. B. Marshall and D. H. Williams, *ibid.*, **23**, 321 (1967).

(19) G. von Mutzenbecher, Z. Pelah, D. H. Williams, H. Budzikiewicz, and C. Djerassi, *Steroids*, **2**, 475 (1963); H. Audier, A. Diara, M. de J. Durazo, M. Fétizon, P. Foy, and W. Vetter, *Bull. Soc. Chim. Fr.*, 2827 (1963); Z. Pelah, D. H. William, H. Budzikiewicz, and C. Djerassi, *J. Amer. Chem. Soc.*, **86**, 3722 (1964).

size increases (65–16%). Ions corresponding to $[M - C_{15}H_{31}]^+$ are not produced from the ester lipids **1** and **2**.

In contrast, ions $[M - H]^+$ from acetals **9–11** actually correspond to $[M - X]^+$ from the ester lipids (Schemes I and II). Ions $[M - H]^+$ are consistently more intense than the parent acetal ions. Specific C-2 deuteration in the ring of a number of representative acetals (**9c**, **10c**, **11a–c**) or perdeuteration of the alcoholic backbone (**11a**) demonstrated that in the formation of $[M - H]^+$ the hydrogen is predominantly lost from the ring C-2, not from the polyol or the alkyl chain (Table II). The isomeric acyl- (**9a**, **10a**), alkyl- (**9b**, **10b**), and acetyl-substituted (**9c**, **10c**) glycerol acetals produce $[M - H]^+$ at *m/e* 551 (**3b**, **4b**, corresponding to $[M - RCOO]^+$ from triglycerides), 537 (**3d**, **4d**, corresponding to $[M - RCOO]^+$ from alkyl diacyl glycerols), and 355, respectively. In contrast to loss of the long alkyl group, expulsion of H-2 from the molecular acetal ion is more favored for the 1,3-dioxanes than it is for the 1,3-dioxolanes, probably because fragmentation of the former involves loss of an axial hydrogen,[20,21] and it is more likely to occur with the cis isomers.

Ions $[M - H]^+$ from diol acetals **11a–d** are identical in composition with ions $[M - RCOO]^+$ produced from diol diesters **2a–d** (see Scheme II and Tables I and II). Hence, the question arises whether they are identical in structure as well. If these ions possess cyclic structures **5b**, **5d**, **5f**, and **5h** postulated in Scheme II, their stabilities are a function of ring size and should be expressed by similar ion-intensity patterns. Although the absolute intensities[14] of both ions differ by a factor of approximately 10, the relative intensity of $[M - H]^+$ as a function of the carbon number of the constituent diol (Figure 1, B) matches almost perfectly that found for $[M - RCOO]^+$ (Figure 1, A). Both show a maximum for the ions having the 1,3-dioxane skeleton, and both exhibit a sharp intensity decline for the ions of larger ring size. Hence, the cyclic structures formulated for $[M - X]^+$ from ester lipids **1** and **2** appear established.

Formation of ions $[M - X]^+$ from esters and ether esters probably takes place by a mechanism involving (a) fragmentation, *i.e.*, extrusion of an acyloxy, alk-1-enyloxy, or alkoxy group from the molecular ion, followed by (b) cyclization of a residual ester radical with the short-chain moiety. All relevant information obtained by specific deuterations in the alcohol moiety (Tables I and II) or at C-2 through C-6 of the acyl functions of triglycerides[5] is consistent with such a mechanism. Hence, the ease of initial cleavage is a contributing factor to the intensity of $[M - X]^+$, as is the stability of the cyclic ion structure. Abstraction of an alk-1-enyloxy group is favored over that of an acyloxy or alkoxy function, while the stability of $[M - X]^+$ is largely a function of ring size. The fragmentation pathways are summarized in Schemes I and II.

The cyclic structures of ions $[M - XH]^+$ from ester lipids cannot be deduced by the same reasoning as for ions $[M - X]^+$ because the corresponding ions are not produced from cyclic acetals. However, the general dependence of ion intensities upon diol carbon numbers in the spectra of diol diesters **2a–e**, as well as the results of deuteration studies (*vide infra*), strongly advocates structures such as **6–8** given in Schemes I and II.

Formation of ions $[M - XH]^+$ proceeds by a pathway independent of that leading to $[M - X]^+$. The fact that $[M - XH]^+$ contributes significantly to the total ion current only for loss of a fatty acid, not alk-1-enol or alkanol, gives credence to an activation mechanism involving hydrogen transfer to the acyloxy carbonyl prior to RCOOH elimination. Complete retention of deuterium in ions $[M - XH]^+$ from the respective esters of perdeuterated glycerol[17] or ethanediol (**2a**-d_4, see Table I) clearly excludes abstraction of hydrogen from the polyol moieties. To define more precisely the origin of the activated hydrogen, the spectra of a series of triglycerides specifically dideuterated in one of the methylene groups at C-2 through C-6 of all three acyl functions were reexamined.[5] In this series, the highest intensity of $[M - RCOOD]^+$ was clearly displayed by the tri-2,2-dideuterioacylglycerol,[22] lending additional support to structures **6–8** proposed in Schemes I and II.

Experimental Section

Low-resolution mass spectra were recorded using a Hitachi Perkin-Elmer instrument RMU-6D. Samples were introduced through the direct inlet system. The source temperature was approximately 250°, the ionizing energy was 70 eV, and the ionizing current was 80 μA. Simultaneous scanning of perfluorokerosene, which was introduced through the inlet for liquid samples, ensured accurate counting of peaks.[14] High-resolution mass spectra were recorded on CEC-21-110B and AEI MS-9 instruments.

All compounds used in the present study were pure as judged by adsorption tlc and/or glc. Triglycerides (**1a**) were purchased from The Hormel Institute Lipids Preparation Laboratory; the synthesis of triglycerides specifically dideuterated in one of the C-2 through C-6 methylene groups of all three acyl functions was previously reported.[5] Alk-1-enyldiacylglycerols (**1b**),[15] alkyldiacylglycerols (**1c**),[23] and dialkylacylglycerols (**1d**),[23] as well as diesters (**2a–e**),[24] alk-1-enyl ether esters (**2f**),[7] and alkyl ether esters (**2g**)[24] of diols, were synthesized as described previously. Long-chain cyclic acetals of glycerol (**9**, **10**) were prepared by acid-catalyzed condensation of hexadecanal and glycerol.[20] Individual stereoisomers were obtained by repeated fractionation of the glycerol acetal acetates (**9c**, **10c**) by adsorption tlc and/or preparative glc. $LiAlH_4$ reduction of the isomeric individual acetates afforded the corresponding hydroxy compounds, which served for the preparation of the alkoxy derivatives (**9b**,**10b**)[20] and for the synthesis of the long-chain esters (**9a**, **10a**) by standard acylation with hexadecanoyl chloride in benzene–pyridine medium. Characteristic data of the acylated glycerol acetals **9a**, and **10a** are as follows.

2-Pentadecyl-4-hexadecanoyloxymethyl-1,3-dioxolanes (9a) had mp 79–80°; R_f 0.39;[25] ir (CS_2, C_2Cl_4)[26] 1736 (s), 1418, 1387 (sh), 1368 (m), 1355 (sh), 1234, 1163 (m), 1141 (s), 1123 (s), 1047 (m),

(20) W. J. Baumann, *J. Org. Chem.*, **36**, 2743 (1971).

(21) W. J. Baumann, T. H. Madson, and B. J. Weseman, *J. Lipid Res.*, **13**, 640 (1972).

(22) Tri-2,2-dideuteriotetradecanoyl glycerol[5] produced $[M - RCOO]^+$ at *m/e* 499 (3.38). The intensity of $[M - RCOOD]^+$ at *m/e* 497 (1.07) was somewhat low, as can be expected for labile C-2 deuteriums.

(23) W. J. Baumann and H. K. Mangold, *Biochim. Biophys. Acta*, **116**, 570 (1966). W. J. Baumann and H. K. Mangold, *J. Org. Chem.*, **29**, 3055 (1964); **31**, 498 (1966).

(24) W. J. Baumann, H. H. O. Schmid, H. W. Ulshöfer, and H. K. Mangold, *Biochim. Biophys. Acta*, **144**, 355 (1967).

(25) Thin layer adsorption chromatography was done on layers of silica gel H (Merck), 0.3 mm thick, in tanks lined with filter paper, using hexane–Et_2O (90:10, v/v) as developing solvent.

(26) Infrared spectra were taken with a Perkin-Elmer Model 21 spectrophotometer. Carbon disulfide served as solvent, except in the ranges 2400–2000 and 1650–1400 cm^{-1}, where tetrachloroethylene was used. Relative intensities are given as s, strong; m, medium; sh, shoulder; weak bands are without designation. Bands associated with vibrations of the aliphatic chains are not listed.

990, 958 cm^{-1}. *Anal.* Calcd for $C_{35}H_{68}O_4$: C, 76.03; H, 12.40. Found:[27] C, 76.26; H, 12.76.

cis-**2-Pentadecyl-5-hexadecanoyloxy-1,3-dioxane** (**10a**) had mp 95–96°; R_f 0.32;[25] ir (CS_2, C_2Cl_4)[26] 1732 (s), 1408, 1340, 1244 (m), 1170, 1152 (s), 1104 (m), 1073 (m), 1008 (m), 950, 902, 791 cm^{-1}. *Anal.* Calcd for $C_{35}H_{68}O_4$: C, 76.03; H, 12.40. Found:[27] C, 76.30; H, 12.70.

trans-**2-Pentadecyl-5-hexadecanoyloxy-1,3-dioxane** (**10a**) had mp 87–89°; R_f 0.65;[25] ir (CS_2, C_2Cl_4)[26] 1740 (s), 1420, 1350 (sh), 1215, 1150 (s), 1115 (m), 1095 (sh), 1075 (sh), 1043 (m), 960, 900 cm^{-1}. *Anal.* Calcd for $C_{35}H_{68}O_4$: C, 76.03; H, 12.40. Found:[27] C, 75.90; H, 12.63.

Cyclic diol acetals **11a–d** were prepared by acid-catalyzed condensation[28] of the corresponding diols with hexadecanal followed by tlc purification with toluene as developing solvent.

(27) Elemental analyses were by I. Beetz, Mikroanalytisches Laboratorium, Kronach, Germany.

(28) P. V. Rao, S. Ramachandran, and D. G. Cornwell, *J. Lipid Res.*, **8**, 380 (1967).

Acknowledgment.—The authors are indebted to Drs. K. Biemann and C. E. Hignite, Massachusetts Institute of Technology, and to Dr. W. E. Baitinger, Purdue University, for recording high-resolution mass spectra.

Registry No.—**1a**, 555-44-2; **1b**, 41562-98-5; **1c**, 41562-99-6; **1d**, 6110-59-4; **2a**, 624-03-3; **2a-d_4**, 34083-13-1; **2b**, 818-21-3; **2c**, 26719-63-1; **2d**, 26933-79-9; **2e**, 23130-50-9; **2f**, 34083-10-8; **2f-d_4**, 41563-08-0; **2g**, 29899-13-6; **2g-d_4**, 41563-10-4; **9a**, 41563-11-5; **9b**, 41563-12-6; *cis*-**9c**, 30889-29-3; *trans*-**9c**, 30889-32-8; **9c-d_1**, 41563-15-9; *cis*-**10a**, 41563-16-0; *trans*-**10a**, 41563-17-1; *cis*-**10b**, 34298-21-0; *trans*-**10b**, 34315-34-9; *cis*-**10c**, 30889-23-7; *cis*-**10c-d_1**, 41563-21-7; *trans*-**10c**, 30889-26-0; *trans*-**10c-d_1**, 41563-23-9; **11a**, 4360-57-0; **11a-d_1**, 41563-25-1; **11a-d_4**, 41563-26-2; **11b**, 17352-27-1; **11b-d_1**, 41563-28-4; **11c**, 41563-29-5; **11c-d_1**, 41563-30-8; **11d**, 41583-11-3.

Phenacyl Photosensitive Blocking Groups

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The *p*-methoxyphenacyl group and α-methylphenacyl group have been found useful photosensitive protecting groups for the carboxyl function. Both types of esters are cleavable in ethanol or dioxane solution at 20° by uv light. The reaction has been applied to esters of N-protected alanine, glycine, phenylalanine, tryptophane, glycylglycine, and benzylaspartylserine and to benzoic acid.

Most useful protecting groups are removed by common chemical reactions. In principle, however, it should be possible to design protecting groups which could be removed by photolysis. In accord with the progress of organic photochemistry, several photosensitive blocking groups have been designed. The advantage of photosensitive blocking groups is that they can be removed under completely neutral and mild conditions.

The first photochemical removal of a blocking group was observed in the photolysis of carbobenzoxyglycine.[1] The irradiation of an aqueous solution of the sodium salt of carbobenzoxyglycine with the 2537-Å mercury line gave a small amount of glycine along with a mixture of other products.

$$PhCH_2OCONHCH_2COONa \xrightarrow{h\nu} H_2NCH_2COONa + \text{mixture}$$

The use of *o*-nitrobenzyl derivatives as photosensitive blocking reagents for amino and carboxyl functions has been reported.[2,3] Irradiation of these derivatives at wavelengths longer than 3200 Å cleaves the protecting group without affecting light-sensitive amino acids.

The potential of certain aromatic azides as photosensitive blocking groups has also been explored.[4] The photolysis of alkyl or acyl derivatives of β-(*o*-azidophenyl)ethyl alcohol yields indole and the corresponding alcohol or acid. This reaction is interesting as a photocyclization reaction. However, since the yield is low, it is not attractive as a photoremoval reaction of a protecting group.

Benzoin esters and other desyl compounds yield 2-phenylbenzofuran upon irradiation with uv light.[5]

A preliminary investigation of the application of this furanization reaction in the unmasking of carboxylic acid esters of appropriately substituted benzoins has been reported.[6] The irradiation of the benzoin derivatives of phthaloylglycine by uv light at 3200 Å formed phthaloylglycine and the corresponding furan derivatives.

These photosensitive blocking groups are all unique and interesting. However they are somewhat complicated to use practically in syntheses, and are far from being widely applicable protecting groups. Since the search for a photosensitive blocking group has just begun, more practical and simple blocking groups can be expected.

Discussion

The phenacyl group has low-lying excited states because of the interaction of the electrons between the carbonyl group and the phenyl ring. Therefore the photolysis of substituted phenacyl esters was first attempted. When *p*-methoxyphenacyl benzoate was irradiated in benzene, no observable reaction occurred and starting material was recovered. But when *p*-methoxyphenacyl benzoate was irradiated in dioxane with a Pyrex filter, the ester cleavage reaction occurred to give benzoic acid in good yield. Encouraged by this observation the photolysis of phenacyl esters was investigated in considerable detail.

(1) J. A. Barltrop and P. Schofield, *Tetrahedron Lett.*, 697 (1962).

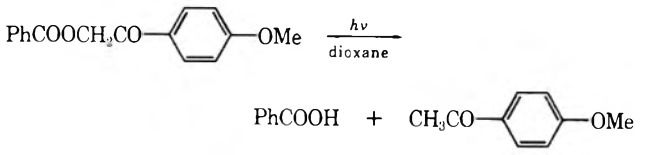
(2) J. A. Barltrop, P. J. Plant, and P. Schofield, *Chem. Commun.*, 822 (1966).

(3) A. Patchornik, B. Amit, and R. B. Woodward, *J. Amer. Chem. Soc.*, **92**, 6333 (1970).

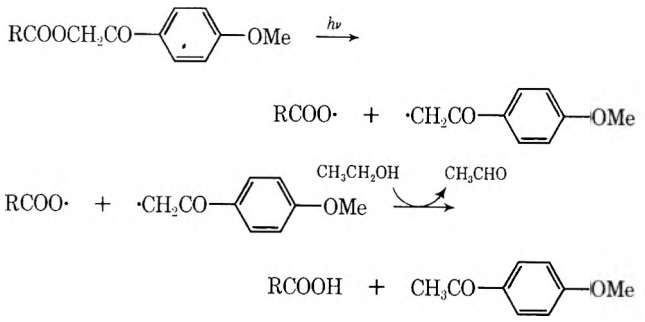
(4) D. H. R. Barton, P. G. Sammes, and G. G. Weingarten, *J. Chem. Soc. C*, 721 (1971).

(5) J. C. Sheehan and R. M. Wilson, *J. Amer. Chem. Soc.*, **86**, 5277 (1964).

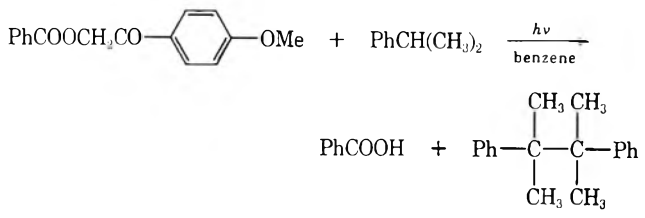
(6) J. C. Sheehan, R. M. Wilson, and A. W. Oxford, *J. Amer. Chem. Soc.*, **93**, 7222 (1971).



In the photocleavage reaction of a phenacyl ester, the other product is acetophenone, which is obtained in good yield. Dioxane serves as a hydrogen donor. Further study showed that ethanol is a better donor, provided that the phenacyl ester is soluble. Ethanol presumably is dehydrogenated to acetaldehyde as the reaction proceeds.[7] The mechanism is considered to be a simple radical scission of the carbon–oxygen bond since in some cases partial decarboxylation was observed.



When a small amount of water was added to the solution, the yield of carboxylic acid was decreased. Photocleavage of phenacyl benzoate also occurred with cumene in benzene to give benzoic acid and 2,3-dimethyl-2,3-diphenylbutane. Cumene is a typical hydrogen radical donor.



These phenomena support the concept of a radical scission.

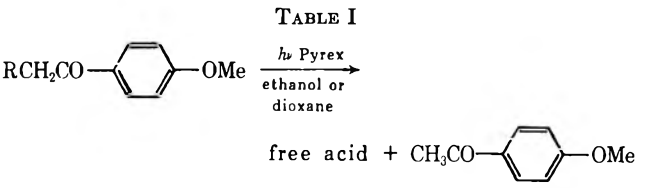
When the photocleavage reaction was carried out in 1 *M* benzophenone or naphthalene in dioxane, the reaction was quenched completely. Benzophenone and naphthalene can quench excited triplet states when their lifetime is longer than 10^{-10} sec.[6] This is evidence that the reaction proceeds through a long-lived triplet state, having a lifetime longer than 10^{-10} sec.

Photolysis of *p*-Methoxyphenacyl Esters.—The phenacyl photocleavage reaction was applied to many blocked amino acids and peptides. The results are summarized in Table I. All these reactions were carried out below room temperature at concentrations of 5×10^{-3}–10^{-2} *M* with a Pyrex filter. Pyrex filters pass uv light of 313 mμ and greater. The reaction is complete in 6 hr in ethanol, and in 11–17 hr in dioxane.

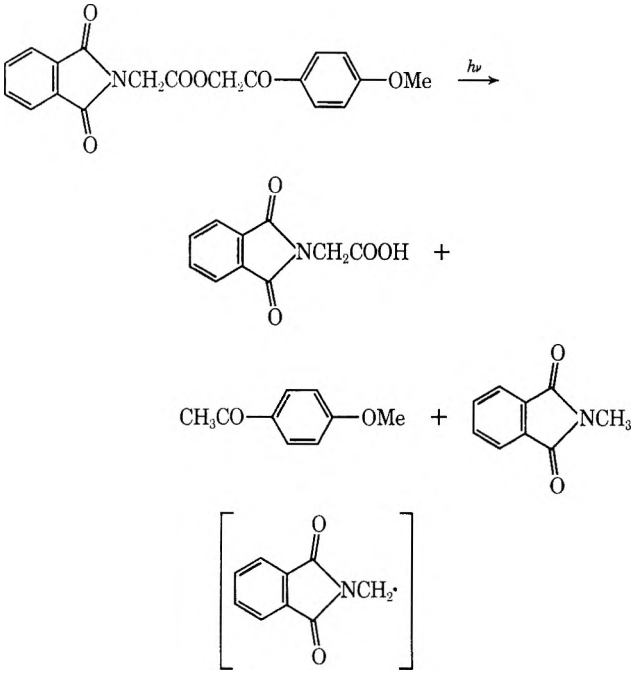
As listed in Table I, under the conditions used for the cleavage, the carbobenzoxy and *tert*-butoxycarbonyl groups are completely stable, although the carbobenzoxy group is sensitive to ultraviolet light of shorter wavelength.[1] However, when phthaloylglycine phenacyl ester was irradiated for 17 hr, partial decarboxylation occurred to give *N*-methylphthalimide. This

(7) R. A. Finnegan and J. A. Matson, *J. Amer. Chem. Soc.*, **94**, 4780 (1972).

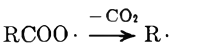
TABLE I



Registry no.	R	Solvent	Irradiation time, hr	Yield of RCOOH, %
41499-11-0	PhCOO	Dioxane	11	78
	PhCOO	Dioxane	17	81
	PhCOO	Ethanol	6	96
41476-77-1	Boc-L-Ala	Dioxane	17	82
	Boc-L-Ala	Ethanol	6	93
41499-12-1	Boc-Gly	Ethanol	6	94
41476-78-2	Boc-L-Phe	Dioxane	17	89
41476-79-3	Z-D, L-Ala	Dioxane	6	84
41558-28-5	Phthaloyl-Gly	Dioxane	17	80
41498-13-2	Tri-Gly	Dioxane	17	58
41476-80-6	Z-L-Trp	Ethanol	4	33
41499-14-3	Z-Gly-Gly	Ethanol	5.5	77
41476-81-7	Z-L-Asp-OBz ⌐L-Ser	Dioxane	9	49



may occur because the phthalimide methylene radical is stabilized by conjugation. When the alkyl radical R· is very stable, partial decarboxylation becomes more likely.



The *N*-trityl group was unstable to uv irradiation to some extent. In the photocleavage reaction of carbobenzoxyglycylglycine phenacyl ester, the peptide bonds were shown to be stable under the reaction conditions. The more complex dipeptide, carbobenzoxy-L-asparagyl-L-serine, was also examined, and gave the desired product in 49% yield. The phenacyl ester of the most photosensitive amino acid, tryptophane, gave only 30% yield after 4-hr irradiation.

The substitution of the phenyl ring of the phenacyl group by electron-donating groups may lower the stability of the derivatives toward acid. Therefore the stability of *p*-methoxyphenacyl ester was examined in trifluoroacetic acid and in 33% hydrogen bromide in acetic acid. It was shown that *p*-methoxyphenacyl acetate was stable under these conditions.

α-Methylphenacyl Blocking Group.—*p*-Methoxyphenacyl esters are more photoreactive than unsubstituted phenacyl esters. One reason could be that the methoxy substitution causes a bathochromic shift and requires radiation of lower energy. The other reason could be that the intermediate radical is stabilized by the electron-donating group.

The α-methylphenacyl blocking group was designed and investigated in accord with the idea of radical stabilization. The results of the photocleavage reactions of α-methylphenacyl esters are summarized in Table II. The treatment is the same as for *p*-

TABLE II

$$RCH(CH_3)COPh \xrightarrow[\text{dioxane or ethanol}]{h\nu} \text{free acid} + CH_3CH_2COPh$$

Registry no.	R	Solvent	Time, hr	Yield of RCOOH, %
1030-23-5	PhCOO	Dioxane	6	78.2
	PhCOO	Ethanol	6	87.4
41499-16-5	Boc-Gly	Ethanol	6	87.3
41476-82-8	Boc-L-Ala	Dioxane	6	95.7
	Boc-L-Ala	Ethanol	6	93.3
41476-83-9	Boc-L-Phe	Dioxane	6	95.6
	Boc-L-Phe	Ethanol	6	85.7
41499-17-6	Phthaloyl-Gly	Ethanol	6	70.6

methoxyphenacyl esters. The α-methylphenacyl group was as reactive as the *p*-methoxyphenacyl group. The cleavage reaction is complete in 6 hr in dioxane. For the α-methylphenacyl blocking group, dioxane seems to be a better solvent than ethanol. The mechanism of the reaction presumably is the same as that of *p*-methoxyphenacyl esters. The coproduct, propiophenone, is obtained in good yield. In the case of phthaloylglycine phenacyl ester, the yield is low because of partial decarboxylation of the product.

Experimental Section

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were recorded on a Hilger-Watts H1200 Infragraph. The nmr spectra were recorded on a Varian T-60. Microanalyses were supplied by Hiroko Hino, Institute of Applied Microbiology, University of Tokyo, and Mrs. Nancy Alvord, MIT. Thin layer chromatography was performed on Baker-Flex silica gel 1B-F plates.

Photolysis Apparatus and Procedures.—The light source was a 450-W Hanovia mercury immersion lamp. The reactions were carried out in a Hanovia no. 19434 quartz immersion well fitted with a Pyrex 7740 absorption sleeve. The apparatus was flushed with nitrogen which had been purified using a sodium anthraquinone-β-sulfonate solution, a solution of sodium hydrosulfite in aqueous potassium hydroxide, and a saturated lead acetate solution.[8]

Photolysis of *p*-Methoxyphenacyl Benzoate. A. In Dioxane.—A solution of 1.20 g (4.45 mmol) of *p*-methoxyphenacyl benzoate in 300 ml of dioxane was irradiated for 17 hr. After the removal of the solvent under reduced pressure, 60 ml of ethyl acetate was added. This solution was extracted with 1 *N* potassium carbonate and the extract was acidified with 2 *N* hydrochloric acid. The product was extracted into ether and the organic layer was dried with anhydrous magnesium sulfate and evaporated to give 0.44 g (81%) of benzoic acid. The identity of the product was confirmed by mixture melting point and comparison of ir spectra. The ethyl acetate solution after the extraction was dried with anhydrous sodium sulfate and evaporated. The residue was chromatographed on 55 g of Florisil (100–200 mesh) using cyclohexane–ethyl acetate (4:1) to give 0.45 g (73%) of *p*-methoxyacetophenone: mp 33–36°; ir ($CHCl_3$) 1670 cm^{-1}; nmr ($CDCl_3$) δ 8.1 (d, 2 H), 7.0 (d, 2 H), 3.9 (s, 3 H), 2.6 (s, 3 H); tlc R_f 0.39 [cyclohexane–EtOAc (4:1)].

B. In Ethanol.—A solution of 1.20 g (4.45 mmol) of *p*-methoxyphenacyl benzoate in 300 ml of ethanol was irradiated for 6 hr. The solution was treated as already described to give 0.52 g (96%) of benzoic acid and 0.38 g (62%) of *p*-methoxyacetophenone.

Photolysis of *p*-Methoxyphenacyl Benzoate with Cumene.—A solution of 0.70 g (2.6 mmol) of *p*-methoxyphenacyl benzoate in 100 ml of cumene and 200 ml of benzene was irradiated for 17 hr. The solution was concentrated under reduced pressure to 150 ml and extracted with 1 *N* aqueous potassium carbonate. Upon acidification of the alkaline extract with 2 *N* hydrochloric acid, the product was extracted with ether. The ether solution was dried with anhydrous magnesium sulfate. After the removal of ether, 0.218 g (69.0%) of benzoic acid was obtained.

***p*-Methoxyphenacyl Benzoate.**—A solution of 1.22 g (0.01 mol) of benzoic acid, 1.01 g (0.01 mol) of triethylamine, and 2.29 g (0.01 mol) of *p*-methoxyphenacyl bromide in 20 ml of dimethylformamide was refrigerated for 24 hr. The mixture was triturated with 140 ml of ice water and the resulting precipitate was filtered and dried. This material was suspended in 80 ml of petroleum ether (bp 40–60°) and stirred for 5 min. The crude product was filtered and recrystallized from ethanol to give 60% colorless needles: mp 108°; ir ($CHCl_3$) 1732, 1700 cm^{-1}; nmr ($CDCl_3$) δ 8.2–6.8 (m, 9 H), 5.5 (s, 2 H), 3.8 (s, 3 H). *Anal.* Calcd for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 71.16; H, 5.18.

***p*-Methoxyphenacyl Esters of N-Blocked Amino Acids.**—The product was prepared in the same way as described for *p*-methoxyphenacyl benzoate.

p-Methoxyphenacyl ester of *tert*-butoxycarbonyl-L-alanine had mp 137°; 71%; ir ($CHCl_3$) 3480, 1760, 1715 cm^{-1}. *Anal.* Calcd for $C_{17}H_{23}NO_6$: C, 60.52; H, 6.87; N, 4.16. Found: C, 60.59; H, 6.78; N, 4.27.

p-Methoxyphenacyl ester of carbobenzoxy-DL-alanine had mp 133°; 85%; ir ($CHCl_3$) 3440, 1755, 1725, 1700 cm^{-1}. *Anal.* Calcd for $C_{20}H_{21}NO_6$: C, 64.68; H, 5.70; N, 3.77. Found: C, 64.56; H, 5.71; N, 3.75.

p-Methoxyphenacyl ester of *tert*-butoxycarbonyl-L-phenylalanine had mp 110°; 80%; ir ($CHCl_3$) 3420, 1750, 1700 cm^{-1}. *Anal.* Calcd for $C_{23}H_{27}NO_6$: C, 66.81; H, 6.58; N, 3.39. Found: C, 67.14; H, 6.52; N, 3.45.

p-Methoxyphenacyl ester of *tert*-butoxycarbonylglycine had mp 73°; yield 65%; ir (CCl_4) 3470, 1765, 1730, 1705 cm^{-1}. *Anal.* Calcd for $C_{16}H_{21}NO_6$: C, 59.43; H, 6.55; N, 4.33. Found: C, 59.04; H, 6.49; N, 4.28.

p-Methoxyphenacyl ester of tritylglycine had mp 169°; 73%; ir ($CHCl_3$) 3450, 1750, 1695 cm^{-1}. *Anal.* Calcd for $C_{30}H_{27}NO_4$: C, 77.40; H, 5.85; N, 3.01. Found: C, 76.35; H, 5.72; N, 2.96.

p-Methoxyphenacyl ester of carbobenzoxy-L-tryptophan had mp 119°; 82%; ir ($CHCl_3$) 3480, 1760, 1720, 1700 cm^{-1}. *Anal.* Calcd for $C_{28}H_{26}N_2O_6$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.12; H, 5.29; N, 5.65.

p-Methoxyphenacyl ester of phthaloylglycine had mp 87°; 30%; ir ($CHCl_3$) 1770, 1730, 1700, 1600 cm^{-1}. *Anal.* Calcd for $C_{19}H_{15}NO_6$: C, 64.64; H, 4.28. Found: C, 64.83; H, 4.34.

***p*-Methoxyphenacyl Esters of N-Blocked Dipeptides.**—The products were prepared from the corresponding N-blocked dipeptides in the same way as described for *p*-methoxyphenacyl *tert*-butoxycarbonylglycinate.

Carbobenzoxyglycylglycine *p*-methoxyphenacyl ester had mp 136–138°; 67%; ir ($CHCl_3$) 3410, 1755, 1725, 1695 cm^{-1}. *Anal.* Calcd for $C_{21}H_{22}N_2O_7$: C, 60.86; H, 5.35; N, 6.76. Found: C, 60.73; H, 5.37; N, 6.83.

(8) L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath, Boston, Mass., 1957, p 299.

Carbobenzoxy-β-benzyl-L-aspartyl-L-serine *p*-methoxyphenacyl ester had mp 145–150°; 75%; ir ($CHCl_3$) 3400, 1755, 1725, 1680 cm^{-1}. *Anal.* Calcd for $C_{31}H_{32}N_2O_{10}$: C, 62.83; H, 5.44; N, 4.73. Found: C, 62.98; H, 5.36; N, 4.65.

Photolysis of *p*-Methoxyphenacyl Esters of N-Blocked Amino Acids and Peptides.—These photocleavage reactions were carried out in the same way as described for *p*-methoxyphenacyl benzoate with solvents and irradiation times as indicated in Table I.

α-Methylphenacyl Esters.—The products were prepared from α-methylphenacyl bromide and the corresponding carboxylic acid in the same way as described for *p*-methoxyphenacyl benzoate.

α-Methylphenacyl benzoate had mp 108°; 76%; ir (CCl_4) 1730, 1705 cm^{-1}. *Anal.* Calcd for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.25; H, 5.39.

α-Methylphenacyl phthaloylglycinate had mp 86°; 76%; ir (CCl_4) 1770, 1740, 1710 cm^{-1}. *Anal.* Calcd for $C_{19}H_{15}NO_5$: C, 67.65; H, 4.48; N, 4.15. Found: C, 67.53; H, 4.49; N, 4.13.

α-Methylphenacyl *tert*-butoxycarbonylglycinate had mp 87°; 91%; ir (CCl_4) 3460, 1760, 1725, 1705 cm^{-1}. *Anal.* Calcd for $C_{16}H_{21}NO_5$: C, 62.52; H, 6.88; N, 4.56. Found: C, 62.48; H, 6.68; N, 4.49.

α-Methylphenacyl ester of *tert*-butoxycarbonyl-L-alanine was recrystallized from petroleum ether: mp 79–83°; 62%; ir (CCl_4) 3450, 1750, 1720, 1710 cm^{-1}. *Anal.* Calcd for $C_{17}H_{23}NO_5$: C, 63.53; H, 7.21; N, 4.36. Found: C, 63.28; H, 7.00; N, 4.72.

α-Methylphenacyl ester of *tert*-butoxycarbonyl-L-phenylalanine was an oil: 80%; ir (CCl_4) 1750, 1725, 1700 cm^{-1}.

Photolysis of α-Methylphenacyl Benzoate.—A solution of 1.06 g (4.0 mmol) of α-methylphenacyl benzoate in 300 ml of dioxane was irradiated for 6 hr at 12°. After removal of the solvent under reduced pressure, 60 ml of ethyl acetate was added. The solution was extracted with 1 *N* aqueous potassium carbonate. Upon acidification of the alkaline extract with 2 *N* hydrochloric acid, the product was extracted with ether. After the removal of ether, the colorless solid was triturated in petroleum ether. Filtration gave 0.382 g (78.2%) of benzoic acid, mp 102°.

The ethyl acetate solution after the extraction was dried and evaporated. The residue was chromatographed on 50 g of Florisil (100–200 mesh) using cyclohexane–ethyl acetate (4:1) to give 0.190 g (35.4%) of propiophenone: ir (CCl_4) 1690 cm^{-1}; nmr δ 8.2–7.9 (m, 2 H), 7.7–7.3 (m, 3 H), 3.1 (q, 2 H), 1.3 (t, 3 H); tlc R_f 0.73 (cyclohexane–EtOAc (4:1)].

The other reactions of α-methylphenacyl esters were similarly conducted with solvents as indicated in Table II.

Quenching Experiments of *p*-Methoxyphenacyl Benzoate Photocleavage Reactions.—A solution of 1.2 g (4.45 mmol) of *p*-methoxyphenacyl benzoate and 38.4 g (0.30 m) of naphthalene in 300 ml of dioxane was irradiated for 17 hr. After the removal of the solvent, 200 ml of benzene was added. The solution was extracted with 1 *N* aqueous potassium carbonate. Upon acidification of the alkaline extract with 2 *N* hydrochloric acid, the solution was extracted with ether. The thin layer chromatography of the ether solution using cyclohexane–ethyl acetate (4:1) showed no product. After the removal of ether, no benzoic acid was obtained.

Acknowledgment.—We are grateful to the Sloan Basic Research Fund for support of this work.

Registry No.—*p*-Methoxyacetophenone, 100-06-1; propiophenone, 93-55-0; benzoic acid, 65-85-0; triethylamine, 121-44-8; *p*-methoxyphenacyl bromide, 2632-13-5.

Reaction Kinetics of 3-Thenoyl Chloride with Anilines in Benzene

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The rate of the reaction of 3-thenoyl chloride with substituted anilines has been measured in benzene at different temperatures. The reaction follows a second-order kinetics. The activation parameters and the slopes of the Hammett (−3.21) and Brønsted (1.08) plots are similar to those of the reactions of benzoyl and 2-thenoyl chlorides with aniline. In the 3-thenoyl chloride reaction the effect of the substituents in the aniline is to modify the activation energy, log *A* remaining approximately constant. The reaction mechanism of the 3-thenoyl chloride with aniline is the same as for the reactions of benzoyl and 2-thenoyl chlorides. 3-Thenoyl chloride, however, does not react as expected from the pK_a of 3-thenoic acid. The Tommila equation points out that the carbonyl carbon atom of 3-thenoyl chloride is less electrophilic than that of benzoyl chloride but more electrophilic than that of 2-thenoyl chloride.

The Hammett relation is valid for correlating the reaction data of 3-thenoic and 3-furoic acid esters.[1]

Oae and Price[2] found that the ethyl ester of 3-thenoic acid saponified as expected from the pK_a of 3-thenoic acid. Imoto and coworkers[3] studied the hydrolysis of thiophene and furancarboxylic acid esters and they found a linear relationship between the hydrolysis rates and the dissociation constants for the 3-carboxylic acids; the 2-analogs, instead, deviated from the straight line. The same results were obtained recently by Ten Thije and Janssen.[4]

In a previous paper we reported the rates of the reaction of 2-thenoyl chloride with various substituted anilines in benzene solution in order to investigate whether 2-thenoyl chloride, in comparison with benzoyl chloride, reacted as expected from the pK_a of 2-thenoic acid.[5] We found that 2-thenoyl chloride reacted more slowly than benzoyl chloride, although 2-thenoic acid was stronger than benzoic acid. The Tommila equation pointed out that the carbonyl carbon atom of 2-thenoyl chloride was less positively charged than that of benzoyl chloride.

Recently we reported the data relating to the reactions of 3-thenoyl 2- and 3-furoyl chlorides with aniline in benzene.[6] We found that only 2-furoyl chloride reacted as expected from the pK_a of 2-furoic acid. The reactivity decreased from benzoyl to 3-thenoyl, 3-furoyl, and 2-thenoyl chlorides, while the order of the acidity constants was 2-thenoic acid > 3-furoic acid > 3-thenoic acid > benzoic acid.

In the present paper we report a study of the reaction

(1) S. Gronowitz, *Advan. Heterocycl. Chem.*, **1**, 80 (1963).

(2) S. Oae and C. C. Price, *J. Amer. Chem. Soc.*, **79**, 2547 (1957).

(3) Y. Otsuji, Y. Koda, M. Kubo, M. Furukawa, and E. Imoto, *Nippon Kagaku Zasshi*, **80**, 1293 (1959).

(4) P. A. Ten Thije and M. J. Janssen, *Recl. Trav. Chim. Pays-Bas*, **84**, 1169 (1965).

(5) A. Arcoria, S. Fisichella, G. Scarlata, and D. Sciotto, *J. Org. Chem.*, **38**, 32 (1973).

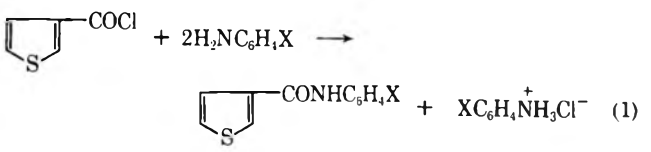
(6) A. Arcoria and S. Fisichella, *Gazz. Chim. Ital.*, in press.

TABLE I
SECOND-ORDER RATE CONSTANTS FOR THE REACTION OF 3-THENOYL CHLORIDE WITH META- AND PARA-SUBSTITUTED ANILINES IN BENZENE

Registry no.	No.	Substituent	pK_a[5]	$k_2 \times 10^2$, l. mol^{-1} sec^{-1} 10°	15°	17.5°	20°	25°	35°	45°
62-53-3	1	H	4.58		2.71			4.38	6.63	
108-44-1	2	*m*-CH_3	4.69		4.86		5.84	7.32	10.6	
106-49-0	3	*p*-CH_3	5.12	9.98		13.0		18.1	25.7	
536-90-3	4	*m*-CH_3O	4.20		1.96		2.49	3.13	4.83	
108-42-9	5	*m*-Cl	3.34					0.257	0.450	0.675
106-47-8	6	*p*-Cl	3.98					1.03	1.61	2.48
99-09-2	7	*m*-NO_2	2.50					0.0272	0.0456	0.0752

between 3-thenoyl chloride and anilines in benzene to give further information about this reaction.

The reaction of the acid chloride with aniline takes place quantitatively according to stoichiometric eq 1.



$$+ 2H_2NC_6H_4X \longrightarrow$$

$$+ XC_6H_4\overset{+}{N}H_3Cl^- \quad (1)$$

X = H, *m*-CH_3, *p*-CH_3, *m*-CH_3O, *m*-Cl, *p*-Cl, *m*-NO_2

The reaction was followed kinetically, as previously described,[5,7] by filtering the completely insoluble aniline hydrochloride, dissolving it in water, and estimating the chloride ion by mercuric nitrate, using a mixture of diphenylcarbazone and bromophenol blue as indicator (see Experimental Section).

We found that the reaction of 3-thenoyl chloride with anilines follows a second-order kinetics. The reaction mechanism of 3-thenoyl chloride with aniline was the same as for benzoylation reaction. The differences in rate were due only to changes in activation energy, log *A* remaining approximately constant.

The 3-thenoyl chloride reaction was slower than that of benzoyl chloride, but it was faster than that of 2-thenoyl chloride. The Tommila equation showed that the carbonyl carbon atom of 3-thenoyl chloride was less electrophilic than that of 2-benzoyl chloride, but more electrophilic than that of 2-thenoyl chloride.

Results and Discussion

The reaction between 3-thenoyl chloride and anilines in benzene took place quantitatively according to eq 1; no other products were observed.

In all cases the compounds gave excellent second-order kinetics. The second-order rate constants were calculated with constant molar ratio of the reactants (1:2): 1 mol of acid chloride with 2 mol of aniline, in agreement with eq 1.

The rate constants at different temperatures, listed in Table I, show that electron-donating substituents accelerate and electron-withdrawing groups retard the reaction.

A comparison of these results with those of the benzoyl[8-10] and 2-thenoyl chlorides[5] reactions shows that 3-thenoyl chloride does not react as expected from the pK_a of 3-thenoic acid. In fact, 3-thenoyl chloride ($k_{25} \times 10^2 = 4.38$ l. mol^{-1} sec^{-1}) is less reactive than benzoyl chloride ($k_{25} \times 10^2 = 6.27$ l. mol^{-1} sec^{-1})[10] but it is more reactive than 2-thenoyl chloride ($K_{25} \times 10^2 = 2.52$ l. mol^{-1} sec^{-1})[5], while the order of the acidity constants of the corresponding acid in aqueous solution is 2-thenoic acid ($pK_a = 3.53$) > 3-thenoic acid ($pK_a = 4.10$) > benzoic acid ($pK_a = 4.21$).[11]

The activation parameters, listed in Table II, were calculated in the usual way[5,7] from a least-squares treatment of log *k* against T^{-1} and they show a regular variation with the substituent in the aniline.

TABLE II
ACTIVATION PARAMETERS FOR THE REACTION RATES IN TABLE I

Substituent	E_A, kcal mol^{-1}	ΔS^* at 25°, cal mol^{-1} °K^{-1}	Log *A*
H	7.49	−41.6	4.12
m-CH_3	6.94	−42.4	3.95
p-CH_3	6.64	−41.6	4.12
m-CH_3O	7.94	−40.7	4.32
m-Cl	9.11	−41.6	4.09
p-Cl	8.27	−41.8	4.08
m-NO_2	10.24	−42.4	3.95

The results show that in the 3-thenoyl chloride reaction, as for that of benzoylation,[11] the effect of the substituents in the aniline is to modify the activation energy, log *A* remaining approximately constant. In Figure 1 log *k* at 25° is plotted against the experimental values of E_A. All the points lie close to the theoretical line of slope $-2.303\,RT$ drawn through the point representing the unsubstituted aniline, showing that the frequency factor is very nearly constant. According to Hinshelwood and coworkers[12,13] the substituent effects are consistent with the assumption that variation of the repulsion between the reactants is the principal factor determining the changes in activation energy.

The large negative entropies of activation are similar to those found for the reactions of benzoyl[10] and 2-thenoyl[5] chlorides with anilines and they are as expected by bimolecular reactions with a highly polar transition state.[14]

The values of the rate constants of the reaction of 3-thenoyl chloride with anilines show that the reaction rate depends on the electron density on the nitrogen atom. Since the basicity also depends on the electron density, one should expect a correlation between rate and basicity of the anilines. It is interesting to

(7) G. Alberghina, A. Arcoria, S. Fisichella, and G. Scarlata, *Gazz. Chim. Ital.*, in press.
(8) E. G. Williams and C. N. Hinshelwood, *J. Chem. Soc.*, 1079 (1934).
(9) F. J. Stubbs and C. N. Hinshelwood, *J. Chem. Soc.*, 71 (1949).
(10) E. Tommila and T. Vihavainen, *Acta Chem. Scand.*, **22**, 3224 (1968).
(11) G. Marino, *Advan. Heterocycl. Chem.*, **13**, 242 (1971).
(12) H. S. Venkataraman and C. Hinshelwood, *J. Chem. Soc.*, 4977 (1960).
(13) H. S. Venkataraman and C. Hinshelwood, *J. Chem. Soc.*, 4986 (1960).
(14) A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed, Wiley, New York, N. Y., 1961, Chapter 7.

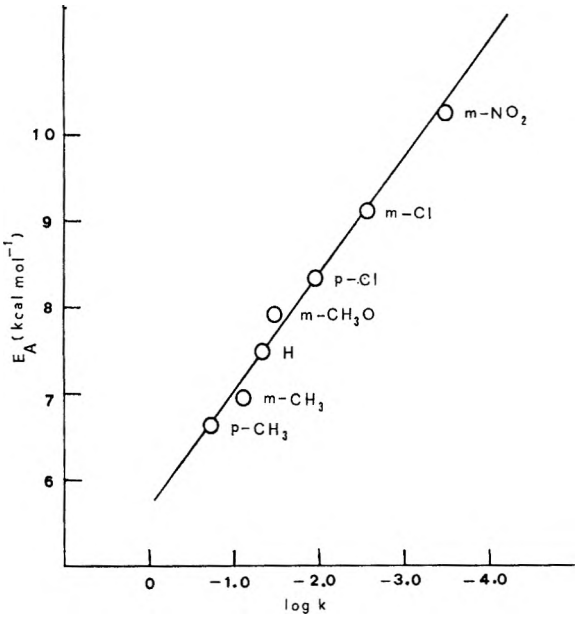


Figure 1.—Plot of the experimental values of E_A against log $k_{25°}$ for the reaction of 3-thenoyl chloride with substituted anilines in benzene. The line is of theoretical slope $-2.303\,RT$.

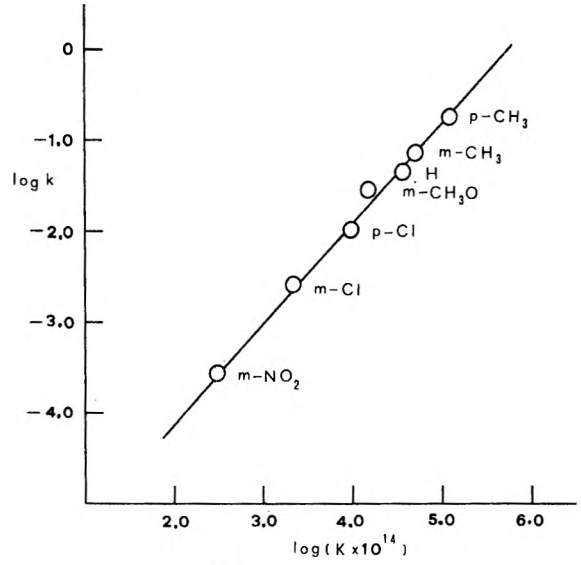


Figure 2.—Plot of log $k_{25°}$ for the reaction of 3-thenoyl chloride with substituted anilines in benzene against the logarithm of their dissociation constants in water at 25° (Brønsted plot).

observe that, as for the 2-thenoyl chloride reaction, for 3-thenoyl chloride was also found a linear relationship between log k at 25° and the pK_a at 25° in water of the corresponding protonated aniline[15] (Figure 2). The sign of the Brønsted slope is as expected for a nucleophilic substitution and its value (1.08) is similar to those found for the benzoylation (0.97) and 2-thenoyl chloride reactions[5] (1.14), but, as previously noted, we cannot discuss the value of the Brønsted coefficient, since the reaction rates were measured in benzene and the pK_a values in water.

The plot of log k at 25° against Hammett's σ constants is linear with a slope of -3.21 (Figure 3). This value is comparable to those found for the reactions of 2-thenoyl[5] and benzoyl[16-18] chlorides with anilines.

(15) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," Wiley, New York, N. Y., 1962, p 144.

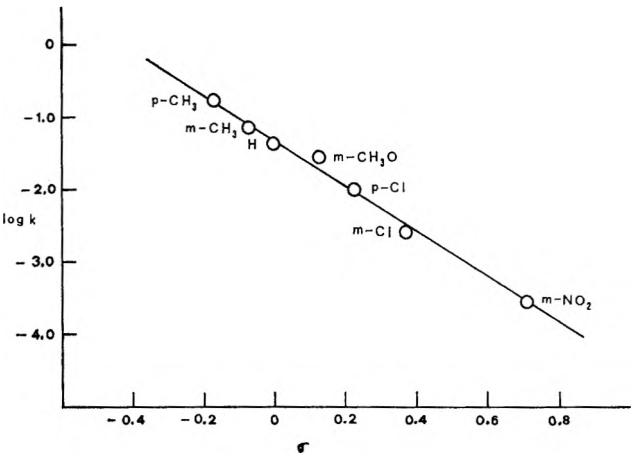
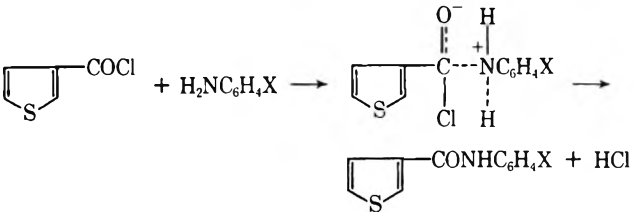


Figure 3.—Hammett plot for the reaction of 3-thenoyl chloride with substituted anilines in benzene at 25°.

From these results we can conclude also that the reaction of 3-thenoyl chloride with aniline in benzene is similar to benzoylation reaction involving the attack of the lone pair of the electrons of the amino group to the carbonyl carbon atom (Scheme I).

SCHEME I



In order to give further information about the reactivity of 3-thenoyl chloride we have made use of a simplified Tommila equation (eq 2),[10,19] where k_s =

$$2.303 \log \frac{k_s}{k_u} = -\frac{e_X \delta e_C}{RT r_j \epsilon} - \frac{\Delta W}{RT} \qquad (2)$$

rate constant of the reaction between 3-thenoyl chloride and aniline and k_u = rate constant of the reaction between benzoyl chloride and the same aniline. The results, listed in Table III, where also the log (k_s/k_u)

TABLE III

VALUES OF LOG (k_s/k_u) AT 25° FOR THE REACTION OF 2- AND 3-THENOYL CHLORIDES WITH META- AND PARA-SUBSTITUTED ANILINES IN BENZENE[a]

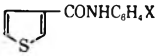
Substituent	3-Thenoyl chloride	2-Thenoyl chloride[b]
H	−0.23242	−0.47250
m-CH_3	−0.27537	−0.58357
p-CH_3	−0.24008	−0.49536
m-Cl	−0.22955	−0.42997
p-Cl	−0.18306	−0.39449
m-NO_2	−0.21281	

[a] The rate constants values at 25° for the reaction of benzoyl chloride with meta- and para- substituted anilines were those from ref 9.

(16) H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).
(17) P. R. Wells, *Chem. Rev.*, **63**, 171 (1963).
(18) G. V. Semenyuk, N. M. Oleinik, and L. M. Litvinenko, *Reakts. Sposobnost Org. Soedin.*, **4**, 760 (1967); *Chem. Abstr.*, **70**, 2931 (1969); *Zh. Obshch. Khim.*, **38**, 2009 (1968); *Chem. Abstr.*, **70**, 19475 (1969).
(19) E. Tommila, *Ann. Acad. Sci. Fennicae, AII*, No. 139 (1967).

TABLE IV

PHYSICAL CONSTANTS OF 3-THIOPHENECARBOXANILIDES[a]



Registry no.	No.	X	Mp, °C	Formula	N, % Calcd	N, % Found	Ref
	1	H	141				b
41507-30-6	2	m-CH_3	126	$C_{12}H_{11}NOS$	6.44	6.38	
41507-31-7	3	p-CH_3	163	$C_{12}H_{11}NOS$	6.44	6.36	
41507-32-8	4	m-CH_3O	138	$C_{12}H_{11}NO_2S$	6.00	6.02	
41507-33-9	5	m-Cl	132	$C_{11}H_8NOSCl$	5.89	5.87	
41559-39-1	6	p-Cl	178	$C_{11}H_8NOSCl$	5.89	5.93	
41507-34-0	7	m-NO_2	172	$C_{11}H_8N_2O_3S$	11.28	11.26	

[a] All the compounds were crystallized from aqueous ethanol. [b] S. Nishimura, R. Motoyama, and E. Imoto, *Bull. Univ. Osaka Prefect., Ser. A-6*, 127 (1958); *Chem. Abstr.*, **53**, 4249 (1959).

values for the reaction of 2-thenoyl chloride with aniline[5] are reported, clearly show that the log (k_s/k_u) values for 2- and 3-thenoyl chlorides are negative, indicating that the effective electric charge of the carbonyl carbon atom of these heterocyclic acid chlorides is less positive than that of benzoyl chloride and, therefore, they are less reactive toward aniline. The log (k_s/k_u) value for 3-thenoyl chloride, less negative than that for 2-thenoyl chloride, shows that the carbonyl carbon atom of 3-thenoyl chloride is more positively charged than that of 2-thenoyl chloride, and, therefore, it is more reactive than 2-thenoyl chloride.

The slower reaction rate of 3-thenoyl chloride, in comparison with that of benzoyl chloride, can be due to the mesomeric interaction between the thiophene ring and the carboxyl group that makes it more stabilized and, therefore, less reactive than the carbonyl group of benzoyl chloride. The reactivity of 3-thenoyl chloride, higher than that of 2-thenoyl chloride, is ascribed to the lower conjugation of the thiophene ring with the carbonyl group in the 3 position than in the 2 position.[6,20]

Experimental Section

Materials.—3-Thenoyl chloride was prepared by refluxing 2 g of 3-thenoic acid (a K & K commercial product) with 10 ml of thionyl chloride for several hours. The excess of thionyl chloride was removed by water-bath distillation and the acid chloride was purified by distillation under reduced pressure, bp 204° (748 mm).[21]

The anilines were purified to constant melting point or boiling point by recrystallization or fractionation. The solvent was benzene (R. P. Carlo Erba).

Kinetic Procedure.—The reaction was followed kinetically, as previously described,[5,7] by filtering the completely insoluble aniline hydrochloride, dissolving it in water, and estimating the chloride with 0.01 *N* mercuric nitrate, using a mixture of diphenylcarbazone and bromophenol blue as indicator.[22,23]

The second-order rate constants are derived from the formula

$$k_2 = \frac{1}{2 \times 60t}\left(\frac{1}{100 - X} - \frac{1}{100}\right)\frac{100}{a}$$

where t is the time in minutes, X is the percentage change, k_2 is the velocity constant (liters/mole seconds), and a is the initial concentration of the acid chloride in moles/liter.[5,7]

For the rate measurements the initial concentrations of the reactants after mixing were thus 3-thenoyl chloride 0.005 *M*, aniline 0.01 *M*. For compounds no. 2 and 3 in Table I, for which the reactions were too fast to be measured accurately at this concentration, the initial concentrations were 0.005 *M* aniline and 0.0025 *M* 3-thenoyl chloride. All compounds gave excellent second-order kinetics. All rates were run in duplicate to the last 80% completion with less than 3% deviation between the two rate constants.

At temperature other than 15 or 25°, rate coefficients were corrected for thermal expansion or contraction of the solvent. All rate constants were calculated by a least-squares computer program with an Hewlett-Packard 9100B. The activation parameters were calculated from a least-squares treatment of log k against T^{-1}.

The estimated precision is *ca.* ±0.5 kcal mol^{-1} in E_A and ±2 cal mol^{-1} $°K^{-1}$ in ΔS^*.

Product Analysis.—Standard solutions of the appropriate aniline and 3-thenoyl chloride in benzene were placed in a glass-stoppered bottle and maintained at the kinetic temperature until completion.

After concentration of the benzenic solution to small volume, the 3-thiophenecarboxanilide was filtered, washed free from aniline hydrochloride with water, dried, and recrystallized from aqueous ethanol. In all cases the amount of 3-thiophenecarboxanilide was ≥95% of that expected from the formation of 1 mol of anilide per mol of acid chloride consumed. Physical constants and analytical data of 3-thiophenecarboxanilides are reported in Table IV.

Acknowledgments.—The authors are grateful to the Consiglio Nazionale delle Ricerche of Italy for financial support.

Registry No.—3-Thenoyl chloride, 41507-35-1; 2-thenoyl chloride, 5271-67-0.

(20) D. P. Ambler, *Phys. Methods Heterocycl. Chem.*, **II**, 312 (1963).

(21) E. Campaigne and W. M. LeSeur, *J. Amer. Chem. Soc.*, **70**, 1555 (1948).

(22) F. E. Clarke, *Anal. Chem.*, **22**, 553 (1950).

(23) A. I. Vogel, "A Textbook of Quantitative Inorganic Analysis," 3rd ed, Longmans, Green and Co., New York, N. Y., 1961, p 274.

Sultone Rearrangements. I. 10-Isobornyl and 4-Methyl-10-isobornyl Sultones

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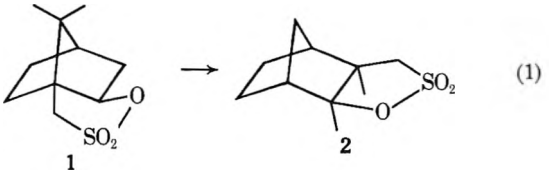
Received May 4, 1973

Thermal rearrangement of 10-isobornyl sultone (1) affords *exo*-camphene sultone (2). In the early stages of the rearrangement *endo*-camphene sultone (8) can be isolated. The stability order for the sultones appears to be 2 > 8 > 1. Two mechanisms are postulated to explain the transformation. One involves an endo-3,2-methyl shift and the other involves a circuitous route of an exo-3,2-methyl shift and several Wagner–Meerwein and 6,2-hydride shifts. A preparation of 4-methyl-10-isobornyl sultone (18) from either camphor or fenchone is described. Sultone 18 rearranges to an endo sultone (29) at moderate temperatures, but the only product found at higher temperatures is an aromatic hydrocarbon, 3,4-dimethylcumene (35). Mechanisms are proposed to account for the aromatization reaction.

A few years ago we discovered a unique thermal rearrangement of a sultone.[1] Upon being heated to its melting point, 10-isobornyl sultone (1) rearranges to *exo*-camphene sultone (2). It was subsequently



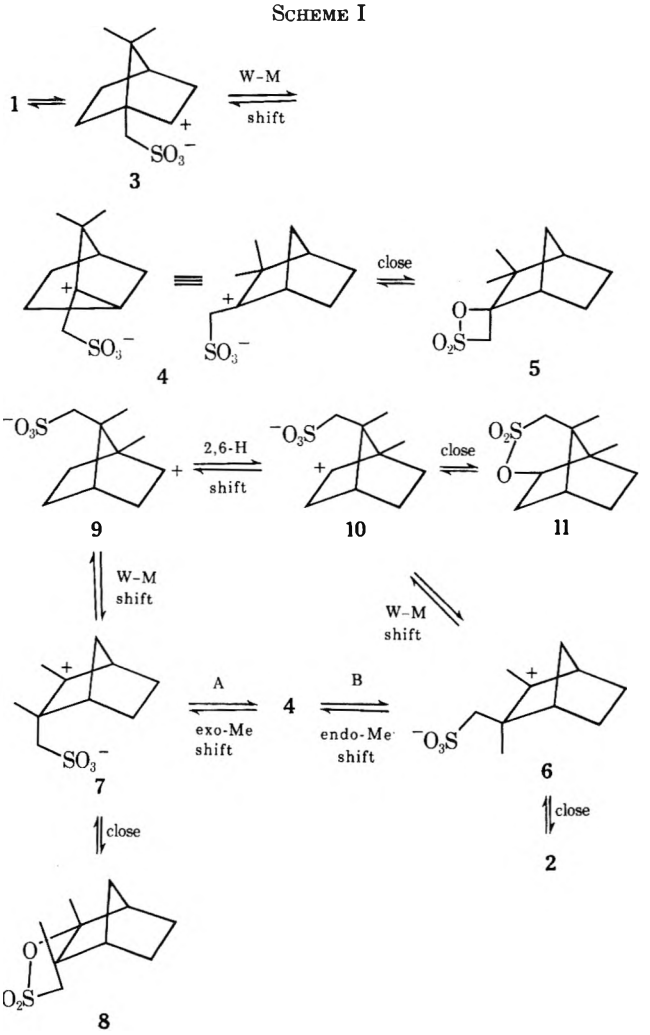
1 2 (1)

found that solid 1 can be transformed to solid 2 at temperatures below the melting point of 1.

Two mechanisms can be envisioned to explain the transformation: (A) an exo-3,2-methyl shift involving several steps or (B) an endo-3,2-methyl shift involving only a couple of simple steps. These mechanisms are shown in Scheme I. It is generally believed[2] that exo-3,2 shifts are lower in energy than endo-3,2 shifts, and on this basis mechanism A should be preferred to mechanism B. There have been, however, some reported cases of endo-3,2 shifts.[3]

Although ionic intermediates are shown in Scheme I, the reactions may be concerted. For example, 1 → 5 and 5 → 2 could proceed by a simultaneous movement of the sulfonate ion across one face of the molecule and an alkyl group across the other face, in an opposite direction. It is not easy to visualize a completely concerted process for pathway A. This paper and the subsequent one describe our attempts to distinguish the two proposed mechanisms, A and B.

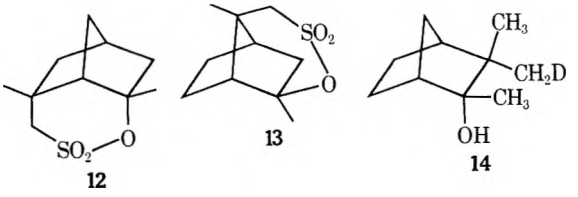
SCHEME I



Results and Discussion

In reexamining the thermal rearrangement of 10-isobornyl sultone, a new sultone was observed in the initial stages of the reaction. Isolation of this new sultone was accomplished by heating 1 for 3–5 min at about 125° (just to a melt) and performing a quick column chromatography of the crude product through basic alumina. Unreacted starting material and sultone 2 were retained on the column, probably due to a rapid hydrolysis of the exposed sultone grouping.

Based on elemental analysis, mass spectrum, and infrared spectrum, the new compound proved to be an isomer of the starting material. An nmr spectrum displayed singlet methyl groups at δ 1.34 and 1.52, an AB pattern for the $-CH_2SO_2-$, one doublet at 2.83 (J = 14 Hz) and the other at 3.38 (J = 14 Hz), and the remaining ring protons spread between 1.55 and 2.45. Several structures appear compatible with these spectral characteristics, namely, 5, 8, and the relatively unlikely structures 12, 13, etc. A simple way to dis-



(1) J. Wolinsky, D. R. Dimmel, and T. W. Gibson, *J. Org. Chem.*, **32**, 2087 (1967).

(2) J. Berson, in "Molecular Rearrangements," P. de Mayo, Ed., Interscience, New York, N. Y., 1963, Chapter 3.

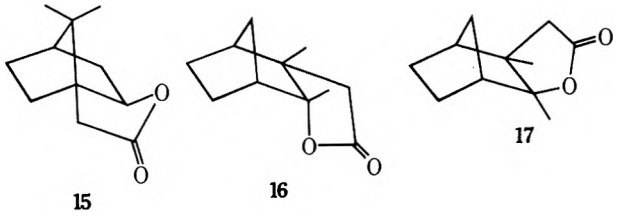
(3) (a) Endo-3,2-methyl shift: S. Rengaraju and K. D. Berlin, *Tetrahedron*, **27**, 2399 (1971); C. W. David, B. W. Everling, R. T. Killian, J. B. Stothers, and W. R. Vaughan, *J. Amer. Chem. Soc.*, **95**, 1265 (1973). (b) Endo-3,2-hydride shift: A. W. Bushwell and P. Wilder, Jr., *ibid.*, **89**, 5721 (1967). (c) Possible endo-3,2-chlorine shift: R. N. McDonald and R. N. Steppel, *ibid.*, **91**, 782 (1969).

tinguish these compounds is desulfurization with $LiAlD_4$.[1] When the experiment was performed, 2-methylcamphenilol was produced. Both nmr and mass spectra clearly showed that one of the geminate dimethyls at C-3 is deuterated; thus, structure **14** was assigned to the reduction product. A trans-2,3-fused sultone ring juncture was considered highly unlikely.

The course of the rearrangement reaction could be conveniently followed by inserting sealed capillaries containing solid **1** into refluxing ethoxyethanol (bp 133–135°) and removing samples at regular time intervals. The crude data, shown in Figure 1, indicate that **1** disappears quite rapidly to **8**, which in a slower reaction goes to **2**. Heating relatively pure **8** afforded **2**. Under the same conditions **2** did not lead to any **8**. Thus, it appears that sultone **2** must be thermodynamically more stable than sultone **8**.

The rearrangement can also be performed in inert solvents like *n*-octane and tetrachloroethylene (TCE). A really simple way to do the rearrangement is to dissolve 10-isobornyl sultone in refluxing *n*-octane (bp 124°) for 2–3 hr, cool, and collect crystalline **2** in 80% yield. The rearrangement in *n*-octane was difficult to follow kinetically; after an induction period of 6 min, sultone **1** was completely converted into a mixture of **2** and **8**. The rearrangement was much slower in refluxing TCE (bp 121°) solvent, and the course of the reaction could be easily followed by nmr. Here again sultone **8** could be observed, and it was possible, using dibenzyl ether as an internal standard, to show that there were no side reactions of **1**, **2**, and **8**, such as formation of camphene.

The crude kinetic data shown in Figure 1 do not tell whether sultone **8** is on the pathway to the formation of **2**, *i.e.*, mechanism A, or just a dead-end product. In other words, does the conversion of **8** → **2** involve **7** → **4** → **6** → **2** or **7** → **9** → **10** → **6** → **2**? It is interesting to note that lactones **15**, **16**, and **17** are known[4]



and that it appears that the thermodynamic stability order is **15** < **16** < **17**. The exo lactone **17** just as the exo sultone **2** has a singlet methylene (CH_2X, X = CO or SO_2) in its nmr spectrum, and the endo lactone **16** like the endo sultone **8** has an AB quartet for this methylene group.

Our first approach to distinguish mechanisms A and B was to synthesize and study the rearrangement of 4-methyl-10-isobornyl sultone (**18**). If **18** were to rearrange *via* an endo-methyl shift mechanism such as B, the product should be **19**; however, if an exo-methyl shift mechanism such as A prevailed, the product should be **20** (eq 2).

The synthesis of **18** is shown in Scheme II. The synthesis of **26** from either fenchone (**21**) or camphor (**27**) represents an improvement of our earlier reported

(4) W. R. Vaughan, J. Wolinsky, R. S. Dueltgen, S. Grey, and F. S. Seichter, *J. Org. Chem.*, **35**, 400 (1970).

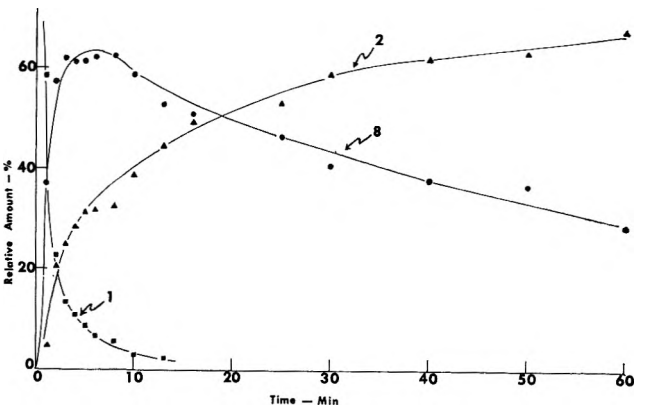
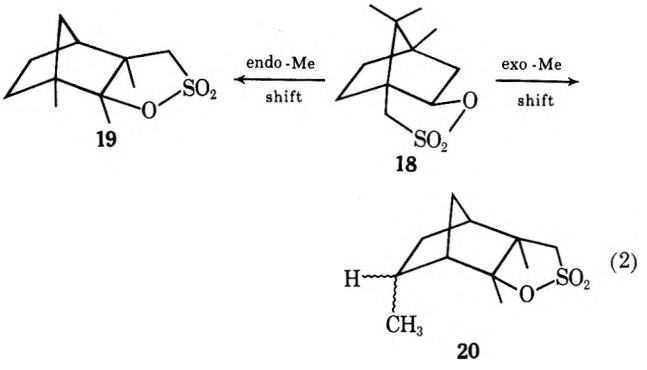


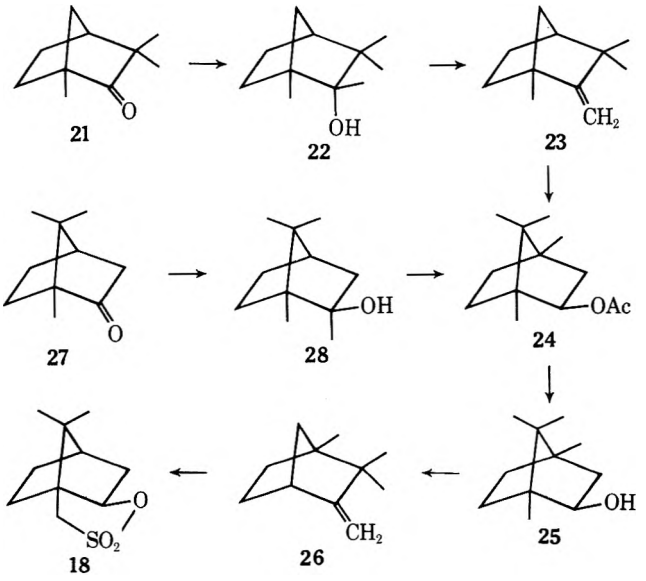
Figure 1.—Product composition resulting from the neat thermal rearrangement of 10-isobornyl sultone (**1**) at 133–135°: ■, amount of sultone **1**; ●, amount of sultone **8**; ▲, amount of sultone **2**.



(2)

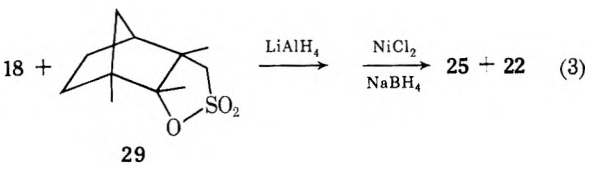
synthesis (see Experimental Section).[1] The thermal rearrangement of **18** was accomplished by heating at 75–85° for 3 hr and subliming out the volatile materials.

Scheme II



The product mixture was found to be composed of one part of **18** to three parts of a new compound, a sultone. An nmr spectrum of the mixture suggested that the new sultone has structure **29**, singlet methyls at δ 1.15, 1.32, and 1.44 and an AB quartet (J = 14 Hz) for the $-CH_2SO_2-$ group, one doublet at 2.83 and the other at 3.41.[4] Reduction of the sultone mixture with $LiAlH_4$, followed by nickel boride, gave a 1:3 mixture of **25**

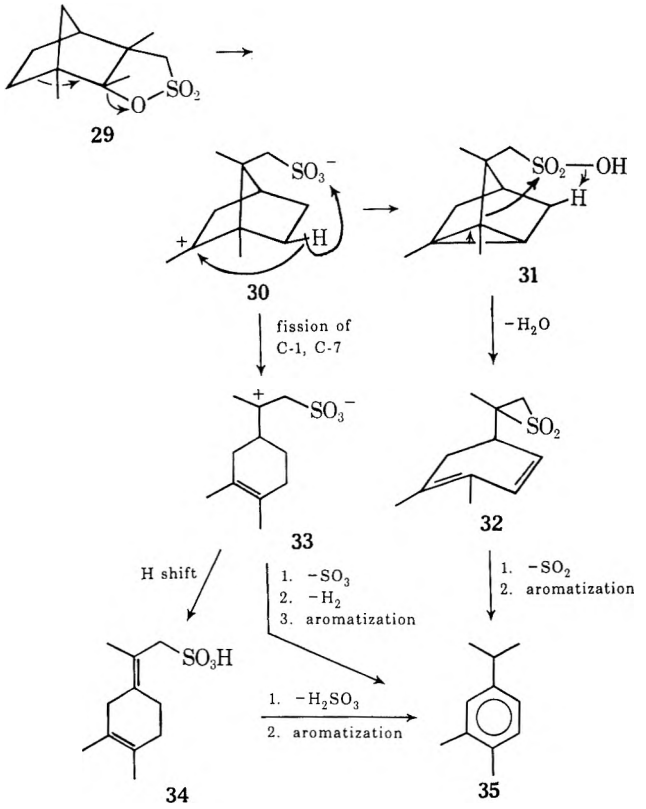
and 1,2-dimethylcamphenilol (22). The endo OH of 22 supports the endo sultone ring juncture of 29.



1-Methylcamphene hydrate (the exo isomer of 22) was shown not to be present.

If 18 or the mixture of 18 and 29 were heated at higher temperatures in an attempt to get either 19 or 20, desulfonation with subsequent aromatization occurred, giving the hydrocarbon 3,4-dimethylcumene (35). The structural proof of this latter compound was based on spectral comparison to reported values.[5] Aromatization of bicyclo[2.2.1]heptanes has occurred in other systems as well.[6,7] The possible mechanisms for this transformation are presented in Scheme III. The

SCHEME III



mechanism involving loss of SO_2 *via* an episulfone extrusion reaction is based on some work of Paquette.[8] Mechanisms involving loss of H_2SO_3 or SO_3 and H_2 can also be envisioned.

Conclusions

The rearrangement of 10-isobornyl sultone (1) not only affords *exo*-camphene sultone (2), as reported earlier,[1] but also *endo*-camphene sultone (8). The endo sultone is formed first in the reaction, but then gradually rearranges to the more stable exo sultone. Although it is tempting to conclude that the endo sultone is an intermediate along the pathway that gives the exo isomer, we cannot rule out the possibility that the endo sultone is a dead-end product which is in equilibrium with an intermediate that gives the exo isomer at a slow rate.

It was anticipated that the thermal rearrangement of 4-methyl-10-isobornyl sultone (18) would allow us to establish the mechanisms of these sultone rearrangements. However, heating 18 only gave the endo sultone 29 at moderate temperatures and 3,4-dimethylcumene (34) at high temperatures. The fact that no exo sultone was observed could be interpreted to favor either an exo- or endo-3,2-methyl shift. The C-4 bridgehead methyl could retard an endo-3,2-methyl shift (pathway B, 4 → 6) by an eclipsing effect[9] that would result between the exo-3-methyl and the bridgehead methyl as the C-3 flattens out. Alternatively, the C-4 methyl could have a large effect on the mechanism of rearrangement if pathway A prevailed. This methyl would end up on the carbonium site of structure 9, *i.e.*, structure 30. The ion now is tertiary and should, therefore, have less tendency to go onto a secondary carbonium ion *via* a 6,2-hydride shift, as depicted in 9 → 10. The longer lived ion 30 might then find alternate ways of reacting, such as shown in Scheme III.

The question of what type of 3,2-methyl shift prevails remains unanswered. Our next paper,[10] dealing with deuterated analogs of 10-isobornyl sultone, attempts to provide the answer.

Experimental Section[11]

Kinetic Measurements of Thermal Rearrangement of 10-Isobornyl Sultone (1). A.—Sealed capillaries containing 1 were immersed in a constant-boiling bath of ethoxyethanol (bp 133–135°). The rate of rearrangment was followed by measuring the relative intensities of the proton nmr signals of the $-CH_2SO_2-$ group.

B.—10-Isobornyl sultone (1.8 g) was dissolved in 12 ml of refluxing tetrachloroethylene (TCE, bp 121°). Samples were withdrawn at regular time intervals and their nmr spectra recorded.

C.—To 10 ml of refluxing *n*-octane (bp 124°) was added 2.5 g of sultone 1. Samples were withdrawn at regular time intervals. Upon cooling, a solid was isolated by filtration. The proton nmr spectra of all the withdrawn samples showed that 8 was not present. In a separate run sultone 2 was isolated in 80% yield after a reaction time of 3 hr.

D.—No side reactions, such as the extrusion of sulfur trioxide to form camphene, were observed in the nmr spectrum. Furthermore, when dibenzyl ether was mixed with 1 in refluxing TCE, the relative ratio of the benzylic protons to $-CH_2SO_2-$ protons remained unchanged under the same reaction conditions as in B.

***endo*-Camphene Sultone (8).**—10-Isobornyl sultone (1.0 g, 4.6 mmol) was heated at 125° for 5 min. The resulting dark brown solid was shown (by nmr) to be a mixture of *exo*- and *endo*-

(5) Sadtler Infrared Spectra Index No. 26046 and Sadtler Nmr Spectra Index No. 420M.

(6) R. P. Lutz and J. D. Roberts, *J. Amer. Chem. Soc.*, **84**, 3715 (1962).

(7) A. Coulombeau, C. Coulombeau, and A. Rassat, *Bull. Soc. Chim. Fr.*, 4389 (1970).

(8) L. A. Paquette, R. E. Wingard, Jr., and R. H. Meisinger, *J. Amer. Chem. Soc.*, **93**, 1048 (1971).

(9) P. v. R. Schleyer, *ibid.*, **89**, 699, 701 (1967).

(10) D. R. Dimmel and W. Y. Fu, *J. Org. Chem.*, **38**, 3782 (1973).

(11) All boiling points and melting points are uncorrected. Infrared spectra were determined with a Perkin-Elmer Infracord spectrophotometer, Model 137B. Nmr spectra were obtained on a Varian A-60A spectrometer, using TMS as an internal standard and CCl_4 as solvent. Mass spectra were obtained using a CEC 21-103 mass spectrometer. Unless otherwise stated, gas chromatographic analyses and preparative vpc were performed on a 6 ft × 0.25 in. aluminum column packed with 20% SE-30 on 60–80 mesh Chromosorb W or an 8 ft × 0.25 in. aluminum column packed with 20% diethylene glycol succinate (DEGS) on3 0–60 mesh Chromosorb W using an F&M Model 700 gas chromatograph. Elemental analyses were performed by Chemalytic, Inc., Tempe, Ariz.

camphene sultones and 10-isobornyl sultone. The mixture was placed on an alumina column (70 g, pH 10.2) and eluted with 140 ml of hexane, followed by 80 ml of 95% hexane–5% benzene, 80 ml of 80% hexane–20% benzene, 240 ml of 60% hexane–40% benzene, and 150 ml of 50% hexane–50% benzene. Fractions of 40 ml each were collected. Upon evaporation of the solvent, fractions 9–16 gave a white residue. Recrystallization of the residue from cold hexane gave 103 mg of a white solid: mp 159.5–160°; nmr (CCl_4) δ 3.38 (d, 1, J = 14 Hz), 2.83 (d, 1, J = 14 Hz), 1.52 (s, CH_3), 1.34 (s, CH_3); ir (CCl_4) 1360, 1185 (SO_2) and 905, 875, 860, 832 cm^{-1} (sultone).

Anal. Calcd for $C_{10}H_{16}O_3S$: C, 55.51; H, 7.46; S, 14.82. Found: C, 55.16; H, 7.60; S, 14.55.

Reduction of *endo*-Camphene Sultone (8).—A 1.0-g (4.6 mmol) sample of a mixture of sultones, shown by nmr to be 50:50 *exo*-(2)-*endo*-camphene sultone (8), was combined with 0.75 g (20 mmol, 80 mequiv) of lithium aluminum hydride in anhydrous tetrahydrofuran (THF) and refluxed for 10 days. After being quenched with saturated aqueous sodium sulfate, the salts were filtered and washed several times with fresh ether. The filtrate was distilled and the residue sublimed. A liquid sublimate was collected which smelled of sulfur. Analysis by vpc and nmr indicated that the product was probably a mixture of hydroxy sulfides.

The crude product mixture was dissolved in a small amount of 95% ethanol and added to a solution of 5.0 g (20 mmol) of hexaaquonickel(II) chloride in 95% ethanol. The solution was swept with nitrogen for 10 min and then cooled in an ice bath. While cold, an aqueous solution of 2.25 g (60 mmol) of sodium borohydride was added dropwise to the stirred solution. When the addition was complete, the ice bath was removed and the reaction mixture refluxed for 4 hr. The solution was then cooled, diluted with water, and filtered. The filtered black catalyst was washed several times with ether. The ether layer was separated from the filtrate, washed, dried ($MgSO_4$), and concentrated and the residue sublimed to yield approximately 100 mg of a mushy solid.

The nmr spectrum of the product indicated that it was a 50:50 mixture of camphene hydrate and 2-methylcamphenilol. After several columns were tried, the two components were partially separated by vpc using a 8 ft × 1/8 in. 20% Quadrol on 60–80 mesh Chromosorb W column. One alcohol had a retention time of 18.5 min and the other 19 min. Enriching the 50:50 sample with either pure alcohol to determine which peak corresponded to which led to a coalescence of the peaks. Another more definitive answer to the structure of sultone 8 is discussed next.

A 175-mg sample of 8, purified by column chromatography and recrystallized from hexane, was dissolved in anhydrous ether and combined with 350 mg (tenfold excess) of lithium aluminum deuteride. The mixture was stirred for 2 weeks at room temperature, quenched with saturated sodium sulfate solution, and filtered. After the salts were washed several times with ether, the filtrate was dried ($MgSO_4$), filtered, evaporated, and sublimed to give 30 mg of solid. An nmr spectrum of the solid agreed with the spectrum of 2-methylcamphenilol except for a decrease in the methyl signal at 53.6 Hz; the other methyl signals at 55.2 and 70.7 Hz were unchanged. A mass spectrum clearly showed that the product was a 2,3,3-trimethyl-2-norbonanol compound with deuterium located on one of the C-3 methyl groups (the m/e 41 shifted substantially to m/e 42; m/e 43 did not shift to m/e 44; and m/e 71, the base peak, was not shifted in comparison to the nondeuterated compound). The solid was assigned the structure 14.

1,2-Dimethylcamphenilol (22).—An ethereal solution of 85 g (0.6 mol) of methyl iodide was added dropwise to 20.0 g (1.67 g-atoms) of magnesium in 100 ml of anhydrous ether. A solution of 53 g (0.35 mol) of fenchone in ether was added dropwise to the freshly prepared Grignard reagent. The resulting dark gray solution was refluxed for 5 hr. The reaction mixture was poured into a beaker of 40 ml of cold, saturated ammonium chloride. The ether layer was separated and the aqueous layer was extracted twice with ether. The combined ether extracts were dried ($MgSO_4$) and concentrated to give 58.1 g (99.2%) of a mixture of 22 and 21: ir 3510, 1095 (–OH), 1740 cm^{-1} (C=O). This mixture was used directly in the next step.

1-Methylcamphene (23).—To an ice-cold solution of 58.1 g of the alcohol–ketone mixture obtained above in 70 ml of anhydrous pyridine was slowly added 40 ml of thionyl chloride. After refluxing for 12 hr the mixture was poured into water and extracted with ether. The ether extracts were washed successively with 5% HCl, 5% $NaHCO_3$, and water. The resulting brown solution was dried ($MgSO_4$), concentrated, and distilled to give 38.5 g of a colorless liquid: bp 125° (110 mm); ir 3080, 1650, 900 cm^{-1} (–C=CH_2) [lit.[12] bp 170–172° (737 mm)]. A small amount of fenchone was present (ir).

1,2,7,7-Tetramethyl-*exo*-2-norbornanol (28).—An ethereal solution of 40 g (0.26 mol) of camphor was slowly added to an ethereal solution of methylmagnesium iodide prepared from 67 g (0.47 mol) of methyl iodide and 20.2 g (1.66 g-atoms) of magnesium. The reaction mixture was refluxed in a nitrogen atmosphere for 40 hr. The mixture was poured into 40 ml of cold and saturated ammonium chloride and the organic layer separated. The aqueous phase was extracted twice with fresh ether. The combined ether extracts were dried ($MgSO_4$) and concentrated to afford 41 g of a mixture of 74% 28 and 26% camphor (by vpc analysis). The mixture was refluxed for 3 hr with 12 g of hydroxylamine hydrochloride, 20 g of potassium hydroxide, and 75 ml of 95% ethanol. The ethanolic solution was poured into 150 ml of cold water, and extracted twice with ether, and the combined ether extracts were washed twice with 10% NaOH, dried ($MgSO_4$), and concentrated to give 35 g (79%) of a solid: mp 164–167°; nmr (CCl_4) δ 1.18 (s, CH_3), 1.06 (s, CH_3) 0.84 (s, CH_3), and 0.80 (s, CH_3) (lit.[13] mp 168°).

4-Methylisobornyl Acetate (24). A. From 1-Methylcamphene (23).—1-Methylcamphene (38.5 g, 0.23 mol) was mixed with 90 ml of glacial acetic acid and 3 ml of 50% H_2SO_4 and kept at 60° for 20 hr. After cooling, the solution was poured into 250 ml of cold water and extracted with ether. The ether extracts were washed with saturated $NaHCO_3$, dried over magnesium sulfate, concentrated, and distilled to give 30.0 g (62%) of a colorless liquid: bp 97–110° (25 mm); ir 1735, 1240 cm^{-1} (acetate); nmr (CCl_4) δ 4.62 (dd, 1, CHOH, J = 4.5, 7.5 Hz), 1.92 (s, CH_3), 0.88 (s, CH_3), 0.83 (s, 2 CH_3), and 0.68 (s, CH_3) [lit.[1] bp 126–128° (28 mm)].

B. From 1,2,7,7-Tetramethyl-*exo*-2-norbornanol (28).—A mixture of 35 g (0.21 mol) of 28, 120 ml of glacial acetic acid, and 6 ml of 50% H_2SO_4 was kept at 60° for 3 days. After cooling, the mixture was poured into 90 g of ice–water slurry and extracted three times with ether. The combined ether extracts were washed successively with 5% NaOH and water until the aqueous wash was neutral to litmus. The ether layer was then dried ($MgSO_4$), concentrated, and distilled to give 25 g (57%) of a colorless liquid whose boiling point and ir and nmr spectra were identical with those obtained from A.

1,4,7,7-Tetramethyl-*exo*-2-norbornanol (25).—A mixture of 30 g (0.14 mol) of 24, 54 ml of water, 54 ml of methanol, and 31 g of potassium hydroxide was refluxed with stirring for 20 hr. The reaction mixture was poured into 200 ml of water and extracted three times with ether. The combined ether extracts were dried ($MgSO_4$) and concentrated to give 15 g (62%) of a white solid: mp 193–194°; ir 3510, 1040 cm^{-1} (–OH); nmr (CCl_4) δ 3.54 (dd, 1, J = 4.5, 7.5 Hz, CHOH), 0.87 (s, 2 CH_3), 0.83 (s, CH_3), 0.66 (s, CH_3); mass spectrum (70 eV) m/e (rel intensity) 150 (10), 135 (16), 125 (17), 109 (100), 107 (20), 55 (34), 43 (37), 41 (63), 39 (33), 29 (30), 27 (37) (lit.[12] mp 190–191°).

β-Methylcamphene (26).—To a cold solution of 24 g (142 mmol) of 25 in 25 ml of freshly distilled pyridine was slowly added 10 ml of thionyl chloride. After being stirred for 3 hr, the mixture was poured into ether and water. The ether layer was separated and washed successively with 5% HCl, saturated $NaHCO_3$, and water. After the ether was removed, the residue was eluted through an alumina column with pentane to give, after sublimation, 16.64 g (78%) of a solid: mp 87–96°; ir 3080, 1650, 1415, 880 cm^{-1} (–C=CH_2); nmr (CCl_4) δ 4.60 (d, 2, J = 12 Hz, –C=CH_2), 2.61 (m, 1, methine proton at C-1), 1.02 (s, CH_3), 0.98 (s, CH_3), 0.92 (s, CH_3) (lit.[12] mp 100–110°). Analysis by vpc (SE-30) showed approximately 55% 26 and 45% tricyclene.

4-Methyl-10-isobornyl Sultone (18).—To a cooled solution of 6 g (75 mmol) of sulfur trioxide in 50 ml of tetrachloroethylene (TCE) was added dropwise with rapid stirring 8.2 g (94 mmol) of *p*-dioxane in 50 ml of TCE. The SO_3–dioxane complex was formed immediately. 4-Methylcamphene (4.0 g, 26.7 mmol) dissolved in 10 ml of TCE was then added slowly with rapid stirring. After stirring at room temperature for 16 hr, the reaction mixture was poured into 60 ml of saturated $NaHCO_3$.

(12) A. I. Sherygin, *Zh. Obshch. Khim.*, **18**, 499 (1948); *Chem. Abstr.*, **42**, 7276h (1948).

(13) M. L. Chapman, W. Chodkiewicz, and P. Cadiot, *Tetrahedron Lett.*, 1619 (1965).

The organic layer was separated and the aqueous phase was extracted with methylene chloride. The combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure at room temperature. The viscous residue was recrystallized twice from pentane to yield 0.402 g (6.7%) of a colorless solid: mp 74–75°; nmr (CCl_4) δ 4.36 (dd, 1, J = 5, 7 Hz, $-CHOSO_2-$), 3.22 (s, 2, $-CH_2SO_2-$), 0.97 (s, 2 CH_3), 0.89 (s, CH_3).

Anal. Calcd for $C_{11}H_{18}O_3S$: C, 57.37; H, 7.88; S, 13.60. Found: C, 57.37; H, 7.91; S, 13.72.

Thermal Rearrangement of 4-Methyl-10-isobornyl Sultone (18).—4-Methyl-10-isobornyl sultone (280 mg) was placed in a sublimer and maintained between 75 and 85° for 3 hr. Sublimation gave 202 mg of a solid [75° (0.1 mm)]. Analysis by nmr showed a 1:3 mixture of **18** and a rearranged sultone, respectively. In addition to the starting material the nmr showed two doublets centered at δ 3.41 (J = 14 Hz) and 2.83 (J = 14 Hz) and three singlet methyls at 1.44, 1.32, and 1.15, which suggested structure **29**.[4]

Reduction of Sultone Mixture 18 and 29.—A procedure similar to the reduction of **8** was used. Thus, 200 mg of the sultone mixture was first treated with 1.1 g (29 mmol) of lithium aluminum hydride in ether and then with 2.4 g (10 mmol) of hexaaquonickel(II) chloride and 1.23 g (33 mmol) of sodium borohydride in absolute ethanol. Analysis by vpc showed a 1:3 mixture. The spectroscopic properties (ir and mass spectrum) of the major component, collected by preparative vpc, were identical with those of **22**. The minor component was likewise isolated by preparative vpc, and its ir and mass spectrum data were identical with those of **25**.

3,4-Dimethylcumene (35) from 4-Methyl-10-isobornyl Sultone (18).—Sultone **18**, 0.25 g, was heated to 100° for 2 hr. The resulting brown solution was found to be an aromatic hydrocarbon: ir 882, 818, 718 cm^{-1} (1,2,4-trisubstituted aromatic); nmr (CCl_4) δ 6.90 (s, 3, aryl protons), 2.78 (m, 1, ArCH), 2.20 (s, 6, 2 CH_3) and 1.21 (d, 6, J = 7 Hz, $-CH(C_3)H_2$); mass spectrum (70 eV) m/e (rel intensity) 149 (3), 148 (25), 134 (13), 133 (100), 117 (12), 105 (13), 91 (14), 77 (8), 51 (6), 41 (11), 39 (12), and 29 (12). The ir and nmr spectra were in complete agreement with those of 2,3-dimethylcumene. A vpc collected sample showed the same spectral properties.[5]

Registry No.—**1**, 13131-57-2; **8**, 41366-78-3; **14**, 41429-86-1; **18**, 41366-79-4; **21**, 1195-79-5; **22**, 28462-85-3; **23**, 13567-57-2; **24**, 10470-41-4; **25**, 41366-83-0; **26**, 13144-43-9; **28**, 2371-42-8; **29**, 41366-86-3; **35**, 4132-77-8; methyl iodide, 74-88-4; camphor, 76-22-2.

Sultone Rearrangements. II. Deuterated Analogs of 10-Isobornyl Sultone. Evidence for Exo-3,2-Methyl Shifts and Discrete 2-Norbornyl Cations

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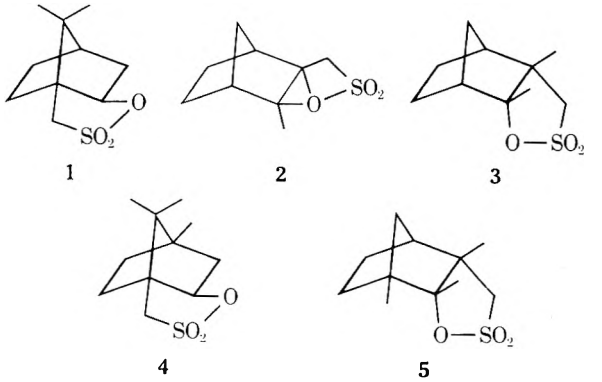
The 3,3-d_2 and 9-d_1 analogs of 10-isobornyl sultone (**1**) were synthesized. There is no scrambling of the deuterium label during the syntheses, even though a 2-norbornyl cation is a likely intermediate in one of the steps. The deuterated 10-isobornyl sultones were thermally converted to deuterated *exo*-camphene sultones (**2**) in hopes of clarifying the nature of the 3,2-methyl shifts which occur during the rearrangement reactions. The label at C-9 is scrambled during the thermal reactions such that a distinction between exo- *vs.* endo-3,2-methyl shifts cannot be made. However, analysis of the deuterium atom position in the product of the thermal rearrangement of 1-3,3-d_2 shows that an exo-3,2-methyl shift prevails over endo shift in the formation of *exo*-camphene sultone. Studies using optically active reagents showed that the two methods of synthesizing 10-isobornyl sultone were highly stereospecific, meaning that the probable 2-norbornyl cation intermediate does undergo racemizing 6,2-hydride shifts. However, racemization does occur during the thermal rearrangement of **1** to **2**.

In the previous paper we described the thermal rearrangement of 10-isobornyl sultone (**1**) to *exo*- and *endo*-camphene sultones (**2** and **3**).[1] Rearrangement of a methyl analog, sultone **4**, gave only an endo sultone **5** and 3,4-dimethylisopropylbenzene and no exo sultone



1 2 3 4 5

comparable to **2**. The formation of the endo sultones **3** and **5** most likely occurs *via* a exo-3,2-methyl shift. The exact manner by which the exo sultone **2** is formed is still in doubt. It was anticipated that its formation may be a result of a relatively rare rearrangement, namely an endo-3,2-methyl shift.[2] Previous results[1] suggested, but did not prove, that the endo sultone **3** may be the precursor of **2** and, consequently, endo-3,2-methyl shifts do not have to be involved.

Since introduction of a methyl group changed the course of the reaction, we decided to keep the structural variations to a minimum by employing deuterium labeling. In order to get deuterium into the structure we had to develop a new way of synthesizing 10-isobornyl sultone. The previous methods[3] usually employed camphene as the starting material and the task of synthesizing specifically labeled camphene derivatives appeared to be both expensive and involved. A synthesis of 10-isobornyl sultone from camphene is shown in eq 1.

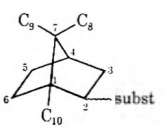
A major problem in specifically deuterating these systems is the ease with which these compounds undergo rapid rearrangements, *i.e.*, Wagner–Meerwein and 6,2- and 3,2-hydride shifts.[4] For example, a rapid

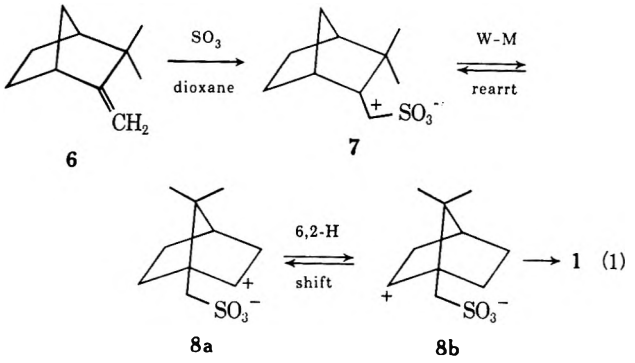
(1) D. R. Dimmel and W. Y. Fu, *J. Org. Chem.*, **38**, 3778 (1973).

(2) See footnote 3 of ref 1.

(3) J. Wolinsky, D. R. Dimmel, and T. W. Gibson, *J. Org. Chem.*, **32**, 2087 (1967).

(4) The number system for bicyclo[2.2.1]heptanes is as follows:



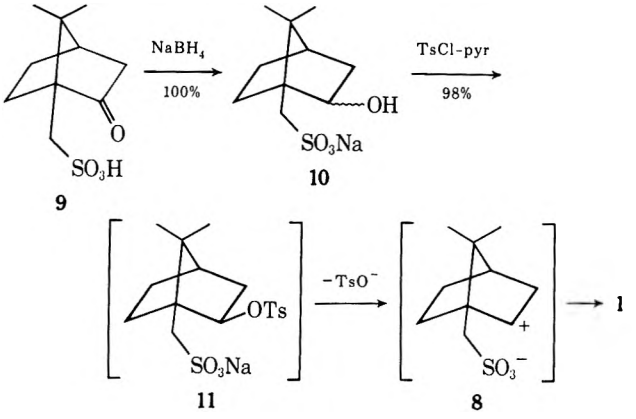


6,2-hydride shift, like **8a** ⇌ **8b**, would render any labeling of the methyl groups useless.[5] We felt we could live with 6,2-hydride shifts if the labels were in the 3 position. This paper describes our syntheses of 3,3-dideuterio- and 9-deuterio-10-isobornyl sultone and their rearrangements to deuterated *exo*-camphene sultone.

Results and Discussion

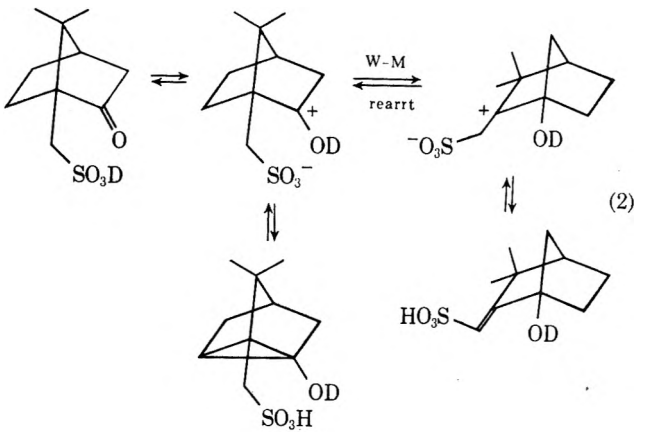
3,3-Dideuterio-10-isobornyl Sultone.—A modification of an earlier method[3] of synthesizing 10-isobornyl sultone from readily available 10-camphorsulfonic acid was developed; this is shown in Scheme I. The reduction of 10-camphorsulfonic acid with sodium borohydride went smoothly, and the product **10** was separated from the inorganic salts by Soxhlet extraction with absolute alcohol. The reaction of **10** with *p*-toluenesulfonyl chloride in pyridine was also quite clean, giving uncontaminated 10-isobornyl sultone in good yield.

SCHEME I



By heating **9** with D_2O twice, 3,3-dideuterio-10-camphorsulfonic acid was obtained; the internal acidity of **9** appears to be sufficient to catalyze the exchange. If homoenolization and/or Wagner–Meerwein rearrangements were occurring, the deuterium label could conceivably become incorporated into the C-6 and C-10 carbons (eq 2). The nmr spectrum, however, gave no indication of deuteriums other than at the C-3 position.

The deuterated 10-camphorsulfonic acid was dissolved in D_2O and added to D_2O–sodium borohydride. These conditions were employed in order to lessen the chance of exchange of the existing label. It was feared



that plain water or alcohol solvent would exchange the C-3 deuterium prior to reaction with the sodium borohydride. The disadvantage of using D_2O as the solvent is the possibility that the following exchange could occur:[6] $NaBH_4 + D_2O \rightleftharpoons NaBH_3D + HOD$. This could lead to some deuterium at the C-2 position (by reduction of the carbonyl). Another problem that could arise is at the completion of the borohydride reduction; the basic solution could possibly promote deuterium exchange of the $-CH_2SO_3Na$ group.[7] Analysis of the nmr spectrum of deuterated **10** for the amount and position of the deuterium was complicated by the fact that **10** is a mixture of exo and endo isomers. Its limited volatility precluded using mass spectroscopy for obtaining the deuterium atom content. Consequently, the material was taken right into the next step, cyclization with tosyl chloride and pyridine to 10-isobornyl sultone.

The most apparent thing about the nmr spectrum of the deuterated 10-isobornyl sultone is the singlet at δ 4.28 which is assigned to the HCO proton. In nondeuterated **1** this proton appears as a doublet of doublets due to unequal coupling to the C-3 hydrogens. The peak is, however, slightly broader than the other singlets in the spectrum. This could be a result of some long-range proton–proton coupling, vicinal deuterium coupling, or an indication that the C-3 position is not fully deuterated.[8]

A comparison of the integrated areas of the peaks in the nmr spectrum of the deuterated 10-isobornyl sultone with the nondeuterated sultone indicated that the deuterium was confined to the 3, 4, 5, and 6 positions. The peaks related to the two methyl groups, the $-CH_2SO_2-$ hydrogens, and the HCO hydrogen, integrated for the same values in both spectra, namely, 3.0, 3.0, 1.81, and 0.82, respectively. The multiplet in the δ 1.2–2.5 region integrated for 6.9 protons in the nondeuterated sultone and 5.0 in the deuterated sultone. The mass spectrum of deuterated **1** was similar to the other sultones that we have encountered in that it dis-

(5) 3,2-Hydride shifts are known to occur much more slowly than 6,2-hydride shifts: M. Saunders, P. v. R. Schleyer, and G. A. Olah, *J. Amer. Chem. Soc.*, **86**, 5680 (1964).

(6) Sodium borohydride apparently does not exchange with D_2O under conditions where impurities are carefully excluded; however, micromolar amounts of heavy metals greatly catalyze the exchange. Several workers have observed exchange under "normal" conditions. See R. E. Davis, J. A. Bloomer, D. R. Cosper, and A. Saba, *Inorg. Chem.*, **3**, 460 (1964).

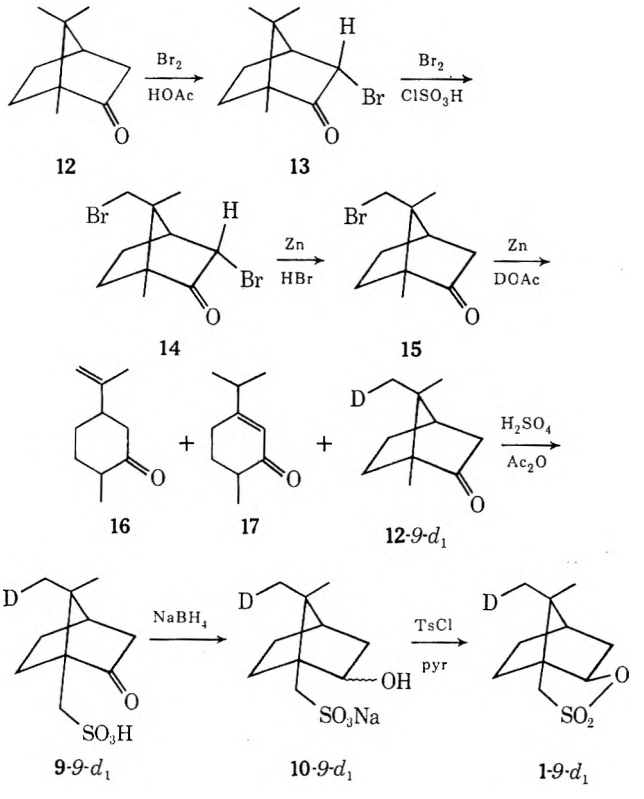
(7) The protons of sodium methanesulfonate undergo exchange with D_2O in the presence of OD^- at 100–160°: J. Hochberg and K. Bonhoefer, *Z. Phys. Chem., Abt. A*, **184**, 419 (1939).

(8) The coupling constant between cis-2,3-endo hydrogens is about 8.5 Hz and between 2-endo,3-exo hydrogens is about 2.5 Hz [A. F. Thomas, R. A. Schneider, and J. Meinwald, *J. Amer. Chem. Soc.*, **89**, 68 (1967)]. One could have possibly 20–30% hydrogen in place of the exo-3 deuterium and not affect the shape of the HCO signal much.

played only a very, very weak molecular ion.[9] A possible useful fragment was the weak peak at m/e 152, which probably corresponds to the loss of SO_2 from 10-isobornyl sultone.[10] This peak shifts significantly to m/e 154 in the deuterated sultone. Because of the weakness of the peaks, it is difficult to completely assess the exact deuterium content; however, there appear to be small amounts (*ca.* 15%) of d_1 and d_3 present in the deuterated sultone. The spectral analysis, however, strongly indicated that the deuterated 10-isobornyl sultone was largely *3,3-d*$_2$.

9-Deuterio-10-isobornyl Sultone.—The success in preparing 1-*3,3-d*$_2$ without scrambling of the label led us to attempt to synthesize 1-*9-d*$_1$. Camphor-*9-d*$_1$ was prepared from *d*-camphor[11] by the following sequence of reactions: (1) bromination of C-3 in acetic acid;[12] (2) bromination of C-9 in chlorosulfonic acid;[13] (3) debromination of C-3 by zinc–hydrogen bromide;[13] and (4) debromination of C-9 by zinc–acetic acid-d_1[14] (Scheme II). The desired product 12-*9-d*$_1$ was contaminated with *ca.* 35% of fragmentation products **16** and **17**. These latter impurities were selectively removed by means of bromination and distillation. The mass spectrum of purified camphor-*9-d*$_1$, mp 179°, showed 19% d_0, 71% d_1, and 10% d_2. The nmr spectrum displayed methyl signals at δ 0.83 (s, C-8), 0.85 (s, C-10), and 0.95 (m, C-9);[15] the multiplet of the latter signal arises because of H/D geminal coupling. Also, since the 0.95 signal integrated for roughly two thirds of the other methyl signals, it is clear that only the C-9 methyl was deuterated.

SCHEME II



Treatment of camphor-*9-d*$_1$ with sulfuric acid in acetic anhydride[16] afforded 10-camphorsulfonic-*9-d*$_1$ acid (**9**-*9-d*$_1$). Reduction of **9**-*9-d*$_1$ with sodium borohydride and subsequent cyclization with *p*-tolylsulfonyl chloride in pyridine gave the desired 10-isobornyl-*9-d*$_1$ sultone (1-*9-d*$_1$). The sultone was contaminated with a small amount (*ca.* 5%) of ethyl tosylate (EtOTs), which probably arose from tosyl chloride reacting with a trace amount of ethanol left over from the previous step.[17] The nmr spectrum of 1-*9-d*$_1$ was identical with the undeuterated sultone **1**, except that the upfield methyl signal at δ 0.95 was broadened due to H/D coupling and integrated for only around two protons relative to the other signals.

Optical Studies.—The fact that the preparations of 9-deuterio- and 3,3-dideuterio-10-isobornyl sultones showed no scrambling of the deuterium label must mean that the deuterated analog of ion **8** closes to the sultone prior to 6,2-hydride shifts. It seems quite likely that ion **8** is an intermediate in the cyclization step, **10** → **1**; regardless of the geometry[18] of the epimeric tosylates **11**, displacement of –OTs by the poor nucleophile RSO_3^- is geometrically prohibited in this system. Although molecular models suggest that both exo and endo closures of **8** are feasible, only an exo sultone **1** is formed. In order to verify these results and determine the actual degree of stereospecificity in the cyclization step, the optical integrity of these reactions was studied. This was accomplished by directly comparing a derivative common to both starting material and product. The reactions are outlined in Scheme III[19] and definitely show that no racemization occurred in the tosylate cyclization since **19** had the same rotation whether derived from **18** or **20**.

A few years ago we observed that sulfonation of camphene, which was partially optically active gave, what appeared to be optically inactive 10-isobornyl sultone (**1**) (eq 1).[3] Since 10-isobornyl sultone (**1**) prepared from 10-camphorsulfonic acid (96% optically pure) had such a small observed rotation, *ca.* 0.05°,[20] it is not surprising that **1** prepared from partially active

(9) At inlet temperatures of *ca.* 100°, **1** rearranges to the other sultones, but one is not certain what the exact composition is and, consequently, the interpretation of the spectrum would be on shaky grounds. A unique spectrum of **1** can be obtained at 100°, but its fragmentation patterns are complicated.

(10) The loss of SO_2 seems to be a reasonable postulate for the m/e 152 peak (weak) but, unfortunately, high resolution spectra were not available to collaborate this. Unsaturated sultones are known to thermally lose SO_2 to give furans: A. Mustafa, in "Organic Sulfur Compounds," Vol. I. N. Kharasch, Ed., Pergamon Press, New York, N. Y., 1961, p 186.

(11) *d*-Camphor was chosen over *dl*-camphor since the 3-bromo derivative (**9**) of *d*-camphor could be obtained crystalline in high yield while the 3-bromo derivative of *dl*-camphor is difficult to crystallize. Problems in purifying racemic **9** have been reported by A. W. Ingersoll and S. H. Babcock, *J. Amer. Chem. Soc.*, **55**, 341 (1933), and references cited therein.

(12) W. L. Meyer, A. P. Lobo, and R. N. McCarty, *J. Org. Chem.*, **32**, 1754 (1967).

(13) E. J. Corey, S. W. Chow, and R. A. Scherrer, *J. Amer. Chem. Soc.*, **79**, 5773 (1957).

(14) K. M. Baker and B. R. Davis, *Tetrahedron*, **24**, 1655 (1968).

(15) The assignment of the methyl signals is based on a shift reagent study of camphor: C. C. Hinckley, *J. Org. Chem.*, **35**, 2834 (1970).

(16) P. D. Bartlett and L. H. Knox, *Org. Syn.*, **45**, 12 (1965).

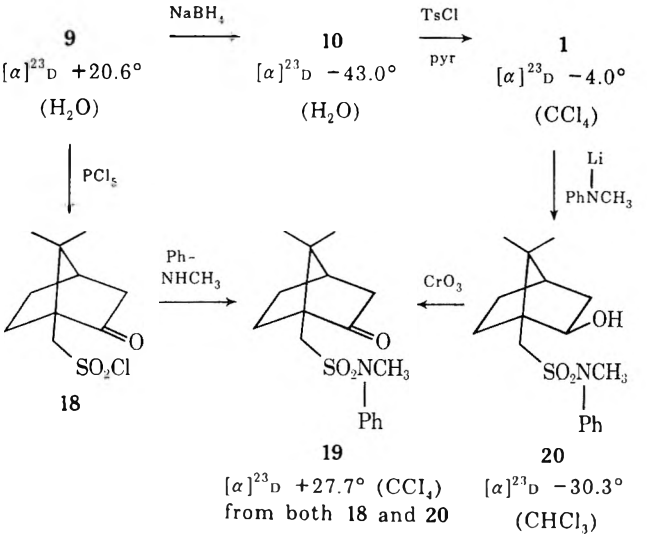
(17) The ethyl tosylate impurity was difficult to separate because its functionality is very similar to that of the sultone. The sultone is quite labile toward various types of chromatography and recrystallization was only partially successful.

(18) A comparison of the nmr spectra of **6** derived from sodium borohydride and sodium/ethanol reduction of **5** showed a 9:1 mixture of isomers in the case of $NaBH_4$ and a 3:2 mixture with Na/EtOH. This similarity to the reductions of camphor suggests that the exo-2-hydroxy sulfonate is the major isomer.

(19) The experimental details for the optically inactive series of some of these reactions are reported in ref 3.

(20) A solution of 0.1541 g of 10-isobornyl sultone in 25 ml of CCl_4 when placed in a 2-dm cell gave an average rotation of −0.05°, but the deviation ranged from 0.00 to −0.10°.

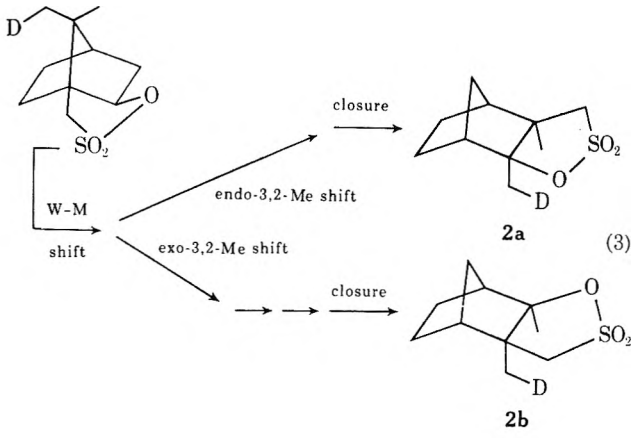
SCHEME III



camphene would appear optically inactive. In order to determine the extent of racemization occurring in the sulfonation reaction, camphene, $[\alpha]^{23}D$ +39.8 ± 0.2° (ether) (38.4 ± 0.2% optically pure),[21] was treated with sulfur trioxide–dioxane complex[19] to afford 10-isobornyl sultone, which in turn was allowed to react with *N*-lithio-*N*-methylaniline to give **20**, $[\alpha]^{23}D$ −11.5 ± 0.5° ($CHCl_3$). Since 96% optically pure **20** has a rotation of $[\alpha]^{23}D$ −30.3 ± 0.7°, the optical purity of **20** obtained from the sulfonation reaction was 36.5 ± 2.4%. Consequently, the sulfonation reaction appears to be at least 95% stereospecific, implying that racemizing 6,2-hydride shifts do not occur to any great extent prior to ion **8** cyclization to sultone **1**.

Wagner–Meerwein rearrangement with the absence of 6,2-hydride shifts has been observed by Winstein and coworkers using poor ionizing solvents.[22] The sulfonations of camphene in tetrachloroethylene–dioxane solvent, as reported here, also appear to be an example of a Wagner–Meerwein rearrangement occurring with the exclusion of 6,2-hydride shifts.

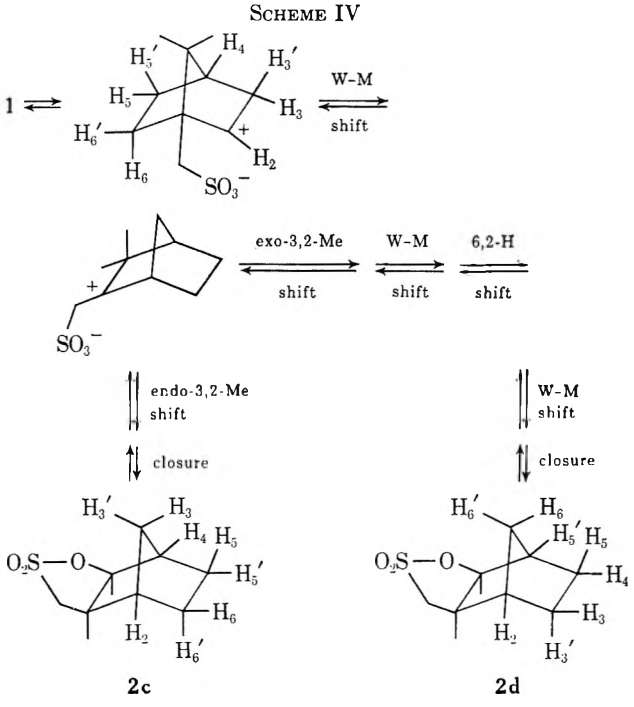
Thermal Rearrangements.—The simplest way to establish which methyl migrates during the rearrangement of **1** to **2** is to label one of the methyl groups and see which one ends up on the C-2 carbon. According to a mechanism involving an endo-3,2-methyl shift, the C-9 methyl of **1** becomes the C-2 methyl of **2**. With an exo-3,2-methyl shift prevailing, the C-9 methyl of **1** would become the C-3 methyl of **2**. Equation 3 indicates the anticipated results.



The neat thermal rearrangement of **1**-*9*-d_1 at 140° for 20 min afforded, after sublimation, *exo*-camphene-d_1 sultone (**2**-d_1). The nmr spectrum of **2**-d_1 was complicated by the fact that there were minor amounts of **3** and EtOTs present; however, even with these substances present, it was clear from the spectrum that the deuterated *exo*-camphene sultone was a 50:50 mixture of **2a** and **2b** (see Experimental Section). Thus, the thermal rearrangement of **2** either involves a nonselective migration of methyl groups, which seems quite unlikely, or rapid 6,2-hydride shifts occur which render the two methyl groups identical. Indeed, the latter possibility appears quite real since the thermal rearrangement of nearly optically pure **1**, $[\alpha]^{23}D$ −4.0°, gave optically inactive **2**, presumably *via* racemizing 6,2-hydride shifts. A derivative of **2**, the hydroxy sulfone **20**, was also optically inactive. Although the rotations of optically pure **2** and **20** were not known, it seems highly unlikely that both compounds would have no rotations at the sodium D line.

Although the rearrangement of **1**-*9*-d_1 did not answer the question as to which methyl migrates, the 3,3-dideuterio derivative could provide the answer. Scheme IV[23] indicates where the hydrogens of **1** would

SCHEME IV



end up in the product, *exo*-camphene sultone, considering the two mechanisms. Assuming ion **8** undergoes rapid 6,2-hydride shifts, the label at C-3 would get spread to the C-5 hydrogens and could, in the case of the exo-methyl shift mechanism, work its way into the C-1 position of the product. Consequently, an observation of about 50% deuterium at C-1 of **2** would establish an exo-methyl shift mechanism, while no

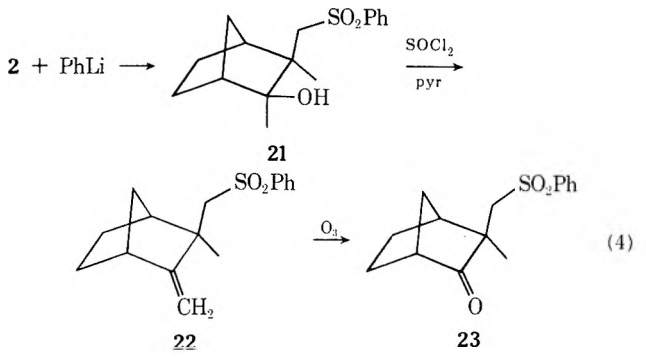
(21) The absolute rotation for *d*-camphene is $[\alpha]^{17}D$ +103.5° in ether: "The Merck Index," 8th ed, P. G. Stecher, Ed., Merck & Co., Rahway, N. J., 1968, p 198.

(22) A. Colter, E. C. Friedrich, N. J. Holness, and S. Winstein, *J. Amer. Chem. Soc.*, **87**, 378 (1965).

(23) Exact details of the various steps in the rearrangement can be found in ref 1.

deuterium at C-1 of **2** would favor the endo-methyl shift mechanism.

It would seem to be a simple task to pick up the extent of label at the C-1 position of **2** by employing the reactions outlined in eq 4. The nmr spectrum of



(4)

nondeuterated keto sulfone **23** displayed signals at δ 3.33 and 2.50, which were assigned to the syn-7 and C-1 protons, respectively. The assignment of these protons to the two signals was based on a comparison of the nmr spectra of **23–28** (Table I). The keto sulfone

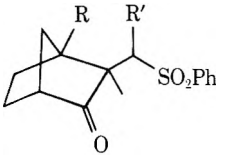
TABLE I

NMR CHEMICAL SHIFTS (δ UNITS) OF SOME SELECTED NORBORNYL DERIVATIVES

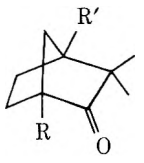
Compd	C-1 H	C-4 H	Syn-7 H
23	2.50	<2.0	3.30
24	2.44		3.05
25[a]	2.59	<2.5	3.54
26	2.45	2.20	<2.0
27	2.45		<2.2
28		2.12	<1.9

[a] The only spectrum taken[3] in $CDCl_3$; all others employed CCl_4 as the solvent.

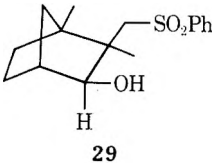
24 was prepared by oxidation of the known hydroxy sulfone **29**.[3] Compound **24**, like **25**, showed two single



24, R = CH_3; R′ = H
25, R = H; R′ = Et



26, R = R′ = H
27, R = H; R′ = CH_3
28, R = CH_3; R′ = H

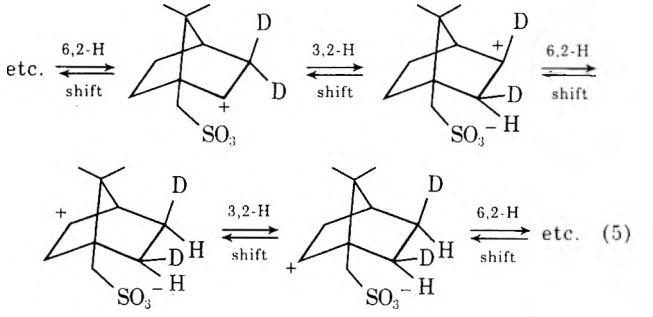


29

proton downfield multiplets; since there is a methyl at C-4 and the signal at δ 2.43 corresponds very closely to the 2.45 signal of **26** and **27**, the only logical candidate for the 3.05 signal is the syn-7 hydrogen. By analogy, the peaks were then assigned to **23**. It is quite possible that the C-4 hydrogen of **23** is shifted upfield just as the C-4 methyl of **24** appears to be. Molecular models prove very beneficial in understanding the large downfield shift of syn-7 hydrogens of **23** and **24**. Based on the premise that there will be strong repulsive forces between the oxygens of the carbonyl and SO_2 group, conformations naturally arise which place the syn-7 hydrogen very close to one of the sulfonyl oxygens.

Heating 10-isobornyl-*3,3-d*$_2$ sultone for 3 hr in refluxing *n*-octane (bp 124°) gave *exo*-camphene-*d*$_2$ sultone. An nmr spectrum of the resulting deuterated sultone showed, relative to the $-CH_2SO_2-$ signal, an approximate decrease of 1.5 protons in the δ 1.2–1.7 region, which contains the methyl groups and the hydrogens attached to C-5, C-6, and anti-C-7, and a decrease of 0.5 proton in the δ 1.9–2.4 region, which probably corresponds to the two bridgehead hydrogens and syn-7 hydrogen. In order to more accurately locate the positions of the deuteriums, *exo*-camphene-*d*$_2$ sultone was converted to deuterated keto sulfone **23**. Relative to the integrated area of the $-CH_2SO_2-$ signal, the nmr spectrum of deuterated **23** was compared to undeuterated **23** to give δ 7.57 and 7.93 (area 5.00, phenyl protons), 3.33 (area 0.96, syn-7 proton), 3.00 (area 2.00, $-CH_2SO_2-$ protons), 2.50 (area 0.59, C-1 proton), 1.35–2.18 (area 4.43, anti-7, C-4, C-5, and C-6 protons), and 1.30 (area 3.00, methyl protons).

The distribution of the deuterium label in the keto sulfone is indicative of an exo-3,2-methyl shift mechanism. The small amount of deuterium at the syn-7 position and less than 50% deuterium at C-1 in **23**-*d*$_2$ may be due to experimental error, the occurrence of small amounts of endo-3,2-methyl shift, or scrambling of the label *via* 6,2- and 3,2-hydride shifts, as shown in eq 5.



(5)

Sultone 1-*3,3-d*$_2$ was also rearranged to *exo*-camphene sultone (2-*d*$_2$) by heating the compound neat at 150° for 30 min. The resulting deuterated sultone was converted to the keto sulfone **23**-*d*$_2$, which had the following nmr spectrum: δ 3.33 (area 0.8) assigned to the syn-7 hydrogen, 3.00 (area 2.0) assigned to the $-CH_2SO_2-$ protons, and 2.50 (area 0.7) assigned to the C-1 bridgehead proton. The incorporation of deuterium at both the syn-7 and C-1 positions can be best explained by a scrambling procedure as outlined in eq 5.

Conclusions

The syntheses of the *3,3-d*$_2$ and *9-d*$_1$ analogs of 10-isobornyl sultone from the corresponding labeled 10-camphorsulfonic acids indicate that a 2-norbornyl cation, **8**, can exist momentarily without undergoing 6,2-hydride (racemization) shifts. The retention of optical activity in going from optically active 10-camphorsulfonic acid to 10-isobornyl sultone to the ketosulfonanilide **19** verifies that the cyclization of **10** to **1**, *via* cation **8**, is highly stereospecific. However, rapid 6,2-hydride shifts do occur in the thermal rearrangement

of **1** to **2**, as proven by the loss of optical activity which accompanies this rearrangement and the scrambling of the deuterium label in the rearrangement of both **1-9-d_1** and **1-3,3-d_2**. Why should racemization reactions occur in the thermal rearrangement of **1** and not in the preparation of **1**? A possible answer is that in the preparation of sultone **1** cyclization of ion **8** is very rapid in comparison to 6,2-hydride shifts, while 6,2-hydride shifts are probably rapid[24] in comparison to the 3,2-methyl shift which is necessary for the conversion of **1** to **2**.

Extensive scrambling of the deuterium, presumably *via* a combination of 6,2- and 3,2-hydride shifts, occurs in the high-temperature neat thermal rearrangement of **1-3,3-d_2**. The milder rearrangement conditions of refluxing *n*-octane do not extensively scramble the label of **1-3,3-d_2** such that the deuterium pattern in the product (and its derivatives) can be deciphered to show that an exo-3,2-methyl shift occurs in preference to an endo-3,2-methyl shift in the formation of sultone **2**. Although it is difficult to come up with an accurate number from the nmr spectrum of **23-d_2**, the proportion of endo-3,2-methyl shift must be at best only a few per cent. Our results are in agreement with those of Vaughan and coworkers,[25] who, by means of carbon-13 nmr, showed that the proportion of endo-3,2-methyl shifts in competition with exo-3,2 shifts is only 0–5%.

Experimental Section[26]

Sodium *l*-10-(2-Hydroxy)bornanesulfonate (10).—An aqueous solution of 46 g (0.20 mol) of *d*-10-camphorsulfonic acid (**9**)[27] in 100 ml of water was slowly added to a large beaker containing an excess of sodium borohydride (14 g, 0.27 mol). After all the sulfonic acid was added, the aqueous solution was concentrated with a rota-evaporator and the residue thoroughly dried in a 110° oven. The powdered solid was placed in a Soxhlet and extracted with absolute alcohol, which removed the sulfonate salt from the inorganic salts. The ethanolic extract was evaporated to afford a quantitative yield of **10**: ir (KBr) 3500, 1150, 1050 cm^{-1}; $[\alpha]^{23}D$ −43.0° (*c* 10, H_2O).[3]

***l*-10-Isobornyl Sultone (1).**—To a rapidly stirred, cold solution of 35 g (0.132 mol) of dried sodium *l*-10-(2-hydroxy)bornanesulfonate (**10**) in 80 ml of anhydrous pyridine was added 45 g (0.236 mol) of recrystallized *p*-tolylsulfonyl chloride. The reaction flask was allowed to warm to room temperature and stirred for 5 hr. The mixture was then poured into 20 g of water–ice slurry, filtered to give 27.7 g (98%) of solid, and recrystallized from hexane to give **1**: mp 116–116.5° (lit.[3] mp 117–119°); $[\alpha]^{25}D$ −4.05° (*c* 10, CCl_4); ir (Nujol) 1340, 1175, 877, 812, and 725 cm^{-1}; nmr (CCl_4) δ 4.30 (d of d, 1, *J* = 4 and 7 Hz, HCO), 3.12 (s, 2, $-CH_2SO_2-$), 1.2–2.5 (m, 6, ring protons), 1.11 (s, 3, syn-CH_3), and 0.94 (s, 3, anti-CH_3).[3]

Preparation of 3,3-Dideuterio-10-isobornyl Sultone (1-3,3-d_2).—A solution of 25 g (0.108 mol) of 10-camphorsulfonic acid (**9**), recrystallized and dried, in 25 ml of 99.7% deuterium oxide was refluxed for 2 days. The solvent was distilled off and the residue dried in a 110° oven overnight. The residue was then combined with a fresh 25 ml of 99.7% D_2O and refluxed for another 2 days. An nmr at this point, in the solvent D_2O, showed δ 3.32 (d, 1, one of the $-CH_2SO_2-$ protons, *J* = 15 Hz), 2.83 (d, 1.1, one of the $-CH_2SO_2-$ protons, *J* = 15 Hz), 1.2–2.6 (m, 5, ring protons), 1.03 (s, 3, syn-7-CH_3), and 0.83 (s, 3, anti-7-CH_3).

The previous D_2O solution of **9-3,3-d_2** was added gradually to 12 g (0.32 mol) of sodium borohydrde dissolved in a little D_2O and kept at ice-bath temperatures. After the addition was complete, the solvent was slowly distilled off. The green residue was dried in an oven to yield a purple solid. This dried material was placed in a Soxhlet extractor and extracted with absolute ethanol. Evaporation of the ethanol gave, after drying, 23 g (90%) of slighly pink solid (**10-3,3-d_2**): nmr (D_2O) δ 4.07 (s, 1, HCO), 3.34 (d, 1, one of the $-CH_2SO_2-$ protons, *J* = 14.5 Hz), 2.82 (d, 1, one of the $-CH_2SO_2-$ protons, *J* = 14.5 Hz), 1.1–1.9 (m, 5, ring protons), 1.02 (s, 3, syn-CH_3), 0.86 (s, 3, anti-CH_3), and singlets at 3.04 and 0.93 for the $-CH_2SO_2-$ and methyls of a minor alcohol (about 10%).

Using the same procedure as the nondeuterated compounds, 6.5 g of deuterated sodium 10-isobornylsulfonate (**10-3,3-d_2**) was cyclized to yield 4.2 g (76%) of deuterated 10-isobornyl sultone: mp 120–121°; nmr (CCl_4) δ 4.28 (s, 0.82, HCO), 3.12 (s, 1.81, $-CH_2SO_2-$), 1.2–2.1 (m, 5.00, ring protons), 1.11 (s, 3.06, syn-CH_3), and 0.95 (s, 3.00, anti-CH_3). The nmr spectrum of nondeuterated 10-isobornyl sultone was identical to the one just described except that the δ 1.2–2.1 region integrated for 6.9 protons and the signal at 4.28 was a doublet of doublets.

4-Methyl-9-(phenylsulfonyl)camphenilone (24).—An ethereal solution of 83 mg (0.3 mmol) of 4-methyl-9-(phenylsulfonyl)-camphenilol (**29**) was treated with 0.3 mmol of Jones reagent. After stirring for 1 hr, the ether was separated, washed with sodium bicarbonate solution and water, dried with sodium sulfate, and evaporated to yield an oily residue: nmr (CCl_4) δ 7.42–7.98 (m, 5, aryl H), 3.05 (m, 1), 2.44 (m, 1), 1.2–1.8 (m, 8, with a singlet methyl at 1.30), and 0.80 (s, 3, CH_3).

D-3-Bromocamphor (13).—This compound was prepared in 81% yield according to the procedure of Meyer, *et al.*[12] The bromo ketone **13** had mp 68–70°; ir 1770 cm^{-1}; nmr (CCl_4) δ 4.54 (d, *J* = 5 Hz), 1.09 (s, 3), 0.97 (s, 6) (lit.[12] mp 76°).

D-3,9-Dibromocamphor (14).—This compound was prepared in 86% yield according to the procedure of Corey, *et al.*[13] The dibromo ketone **14** had mp 147–152°; ir 1745 cm^{-1}; nmr (CCl_4) δ 4.54 (d, *J* = 5 Hz), 3.68 and 3.28 (neq,[29] *J* = 10 Hz), 1.14 (s, 6) (lit.[27] mp 152–153°).

D-9-Bromocamphor (15).—This compound was prepared in 45% yield according to the procedure of Corey, *et al.*[13] The bromo ketone **15** had mp 71–75°; ir 1750 cm^{-1}; nmr (CCl_4) δ 3.60 and 3.17 (neq, *J* = 10 Hz), 1.01 (s, 3), 0.92 (s, 3) (lit.[28] mp 93–94°).

Camphor-9-d_1 (12-9-d_1).[14]—To a mixture of 50 g (2.5 mol) of deuterium oxide and 253 g (2.48 mol) of freshly distilled acetic anhydride was added 25.5 g (0.11 mol) of 9-bromocamphor. The mixture was stirred and kept cold on an ice bath in an inert atmosphere (nitrogen and drying tube). Zinc powder (49 g) was added in small portions such that the exothermic reaction was kept under control. The mixture was stirred for 48 hr at 40° and filtered. The filtrate was neutralized with $NaHCO_3$ and extracted three times with ether; the combined ether extracts were washed with saturated $NaHCO_3$ and water. The ether solution was dried ($MgSO_4$) and concentrated to give 14 g (83%) of a yellow liquid. Vpc analysis showed 65% camphor, 29% dihydrocarvone (**16**), and 6% of an unidentified material assumed to be **17**.[14] A flask containing 5 g of the above mixture in ether was kept in the dark at 5°. Bromine was added dropwise to the mixture with stirring. The ether solution was washed with saturated $NaHSO_3$, dried ($MgSO_4$), concentrated, and dis-

(24) J. A. Berson, J. H. Hammons, A. W. McRowe, R. G. Bergman, A. Remanick, and D. Houston, *J. Amer. Chem. Soc.*, **89**, 2590 (1967). A careful examination of the solvolysis products of *d*-3-*exo*-methyl-2-norbornyl cation reveals that Wagner–Meerwein and 6,2-hydride shifts are more rapid than either 3,2-methyl or hydride shifts. The retention of optical purity of the product 2-*endo*-methyl-2-*exo*-norbornyl acetate suggests the preference for a circuitous route of Wagner–Meerwein, 6,2-hydride, Wagner–Meerwein and 3,2-hydride shifts; a 3,2-methyl shift, *i.e.*, racemization, is stringently avoided.

(25) C. W. David, B. W. Everling, R. T. Killian, J. B. Stothers, and W. R. Vaughan, *J. Amer. Chem. Soc.*, **95**, 1265 (1973).

(26) All boiling points and melting points are uncorrected. Infrared spectra were determined with a Perkin-Elmer Infracord spectrophotometer, Model 137B. Nmr spectra were obtained on a Varian A-60A spectrometer, using TMS or DSS as internal standards and D_2O or CCl_4 as solvents. Mass spectra were obtained using a CEC 21-103 mass spectrometer. Optical rotations at the sodium-D line were measured in water or CCl_4, using a Rudolph Model 70 polarimeter and a 1-dm polarimeter tube. Deuterium oxide, 99.7%, was supplied by Aldrich Chemical Co. Gas chromatographic analyses were performed on a 6 ft × 0.25 in. aluminum column packed with SE-30 on 60–80 mesh Chromosorb W or an 8 ft × 0.25 in. aluminum column packed with DEGS on 30–60 mesh Chromosorb W, using an F&M Model 700 gas chromatograph.

(27) The *d*-10-camphorsulfonic acid was purchased from Aldrich Chemical Co., Milwaukee, Wis., and recrystallized prior to use. The observed specific rotation was +20.6° as a concentrated solution in water. The reported rotation is $[\alpha]^{20}D$ + 21.5° (H_2O); "The Merck Index," ref 21, p 199.

(28) F. S. Kipping and W. J. Pope, *J. Chem. Soc.*, **67**, 371 (1895).

(29) Nonequivalent methylene protons.

tilled to yield 2.50 g of a crude yellow solid [95–100° (0.4 mm)], which was further purified by sublimation at atmospheric pressure to afford 1.70 g of product: mp 176–179°; nmr (CCl_4) indicated that the deuterium was located at the C-9 methyl;[16] a mass spectrum showed 11% d_0, 79% d_1, and 10% d_2.

9-Deuterio-10-isobornyl Sultone (1-9-d_1).—9-Deuterio-10-camphorsulfonic acid (9-9-d_1) was prepared in 51% yield according to the procedure of Bartlett and Knox.[16] The sulfonic acid 9-9-d_1 was reduced with sodium borohydride and cyclized with *p*-tolylsulfonyl chloride in pyridine according to our procedure reported earlier in this paper. The desired sultone 1-9-d_1 was contaminated with a small amount (*ca.* 5%) of ethyl tosylate (EtOTs). This mixture was repeatedly washed with hot hexane. The hexane solution was concentrated to afford 0.2 g of 1-9-d_1, still containing *ca.* 2% EtOTs. Its nmr spectrum (CCl_4) showed δ 4.30 (d of d, 1, J = 4 and 7 Hz, HCO), 3.12 (s, 2, $-CH_2SO_2-$), 1.2–2.5 (m, 6, ring protons), 1.11 (s, 3, syn-CH_3), and 0.95 (m, 2, anti-CH_2D).

***exo*-Camphene Sultones (2a and 2b).**—9-Deuterio-10-isobornyl sultone (1-9-d_1) (0.1 g), containing *ca.* 2% EtOTs, was warmed at 140° for 20 min and sublimed (0.4 mm) to afford *ca.* 50 mg of a mushy solid: ir (CCl_4) 1330, 1280, 868 cm^{-1}; nmr (CCl_4) δ 7.21–7.7 (m), 4.08 (q, J = 7 Hz), 3.36 and 2.80 (neq J = 14 Hz), 3.00 (s), 1.50 (s), 1.28 (m). The ratio of exo isomer to endo isomer and to EtOTs in this mixture was 47:35:18, as ascertained by integration of the $-CH_2SO_2-$ resonances of exo sultone (2-d_1) (δ 3.00), the endo sultone (3-d_1) (δ 3.36 and 2.80), and the $-CH_2O$ resonance of EtOTs (δ 4.08). The methyl signal of the sultone 2-d_1 at δ 1.28 was masked by the triplet methyl signal of EtOTs at δ 1.29. A mixture of sultones 2 and 3 and EtOTs in a ratio of 47:34:19 was prepared; the nmr (CCl_4) of this mixture was identical with the deuterated mixture. The integration ratio of the two methyl signal at δ 1.50 and 1.28 (39:27) was also identical with the methyl signal ratio of the deuterated mixture.

An nmr spectrum of a small amount of material which was not sublimed in the above procedure was identical with the nmr spectrum of nondeuterared *exo*-camphene sultone; the impurities of sultone 3 and ethyl tosylate were apparently sublimed out. The great similarity of what is supposed to be deuterated 2 with nondeuterated 2 adds additional support for the deuterium label being spread equally between the two methyl groups. (A content of 40% deuterium in one of three hydrogens of a methyl group may not significantly change the shape of the signal.)

Solution Rearrangement of 10-Isobornyl-3,3-d_2 Sultone.—A solution of 4.0 g of 10-isobornyl-3,3-d_2 sultone (1-3,3-d_2) in approximately 25 ml of *n*-octane was refluxed for 3 hr. The hot octane solution was decanted from the black residue and cooled to give 0.7 g of colorless crystals of *exo*-camphene sultone (2-d_2). A comparison of the integrated areas of 2 with 2-d_2 showed that the latter compound had the following nmr spectrum: δ (CCl_4) 3.00 (s, 2.0, $-CH_2SO_2-$), 1.9–2.4 (m, 2.5, probably C-1, C-4, and syn-C-7 protons), and 1.2–1.7 (m with 2 s at 1.28 and 1.50, 9.5, remaining ring hydrogens and 2 methyls); mass spectrum (70 eV) *m/e* (rel intensity) 39 (19), 41 (25), 42 (18), 43 (100), 44 (17), 67 (31), 68 (41), 69 (50), 84 (25), 85 (16), 111 (27), 148 (29), and 149 (19). The octane filtrate was added to the black residue and evaporated. The resulting residue was extracted several times with hot hexane and cooled to give an additional 1.5 g (55% overall isolated yield) of solid which had the same spectral characteristics as those described above.

Using previously described procedures,[3] the deuterated *exo*-camphene sultone was converted to the deuterated keto sulfone 23-d_2. A comparison of the nmr spectrum of 23 and 23-d_2 gave the following results for 23-d_2: nmr (CCl_4) δ 7.93 (m, 2.00, *o*-H of Ph), 7.57 (m, 3.00, *m*- and *p*-H of Ph), 3.33 (m, 0.96, syn-7 proton), 3.00 (s, 2.00, $-CH_2SO_2-$), 2.50 (m, 0.59, C-1 proton), 1.35–2.18 (m, 4.43, anti-7, C-4, 5 and 6 protons), and 1.30 (s, 3.00, CH_3).

Neat Rearrangement of 10-Isobornyl-3,3-d_2 Sultone.—In a 50-ml round-bottom flask under a N_2 atmosphere 1 g of 10-isobornyl-3,3-d_2 sultone (1-3,3-d_2) was heated at 150° for 30 min. It took about 2 min for the solid to melt and another 2 min for it to turn brown. The dark-colored solid was recrystallized twice from hexane to give 0.44 g of colorless solid, mp 131–133°. The nmr and mass spectra were similar to the other sample of 2-d_2 prepared above. This sultone was converted to the keto sulfone 23-d_2, which showed an nmr spectrum very similar to the other sample of 23-d_2 prepared above except that the δ 3.33 and 2.50 multiplets integrated for 0.8 and 0.7 protons, respectively.

Registry No.—1, 41348-33-8; 1-9-d_1, 41348-34-9; 1-3,3-d_2, 41348-35-0; 2-d_2, 41348-30-5; 2a, 41348-36-1; 2b, 41348-37-2; 3-d_1, 41348-31-6; 9, 3144-16-9; 9-9-d_1, 41348-39-4; 9-3,3-d_2, 41348-40-7; 10, 41348-41-8; 10-3,3-d_2, 41348-42-9; 12-9-d_1, 41348-43-0; 13, 41348-44-1; 14, 10293-10-4; 15, 10293-09-1; 23-d_2, 41348-32-7; 24, 41348-47-4; 29, 41523-55-1.

Carbon-13 Nuclear Magnetic Resonance Spectra of Keto Steroids

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Fourier transform C-13 nuclear magnetic resonance spectra have been obtained and assigned for a complete series of keto steroids—the steroid skeletons being those of androstane and cholestane. The assignments were performed by comparing the spectra of these closely related compounds and correlating the shifts due to differences in structure, and by use of off-resonance decoupled spectra. Furthermore, the spectra of a series of specific deuterium-labeled analogs have been obtained for assignment purposes. The assignments show strong internal consistency. It is shown that previous assignments to C-12 and C-16 in these systems is erroneous. The effects of deuterium substitution in the steroid system are described, and the observed deuterium isotope shifts are presented.

While it is now possible to obtain high-resolution carbon-13 nuclear magnetic resonance (cmr) spectra of larger molecules such as steroids within a reasonably short time using pulsed Fourier transform technique, the task of assigning the spectra even of known steroids is still far from routine; day-to-day use of cmr with the purpose of structure elucidation in the steroid field is therefore not yet possible, even though it is quite apparent that cmr spectroscopy has great potential in this respect, as illustrated by the cmr spectra of some 30 steroids investigated by Roberts, *et al.*[2] A few other investigations have dealt with cmr of steroids,[3-6] but a considerable amount of well-documented (empirical) correlations of chemical shifts are needed before it is possible to predict the cmr spectrum of a given ste-

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roidal structure, a necessary prerequisite before applying cmr spectroscopy to routine structural elucidation. This has led us to undertake a systematic investigation of the cmr spectra of steroids, and in this paper we describe the results obtained for steroidal ketones.

Experimental Section

The Fourier transform cmr spectra were recorded using a Varian XL-100-15 spectrometer operating at 25.2 MHz, equipped for pulsed Fourier transformation. The instrument was controlled *via* a Varian 620i computer.

Spectra were obtained in $CDCl_3$ solution with internal TMS as standard. Field frequency lock was established *via* the deuterium resonance of the solvent. Sample concentrations varied from 0.1 to 1.0 *M* solutions. To examine the influence of concentration on chemical shifts, the cmr spectra of 1.0, 0.5, and 0.25 *M* solutions of 7-cholestanone were recorded. The shieldings of all carbons, except the carbonyl carbon, remained within the limits of the experimental reproducibility (less than 0.1 ppm). The chemical shift of the carbonyl carbon exhibited a small but significant concentration dependence, becoming 0.2 ppm more deshielded for each 1:1 dilution. Probe temperature for all experiments was *ca.* 30°.

The steroids used in this investigation were all prepared in this laboratory by already published methods. Most of the labeled compounds studied have been described previously (see Table II). Compounds **7**, **8**, **12**, and **14**–**16** were prepared by base-catalyzed exchange of enolizable hydrogen atoms with $MeOD/MeO^-$ or $MeOD/OD^-$.[7] **2** was prepared by reduction of 17-androstanone to 17-d_1-17-androstanol with lithium aluminum deuteride, conversion to the *N*,*N*,*N*′,*N*′-tetramethylphosphorodiamidate, and reduction of this as given by Ireland, *et al.*[8] Compound **4** was similarly prepared by lithium aluminum hydride reduction of **13** followed by reduction *via* the phosphate.[8,9]

Results

The compounds examined together with their C-13 chemical shift data are presented in Table I, while Table II lists the specific deuterium-labeled steroids for

TABLE I

C-13 CHEMICAL SHIFTS IN 5α-KETO STEROIDS[a]

Steroid	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
Androstane (A)	38.8	22.3	26.9	29.2	47.1	29.2	32.6[b]	36.0[c]	55.1[b]	36.4	20.9[c]	39.0[b]	40.8[c]	54.7	25.5	20.5[c]	40.5[b]	17.6	12.3								
Cholestane (B)	38.8	22.3	26.9[b]	29.2[c]	47.1	29.2	32.2	35.6	54.9	36.3	20.9	40.2	42.6	56.7	24.2	28.3	56.4	12.2	12.2	35.9	18.7	36.3	24.0	39.6	28.0	22.5	22.8
1-Androstanone (C)	215.8	38.3	28.0	28.0	49.8[b]	28.0	31.5[b]	36.2[c]	47.2	52.0	22.7	38.8	41.0	54.4	25.5	20.4	40.4	17.8	12.3								
2-Cholestanone (D)	54.1[b]	211.7	41.4[b]	28.3[c]	45.4	29.3	31.8	35.0	54.1	40.6[c]	21.0	39.9	42.6	56.4	24.3	28.3	56.4	12.1	12.6	35.8	18.7	36.2	23.9	39.6	28.1	22.5	22.8
3-Androstanone (E)	38.7[c]	38.1[b]	211.0	44.6[b]	46.7	29.0	32.1	35.7	54.1	35.7	21.5	38.8	40.8	54.3	25.5[c]	20.5[b]	40.3[b]	17.5	11.4								
3-Cholestanone (F)	38.5	38.1	211.2	44.6	46.7	29.0	31.7	35.6	53.8	35.4	21.4	39.9	42.5	56.2	24.2	28.2	56.2	12.1	11.4	35.7	18.7	36.1	23.8	39.5	28.0	22.5	22.8
4-Androstanone (G)	37.8[c]	20.5[b]	41.2[b,c]	212.6	59.3[c]	22.7[b,c]	30.9[b,c]	35.5[c]	54.5	42.6	21.8	38.9	40.8	54.8	25.5	20.5	40.4	17.6	13.8								
4-Cholestanone (H)	37.6	20.5	41.2	212.6	59.2	22.7	30.5	35.1	54.5	42.5	21.7	40.0	42.5	56.3	24.1	28.2	56.3	12.1	13.8	35.8	18.7	36.2	23.9	39.5	28.0	22.7	22.7
6-Androstanone (I)	38.3*	21.5	25.3	20.4	58.8	211.8	47.1	38.3	55.1*	41.8	21.2	38.5*	41.2	54.7*	25.3	20.5	40.2	17.5	13.1								
7-Cholestanone (J)	38.9*	21.8	26.5	29.2	49.1[c]	46.6[b]	211.3	50.1[b]	49.1	36.7	21.3	38.3*	42.5	55.1	25.0	28.5	56.2	12.1	11.6	35.7	18.8	36.2	23.8	39.5	28.0	22.5	22.8
11-Androstanone (K)	37.8	21.9	26.8	28.8*	46.9	28.5*	33.2	37.4	64.9[b]	36.0[c]	210.7	56.9[b]	44.9	54.2	24.9	20.9	39.3	18.2	12.1								
12-Androstanone (L)	38.3	21.9	26.6	28.8	47.0	28.8	31.7	35.0	56.5[c]	36.9	37.5[b]	215.3	54.9	54.6	24.8	19.5	31.9	17.7	11.9								
15-Androstanone (M)	38.7	22.2	26.8	29.0*	47.3	28.6*	30.8	32.5	55.0	36.5	20.4	39.4	39.2	63.4	216.1	35.1*	35.4*	18.3	12.2								
15-Cholestanone (N)	38.7	22.2	26.8	29.0*	47.2	28.7*	30.9	32.1	54.5	36.4	20.5	40.1	42.4	66.1	215.6	42.0	51.7	13.1	12.2	35.4	19.1	36.1	23.9	39.4	28.0	22.5	22.8
16-Androstanone (O)	38.4	22.1	26.8	29.0*	47.0	28.8*	32.4	35.0	54.7	36.5	20.4	38.4	39.2	51.9	39.3[b]	218.3	55.9[b]	18.1	12.3								
17-Androstanone (P)	38.6	22.1	26.7	29.0	47.0	28.8	31.7	35.1	54.9	36.4	20.1	31.0	47.7	51.6	21.7[c]	35.7[b]	220.4	13.8	12.2								

[a] In parts per million relative to TMS. Assignment of chemical shifts for close-lying peaks marked with an asterisk may be reversed. [b] Deuteration at this position causes the peak to "disappear." [c] Isotope shift observed upon deuteration at a neighboring carbon atom.

TABLE II

DEUTERIUM-LABELED STEROIDS EXAMINED

Compd no.	Compd
1	7β-d_1-Androstane[a]
2	17-d_1-Androstane
3	3α-d_1-Cholestane[a]
4	9α,12α-d_2-Androstane
5	5α-d_1-1-Androstanone[b]
6	7-d_1-1-Androstanone[b]
7	1,1,3,3-d_4-2-Cholestanone
8	2,2,4,4-d_4-3-Androstanone
9	16,16-d_2-3-Androstanone[c]
10	2,2,6,6-d_4-4-Androstanone[d]
11	3,3,7,7-d_4-4-Androstanone[d]
12	6,6,8-d_3-7-Cholestanone
13	9α,12α-d_2-11-Androstanone[e]
14	11,11-d_2-12-Androstanone
15	17,17,15,15-d_4-16-Androstanone
16	16,16-d_2-17-Androstanone

[a] L. Tökés and C. Djerassi, *J. Amer. Chem. Soc.*, **91**, 5017 (1969). [b] H. Powell, D. H. Williams, H. Budzikiewics, and C. Djerassi, *J. Amer. Chem. Soc.*, **86**, 2623 (1964). [c] L. Tökés, G. Jones, and C. Djerassi, *J. Amer. Chem. Soc.*, **90**, 5465 (1968). [d] J. Gutzwiller and C. Djerassi, *Helv. Chim. Acta*, **49**, 2108 (1966). [e] D. H. Williams, J. M. Wilson, H. Budzikiewicz, and C. Djerassi, *J. Amer. Chem. Soc.*, **85**, 2091 (1963).

(7) R. H. Shapiro, D. H. Williams, H. Budzikiewicz, and C. Djerassi, *J. Amer. Chem. Soc.*, **86**, 2837 (1964).

(8) R. E. Ireland, D. C. Muchmore, and U. Hengartner, *J. Amer. Chem. Soc.*, **94**, 5098 (1972).

(9) R. M. Muccino and C. Djerassi, unpublished results.

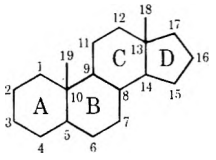
which supporting cmr data have been obtained. In some cases changes in the chemical shifts caused by deuterium substitution were measured; these are discussed below.

Cmr spectra have previously[2] been reported for two of the compounds in Table I, cholestane and 3-cholestanone. The chemical shifts reported earlier differ somewhat from ours, which are all displaced 0.1–0.7 ppm toward lower field, except for the carbonyl carbon in 3-cholestanone, which is 1.8 ppm more shielded. These differences are probably caused by the difference in solvent employed (dioxane–chloroform *vs.* chloroform) and the different instrumentation used.

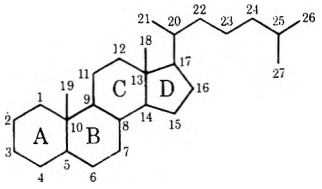
Androstane and Cholestane.—Since androstane and cholestane (Chart I) are the parent hydrocarbons of the

CHART I

STRUCTURES OF THE STEROID SKELETONS EMPLOYED, WITH THE STANDARD NUMBERING SYSTEM



androstane



cholestane

steroids studied in the present investigation, we found it important to establish the assignments of the cmr spectra of those compounds with a great deal of certainty. For androstane, the assignment was greatly facilitated by comparison with the off-resonance decoupled spectrum and with spectra of specifically labeled analogs (see Table II). By substitution of hydrogen by deuterium the intensity of the cmr signal for the carbon bearing the deuterium decreases dramatically.[2,10] This is a consequence of a combination of quadrupolar broadening, spin–spin coupling, and a decrease in the nuclear Overhauser enhancement. As a result the signals for deuterated carbon atoms have a very low intensity; this is the case even for carbon atoms not fully deuterated (see below).

The chemical shift values of the carbons C-1–C-10 and C-19 in androstane are expected to be nearly identical with those of cholestane, which have previously[2] been assigned, and a 1:1 correspondence is also found. These assignments are all in accordance with the off-resonance decoupled spectra and with the cmr data for the deuterated compounds **3**, **1**, and **4**, which allow unambiguous identification of the peaks due to C-3, C-7, and C-9. Furthermore, the isotope shifts often observed at carbons next to a deuterated carbon (see below) also corroborate this assignment. Of the remaining eight peaks in the androstane spectrum, one peak becomes a singlet (C-13), one a doublet (C-14), and one a quartet (C-18) in the off-resonance decoupled spectrum; the last five all become triplets. Among these, the peaks corresponding to C-12, C-16, and C-17 were identified from the spectra of the deuterated compounds **4**, **9**, and **2**. The C-11 position was distinguished from C-15 by comparison with the spectra of 1- and 16-androstanone. The peak assigned to C-11 is virtually unshifted in the spectrum of the 16-keto derivative, but shifts in the spectrum of 1-androstanone, whereas the position of the other peak remains unchanged by introduction of a keto group in the 1 position and changes when the keto group is in the 16 position; the latter is consequently assigned to C-15. The small isotope shift for C-11 observed in *9α,12α-d*$_2$-androstane confirms this assignment.

A comparison of the chemical shifts for the carbon atoms in rings C and D in androstane with those given[2] for cholestane appears to yield some very unusual substituent parameters for introduction of the C-17 side chain. Position 12, which is a γ carbon atom in relation to the 17-alkyl substituent, apparently shifts by −10.7 ppm, and C-16, which is β to the substituent, shifts by −19.7 ppm. Since the chemical shifts of these two atoms in the androstane spectrum have been unequivocally determined by the labeling data, we have reexamined the spectrum of cholestane. It appears that, if the previous[2] assignments for C-12 and C-16 are reversed, more reasonable (from the viewpoint of chemical shift theory) substituent values appear: +1.2 ppm for C-12 and +7.8 ppm for C-16. This (reversed) assignment for C-12 and C-16 (C-12, 40.2 ppm, and C-16, 28.3 ppm; *cf.* Table I) in cholestane is supported by several observations. For example, the spectrum of 15-cholestanone still retains the peak at 40 ppm while there is one less around 28 ppm, compared to the spectrum of cholestane. Furthermore, the chemical shift value for C-12 is expected to be close to the value for C-1 (which is found to be around 39 ppm), as C-1 and C-12 have very similar geometrical environments; likewise the chemical shift for C-16 should not be far from that of C-15. The argumentation given by Roberts, *et al.*,[2] in support of their assignment of C-12 and C-16 deals with steroids having keto or hydroxyl groups in the 17 position, and the assignments for C-12 and C-16 in those compounds agree very well with the results found in our work. Apparently, the chemical shift values for C-16 (36 ppm) and C-12 (31 ppm) observed in the spectra of 17-keto steroids have been the reason for the assignment of these two carbon resonances in the cholestanes examined, but a detailed argumentation was not given. Furthermore, the suggested assignment requires that the difference in substituent parameters for the side chain and a keto group be small in contrast to previous results.[11–13] We have found, however, that introduction of a keto group in the steroid skeleton shifts a CH_2 β carbon atom about 15 ppm downfield and that a CH_2 γ carbon atom eclipsed to the keto group, as C-12 is to a 17-keto group, is shifted 6–10 ppm upfield, in agreement with the results of Weigert and Roberts[11] for cycloalkanones. These substituent parameters, together with usual[12,13] values for alkyl substitution, provide further evidence for the reversed assignment for C-12 and C-16. The

(10) H. Spiesecke and W. G. Schneider, *J. Chem. Phys.*, **35**, 731 (1961).

(11) F. J. Weigert and J. D. Roberts, *J. Amer. Chem. Soc.*, **92**, 1347 (1970).
(12) L. P. Lindeman and J. Q. Adams, *Anal. Chem.*, **43**, 1245 (1971).
(13) D. M. Grant and E. G. Paul, *J. Amer. Chem. Soc.*, **86**, 2984 (1964).

reassigned cholestane spectrum has been used as reference for the cholestanones included in Table I. It should be noted that the earlier assignment for C-12 and C-16 in cholestanes has been used in other cmr work on steroids.[3,4,6,14]

Keto Steroids.—The assignment of chemical shift values to specific carbon atoms, as given in Table I, has been based on considerations given below.

In general, we have found that the effect of an oxo group in the steroid skeleton is limited to the chemical shifts of the α, β, γ, and δ carbon atoms (α being the carbonyl carbon), while the rest of the carbon atoms were found to give rise to resonances in essentially the same positions as in the corresponding hydrocarbon. The assignment of carbons remote from the carbonyl group to specific resonances is hence straightforward. Likewise, where labeled analogs were available (see Table II), the assignment of the labeled carbon atoms presents no problem. In many cases shielding effects are observed at carbon atoms that are neighbors to the labeled site (see footnotes to Table I); this effect has been utilized whenever present for assignment purposes.

The carbonyl carbon resonances are unequivocally identified, as they always appear in the lowest field region of the cmr spectra.[15]

Several alkyl-substituted cyclohexanones and cyclopentanones have been examined by Weigert and Roberts.[11] They report that the substituent parameters for the oxo group in these systems range from +11 to +18 ppm for β carbon atoms and from −3 to +3 ppm for γ and δ carbon atoms, except in one case, where a γ-carbon atom is eclipsed to the keto group, in which case a shift of −9 ppm was found. For a number of the steroids, substituent parameters could be extracted directly from the cmr spectra of deuterated analogs and were found to agree well with those found[11] for the simpler systems. These parameters were then used as rough guidelines for assignments in the remaining compounds.

Comparison of the spectra of closely related compounds, *e.g.*, androstanones and cholestanones, with the carbonyl group at the same position, together with data from off-resonance decoupled spectra, data from spectra of labeled compounds, and simple chemical shift considerations, was sufficient to allow complete assignment in all but a few cases. 11-Androstanone is such a case, where differentiation between C-1 and C-17 is not immediately possible. To clarify this point the cmr spectrum of 3β-hydroxy-11-androstanone was obtained, and the unshifted one of the two peaks in question was assigned to C-17. Likewise, in the spectrum of 12-androstanone distinction between the C-9 and C-14 and the C-7 and C-17 resonances was not obvious. A comparison with the spectrum of 5α,12-pregnanone allows the assignment to be made, since only C-14 and C-17 are expected to shift significantly as a result of introduction of the C-17 side chain. Differentiation between close-lying peaks is not always possible, nor always meaningful; such pairs of peaks are designated with asterisks in Table I.

(14) A. Allerhand, D. Doddrell, and R. Komoroski, *J. Chem. Phys.*, **55**, 189 (1971).

(15) See, for example, G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists," Wiley-Interscience, New York, N. Y., 1972.

Discussion

The influence of different structural environments on the chemical shift of the carbonyl carbon is well illustrated in this series with keto groups at all possible positions of the steroid skeleton. It has previously[11,16,17] been found that the carbonyl carbon atom frequency in cyclopentanones is shifted about 5 ppm downfield relative to cyclohexanones, and that the effect of alkyl substitution on the carbonyl resonance is relatively small. These observations have been found to hold also for the keto steroids examined in this paper. Steroids with the carbonyl group in positions 2 to 11 all give a constant chemical shift value of 212 ppm (±1). On the other hand, if the carbonyl group is next to one of the two quaternary carbon atoms, as in 1-, 12-, and 17-keto steroids, a further downfield shift of 3–4 ppm is observed. The shielding of carbonyl carbon atoms located in ring D appear to be more sensitive to substitution, as seen, *e.g.*, by the 2.6-ppm difference in chemical shift between the carbonyl carbon atoms in 16-androstanone and 15-androstanone. However, even though some structural information is contained in the small changes of the carbonyl chemical shifts, it should be kept in mind that these shifts are quite sensitive to solvent and concentration changes.[18–20]

The influence of a keto group on the chemical shift of β-carbon atoms varies with the branching at this atom, and the shifts observed are generally smaller when the keto group is located in the five-membered ring than when it is found in one of the three six-membered rings. Average substituent values are 16 ppm for methylene and quaternary carbons and 12 ppm for methine carbon atoms. For keto groups in the five-membered ring these values are reduced by 2–3 ppm except for the quaternary carbon atom, which shows a remarkably low β substituent parameter of only 7 ppm.

The shifts observed at γ-carbon atoms vary greatly in magnitude and direction, covering a range from +6.3 to −9.5 ppm, even though half of the γ shifts observed are within ±2 ppm. The largest upfield shifts appear when the γ-carbon atom is eclipsed or nearly eclipsed to the keto group (*e.g.*, C-4 in 6-androstanone), while the other large up- and downfield γ shifts are observed for bridgehead carbon atoms (*e.g.*, C-10 in 2-cholestanone and C-9 in 7-cholestanone), that are approximately trans to the carbonyl oxygen atom. In a few cases (*e.g.*, C-10 in 11-androstanone) only small upfield shifts are observed at γ-carbon atoms eclipsed to keto groups, but in these cases the γ-carbon atoms are also ring junctions; the smaller upfield shifts for these carbon atoms may be the result of two opposing effects. γ shifts have been found to be caused by 1–4 nonbonded gauche interactions[21] resulting in an upfield shift of the γ-carbon resonance; trans γ-carbon atoms are usually not affected. The large up- and downfield γ shifts observed at (approximately) trans bridgehead carbon atoms probably reflect geometrical changes that take place upon introduction of a carbonyl group in a rigid

(16) J. B. Grutzner, M. Jautelat, J. B. Dence, R. A. Smith, and J. D. Roberts, *J. Amer. Chem. Soc.*, **92**, 7107 (1970).

(17) D. H. Marr and J. B. Stothers, *Can. J. Chem.*, **46**, 225 (1967).

(18) G. E. Maciel and J. J. Natterstad, *J. Chem. Phys.*, **42**, 2752 (1965).

(19) W. H. deJeu, *J. Phys. Chem.*, **74**, 822 (1970).

(20) H. E. Maciel and G. C. Ruben, *J. Amer. Chem. Soc.*, **85**, 3903 (1963).

(21) D. M. Grant and B. V. Cheney, *J. Amer. Chem. Soc.*, **89**, 5315 (1967).

framework as the steroid skeleton as opposed to a more flexible system as, *e.g.*, cyclohexane.

All δ-carbon shifts were found to be within ±2 ppm.

Isotope Effects.—The cmr spectra of the 16 deuterium-labeled compounds included in this study (see Table II) reveal, in accordance with previous reports,[22-26] that the introduction of deuterium atoms influences the chemical shifts of the labeled carbon as well as its neighbors. As noted above, the intensity of the cmr signal due to a deuterated carbon atom is very low; this is especially true when the carbon carries two deuterium atoms [*e.g.*, C-2 and C-6 in **10** (Table II)], since the splitting due to spin–spin coupling then becomes very extensive, and it has not been possible in these cases to measure a direct isotope shift. When a carbon has only one deuterium atom attached (*e.g.*, C-9 and C-12 in **13**), upfield isotope shifts of 0.3–0.5 ppm have been found, with the exception of 5α-d_1-1-androstanone, in which an isotope shift could not be detected.

The shifts observed at carbon atoms adjacent to labeled sites depend on the number of deuterium atoms introduced; a single deuterium atom on an sp^3 carbon atom, as in **1**, causes a geminal isotope shift of 0.1 ppm, while two deuterium atoms (*e.g.*, **9**) give rise to a shift of 0.2 ppm, in both cases toward higher field. These isotope shifts are of the same magnitude and direction as those reported.[22-26] Stothers, *et al.*,[26] have found spin–spin splitting and significantly broadened peaks in the spectra of 3-d_1-camphor and 3-d_1-5,6-dimethylnorbornan-2-ones owing to vicinal ^{13}C–^2H couplings. Similar spin–spin splitting, or peak broadenings, have not been observed for any of the labeled steroids examined, even though several compounds (*e.g.*, **1**) are included in which carbon atoms are trans to the deuterium, where the ^{13}C–^2H vicinal coupling constant would be expected to have its maximum value.[26] In contrast, upon deuteration we have observed drastic peak intensity changes at carbon atoms other than those deuterated (*e.g.*, C-2 and C-10 in **7**). Generally, the carbonyl carbon signal decreases upon deuterium exchange at the neighboring carbon atoms, rendering it nondetectable under experimental conditions where the undeuterated compound gives a carbonyl peak with a signal to noise ratio of about 15:1. Geminal isotope shifts have therefore not been measured for the sp^2 carbons. The intensity reduction may in these cases be a consequence of the decreased nuclear Overhauser enhancement, since the dipolar interaction between the carbon atom and the nearest hydrogen atoms is distance dependent ($1/r^6$). However, we observe a similarly reduced intensity by up to a factor of 10 relative to the unlabeled compound when introducing only one or two deuterium atoms adjacent to carbon atoms with no directly bonded protons (*e.g.*, C-13 in **2**, C-10 and C-13 in **4**, C-10 in **5**). This would not appear to be a result of simple reduction of the nuclear Overhauser enhancement, since in these cases only one or two out of seven or eight adjacent hydrogens are replaced by deuterium; whether the intensity decrease is then a consequence of peak broadenings caused by a geminal C–D coupling or other effects are involved is currently under investigation.

Acknowledgment.—The nmr spectrometer was purchased under Grant No. GP-28142 from the National Science Foundation. Financial assistance by Grant No. RR-612-07 from the National Institutes of Health is also gratefully acknowledged.

Registry No.—Table I: A, 438-22-2; B, 481-21-0; C, 1755-29-9; D, 570-67-2; E, 1224-95-9; F, 566-88-1; G, 13583-70-5; H, 566-51-8; I, 3676-06-0; J, 567-71-5; K, 1755-32-4; L, 3676-09-3; M, 734-68-9; N, 40071-71-4; O, 1032-16-2; P, 963-74-6.

(22) G. E. Maciel, P. D. Ellis, and D. C. Hofer, *J. Phys. Chem.*, **71**, 2160 (1967).

(23) G. L. Lebel, J. D. Laposa, B. G. Sayer, and R. A. Bell, *Anal. Chem.*, **43**, 1500 (1971).

(24) R. A. Bell, C. L. Chan, and B. G. Sayer, *J. Chem. Soc., Chem. Commun.*, 67 (1972).

(25) D. Doddrell and I. Burfitt, *Aust. J. Chem.*, **25**, 2239 (1972).

(26) J. B. Stothers, C. T. Tan, A. Nickon, F. Huang, R. Sridhar, and R. Weglein, *J. Amer. Chem. Soc.*, **94**, 8581 (1972).

Notes

Interaction of Pyridoxal with Cyanide[1]

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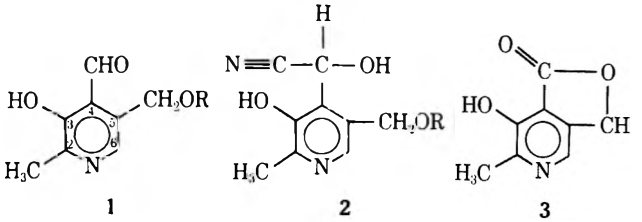
Pyridoxal (**1a**) and its 5′-phosphate (**1b**) are the most important forms of vitamin B_6. The 5′-phosphate serves as a cofactor for a number of enzymes, most of which are involved in the metabolism of amino acids; these enzymes include transaminases, decarboxylases, and racemases.[2]

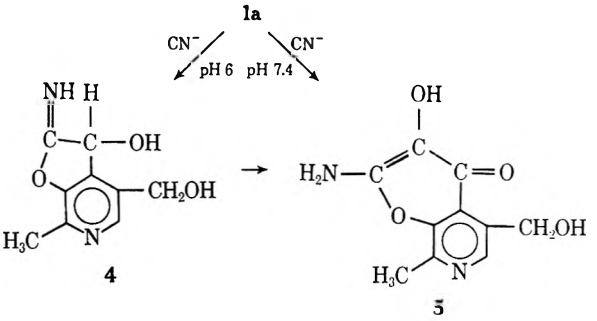


1 **2** **3**

a, R = H
b, R = PO_3^{2-}

We are interested in obtaining the cyanohydrin (2a) of pyridoxal as a convenient starting material for the synthesis of some potential antagonists for this vitamin. Indeed, Bonavita reported formation of the presumed cyanohydrin **2** by the interaction of **1a** or **1b** with KCN at pH 7.2, giving a fluorescent compound.[3] Subsequently this reaction became one of the standard fluorometric methods for the determination of **1b** in biological material.[4] More recently, however, Oishi and Fukui reexamined the reaction, and found pyridoxic acid lactone (**3**) to be the end product.[5] Thus the fluorescence observed is due to this lactone. About the same time, Takanishi, *et al.*, reported formation of the cyclic imine derivative **4**, with a five-membered ring, from a similar reaction, and determined the structure by X-ray crystallography.[6] However, they did not provide experimental details.

We have investigated the reaction in the hope of obtaining precursors of the lactone **3**. Tlc of a reaction mixture obtained on treating pyridoxal with cyanide at pH 7.4 indicated the formation of a mixture consisting of at least five products; on heating to 50°,



4 **5**

crystals precipitated, and the product, obtained in 47% yield, had two extra carbon atoms, as indicated by its mass spectrum and by elemental analyses. Other physical methods and degradation experiments (reported in the present paper) did not provide definitive information concerning the structure of this unexpected product, and X-ray crystallography[7] finally identified the substance as the azachromone derivative **5** (see Experimental Section). The new compound was found to be stable in acid, giving a yellow solution, but was readily degraded in 1 *N* NaOH to pyridoxic acid and HCN. It was further characterized as a crystalline triacetyl derivative and as the hydrobromide salt.

While X-ray crystallographic study was in progress, we carried out mild degradation experiments on **5** to learn what we could about its structure. Mild acid hydrolysis gave a mixture of products. When **5** was dissolved in 0.1 *N* HCl and treated with "nitrous fumes" generated from HNO_3 and As_2O_3,[8] a crystalline product was formed immediately. This product was condensed with phenylenediamine, and the resulting product in turn was acetylated. The structures of the degradation product and this derivative could not be established unequivocally, but the experiments leading to the two compounds are described (see Experimental Section).

Reaction of pyridoxal with cyanide in a potassium acetate buffer at pH 6 gave a product in 79% yield, and the composition of the product corresponded to that of the "normal" cyanohydrin **2**. Since the uv spectra of the new compound in acidic and neutral solutions are almost identical, we can assume that the phenolic hydroxyl is substituted. This assumption alone makes the structure **4** very probable, particularly since it is reasonable to postulate an intramolecular addition of the phenolic hydroxyl to the cyano group to form the five-membered ring. The compound is most likely the one described by Takanishi, *et al.*,[6] although the details reported by Takanishi's group are insufficient to establish this conclusion beyond any doubt. A structure of this type has been postulated as an intermediate in the interaction of salicylaldehyde with cyanide.[9] The structure of **4** has also been con-

(1) Chemistry and Biology of Vitamin B_6. 34. Previous paper in this series: W. Korytnyk, S. C. Srivastava, N. Angelino, P. G. G. Potti, and B. Paul, *J. Med. Chem.*, **16**, 1096 (1973).

(2) E. E. Snell in "Comprehensive Biochemistry," Vol. 11, M. Florkin and E. H. Stotz, Ed., Elsevier, Amsterdam, 1963, p 48.

(3) V. Bonavita, *Arch. Biochem. Biophys.*, **88**, 366 (1960).

(4) (a) C. A. Storvick and J. M. Peters, *Vitam. Horm. (New York)*, **22**, 833 (1964); (b) C. A. Storvick, E. M. Benson, M. A. Edwards, and M. J. Woodring, *Methods Biochem. Anal.*, **12**, 183 (1964); (c) Z. Tamura and S. Takanishi, *Methods Enzymol.*, **18A**, 471 (1970); (d) K. M. Grigor, D. von Redlich, and D. Glick, *Anal. Biochem.*, **50**, 28 (1972).

(5) S. Oishi and S. Fukui, *Arch. Biochem. Biophys.*, **128**, 606 (1968).

(6) S. Takanishi, Z. Tamura, A. Yoshino, and Y. Iidaka, *Chem. Pharm. Bull.*, **16**, 758 (1968).

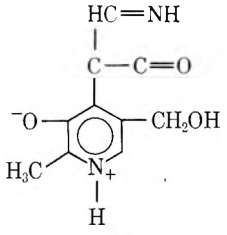
(7) G. Kartha, H. Ahrens, and W. Korytnyk, Abstracts, 23rd International Congress of Pure and Applied Chemistry, Boston, Mass., 1971, pp 134, 135.

(8) R. Möhlau, *Chem. Ber.*, **15**, 2472 (1882).

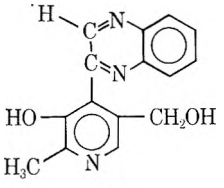
(9) K. Ladenburg, K. Folkers, and R. T. Major, *J. Amer. Chem. Soc.*, **58**, 1292 (1936).

firmed by the nmr and mass spectra. 5-Deoxypyridoxal also reacted with cyanide in a similar manner at pH 6, indicating that the 5′-OH group is not involved in the reaction. The compound **4** was found to be a powerful reducing agent, as indicated by immediate precipitation of silver on treatment with Tollens' reagent. It proved to be very unstable, decomposing in either acid or alkali to pyridoxic acid, even in chromatography on silica gel. Surprisingly, when a slightly alkaline solution of **4** was heated at 50° for 30 min, it was converted into **5** in about 50% yield.

These somewhat unexpected reactions can be rationalized by the assumption that the cyanohydrin **2** is too reactive to be capable of independent existence, and at pH 6 is converted into the cyclic imine **4**, with a five-membered ring. It is apparent that the formation of **5** from pyridoxal and cyanide involves two consecutive additions, since **5** has two extra carbon atoms. The formation of **5** from **4** probably involves a disproportionation reaction: part of **4** is degraded to pyridoxic acid, liberating CN^-, which in turn adds to an appropriate intermediate derived from **4**, forming **5**. Reaction of pyridoxal with CN^- at pH 7.4 was followed by tlc. Initially, an intermediate was detected as the main spot, but could not be isolated, presumably because of its instability. Since it was expected to have the α-ketoimine structure **6** (existing probably in the hemiketal form), the reaction mixture was treated with phenylenediamine, when the quinoxaline **7** precipi-



6

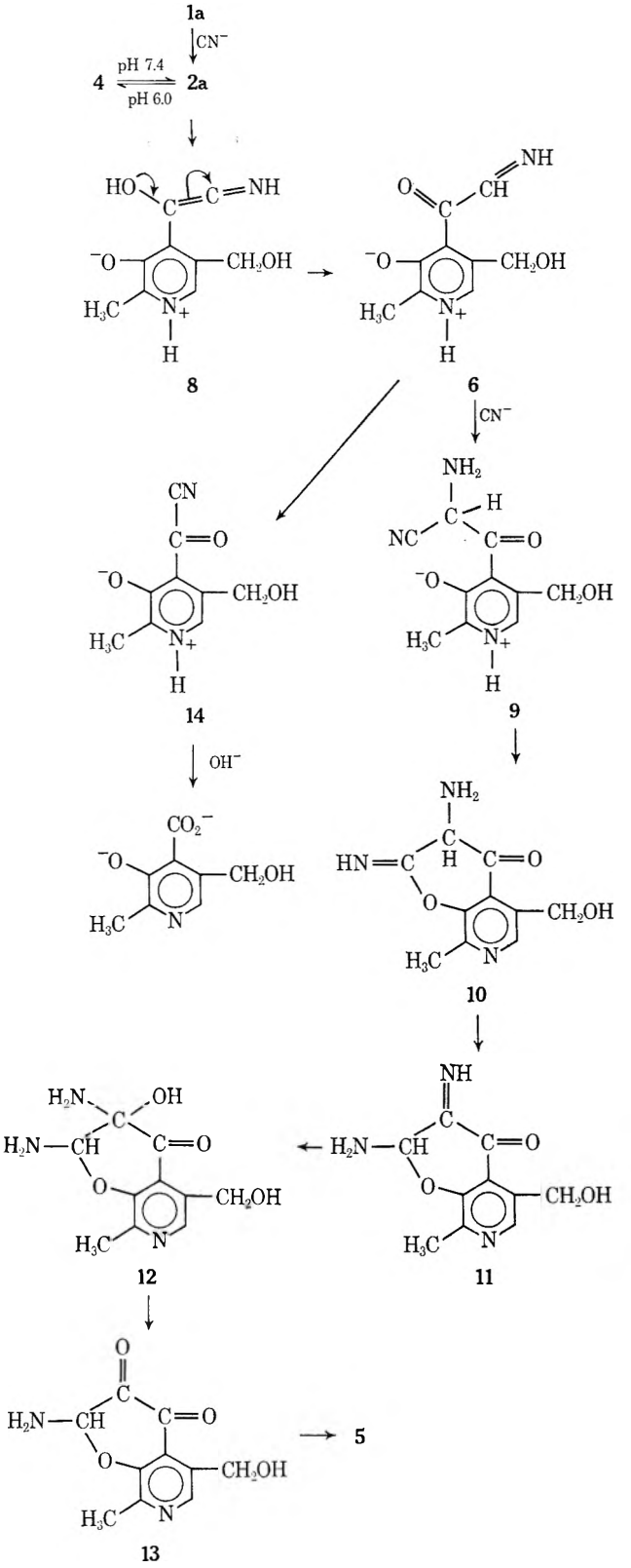


7

tated in 51% yield. The structure of **7** was proved by nmr spectroscopy and reaction of the phenolic OH with *p*-nitrobenzenesulfonyl chloride.

Formation of **6** from the initial cyanohydrin **2a** can be envisaged as occurring *via* the tautomeric ketoimine **8**,[10] which then undergoes an internal oxidation–reduction reaction to **6** (Scheme I). The imine **6** next reacts with CN^-, forming the α-aminonitrile **9**,[11] which then reacts intramolecularly with the phenolic hydroxyl, giving the amino imino intermediate **10**. Subsequently the latter tautomerizes to **11**, which adds H_2O to its imino group, giving **12**, which finally eliminates NH_3, giving **13**, a tautomer of **5**.[12] Conversion of **4** into **5** and pyridoxic acid can be assumed to proceed also by way of the cyanohydrin **2a**, forming the α-ketoimine **8**. It seems probable that the latter is readily oxidized by air to the acyl cyanide **14**, which hydrolyzes under mild alkaline conditions to pyridoxic acid and CN^-. While this process is under way, the liberated CN^- could at-

SCHEME I



tack the remaining **6**, forming **5** by the mechanism already discussed.

The suggested mechanism should be considered a rationalization based on analogies found in the literature and on observed facts. Although other interpretations are admissible, we would like to point out the participation of the nucleophilic phenolic hydroxyl group, in preference to the less nucleophilic 5′-hydroxyl group, as an interesting feature of these reactions.

(10) D. J. Cram and L. Gosser, *J. Amer. Chem. Soc.*, **86**, 2950 (1964), have postulated this type of ketenimine tautomer in the racemization of a nitrile by the so-called "conducted tour mechanism."

(11) There are a number of examples of additions of CN^- to imines giving aminonitriles: *e.g.*, G. E. P. Smith and F. W. Bergstrom, *J. Amer. Chem. Soc.*, **56**, 2095 (1934).

(12) Hydrolysis of a similar type of imines appears to be important in the Kiliani–Fischer cyanohydrin synthesis: R. Varma and D. F. French, *Carbohyd. Res.*, **25**, 71 (1972).

The latter group has been found to be important for the formation of the hemiacetal and for other reactions,[13] but apparently does not participate in any important manner in the reactions discussed here.

In connection with the "cyanohydrin reaction" as developed originally by Bonavita, it is significant that both **4** and **5** give rise to pyridoxic acid, the end product. This result suggests that a number of intermediates produced in the initial stages of the reaction, as indicated by our tlc studies, may be degraded to pyridoxic acid.[14] The synthesis of both **4** and **5** in a single step from the readily available pyridoxal provides readily available intermediates for synthesizing some unusual vitamin B_6 analogs.

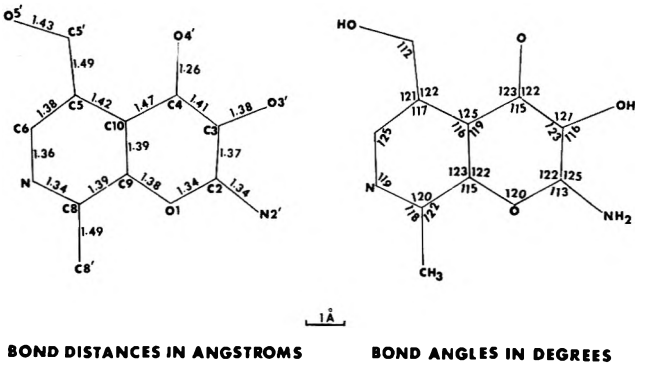


Figure 1.—2-Amino-3-hydroxy-5-(hydroxymethyl)-8-methyl-7-azachromone.

Experimental Section

Ir spectra were determined with a Perkin-Elmer 457 spectrometer, uv spectra with a Perkin-Elmer 202 instrument, and nmr spectra with a Varian A-60A instrument. Some mass spectra were determined by Dr. D. C. DeJongh, of Wayne State University, with an Atlas CH4 mass spectrometer, the ionizing potential being 70 eV and the ionizing current 19μA; others were determined at Roswell Park with a CEC 21-491 mass spectrometer under similar conditions. Tlc (silica gel) was used routinely, as described earlier.[15]

Reaction of Pyridoxal with KCN at pH 7.4. 2-Amino-3-hydroxy-5-(hydroxymethyl)-8-methyl-7-azachromone (5).—To a well-stirred solution of pyridoxal hydrochloride (1.05 g) in water (5 ml) a solution of potassium cyanide (650 mg) in water (5 ml) was added, the pH being carefully followed with a pH meter. Immediately after the addition of cyanide, the pH of the solution was adjusted to 7.4 with 6 *N* HCl and was kept at pH 7.8–7.4 by continued addition of 2 *N* HCl. After 10 min at room temperature, flurries of solid material began to appear. Tlc of the reaction mixture (1:1 MeOH–$CHCl_3$) gave six Gibbs-positive spots. The main spot (R_f 0.65) coincided with some unreacted pyridoxal, as indicated by a positive phenylhydrazine test. The reaction mixture was heated to 45–55° for 40 min to complete the formation of the crystalline precipitate, cooled in ice for 2 hr, and filtered; the precipitate was washed with ice–water. The yield was 530 mg (46%): mp 270–280°; R_f 0–0.1 in 1:1 MeOH–$CHCl_3$, and 0.38 in 0.1 *N* HCl. The Gibbs test gave a strong violet spot. The solution of the compound is strongly yellow at acid pH, but colorless at neutral or alkaline pH. In 1 *N* NaOH, the compound is rapidly converted into 4-pyridoxic acid: nmr (DMSO-d_6) 156 (CH_3), 296 (CH_2OH), 500 (pyridine α-H), 463 (broad singlet, OH), 300 (broad, OH); nmr (1 *N* DCl) 173 (CH_3), 314 (CH_2OH), 512 (α-pyridine H); ir 3400–2600 (very broad peak), 1650 cm^{-1} (C=O stretching); uv $\lambda_{max}^{0.1\ N\ HCl}$ 266 nm (ϵ 14,200), 404 (750), shoulder at 310; in phosphate buffer (pH 7.0), there is a change in spectrum, λ_{max} 252 and 318 nm being recorded after 45 min.

Anal. Calcd for $C_{10}H_{10}N_2O_4$: C, 54.06; H, 4.53; N, 12.61. Found: C, 53.91; H, 4.58; N, 12.66.

X-Ray Determination of the Structure of 5.—One very fine elongated yellow crystal, obtained from a dilute aqueous phosphoric acid solution, was used in the X-ray crystallographic determination of the structure of **5**. The crystal had an orthorhombic unit cell, with parameters a = 18.36, b = 7.12, c = 17.34 Å, and Z = 8. The three-dimensional X-ray diffraction data were collected to a Bragg angle of 75° on a General Electric automatic diffractometer, using Cu K_α radiation and the stationary crystal, stationary counter method. Of the 2688 reflections measured, 2154 (about 80%) were considered observed. Systematic absences indicated P_{bcn} as the most probable space group.

The chemical formula and the structure of the molecule being uncertain at the beginning of the investigation, initial attempts to establish the crystal structure by interpretation of the Patterson map on the basis of known molecular features were unsuccessful. Finally, the correct solution was obtained by utilizing the multisolution tangent refinement techniques that required minimal prior knowledge concerning the structure.[16] Using 151 reflections of E greater than 1.75, 32 phase sets were computed, and the E map with the most consistent set was calculated. This map revealed probable atomic positions for 14 atoms belonging to a planar molecule. Iterative cycles of calculation of structural factors, assigning carbon scattering factors to all atoms, followed by least-squares refinement and calculations of electron density, revealed two more atoms belonging to the molecule. In addition, two water molecules were located in the asymmetric unit of the cell. Detailed inspection of the intramolecular bond lengths and angles, as well as the peak heights in the electron density maps, enabled the correct atomic types (C, N, and O) to be established. Further least-squares refinement of the parameters, followed by difference electron density maps, gave the locations of all of the hydrogen atoms in the molecule. The reliability index R at this stage of refinement is 0.088, and the fractional atomic coordinates are given in Table I. The estimated standard deviations in the atomic positions are also given in Table I. The thermal parameters for these atoms are given in Table II.

Table I

Fractional Coordinates of Nonhydrogen Atoms

Atom	X/a	Y/b	Z/c	ESD in position, Å
O_1	0.3113	0.0745	0.3952	0.003
$O_{4'}$	0.3141	0.2203	0.6236	0.003
$O_{5'}$	0.0869	0.2391	0.6450	0.004
$O_{3'}$	0.4437	0.1719	0.5412	0.003
W_1	0.9872	0.0910	0.3356	0.004
W_2	0.4169	0.0598	0.7301	0.004
N_7	0.1184	0.0964	0.4192	0.004
$N_{2'}$	0.4324	0.0727	0.3837	0.004
C_8	0.1843	0.0750	0.3878	0.004
C_9	0.2462	0.1002	0.4332	0.004
C_{10}	0.2435	0.1505	0.5104	0.004
C_5	0.1728	0.1696	0.5430	0.004
C_6	0.1137	0.1440	0.4947	0.004
$C_{5'}$	0.1620	0.2156	0.6233	0.004
$C_{8'}$	0.1884	0.0190	0.3049	0.005
C_4	0.3120	0.1769	0.5530	0.004
C_3	0.3757	0.1530	0.5039	0.004
C_2	0.3741	0.1010	0.4331	0.004

The analysis shows that the molecule is 2-amino-3-hydroxy-5-(hydroxymethyl)-8-methyl-7-azachromone. It is essentially a planar molecule, with none of the 16 nonhydrogen atoms being away from the least-squares plane by more than 0.03 Å. The intramolecular bond lengths and angles are shown in Figure 1. The C–O bonds obtained correspond to the value usually found in aromatic rings. The C_3–C_4 bond shows appreciably more sp^2 character, both from consideration of bond length and bond angles compared to the C_4–C_{10} bond. Bond length C_4=$O_{4'}$ is

(13) W. Korytnyk and H. Ahrens, *J. Med. Chem.*, **14**, 947 (1971).

(14) Certain aliphatic cyanohydrins have been found to be degraded to carboxylic acids by an intramolecular oxidation–reduction reaction; *cf.* V. Franzen and L. Fikentscher, *Justus Liebigs Ann. Chem.*, **623**, 68 (1959).

(15) H. Ahrens and W. Korytnyk, *Methods Enzymol.* **18A**, 489 (1970).

(16) G. Germain, P. Main, and M. M. Woolfson, *Acta Crystallogr., Sect. B*, **26**, 276 (1970).

TABLE II

THERMAL PARAMETERS OF ATOMS[a]

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O_1	0.0207	0.0506	0.0249	0.0003	0.0000	−0.0010
$O_{4'}$	0.0308	0.0569	0.0254	0.0013	−0.0004	−0.0024
$O_{5'}$	0.0257	0.0605	0.0489	−0.0013	0.0014	0.0049
$O_{3'}$	0.0203	0.0689	0.0370	0.0011	−0.0006	−0.0041
W_1	0.0276	0.0649	0.0539	0.0008	−0.0008	−0.0013
W_2	0.0576	0.0526	0.0402	−0.0023	−0.0003	−0.0003
N_7	0.0247	0.0440	0.0328	0.0002	−0.0005	0.0000
$N_{2'}$	0.0245	0.0730	0.0338	0.0005	0.0006	−0.0029
C_8	0.0244	0.0362	0.0328	0.0000	−0.0004	−0.0006
C_9	0.0221	0.0315	0.0274	0.0007	0.0001	0.0005
C_{10}	0.0237	0.0278	0.0266	0.0001	0.0001	0.0008
C_5	0.0230	0.0288	0.0314	0.0000	0.0003	0.0007
C_6	0.0243	0.0412	0.0366	0.0004	−0.0003	−0.0011
$C_{5'}$	0.0245	0.0451	0.0364	−0.0001	0.0007	−0.0013
$C_{8'}$	0.0358	0.0594	0.0344	−0.0003	−0.0004	−0.0013
C_4	0.0237	0.0346	0.0278	0.0009	−0.0002	−0.0003
C_3	0.0214	0.0432	0.0279	0.0004	−0.0005	−0.0004
C_2	0.0205	0.0397	0.0312	0.0005	0.0003	−0.0008

[a] $T = \exp[-2\pi^2(U_{11}h^2a^{*2} + U_{22}k^2b^{*2} + U_{33}l^2c^{*2} + 2U_{12}hka^*b^* + 2U_{13}hla^*c^* + 2U_{23}klb^*c^*)]$.

the zwitterion type, presumably due to the hydrogen bonding between $O_{4'}$ and the water molecule. In addition to the intermolecular hydrogen bonding through the water molecules there is also a weak intramolecular hydrogen bond between $N_{2'}$ and $O_{3'}$.

The eight molecules in the unit cell are stacked together in the crystal in a parallel fashion in two layers at a stacking distance of 3.48 Å. A view of the crystal packing viewed down the b axis is shown in Figure 2.[17] The crystal is stabilized by many hydrogen bonds involving water molecules. Table III shows the relevant lengths and angles involving the intermolecular hydrogen bonds.

TABLE III

H BONDING DISTANCES (Å) AND BOND ANGLES (DEGREE) IN 2-AMINO-3-HYDROXY-5-(HYDROXYMETHYL)-8-METHYL-7-AZACHROMONE

X—H···Y	X—H	H···Y	X—Y	∠X-H-Y	∠H-X-Y
O_{w1}—H···N_7	0.99	2.20	2.81	145	23
$O_{3'}$—H···O_{w1}	1.00	1.90	2.84	148	21
$O_{5'}$—H···O_{w1}	1.08	1.67	2.74	176	3
O_{w2}—H···$O_{5'}$	1.00	1.74	2.72	170	7
O_{w2}—H···$O_{4'}$	0.99	1.99	2.88	142	25
$N_{2'}$—H···O_{w2}	0.99	1.94	2.91	163	7

Hydrobromide of 5.—Compound **5** (83 mg, free base) was added in small portions to an aqueous HBr solution (0.5 ml of 48% HBr and 0.5 ml of water) and the reaction mixture was kept at 4° for 1 hr. The resulting brown crystals were filtered, washed with ether, and dried, yielding 38 mg of material. Addition of ether precipitated an additional 37 mg of the hydrobromide. The combined fractions were dissolved in boiling ethanol (150 ml), and the solution was filtered. The filtrate was evaporated to 50 ml, when the compound crystallized. It decomposed over the range 240–245°. It gave the same tlc spot and uv spectrum (in 0.1 *N* HCl) as did the free base **5** and ir λ_{max}^{KBr} 3420, 2650 (broad, OH), 1650, 1620, 1590 (broad bands C=O).

Anal. Calcd for $C_{10}H_{11}N_2O_4Br$: C, 39.64; H, 3.66; N, 9.25; Br, 26.04. Found: C, 39.50; H, 3.66; N, 8.96; Br, 26.37.

Acetylation of 5.—Compound **5** (170 mg) was stirred with acetic anhydride (5 ml) in pyridine (dry, 7 ml) for 24 hr. In addition to the triacetyl derivative of **5** (R_f 0.30 in EtOAc), a spot of high R_f, 0.77, was formed; both spots were Gibbs positive after spraying with HCl and heating, but the triacetyl derivative appeared to predominate. After evaporation, the resulting oil was kept at 0.1 Torr for 2 hr to remove most of the acetylation reagents. The oil was then dissolved in EtOAc (1.0 ml), and 0.1 ml of the solution was subjected to preparative tlc. The two zones (R_f 0.15–0.35 and 0.40–0.65) were scraped off, and the scrapings were eluted with EtOAc. Both eluates show the same spot (R_f 0.30), indicating that the material of higher R_f has been converted into the triacetate (R_f 0.30). From these eluates, 14.4 mg of crystalline material, mp 179°, was isolated. The rest of the EtOAc solution was crystallized on the addition of petroleum ether. A total of 176.4 mg (66%) of crystalline triacetate was obtained (several recrystallizations from mixtures of chloroform with petroleum ether and of THF with petroleum ether gave the raised mp 180°); ir λ_{max}^{KBr} 1781, 1739, 1688, 1660, 1620 (split), 1590, 1554 (C=O), 3190 and 2325 cm^{-1} (broad, NH and C–H, respectively); uv λ_{max}^{EtOH} 233 mμ (ε 2.14 × 10^4), 247 (sh, 1.28 × 10^4), 316 (1.38 × 10^4); $\lambda_{max}^{0.1\ N\ HCl}$ 234 mμ (ε 1.94 × 10^4), 265 (sh, 6.7 × 10^3), 327 (9.7 × 10^3); nmr ($CDCl_3$), 131 and 141.5 (acetyl CH_3), 166 (8-CH_3), 347 (5-CH_2OH), 481 (NH, exchanged with D_2O), 510 (C_6H); mass spectrum 348 (molecular ion).

Anal. Calcd for $C_{16}H_{16}N_2O_7$: C, 55.17; H, 4.63; N, 8.04. Found: C, 55.34; H, 4.63; N, 8.30.

Degradation of 5. A. Treatment with 0.1 *N* HCl.—The hydrobromide of **5** was dissolved in 0.1 *N* HCl, and the solution was left standing at room temperature for 24 hr. The peak at 404 nm disappeared, and new peaks at 258 and 357 nm appeared. Tlc (1:1 MeOH–$CHCl_3$) gave three spots of low R_f. A well-defined product could not be isolated.

B. Treatment of 5 with "Nitrous Fumes" in 0.1 *N* HCl.—A stream of "nitrous fumes," generated from nitric acid and As_2O_3,[8] was passed through a solution of **5** (100 mg) in ice-cold 0.1 *N* HCl (4 ml). After a few minutes, tlc showed essentially one spot (R_f 0.4 in 1:1 MeOH–$CHCl_3$). After evaporation *in vacuo*, water was added, and the new compound crystallized. It was recrystallized from hot DMF and decomposed above 140°: uv $\lambda_{max}^{0.1\ N\ HCl}$ 292 and 340 nm (broad, weak band); ir λ_{max}^{KBr} 3455, 3338, 2150, 710 cm^{-1} (C=O); molecular ion *m/e* 238.

Anal. Calcd for $C_{10}H_{10}O_5N_2$: C, 50.41; H, 4.23; N, 11.76. Found: C, 50.72; H, 4.57; N, 11.69.

Condensation of the "Nitrous Acid" Degradation Product with *o*-Phenylenediamine.—To *o*-phenylenediamine (370 mg) in 10% acetic acid (2.5 ml) a solution of the preceding degradation product (110 mg) was gradually added, with stirring. After 3 hr, the resulting precipitate was filtered and washed with water, acetone, and ether; it was recrystallized twice from hot DMF: yield 55%; mp 293–300° dec; ir λ_{max}^{KBr} 1770 (C=O), 3200 cm^{-1} (broad); molecular ion peak at 295.

Anal. Calcd for $C_{16}H_{13}N_3O_3$: C, 65.15; H, 4.44; N, 14.24. Found: C, 65.12; H, 4.19; N, 14.39.

Acetylation of Phenylenediamine Condensation Product.—The phenylenediamine condensation product (86 mg) was heated with a mixture of pyridine (3 ml) and acetic anhydride (3 ml). Then the reagents were evaporated, and the residue was dissolved in $CHCl_3$. After being washed with H_2O, the $CHCl_3$ solution was dried ($MgSO_4$) and was evaporated to an oil. The oil was crystallized from hot dimethylformamide (DMF): mp 248–253°; ir λ_{max}^{KBr} 1742 and 1765 cm^{-1} (C=O).

(17) See paragraph at end of paper regarding supplementary material.

Anal. Calcd for $C_{18}H_{15}N_3O_4$: C, 64.15; H, 4.49; N, 12.47. Found: C, 63.93; H, 4.24; N, 12.54.

Reaction of Pyridoxal with KCN at pH 6.0. 2,3*H*-2-Imino-3-hydroxy-4-(hydroxymethyl)furo[2,3-*c*]pyridine (4).—To a solution of KOAc (1.0 g) and KCN (1.0 g) in water (10 ml), glacial acetic acid was added until pH 7.0 was reached (*ca.* 0.9 ml). Now pyridoxal HCl (0.5 g) was added to the solution, lowering the pH to about 6.0. The solution became darker and started depositing crystals. After cooling for 2 hr in ice, the resulting acetate salt of **4** was filtered, washed with acetone and ether, and dried. The yield was 0.49 g (79%): mp 149° dec (the compound could not be recrystallized, since it readily decomposes to 4-pyridoxic acid lactone); nmr (DMSO-d_6) 114 (CH_3, ionic acetate), 147 (2-CH_3), 298 (4-CH_2CH), 476 (C_7 H); ir λ_{max}^{KBr} 1650 (C=N), 1750 cm^{-1} (ionic acetate); uv λ_{max}^{DMSO} 315 nm (ϵ 5700); $\lambda_{max}^{0.1\ N\ HCl}$ 249 nm (ϵ 8150), 352 (18,900); $\lambda_{max}^{pH\ 7.0}$ 251 nm (ϵ 6800), 357 (8350).

Anal. Calcd for $C_9H_{11}N_2O_3{}^+CH_3COO^-$: C, 51.98; H, 5.55; N, 11.08. Found: C, 52.25; H, 5.56; N, 11.08.

Picrate of 4.—With picric acid, **4** forms a violet picrate, mp 176° dec.

Anal. Calcd for $C_{15}H_{13}N_5O_{10}$: C, 42.55; H, 3.10; N, 16.54. Found: C, 42.84; H, 3.27; N, 16.80.

Hydrobromide of 4.—To a solution of **4** (acetate salt, 220 mg) in water (2.0 ml), 48% HBr (1.0 ml) was added. After a short time, brown crystals precipitated. The reaction mixture was kept in a refrigerator for 2 hr and filtered, and the precipitate was recrystallized from a mixture of ethanol and petroleum ether: mp 165–170° dec.

Anal. Calcd for $C_9H_{11}BrN_2O_3$: C, 39.30; H, 4.03; N, 10.19. Found: C, 39.41; H, 3.96; N, 10.50.

Quinoxaline Derivative (7).—Initially the reaction was carried out as for **5**, using the same amounts of reagents. After the addition of KCN (pH 7.4), about 5 min was allowed to elapse before *o*-phenylenediamine (0.56 g, 5.15 mmol) was added. Then the pH was lowered to 5 with 6 *N* HCl, and the reaction mixture was left standing in the cold for 4 hr. Since no precipitate formed, the pH was raised to 7.5 with NaOH solution, and the reaction mixture was left standing in a refrigerator overnight. The next day, 0.58 g of product had precipitated. The product was then washed with ethanol and ether. Additional material was isolated from the mother liquors, increasing the yield to 0.72 g (51%): mp 228–230° dec; tlc R_f 0.3 (9:1 $CHCl_3$–CH_3OH); the Gibbs test gives a green spot, which changes to purple on standing; nmr (DMSO-d_6) 151 (2-CH_3), 265.5 (5-CH_2OH), 469–492 (multiplet of unresolved quinoxaline phenyl protons and of C_6 H of pyridoxine), 534 (quinoxaline diazine C–H); uv λ_{max}^{EtOH} 215, 243, 323, 390 nm; $\lambda_{max}^{0.1\ N\ HCl}$ 211, 240, 260, 305–325 nm; $\lambda_{max}^{0.1\ N\ NaOH}$ 222, 239.5, 312, 386 nm.

Anal. Calcd for $C_{15}H_{13}N_3O_2\cdot 0.5H_2O$: C, 65.20; H, 5.10; N, 15.20. Found: C, 65.44; H, 5.07; N, 14.94.

The *p*-nitrobenzenesulfonyl derivative of the preceding compound was prepared by treating the compound (90 mg, 0.33 mmol) in ice-cold pyridine (4 ml) with *p*-nitrobenzenesulfonyl chloride (73 mg, 0.37 mmol). After the reaction mixture had been left standing overnight, pyridine was evaporated *in vacuo*, the residue was dissolved in chloroform, and the solution was washed with a bicarbonate solution and water. After drying (Na_2SO_4) and evaporating off the $CHCl_3$, the oil was dissolved in ethanol. The yield was 24 mg (30%): mp 186–188°; tlc (in ethyl acetate, R_f 0.5) gave one spot, which was Gibbs-negative, indicating substitution on the phenolic hydroxyl. When the tlc plate was sprayed with an NaOH solution and heated, the Gibbs test was positive, indicating hydrolysis of the sulfonate ester. The nmr spectrum is consistent with the structure.

Anal. Calcd for $C_{21}H_{16}N_4O_6S$: C, 55.74; H, 3.56; N, 12.38. Found: C, 56.60; H, 3.70; N, 12.17.

Acknowledgment.—This work was supported in part by Grant No. CA-08793 from the U. S. Public Health Service awarded to W. Korytnyk and Grant No. GB-25981 from the National Science Foundation and AM-3942 from the U. S. Public Health Service awarded to G. Kartha. Thanks are also due Miss K. T. Go for assistance in the collection of X-ray diffraction data.

Registry No.—**1a**, 66-72-8; **4**, 41203-44-5; **4** picrate, 41203-45-6; **4** acetate salt, 41203-46-7; **4** HBr, 19839-38-4; **5**, 41203-47-8; **5** HBr, 41203-48-9; **5** triacetate, 41203-49-0; **7**, 41203-50-3; **7**, *p*-nitrobenzenesulfonyl derivative, 41296-58-6; KCN, 151-50-8; *p*-nitrobenzenesulfonyl chloride, 98-74-8.

Supplementary Material Available.—Figure 2 and a table of structure factors will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 20 × reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $4.00 for photocopy or $2.00 for microfiche, referring to code number JOC-73-3793.

6α- and 6β-Hydroxyestradiol. Circular Dichroism and Substantiation of Configurational Assignments

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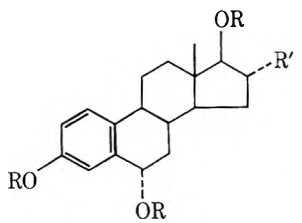
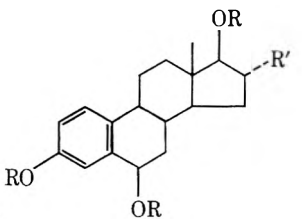
Recently we reported[2] the stereospecific syntheses of 6α- and 6β-hydroxyestriol[3] (**1a** and **2a**) and made configurational assignments by a comparison of the C-6 pmr signals of the respective tetraacetates (**1b** and **2b**). A broad, poorly defined triplet (spacing 8 Hz) was assigned to the pseudoaxial proton at C-6 in **1b**, while a narrow doublet (spacing 2.5 Hz) was assigned to the pseudoequatorial proton at C-6 in **2b**. The CD spectra of **1a** and **2a** show a strong and configurationally specific effect of the 6-hydroxyl substituent on the ^1L_b and ^1L_a dichroic absorption bands associated with the aromatic chromophore. While estradiol[4] and estriol each display ^1L_b and ^1L_a dichroic absorption of opposite sign (negative and positive, respectively), both CD maxima are negative for **1a** ($[\theta]_{283}^{EtOH}$ −1700 and $[\theta]_{229}^{EtOH}$ −5200) and positive for **2a** ($[\theta]_{280}^{EtOH}$ +620 and $[\theta]_{227}^{EtOH}$ +20,000). In the light of these data, a report[5] that the ORD spectrum of 6β-hydroxyestradiol (**2c**) shows a weak negative Cotton effect centered at 272 nm and a strong positive Cotton effect centered at 221 nm is puzzling. Since the C-16 hydroxyl group is so remote as to have little effect on the CD absorption within either the ^1L_b or the ^1L_a band,[6] one would predict that **2c** should display two positive Cotton effects, in strict analogy to **2a**.

The synthesis of the two epimeric 6-hydroxyestradiols, mp 239–249 and 191–195°, was reported by Wintersteiner and Moore in 1959,[7] and the higher melting triol was tentatively assigned the thermodynamically more stable 6α configuration on the basis of its method of preparation. It was noted, however, that the observed order of elution of the two triacetates **1d** and **2d** from alumina was opposite to that expected

(1) Supported by NIH Grant HD-05797.
(2) E. P. Burrows, D. L. Di Pietro, and H. E. Smith, *J. Org. Chem.*, **37**, 4000 (1972).
(3) Estriol is the trivial name for 1,3,5(10)-estratriene-3,16α,17β-triol.
(4) Estradiol is the trivial name for 1,3,5(10)-estratriene-3,17β-diol.
(5) P. Crabbé and W. Klyne, *Tetrahedron*, **23**, 3449 (1967).
(6) G. Snatzke and P. C. Ho, *Tetrahedron*, **27**, 3645 (1971).
(7) O. Wintersteiner and M. Moore, *J. Amer. Chem. Soc.*, **81**, 442 (1959).



1a, R = H; R′ = OH
b, R = Ac; R′ = OAc
c, R = R′ = H
d, R = Ac; R′ = H



2a, R = H; R′ = OH
b, R = Ac; R′ = OAc
c, R = R′ = H
d, R = Ac; R′ = H

on the basis of this assignment. The ORD spectrum of **2c** was reported by Crabbé and Klyne in 1967.[5] This sample of **2c** was obtained from Wintersteiner, but no physical constants or other spectral data were given for the material.

In order to remove these uncertainties and to establish unambiguously the configurations of the 6-hydroxyestradiols, we obtained pure samples of **1c** and **2c** by the methods and criteria described for **1a** and **2a**.[2] The physical constants of these samples are in good agreement with those reported earlier,[7] and the pmr spectra of triacetates **1d** and **2d** (Table I) demonstrate that the higher melting and the lower melting triols are **1c** and **2c**, respectively, in accord with the original tentative assignments. The CD spectra of triols **1c** and **2c** (Table II) are strictly analogous to those of **1a** and **2a**. The observed consistency of the Cotton effects (both negative for **1a** and **1c**, both positive for **2a** and **2c**) suggests a reliable means of configurational identification of minute amounts of the 6-hydroxyestradiol and the 6-hydroxyestriol isolated as metabolites in rats[8] and humans.[9]

TABLE I

PMR DATA FOR 6-HYDROXYESTRADIOLS IN CHLOROFORM-*d*

	δ, ppm[a]				
Compd	C-6 H	C-17 H[b]	C-3 CH_3CO[c]	C-6 CH_3CO[c]	C-17 CH_3CO[c]
6α-Hydroxyestradiol triacetate (1d)	6.08[d]	4.74	2.28	2.13	2.05
6β-Hydroxyestradiol triacetate (2d)	6.08[e]	4.74	2.28	2.05	2.05

[a] Chemical shift downfield from TMS. [b] Multiplet. [c] Singlet. [d] Triplet, spacing 8 Hz. [e] Doublet, spacing 3 Hz.

TABLE II

SPECTRAL DATA FOR ESTRADIOL DERIVATIVES IN ABSOLUTE ETHANOL[a]

Compd	Uv max, λ, nm (ε)	CD max, λ, nm ([θ])
6α-Hydroxyestradiol (1c)	288[b] (2000)	289 (−1300)
	282 (2200)	283 (−1300)
	229[b] (5900)	230 (−3300)
	222 (7700)	
6β-Hydroxyestradiol (2c)	288[b] (1900)	288 (+500)
	282 (2100)	280 (+600)
	228[b] (5900)	228 (+20,000)
	221 (7400)	
6-Oxoestradiol diacetate (3)		366 (+850)
		352 (+4000)
		338 (+8300)
		326 (+10,000)
	298 (2100)	296 (−15,000)
	247 (10,000)	247 (−15,000)
6-Oxoestradiol (4)	327 (3000)	345 (+22,000)
		311 (−20,000)
	256 (8900)	252 (−10,000)
	222 (20,000)	223 (+26,000)

[a] *c* 0.0043–0.021 g/100 ml; *l* = 1 cm; temperature 25°. [b] Shoulder.

Experimental Section

Melting points were taken in open capillary tubes and are corrected. Tlc systems (silica gel HF-254) were 9:1 C_6H_6–EtOAc (system 1) or 4:1 C_6H_6–MeOH (system 2). Pmr spectra were determined with a JEOL MH-100 spectrometer and uv spectra with a Cary Model 14 spectrophotometer. CD spectra were measured using a Cary Model 60 spectropolarimeter equipped with a CD Model 6001 accessory.

6-Oxoestradiol (4).—Estradiol diacetate (4.83 g, 13.6 mmol) was oxidized as described previously for estriol triacetate[2] using CrO_3 (4.08 g, 40.8 mmol) in glacial HOAc (42 ml) and H_2O (3.5 ml). The mixture of products (4.25 g) was combined with 4.77 g from a similar oxidation and chromatographed on 200 g of silica gel as described previously to give 1.13 g (10%) of crude 6-oxoestradiol diacetate (**3**), pure by tlc (R_f 0.6, system 1). A sample recrystallized from MeOH had mp 170–171° (lit.[10] mp 173–175°). A solution of **3** (1.13 g, 3.05 mmol) in 0.5 *N* 95% methanolic KOH (12 ml) was allowed to stand for 10 hr at room temperature and then was evaporated to near dryness. The residue was diluted with H_2O and acidified with 5% HCl, yielding **4** (0.77 g, 89%), pure by tlc (R_f 0.5, system 2). A sample recrystallized from MeOH had mp 267–268° (lit.[10] mp 281–283°).

6β-Hydroxyestradiol (2c).—A solution of **4** (100 mg, 0.349 mmol) in absolute EtOH (15 ml) was hydrogenated for 18 hr over Pt (from 45 mg of PtO_2). Tlc of the residue after filtration through Celite and evaporation of the filtrate to dryness revealed a major component (R_f 0.4, system 2) which was isolated by preparative tlc. This sample of **2c** (38 mg, homogeneous to tlc) would not crystallize but was converted to the readily crystalline triacetate **2d**: mp 173–176°; $[\alpha]^{25}D$ + 56° (*c* 1.05, absolute EtOH) [lit.[7] mp 176–178°; $[\alpha]^{24}D$ + 53° (*c* 0.860, $CHCl_3$)]. Alkaline hydrolysis (0.2 *N* 95% methanolic KOH) then yielded crystalline **2c**, which after recrystallization from MeOH melted at 125–135° followed by resolidification and melting at 195–200°, $[\alpha]^{25}D$ + 31° (*c* 0.64, absolute EtOH) [lit.[7] mp 126–134° followed by resolidification and melting at 191–195°, $[\alpha]^{25}D$ +29° (c 0.487, EtOH)].

6α-Hydroxyestradiol (1c), purchased from Steraloids, was homogeneous to tlc (R_f 0.4, system 2): mp 230–235°; $[\alpha]^{25}D$ +85° (*c* 1.09, absolute EtOH) [lit.[7] mp 233–246°, $[\alpha]^{23}D$ +78° (c 0.746, EtOH)]. Acetic anhydride–pyridine treatment gave the triacetate **1d**: mp 141–143°; $[\alpha]^{25}D$ +35° (*c* 1.05, absolute EtOH) [lit.[7] mp 143–144°, $[\alpha]^{23}D$ +40° (*c* 0.944, $CHCl_3$)].

Registry No.—**1a**, 7291-49-8; **1c**, 1229-24-9; **1d**, 6626-42-2; **2a**, 36615-04-0; **2c**, 3583-03-7; **2d**, 6944-48-5; **3**, 3434-45-5; **4**, 571-92-6.

(8) G. C. Mueller and G. Rumney, *J. Amer. Chem. Soc.*, **79**, 1004 (1957).
(9) J. Breuer, F. Breuer, H. Breuer, and R. Knuppen, *Z. Physiol. Chem.*, **346**, 279 (1966).
(10) B. Longwell and O. Wintersteiner, *J. Biol. Chem.*, **133**, 219 (1940).

An Intramolecular Rearrangement Involving Neighboring Ether Oxygen

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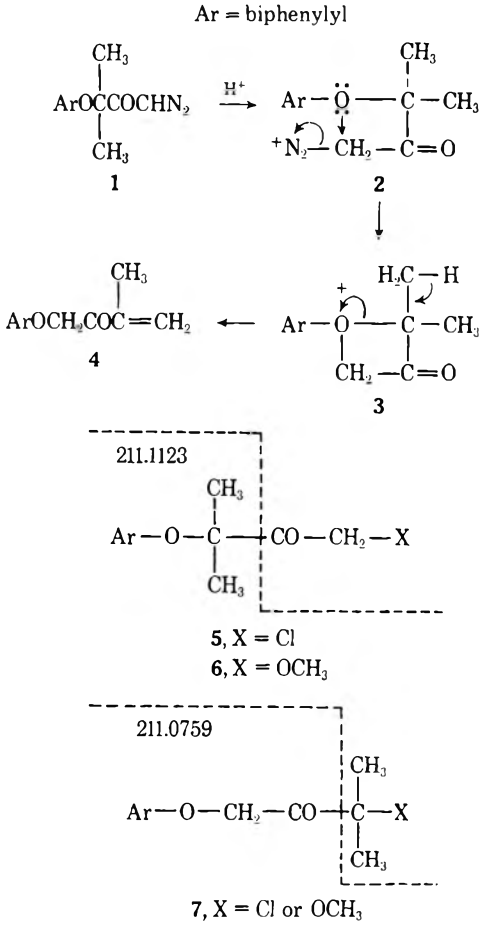
This paper describes a molecular rearrangement involving neighboring-group participation by an ether oxygen. While investigating carbenoid reactions from

copper-catalyzed decompositions of diazo ketones, we had occasion to prepare the diazo ketone **1**. In one preparation of **1**, the diazo ketone was contaminated (as deduced by subsequent events) by its precursor, 2-(4-biphenylyloxy)-2-methylpropionyl chloride. An attempt to recrystallize the crude diazo ketone from methanol resulted in its complete destruction and formation of four major products which were separated by chromatography. Three of the products were those to be expected, namely, methyl 2-(4-biphenylyloxy)-2-methylpropionate (from reaction of the above-mentioned acid chloride with methanol), the chloro ketone **5** (from reaction of the diazo ketone **1** with hydrogen chloride), and the methoxy ketone **6** (from acid-catalyzed reaction of the diazo ketone **1** with methanol).

Analytical and spectroscopic data indicate that the fourth product was 1-(4-biphenylyloxy)-3-methyl-3-buten-2-one (**4**). Hydrogenation of this substance afforded the expected dihydro compound, 1-(4-biphenylyloxy)-3-methyl-2-butanone, the identity of which was confirmed by analytical and spectroscopic means. The unsaturated ketone **4** was obtained in higher yield by subjecting the diazo ketone **1** to perchloric acid cat-



5, X = Cl
6, X = OCH_3

7, X = Cl or OCH_3

alyzed rearrangement under essentially aprotic conditions (tetrahydrofuran with a trace of water from the acid).

While no kinetic studies of this rearrangement have been undertaken, it is possible to construct a likely mechanistic course of reaction. Protonation of the diazo ketone can lead to intermediate **2** which, on loss of nitrogen and ring closure, would afford the oxonium ion **3**.[1-3] Loss of a proton and scission of the four-membered ring, as indicated in **3**, would lead to the observed product **4**. Ion **2** is the probable precursor of products **5** and **6**; however, it should be recognized that attack of chloride ion or methanol on the methylene carbon of **3** may account for a portion of these products.[4]

The possibility of chloride ion or methanol attacking the quaternary carbon of **3**, while less likely, could lead to products of type **7**, which would not be readily distinguishable (by nmr) from the actual products **5** and **6**. Low resolution mass spectra of the chloro ketone and methoxy ketone are reasonably consistent for structures of type **5** and **6**. However, compounds **5**, **6**, or **7** should all suffer significant fragmentation on electron impact to give ions of mass 211. In the case of the methoxy ketone (assumed to be representative), a high resolution mass spectrum ruled in favor of structure **6** when a single ion peak of nominal mass 211 was observed at 211.1116.

Experimental Section

Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected. The nmr spectra were obtained with a Varian A-60 spectrometer and significant signals are located in parts per million (δ) downfield from internal TMS. Low resolution mass spectra were obtained with an Atlas MAT CH4 spectrometer and the high resolution mass spectrum was obtained with a CEC 21-110 spectrometer; data are reported as m/e for M^+ and significant fragment ions.

Products from the Reaction of 2-(4-Biphenylyloxy)-2-methylpropionyl Chloride and 3-(4-Biphenylyloxy)-1-diazo-3-methyl-2-butanone (1) in Methanol.—A solution of 10 g of 2-(4-biphenylyloxy)-2-methylpropionyl chloride[5] in 100 ml of dry benzene was added to ethereal diazomethane prepared from 25 g of *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine. The mixture was stirred overnight at room temperature and then concentrated *in vacuo*. Attempted recrystallization of the crude diazo ketone residue from methanol[6] afforded 8 g of a mixture consisting of four major products as detected by thin layer chromatography on silica gel with 10% ethyl acetate in cyclohexane. The mixture was chromatographed in a column prepared by wet packing 1400 g of silica gel (E. Merck) with 10% ethyl acetate in cyclohexane. Elution of the column with 4 l. of the same solvent followed by 4 l. of 15% ethyl acetate in cyclohexane gave the following products.

A. 3-(4-Biphenylyloxy)-1-chloro-3-methyl-2-butanone (5).—Band 1 afforded 1 g of material which, on recrystallization from methanol, gave 0.41 g of **5**, mp 135–136°. The analytical sample of chloro ketone was crystallized from methanol and had mp 136–137°; nmr ($CDCl_3$) δ 4.63 (s, 2, $COCH_2Cl$), 1.53 [s, 6, $C(CH_3)_2$]; mass spectrum (70 eV) 288 and 290 (ratio 3:1, M^+), 211 [C_6H_5-C_6H_4O=$C(CH_3)_2$]$^+$, and other ions at 170, 153, and 152.

Anal. Calcd for $C_{17}H_{17}ClO_2$: C, 70.70; H, 5.94. Found: C, 70.46; H, 6.06.

B. Methyl 2-(4-Biphenylyloxy)-2-methylpropionate.—Band 2 afforded 3 g of material, mp 83.5–85°, which is identical with an authentic sample of methyl 2-(4-biphenylyloxy)-2-methylpropionate prepared by treatment of 2-(4-biphenylyloxy)-2-methylpropionic acid with diazomethane and recrystallization of the product from ether–hexane: mp 84–85°; nmr ($CDCl_3$) δ 3.73 (s, 3, OCH_3), 1.62 [s, 6, $C(CH_3)_2$].

(1) Analogous ions are formed from MeO-4 participation in solvolysis reactions; see P. G. Gassman and J. L. Marshall, *Tetrahedron Lett.*, 2429 (1968).

(2) For a recent leading reference on stereochemical aspects of ether oxygen participation, see L. A. Paquette, I. R. Dunkin, J. P. Freeman, and P. C. Storm, *J. Amer. Chem. Soc.*, **94**, 8124 (1972).

(3) The carbonium ion character of acid-catalyzed reactions of diazo compounds has been reviewed: R. A. More O'Ferrall, *Advan. Phys. Org. Chem.*, **5**, 331 (1967).

(4) *Cf.* L. A. Paquette and R. W. Begland, *J. Amer. Chem. Soc.*, **87**, 3784 (1965), and references contained therein.

(5) Prepared from 2-(4-biphenylyloxy)-2-methylpropionic acid [A. Buttini, G. Carminati, P. Galimberti, V. Gerosa, and M. Melandri, *Boll. Chim. Farm.*, **101**, 354 (1962)] by the method of Merck and Co., Inc. Neth. Appl: 6,500,136 (Aug. 2, 1965); *Chem. Abstr.*, **64**, P3422*g* (1966).

(6) In later work, the diazo ketone was crystallized from acetonitrile and had mp 131° dec.

Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.60; H, 6.48.

C. 1-(4-Biphenylyloxy)-3-methyl-3-buten-2-one (4).—Band 3 afforded 1.8 g of material which, on recrystallization from methanol, gave 1.23 g of **4**, mp 79–82°. The analytical sample of **4** was crystallized from methanol and had mp 81–82.5°; nmr ($CDCl_3$) δ 6.77–7.60 (m, 9), 6.02 (m, 1, A portion of AMX_3 pattern for isopropenyl), 5.83 (m, 1 M portion of the AMX_3 pattern), 4.97 (s, 2, OCH_2CO), 1.90 (m, 3, X_3 portion of the AMX_3 pattern); mass spectrum (70 eV) 252 (M^+), 183 ($C_6H_5C_6H_4O{=}CH_2^+$), and other ions at 169, 153, 152, 83, and 69.

Anal. Calcd for $C_{17}H_{16}O_2$: C, 80.92; H, 6.39. Found: C, 81.00; H, 6.54.

D. 3-(4-Biphenylyloxy)-1-methoxy-3-methyl-2-butanone (6).—Band 4 afforded 0.8 g of material which was recrystallized from methanol to give 0.25 g of **6**, mp 93–94°. The analytical sample of **6** was crystallized from methanol and had mp 94–95°; nmr ($CDCl_3$) δ 4.55 (s, 2, OCH_2CO), 3.42 (s, 3, OCH_3), 152 [s, 6, $C(CH_3)_2$]; mass spectrum (70 eV) 284 (M^+), 211 [$C_6H_5C_6H_4O{=}C(CH_3)_2^+$], and other ions at 170, 153, 152 and 45. High resolution peak matching at mass 211 for this product showed a single ion at m/e 211.1116 (calcd for $C_{15}H_{15}O$: 211.1123).

Anal. Calcd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 76.12; H, 7.18.

1-(4-Biphenylyloxy)-3-methyl-3-buten-2-one (4).—To a mixture of 20 g **1** and 300 ml of tetrahydrofuran at 0° was added a solution of 1 ml of 70% perchloric acid in 25 ml of tetrahydrofuran. The mixture was stirred at room temperature for 2 hr at which time 2 ml of pyridine was added and the mixture was concentrated *in vacuo*. An ethereal solution of the residue was washed with dilute acid, dilute base, and water and then dried. The crude product was chromatographed in a column prepared by wet packing 2 kg of silica gel (E. Merck) with 15% ethyl acetate in cyclohexane. Elution of the column with the same solvent and concentration of appropriate fractions (as determined by thin layer chromatography) gave material which, on recrystallization from methanol, yielded 8.4 g of product **4**, mp 80.5–82°, identical with this substance described above.

1-(4-Biphenylyloxy)-3-methyl-2-butanone.—A mixture of 100 mg of **4**, 50 ml of tetrahydrofuran, and 100 mg of 10% palladium on carbon was shaken in a Parr hydrogenation apparatus at an initial hydrogen pressure of 15 psi. After the hydrogen uptake ceased (1 hr), the catalyst was removed by filtration and the filtrate concentrated *in vacuo*. The residue was crystallized from methanol and gave 72 mg of 1-(4-biphenylyloxy)-3-methyl-2-butanone: mp 62–63°; nmr ($CDCl_3$) δ 4.62 (s, 2, OCH_2CO), 2.93 (septuplet, 1, J = 7 Hz, A portion of AX_6 pattern for isopropyl), 1.13 (d, 6, J = 7 Hz, X_6 portion of the AX_3 pattern); mass spectrum (70 eV) 254 (M^+), 183 ($C_6H_5C_6H_4OCH_2^+$), and other ions at 153, 152, 71 and 43.

Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 80.44; H, 6.91.

Acknowledgment.—Appreciation is expressed to our analytical section for elementary analyses and especially to L. Baczynskyj, M. F. Grostic, L. M. Humphrey, and R. J. Wnuk for mass spectral measurements and helpful discussions.

Registry No.—**1**, 41507-63-5; **4**, 41507-64-6; **5**, 41507-65-7; **6**, 41507-66-8; 2-(4-biphenylyloxy)-2-methylpropionyl chloride, 4878-10-8; diazomethane, 334-88-3; methyl 2-(4-biphenylyloxy)-2-methylpropionate, 41507-68-0; 1-(4-biphenylyloxy)-3-methyl-2-butanone, 41507-69-1.

Dehydrobromination by *N*-Phenylbenzamidine

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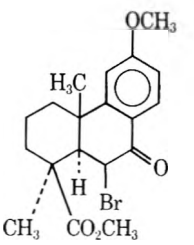
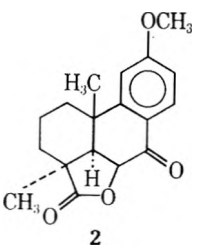
In connection with the synthesis of diterpenoid intermediates an improved yield of lactone **2** from bromo ketone **1** was required. The transformation of bromo ketone **1** to a mixture of lactone **2** (47% yield) and ester **3** (40% yield) by refluxing in collidine has been previously reported[2] along with the observation that treatment of bromo ketone **1** with sodium methoxide yields only elimination product **3**. The suggestion was offered that a major factor in the contrasting behavior of sodium methoxide and collidine might be the steric requirements of the bases for proton abstraction.[2] Thus we initiated an investigation into the improvement of the yield of lactone **2** by utilizing a variety of bases[3,4] that have greater steric requirements than collidine. As a result of this study, we now wish to report that the base *N*-phenylbenzamidine is useful for inducement of dehydrobromination.

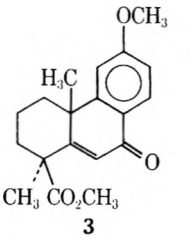


1



2

Reaction of bromo ketone **1** with 3.5 equiv of *N*-phenylbenzamidine in 25 equiv of *o*-xylene at reflux (148°) for 3 hr gave product **3** in 91% yield in the form of a white, crystalline solid, mp 175–177°. The infrared spectrum showed absorptions at 1725, 1645, 1600, and 1575 cm^{-1} for the ester, α,β-unsaturated ketone, and aromatic functional groups. The nmr spectrum exhibited resonance signals for singlets at δ 1.56 and 1.76 for the two tertiary methyl groups, singlets at δ 4.33 and 4.58 for the two methoxy groups, a singlet at δ 7.71 for the vinylic proton, a multiplet at δ 8.15 for the C-13 and C-14 protons, and a doublet (J = 8 Hz) at δ 9.58 for the C-11 proton. Neither lactone **2** nor decarbomethoxylation product **4** were found in the reaction mixture.



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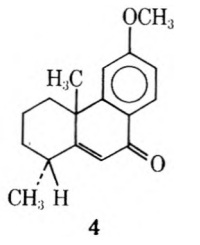

4

The same reaction could be effected in approximately the same yield under milder conditions. Reaction of bromo ketone **1** with 3.5 equiv of *N*-phenylbenzamidine in 35 equiv of benzene at reflux (83°) for 48 hr gave product **3** in 90.5% yield.

Significantly, *N*-phenylbenzamidine gives much higher yields of **3** than the stronger base sodium methoxide[2] and without the concomitant *O*-alkyl cleavage

(1) National Defense Education Act Graduate Fellow, 1971–1973.

(2) E. Wenkert, *et al.*, *Can. J. Chem.*, **41**, 1924 (1963).
(3) D. H. Miles and E. J. Parish, *Tetrahedron Lett.*, 3987 (1972).
(4) E. J. Parish and D. H. Miles, *J. Org. Chem.*, **38**, 1223 (1973).

reported[3,4] for dehydrohalogenating agents[5-9] 1,5-diazabicyclo[5.4.0]undecene-5 (DBU) and 1,5-diazabicyclo[4.3.0]nonene-5 (DBN).

The generality of the dehydrobrominating reagent is demonstrated by the application of *N*-phenylbenzamidine to the two bromides 1-bromoheptane and bromocyclohexane. A mixture of 3.5 equiv of *N*-phenylbenzamidine and 1 equiv of the appropriate bromide was dissolved in 25 equiv of *o*-xylene and refluxed (148°) for 8 hr. The resulting olefins were obtained in 98% yield by glc analysis and were identical by ir, nmr, and glc comparison with authentic samples.

Attempts to bring about dehydrochlorination with *N*-phenylbenzamidine gave poor yields of products. Thus *N*-phenylbenzamidine is a relatively mild and selective dehydrobrominating agent.

Experimental Section

Melting points were obtained on a Fisher-Johns apparatus and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Nuclear magnetic resonance spectra were obtained using a Jeolco minimar spectrometer. Tetramethylsilane was used as an internal standard. Infrared spectra were obtained using a Perkin-Elmer Model 137 G spectrophotometer. Gas–liquid chromatography (glc) was performed using a Hewlett-Packard Model 402 gas chromatograph with a hydrogen flame detector. A glass column (6 ft × 0.25 in. o.d.) bent in a U shape and packed with 3% SE-30 on 100/120 mesh GCQ at a column temperature of 270 or 60° with a helium flow rate of 90 ml/min was used for all glc analyses.

Dehydrobromination of Bromo Ketone 1 in *o*-Xylene.—Bromo ketone 1 (250 mg, 0.63 mmol) was added to a solution of *N*-phenylbenzamidine (412 mg, 2.22 mmol) and 1.87 ml of *o*-xylene. The reaction solution was refluxed (148°) for 3 hr. The ether extract of the acidified (5% HCl) reaction mixture was washed with 5% aqueous sodium carbonate and water, dried over anhydrous sulfate, and evaporated *in vacuo*. Crystallization of the residue from aqueous methanol solution yielded 181 mg (91%) of the crystalline solid **3**: mp 175–177° (lit.[2] mp 173–175°); λ_{max}^{KBr} 1725, 1645, 1600, 1575 cm^{-1}; δ nmr ($CHCl_3$) 1.56 (3 H), 1.76 (3 H), 4.33 (3 H), 4.58 (3 H), 7.71 (1 H), 8.15 (2 H, multiplet), 9.58 (1 H, d, J = 8 Hz). *Anal.* Calcd for $C_{19}H_{22}O_4$: C, 72.50; H, 7.01. Found: C, 72.86; H, 7.14.

Dehydrobromination of Bromo Ketone 1 in Benzene.—Bromo ketone 1 (250 mg, 0.63 mmol) was added to a solution of *N*-phenylbenzamidine (412 mg, 2.22 mmol) and 2.05 ml of benzene which was refluxed (83°) for 48 hr. Following work-up in the manner described above, crystallization from aqueous methanol yielded 180 mg (90.5%) of the crystalline solid **3**, mp 175–177°.

General Procedure for Dehydrobromination. 1-Bromoheptane and Bromocyclohexane.—A mixture of *N*-phenylbenzamidine (996 mg, 5.37 mmol) and 1.53 mmol of the appropriate bromide was dissolved in 4.58 ml of *o*-xylene and refluxed at 148° for 8 hr. The usual work-up of the ether extract of the acidified reaction mixture yielded the corresponding olefin (98% glc) which was identical by ir, nmr, and glc comparison with authentic samples.

Acknowledgments.—We wish to thank the graduate school and the Biological and Physical Sciences Institute for partial financial support. We express our sincere appreciation to Dr. Ian K. Walker, Department of Scientific and Industrial Research, Wellington, New Zealand, for generous supplies of podocarpic acid.

Registry No.—**1**, 37931-64-9; **3**, 37931-65-0; *N*-phenylbenzamidine, 1527-91-9.

(5) E. Truscheit and K. Eiter, *Justus Liebigs Ann. Chem.*, **65**, 658 (1962).
(6) E. Vogel, R. Schubart, and W. A. Boll, *Angew. Chem., Int. Ed. Engl.*, **3**, 510 (1964).
(7) K. Eiter and H. Oediger, *Justus Liebigs Ann. Chem.*, **682**, 62 (1965).
(8) H. Oediger, H. J. Kable, F. Moller, and K. Eiter, *Ber.*, **99**, 2012 (1966).
(9) E. Vogel and F. G. Klarner, *Angew. Chem., Int. Ed. Engl.*, **7**, 374 (1968).

The Photochemistry of 2-Vinylbiphenyl and 4-Vinylphenanthrene[1]

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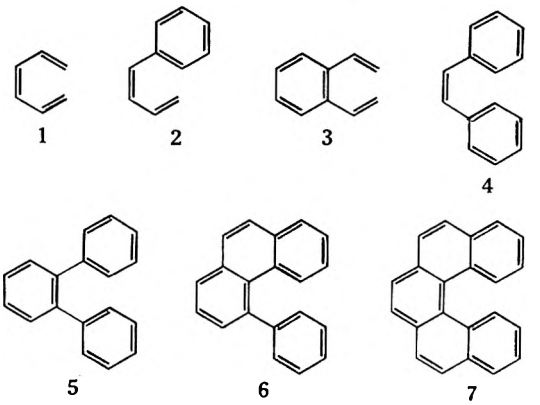
The photochemistry of hexatriene (**1**) and the related compounds, 1-phenyl-1,3-butadiene (**2**), 1,2-divinylbenzene (**3**), stilbene (**4**), *o*-terphenyl (**5**), 4-phenylphenanthrene (**6**), and dibenzo[*c*,*g*]phenanthrene (**7**),



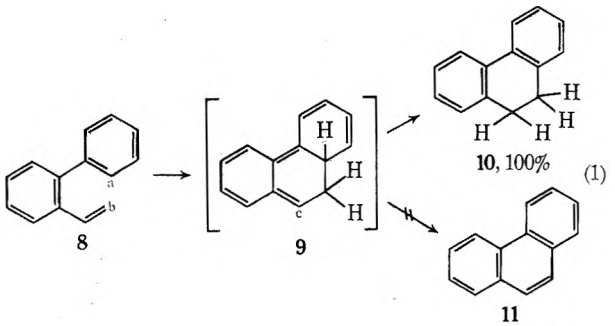
whose structures may be considered as possessing a disguised hexatriene system, have been investigated.[2] In these compounds the hexatriene system gradually loses its separate identity by successive fusion of benzene rings. We now wish to report some observations on the photochemistry of the other two members of this series: 2-vinylbiphenyl (**8**) and 4-vinylphenanthrene (**12**).

The relative ease of photocyclization of hexatriene analogs has been related to the sum of the free-valence indices in the first excited state, ΣF^*, at the two positions which become bonded during the cyclization.[3,4] Generally, photocyclization is only observed if $\Sigma F^* > 1.0$. The photocyclization of both **8** and **12** at the two positions indicated as a and b should be very favorable since ΣF^* is 1.63 and 1.48 for **8** and **12**, respectively. These values are calculated for planar molecules in the usual way and are based on the HMO approximation.

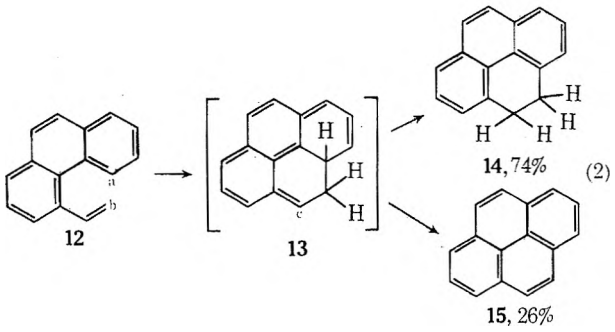
Irradiation of a benzene solution of **8** for 1 hr, in the presence of atmospheric oxygen (aerobic irradiation), gave complete conversion to 9,10-dihydrophenanthrene (**10**); there was no evidence of the formation of phen-

(1) Photocyclization of Stilbene Analogs. III. Part II: D. D. Morgan, S. W. Horgan, and M. Orchin, *Tetrahedron Lett.*, 1789 (1972).
(2) The photochemistry of acyclic polyenes and of stilbenes is reviewed by G. J. Fonken and F. R. Stermitz, respectively, in "Organic Photochemistry," Vol. 1, O. L. Chapman, Ed., Marcel Dekker, New York, N. Y., 1967. See R. J. Hayward, A. C. Hopkinson, and C. C. Leznoff, *Tetrahedron*, **28**, 439 (1972), and references therein for the photochemistry of phenyl-substituted 1,3-butadienes. The photochemistry of divinylbenzene is discussed by M. Pomerantz, *J. Amer. Chem. Soc.*, **89**, 695 (1967), and J. Meinwald and P. H. Mazzocchi, *ibid.*, 696; that of *o*-terphenyl by N. Kharasch, T. G. Alston, H. B. Lewis, and W. Wolf, *Chem. Commun.*, 242 (1965); that of 4-phenylphenanthrene by R. J. Hayward and C. C. Leznoff, *Tetrahedron*, **27**, 2085 (1971); and that of dibenzo[*c*,*g*]phenanthrene by C. Goedicke and H. Stegemeyer, *Ber. Bunsenges. Phys. Chem.*, **73**, 782 (1969).
(3) M. Scholz, M. Mühlstädt, and F. Dietz, *Tetrahedron Lett.*, 665 (1967); F. Dietz and M. Scholz, *Tetrahedron*, **24**, 6845 (1968).
(4) W. H. Laarhoven, Th. J. H. Cuppen, and R. J. F. Nivard, *Recl. Trav. Chim. Pays-Bas*, **87**, 687 (1968).

anthrene (11) (eq 1), the product expected under oxidative conditions.



(1)



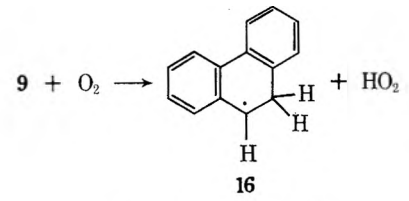
(2)

Irradiation of a solution of 12 under the conditions described for 8 gave a mixture consisting of 26% pyrene (15) and 74% rearrangement product, 4,5-dihydropyrene (14) (eq 2). Two control experiments were run to determine the origin of pyrene. In the first a 10^{-2} *M* solution of 12 in benzene was degassed and irradiated for 1 hr (anaerobic irradiation). Gas chromatographic analysis showed the presence of 14; there was no evidence of pyrene. In the second experiment a 5×10^{-4} *M* solution of 14 in benzene, containing 1% pyrene, was subjected to aerobic irradiation. No increase in the pyrene concentration was observed. These experiments demonstrate that oxygen is required for the formation of pyrene and that pyrene is not formed from a photoreaction of 4,5-dihydropyrene (14).

We assume that dihydrophenanthrene (9) and dihydropyrene (13) are intermediates in the photocyclization of 8 and 12, respectively, and these intermediates lead to isolable compounds by ground-state reactions. Anaerobic irradiation of 8 and 12 did not, however, give spectroscopically detectable quantities of the dihydroforms 9 and 13. The formation of 10 from 9 and 14 from 13 may be explained by a rapid 1,5-sigmatropic shift of the tertiary hydrogens to position c, an allowed ground-state process.[5] A similar rearrangement in a more complicated hexatriene system has also been reported.[6]

A possible alternate mechanism for the formation of 10 and 14 involves a radical-chain mechanism. Thus, if oxygen were to abstract a hydrogen atom from 9, 16 would be produced which could then act as a chain carrier (eq 3). A radical reaction has been shown to occur in the photochemical isomerization of suitably substituted stilbenes to 9,10-dihydrophenanthrenes.[7]

However in separate experiments it was shown that, after 0.5 hr of aerobic irradiation of 8, no H_2O_2 was



(3)

16 + 9 → 10 + 16

present,[8] and the presence of PhSe radicals,[9] generated from the irradiation of solutions containing Ph_2Se_2, had no effect on the reaction.

It is not clear why 12 gives both 14 and 15, whereas 8 gives only the dihydro product 10. If the rate of the 1,5-sigmatropic rearrangement in 9 were faster than in 13, some of the latter could persist long enough to undergo oxidative dehydrogenation to pyrene. However, it is not clear why the rate of migration of the tertiary hydrogens in 9 and 13 to positions of similar electron density should be significantly different.[10] The thermal abstraction of a tertiary allylic hydrogen from 9,10-cyclopentano-4a,4b-dihydrophenanthrene by molecular oxygen has been shown to have a rather large negative entropy of activation.[8] The slight structural difference between 9 and 13 may be sufficient to produce a significant difference in the configuration of the transition states for hydrogen abstraction, and hence a larger negative entropy of activation, for the conversion of 9 relative to that of 13.

Experimental Section

Melting points are uncorrected. Uv absorption spectra were obtained on a Cary 14 spectrophotometer and, for the pmr spectra, a Varian T60 instrument was used. Gas chromatographic analyses were performed on a Varian Model 1200 flame ionization instrument using a 3 ft × 1/8 in. glass column packed with 2% Versimid 900 on 100–120 Chromosorb W. Gas chromatographic retention times and the pmr spectra of 10, 14, and 15 were checked against those of authentic samples. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. A 550-W medium-pressure mercury arc (Hanovia 673A) contained in a water-cooled Vycor jacket was used as the light source. In some experiments a merry-go-round apparatus surrounded the light source and contained the sample tubes. The sample tubes were Pyrex test tubes (1-cm o.d.) fitted with an adapter for attachment to a high-vacuum line when necessary. For anaerobic irradiations the samples were degassed by five freeze–pump–thaw cycles at 10^{-5} Torr.

2-Vinylbiphenyl.—This compound was prepared by a published procedure.[11]

4-Phenanthrenecarboxaldehyde.—A mixture of 4.5 g of 4-methylphenanthrene,[12] 4.63 g of *N*-bromosuccinimide, 50 mg of benzoyl peroxide, and 100 ml of carbon tetrachloride was stirred and refluxed for 2 hr. Succinimide was removed by filtration and the filtrate evaporated *in vacuo* on a steam bath. The residue of crude 4-bromomethylphenanthrene was dissolved in 50 ml of acetic acid–water (1:1), and 6.6 g of hexamethylenetetraamine added. The mixture was stirred and refluxed for 2 hr. Hydrochloric acid (20 ml) was then added and refluxing continued for 15 min. After cooling to room temperature, the mixture was extracted with 300 ml of chloroform, the extract washed with water, dried over magnesium sulfate, and filtered, and the filtrate evaporated to dryness. The crude aldehyde was recrystallized three times from ether–hexane: yield 2.4 g (49.9%), mp 82–84°.

(5) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry," Verlag Chemie Gmbtl, Weinheim, Germany, 1970.
(6) H. G. Heller and K. Salisbury, *Tetrahedron Lett.*, 2033 (1968).
(7) R. Srinivasan and J. N. C. Hsu, *J. Amer. Chem. Soc.*, **93**, 2816 (1971).
(8) A. Bromberg and K. A. Muszkat, *J. Amer. Chem. Soc.*, **91**, 2860 (1969).
(9) E. J. Levi and M. Orchin, *J. Org. Chem.*, **31**, 4302 (1966).
(10) The free-valence indices, in the ground state, at position c are 0.989 and 0.994 for 9 and 13, respectively.
(11) C. K. Bradsher and R. W. Wert, *J. Amer. Chem. Soc.*, **62**, 2806 (1940).
(12) W. E. Bachmann and R. C. Edgerton, *J. Amer. Chem. Soc.*, **62**, 2219 (1940).

Anal. Calcd for $C_{15}H_{10}O$: C, 87.35; H, 4.98. Found: C, 87.47; H, 5.00.

4-Vinylphenanthrene.—A mixture of 175 mg of methyltriphenylphosphonium bromide, 0.25 ml of 1.91 *M* phenyllithium, and 20 ml of dry ether were stirred and refluxed under nitrogen for 0.5 hr. A solution of 100 mg of 4-phenanthrenecarboxaldehyde in 20 ml of ether was added dropwise over a period of 15 min, and the mixture was then stirred and refluxed for 2 hr. The reaction mixture was filtered, the filtrate diluted with 200 ml of ether, washed with water, dried, and filtered, and the ether removed *in vacuo*. The residue was chromatographed on alumina using hexane as the eluent to give an oil which was further purified and analyzed *via* the picrate: 125 mg (59.1% yield), mp 112–113°.

Anal. Calcd for $C_{22}H_{15}N_3O_7$: C, 60.97; H, 3.49; N, 9.70. Found: C, 60.85; H, 3.49; N, 9.53.

Photocyclization of 2-Vinylbiphenyl.—A 10^{-3} *M* solution of **8** in benzene was placed in a Pyrex test tube and irradiated under aerobic conditions for 1 hr. Gas chromatographic analysis of the reaction mixture showed it to consist entirely of **10**. In a second experiment a solution of 2.0 g of **8** in 1 l. of benzene was stirred and irradiated through a Vycor immersion well. The course of the reaction was followed using pmr and uv spectroscopy. The reaction was stopped after 12 hr, at which point it was ~70% complete. Judging by the color of the solution, considerable photodecomposition had occurred. The solvent was removed *in vacuo* and the residual liquid vacuum distilled to give 400 mg [bp 181–183° (4.5 Torr)] of material. A pmr spectrum of this mixture showed it to consist of **8** and **10**. No further attempts were made to isolate the low melting **10**.

Photocyclization of 4-Vinylphenanthrene.—A 10^{-2} *M* solution of **12** in benzene was placed in a Pyrex test tube and irradiated under aerobic conditions for 1 hr. The reaction mixture was analyzed by gas chromatography and contained 26 ± 2% **15** and 74 ± 2% **14**. There was no detectable amount of starting material or other compounds present. Irradiation of solutions of **12** under anaerobic conditions, followed by gas chromatographic analysis, showed the presence of **14**; there was no evidence of pyrene.

Isolation of 4,5-Dihydropyrene.—Four 20-ml benzene solutions, each 2×10^{-3} *M* in **12**, were placed in Pyrex test tubes, degassed, and irradiated for 0.5 hr. The solutions were combined, the solvent was removed *in vacuo*, and the residue was sublimed. 4,5-Dihydropyrene, **14**, sublimed at 75° (2.0 Torr): mp 132–134° (lit.[13] 131–132°); pmr δ 3.29 (s, 4 H), 7.55 (m, 8 H).

Registry No.—**8**, 1587-22-0; **12**, 41498-39-9; **12** picrate, 41498-40-2; **14**, 6628-98-4; 4-methylphenanthrene, 832-64-4; 4-phenanthrenecarboxaldehyde, 41498-43-5.

(13) M. S. Newman and H. W. Whitehouse, *J. Amer. Chem. Soc.*, **71**, 3664 (1949).

Photosensitized Cyclodimerization of Phenyl Vinyl Ethers

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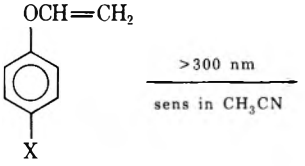
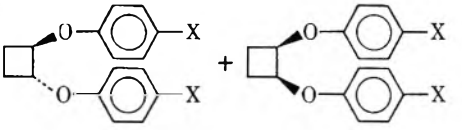
Recently we have reported that aromatic esters, substituted with electron-withdrawing groups, undergo photocycloadditions to olefins to yield oxetanes[1a,b] or ladder compounds,[1c] and that these esters are readily photoreduced by various aromatic hydrocarbons.[2] In the course of a continuing study we also found that aromatic esters acted as sensitizers for cyclodimerization of phenyl vinyl ether **1a** to give its head-to-head cyclodimers **2a** and **3a**.[3] For some olefins having an electron-withdrawing group, such as acrylonitrile, photosensitized cyclodimerization is well known,[4] but, for olefins having an electron-donating group, such a reaction is very unique.

In this paper, we wish to report that in the presence of aromatic esters some para-substituted phenyl vinyl ethers **1b–d** also undergo photosensitized cyclodimerizations to afford head-to-head cyclodimers. Furthermore, we examined the availability of various sensitizers to effect this reaction and the quenching efficiency of a sensitizer's (dimethyl terephthalate, **4**) fluorescence by the ethers **1a–e** in order to clarify the reaction mechanism.

Irradiation of an acetonitrile solution of **1** and a sensitizer such as dimethyl terephthalate (**4**) gave a mixture of trans- and cis-1,2-di-para-substituted phenoxycyclobutanes **2** and **3** (3:4) as the result of head-to-



1a, X = H
b, X = CH_3
c, X = Cl
d, X = Br



2a, X = H	**3a**, X = H
b, X = CH_3	**b**, X = CH_3
c, X = Cl	**c**, X = Cl
d, X = Br	**d**, X = Br

head cyclodimerization of **1**. The structures of the cyclodimers were determined by their mass and nmr spectra. From mass spectra, they were characterized to be the head-to-head cyclodimers due to the reverse [2 + 2] cleavage ($M^+ - C_2H_4$). The stereochemistry of **2** and **3** was confirmed by comparison of their nmr spectra with those of *trans*- and *cis*-1,2-dibromocyclobutanes. A methine proton chemical shift of **2** was more upfield by *ca.* 0.2 ppm than that of **3**. In addition, the former had a broad four-proton methylene peak, while the latter had a sharp and sometimes distinct triplet methylene peak. These features of nmr spectra are very similar to those of *trans*- and *cis*-1,2-dibromocyclobutanes whose stereochemistry is confirmed.[5] On the basis of these nmr data, **2** and **3** were assigned to the trans and cis isomers, respectively.

On the other hand, irradiation of **1** without the sensitizer gave no cyclodimer but only polymers.[6] This indicates that the cyclodimerization of **1** proceeds ex-

(1) (a) Y. Shigemitsu, H. Nakai, and Y. Odaira, *Tetrahedron*, **25**, 3039 (1969); (b) Y. Shigemitsu, Y. Katsuhara, and Y. Odaira, *Tetrahedron Lett.*, 2887 (1971); (c) Y. Katsuhara, T. Nakamura, A. Shimizu, Y. Shigemitsu, and Y. Odaira, *Chem. Lett.*, 1215 (1972).

(2) (a) K. Fukui and Y. Odaira, *Tetrahedron Lett.*, 5255 (1969); (b) K. Fukui, K. Senda, Y. Shigemitsu, and Y. Odaira, *J. Org. Chem.*, **37**, 3176 (1972).

(3) S. Kuwata, Y. Shigemitsu, and Y. Odaira, *J. Chem. Soc., Chem. Commun.*, 2 (1972).

(4) S. Hosaka and S. Wakamatsu, *Tetrahedron Lett.*, 219 (1968).

(5) P. I. Abell and C. Chiao, *J. Amer. Chem. Soc.*, **82**, 3610 (1960).

(6) Cyclodimers **2** and **3** remained unchanged upon similar irradiation.

clusively through photosensitization. To ascertain the dependence of the nature of sensitizer on this cyclodimerization, **1a** was irradiated in the presence of various sensitizers. The results are summarized in Table I.

TABLE I
RESULTS OF PHOTOSENSITIZED REACTIONS OF **1a** WITH SOME SENSITIZERS

Sensitizer	E_T, kcal/mol	Nature of lowest triplet state	2a and 3a
Methyl benzoate	77.9	$\pi-\pi^*$	Yes
Dimethyl terephthalate[a]	73.1	$\pi-\pi^*$	Yes
Benzonitrile	77	$\pi-\pi^*$	Yes
Benzene[b]	85	$\pi-\pi^*$	No
Anisole	80.7	$\pi-\pi^*$	No
Acetophenone[a]	73.6	$n-\pi^*$	No
Benzophenone[a]	69.5	$n-\pi^*$	No

[a] Irradiated through Pyrex. Others were irradiated through quartz. [b] Irradiated in the benzene solution.

As shown in Table I, effective sensitizers for the cyclodimerization are aromatic esters and benzonitrile, which have $\pi-\pi^*$ type lowest excited states and have an electron-withdrawing group in their benzene ring. Furthermore, the possibility of exothermic triplet–triplet energy transfer from these sensitizers to **1a** should be eliminated, because the E_T of **1a** is estimated at 80.2 kcal/mol from the 0–0 band of phosphorescence (MeOH–EtOH glass), which is above that of the sensitizer. On the other hand, acetophenone and benzophenone having $n-\pi^*$ type lowest excited states do not sensitize this cyclodimerization but only undergo well-known Paterno–Büchi reaction to yield oxetane derivatives.[7] This dramatic dependency of cyclodimerization on the nature of the sensitizer could be of much help for determining reaction mechanism.

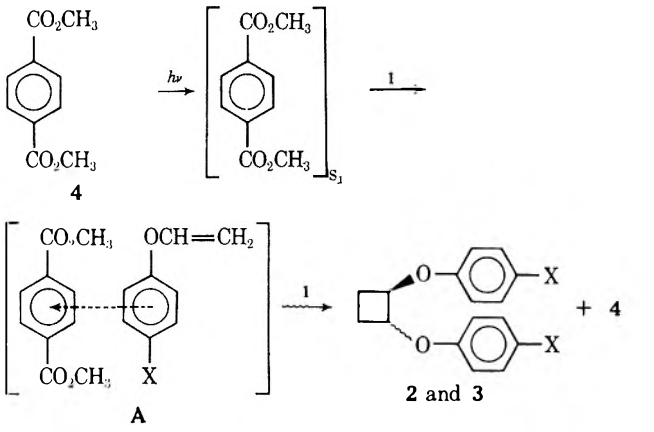
Uv spectra showed no evidence for a charge-transfer complex of the sensitizer with the ether. Although these results suggest the participation of an excited singlet state of the sensitizer, it is still in question how this state acts in the primary step of the photosensitized reaction. Thus we conducted a quenching experiment of the fluorescence of a sensitizer **4** by **1**. The Stern–Volmer plots showed comparatively good linearity, and $k_q\tau$ values are given in Table II. From this table, we

TABLE II
$k_q\tau$ VALUES OF PHENYL VINYL ETHERS FOR FLUORESCENCE QUENCHING OF DIMETHYL TEREPHTHALATE (**4**) IN ACETONITRILE

Quencher	$k_q\tau \times 10^{-1}$, M^{-1}
1a	3.6
1b	4.6
1c	3.7
1d	4.0
m-Chlorophenyl vinyl ether (**1e**)	3.6
Anisole	5.1
Phenetole	4.5

can find (1) that the $k_q\tau$ value of phenetole, having no vinyl group, is very close to those of **1**; (2) that the $k_q\tau$ value of **1** follows the order of increasing electron density on the benzene ring of **1**. From these facts we conclude that the primary step toward product formation may be exciplex formation between an excited singlet sensitizer and a ground-state ether **1** (A), and that the interaction may localize between both benzene rings where the one of the sensitizer may act as the acceptor and that of the second as the donor.

At the present time we would like to propose the following reaction scheme for cyclodimerization of **1**.



Further studies on the detailed mechanism for this reaction are in progress and will be published shortly.

Experimental Section

All melting points are uncorrected. Ir spectra were obtained on a Japan Spectroscopic Model IR-G spectrophotometer in a potassium bromide pellet. Nmr spectra were obtained with a Nippon Denshi Model JNM-3H 60 spectrometer in carbon tetrachloride using tetramethylsilane as an internal standard. Mass spectra were obtained with a Hitachi Model RMU-6E mass spectrometer. Uv spectra were obtained with a Hitachi 124 spectrophotometer in acetonitrile solution. Fluorescence spectra were obtained with a Hitachi fluorescence spectrophotometer MPF-3 in acetonitrile solution.

Materials.—Phenyl vinyl ethers were prepared by the method of McElvain[8] from ethylene dibromide and appropriate substituted or nonsubstituted phenols. Appropriate β-bromophenetoles were given by refluxing a mixture of ethylene dibromide, sodium hydroxide, and phenols in water. They were purified by distillation and dehydrobrominated to appropriate phenyl vinyl ethers by heating at *ca.* 200° with a nearly equal amount (in weight) of powdered potassium hydroxide in a copper flask. The phenyl vinyl ethers were purified by distillation: **1a**, bp 154° (760 mm), $n^{22.5}$D 1.5212, uv max 269 nm (ϵ 1.0 × 10^3); **1b**, bp 71–76° (18 mm), $n^{21.5}$D 1.5170, uv max 274 nm (ϵ 1.09 × 10^3); **1c**, bp 70–72° (13 mm), $n^{20.5}$D 1.5408, uv max 278 nm (ϵ 1.23 × 10^3); **1d**, bp 101.5–104° (24 mm), $n^{23.5}$D 1.5658, uv max 279 nm (ϵ 1.18 × 10^3); **1e**, bp 89.5–93.5° (26–26.5 mm), $n^{26.5}$D 1.5354, uv max 273 nm (ϵ 1.29 × 10^3), 280 (1.15 × 10^3). The sensitizers were purified by distillation or recrystallization before use.

Reaction of Phenyl Vinyl Ether (1a).—A solution of **1a** (6.0 g, 0.05 mol) and **4** (4.0 g, 0.021 mol) in 150 ml of acetonitrile was irradiated for 15 hr with a 500-W high-pressure mercury arc through Pyrex under nitrogen at room temperature. After evaporation of the solvent *in vacuo*, the resulting precipitate of **4** (3.5 g) was removed by filtration and washed with a few portions of cooled ether. The filtrate combined with the ether portions was concentrated and distilled under reduced pressure, recovering unreacted **1a** (2.9 g). The resulting brown-colored oily residue was chromatographed on a silica gel. The cyclodimers **2a** and **3a** (0.92 g, **2a**:**3a** *ca.* 3:4, 30%) were eluted with benzene–petroleum ether (bp 30–60°) (1:49) and recrystallized from petroleum ether. **2a** had mp 66–68°; ir 1595, 1585, 1490, 1480, 1240, 1220, 1065, 920, 745, 685 cm^{-1}; nmr τ 2.6–3.3 (m, 10 H), 5.2–5.5 (m, 2 H),

(7) S. Kuwata, unpublished results.

(8) S. M. McElvain and B. Fajardo-Pinzón, *J. Amer. Chem. Soc.*, **67**, 650 (1945).

7.4–8.0 (broad m, 2 H), 8.0–8.75 (broad m, 2 H); mass spectrum *m/e* 240 (M^+), 212 ($M^+ - C_2H_4$), 120 ($M^+/2$).

Anal. Calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 80.11; H, 6.80.

3a had mp 80.0–80.5°; ir 1600, 1585, 1490, 1235, 1210, 1090, 915, 750, 690 cm^{-1}; nmr τ 2.7–3.4 (m, 10 H), 5.1–5.35 (m, 2 H), 7.65–7.85 (d, with shoulder, 4 H); mass spectrum *m/e* 240 (M^+), 212 ($M^+ - C_2H_4$), 120 ($M^+/2$).

Anal. Calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 79.91; H, 6.91.

Similar experimental procedures were used for the photosensitized cyclodimerizations of **1b–d** with **4** unless otherwise stated. Trans and cis cyclodimers were always obtained in *ca.* 3:4 ratio and recrystallized from petroleum ether.

Cyclodimers 2b and 3b.—Cyclodimers **2b** and **3b** were obtained in 15% yield. **2b** had mp 64–65°; ir 1610, 1580, 1500, 1240, 1220, 1055, 915, 810 cm^{-1}; nmr τ 2.9–3.4 (double d, 8 H), 5.25–5.65 (m, 2 H), 7.45–8.05 (broad m, 2 H), 8.05–8.6 (broad m, 2 H), 7.75 (s, 6 H); mass spectrum *m/e* 268 (M^+), 240 ($M^+ - C_2H_4$), 134 ($M^+/2$).

Anal. Calcd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.61; H, 7.56.

3b had mp 47–47.5°; ir 1610, 1580, 1500, 1220, 1100, 905, 805 cm^{-1}; nmr τ 2.95–3.55 (double d, 8 H), 5.1–5.4 (m, 2 H), 7.65–7.9 (hindered by CH_3 proton peak, 4 H), 7.75 (s, 6 H); mass spectrum *m/e* 268 (M^+), 240 ($M^+ - C_2H_4$), 134 ($M^+/2$).

Anal. Calcd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.52; H, 7.38.

Cyclodimers 2c and 3c.—Similar irradiation of **1c** with tetramethyl pyromellitate as a sensitizer afforded cyclodimers **2c** and **3c** in 17% yield. **2c** had mp 89–90.5°; ir 1590, 1580, 1485, 1240, 1220, 1050, 920, 820 cm^{-1}; nmr τ 2.75–3.05 (d, 4 H), 3.10–3.40 (d, 4 H), 5.30–5.65 (m, 2 H), 7.40–7.95 (broad m, 2 H), 7.95–8.60 (broad m, 2 H); mass spectrum *m/e* 308 (M^+), 280 ($M^+ - C_2H_4$), 154 ($M^+/2$).

Anal. Calcd for $C_{16}H_{14}Cl_2O_2$: C, 62.15; H, 4.56. Found: C, 62.14; H, 4.46.

3c had mp 76–77°; ir 1590, 1485, 1230, 1080, 920, 820, 805 cm^{-1}; nmr τ 2.75–3.10 (d, 4 H), 3.20–3.55 (d, 4 H), 5.10–5.40 (m, 2 H), 7.65–7.85 (t, 4 H); mass spectrum *m/e* 308 (M^+), 280 ($M^+ - C_2H_4$), 154 ($M^+/2$).

Anal. Calcd for $C_{16}H_{14}Cl_2O_2$: C, 62.15; H, 4.56. Found: C, 62.32; H, 4.50.

Cyclodimers 2d and 3d.—Cyclodimers **2d** and **3d** were obtained in 7% yield. **2d** had mp 81–81.5°; ir 1585, 1480, 1230, 1050, 915, 815 cm^{-1}; nmr τ 2.6–2.9 (d, 4 H), 3.15–3.45 (d, 4 H), 5.2–5.6 (m, 2 H), 7.4–8.0 (broad m, 2 H), 8.0–8.5 (broad m, 2 H); mass spectrum *m/e* 400 ($M^+ + 4$), 398 ($M^+ + 2$), 396 (M^+), 368 ($M^+ - C_2H_4$), 198 ($M^+/2$).

Anal. Calcd for $C_{16}H_{14}Br_2O_2$: C, 48.24; H, 3.52. Found: C, 48.12; H, 3.47.

3d had mp 102.5–103.5°; ir 1580, 1480, 1225, 1065, 920, 820, 805 cm^{-1}; nmr τ 2.65–2.95 (d, 4 H), 3.25–3.55 (d, 4 H), 5.1–5.4 (m, 2 H), 7.65–7.80 (t, 4 H); mass spectrum *m/e* 400 ($M^+ + 4$), 398 ($M^+ + 2$), 396 (M^+), 368 ($M^+ - C_2H_4$), 198 ($M^+/2$).

Anal. Calcd for $C_{16}H_{14}Br_2O_2$: C, 48.24; H, 3.52. Found: C, 48.43; H, 3.57.

Photolysis of 1a.—An acetonitrile solution (45 ml) of **1a** (2.4 g, 0.02 mol) was irradiated for 98 hr with a 500-W high-pressure mercury arc through quartz under nitrogen at room temperature. After removal of the solvent *in vacuo*, unreacted **1a** (1.1 g) was recovered by distillation under reduced pressure. The resulting oily residue was chromatographed on 25 g of silica gel; cyclodimers **2a** and **3a** were not obtained but only polymers.

Reaction of 1a with Various Sensitizers.—An acetonitrile solution of **1a** was irradiated with a 500-W high-pressure mercury arc under nitrogen in the presence of benzonitrile, benzene (neat), anisole, acetophenone, or benzophenone under the conditions that a sensitizer predominantly absorbed the light. The cyclodimers **2a** and **3a** were identified by means of glc. The results are summarized in Table I.

Quenching of Fluorescence of 4.—The broad fluorescence of **4** in acetonitrile (0.085 *M*) was observed at 380 nm, which was quenched by the addition of **1** ($2.5 \sim 13 \times 10^{-3}$ *M*). The intensity of emission (F) was compared to the intensity (F_0) in the absence of **1**. Typical Stern–Volmer quenching plots (F_0/F *vs.* molarity of **1**) were obtained. The slopes of plots give values for $k_q\tau$, where k_q is a rate constant for fluorescence quenching of **4** by **1** and τ is the lifetime of fluorescence in the absence of **1**. The results are given in Table II.

Acknowledgment.—The authors wish to thank Miss J. Maenaka, Mrs. T. Muneishi, and Mr. K. Muneishi for the elemental analyses, Miss Y. Sato and Mr. H. Miyamoto for the nmr measurements, and Mr. H. Moriguchi for the mass analyses.

Registry No.—**1a**, 766-94-9; **1b**, 1005-62-5; **1c**, 1074-56-2; **1d**, 1005-61-4; **1e**, 1005-41-0; **2a**, 35370-70-8; **2b**, 41507-17-9; **2c**, 41507-18-0; **2d**, 41507-19-1; **3a**, 35370-71-9; **3b**, 41507-21-5; **3c**, 41507-22-6; **3d**, 41507-23-7; **4**, 120-61-6.

On the Photodecarbonylation of β,γ-Epoxy Ketones

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In contrast to the extensive investigation of the photochemistry of α,β-epoxy ketones,[1] β,γ-epoxy ketones have received relatively little attention. Padwa and his coworkers have reported that irradiation of *trans*-1,4-diphenyl-3,4-epoxybutan-1-one affords products derived from Norrish type II processes, but the cis isomer gives only recovered starting material.[2] In 10-oxatricyclo[4.3.1.$0^{1,6}$]decan-8-one, Norrish type II processes are not possible, and photolysis of this compound provides small amounts (less than 0.2 mol/mol of ketone) of a mixture of carbon monoxide and carbon dioxide, and a mixture of unidentified products.[3] Analogous to their cyclopropyl counterparts,[4] 2-(oxiranyl)cycloalkanones give (among other products) unsaturated macrolides by a three-atom photochemical ring expansion.[5]

Recently, Chambers and Marples have noted the photodecarbonylation of a β,γ-epoxy ketone.[6] Irradiation of 9α,10α-epoxy ketone **1** results in the formation of unsaturated epoxide **2** (20%), the B-nor epoxide **3** (3%), and several minor products.[6] We now wish to report the photochemistry of two β,γ-epoxy ketones which also undergo photodecarbonylation to provide unsaturated epoxides. However, these reactions proceed in high chemical yield and by a mechanism clearly different from that reported by Chambers and Marples for the photodecarbonylation of **1**.

Treatment of hexamethylbenzobicyclo[2.2.2]octadienone **4**[7] with *m*-chloroperbenzoic acid gives epoxy

(1) For reviews see A. Padwa, *Org. Photochem.*, **1**, 91 (1967); R. O. Kan, "Organic Photochemistry," McGraw-Hill, New York, N. Y., 1966, pp 129–140; J. A. Waters, Y. Kondo, and B. Witkop, *J. Pharm. Sci.*, **61**, 321 (1972).

(2) A. Padwa, D. Crumrine, R. Hartman, and R. Layton, *J. Amer. Chem. Soc.*, **89**, 4435 (1967).

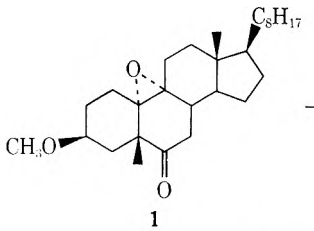
(3) J. E. Starr and R. H. Eastman, *J. Org. Chem.*, **31**, 1393 (1966).

(4) R. G. Carlson and E. L. Biersmith, *Chem. Commun.*, 1049 (1969).

(5) R. G. Carlson, J. H.-A. Huber, and D. E. Henton, *Chem. Commun.*, 223 (1973).

(6) R. J. Chambers and B. A. Marples, *Chem. Commun.*, 1122 (1972).

(7) A. C. Gripper-Gray and H. Hart, *J. Amer. Chem. Soc.*, **90**, 2569 (1968).



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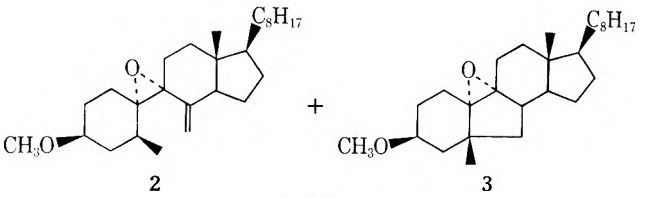
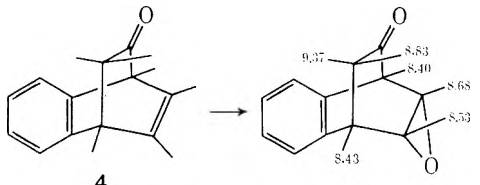


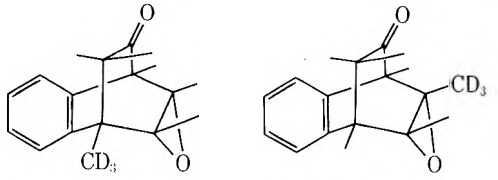
2 3

ketone **5**: mp 83–85°; $\nu_{C=O}^{CCl_4}$ 1720 cm^{-1}; pmr ($CDCl_3$) three-proton singlets at τ 9.37, 8.83, 8.68, 8.53, 8.43, and



4 5

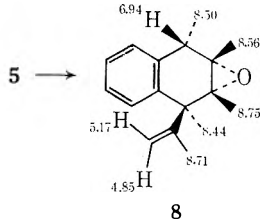
8.40, and a four-proton aromatic multiplet, τ 2.92–2.60. As the signals at τ 8.43 and 8.68 are absent in the pmr spectra of **6** and **7**, respectively, the pmr signals of **5**



6 7

can be assigned as indicated in the figure. The chemical shifts, and the difference in chemical shifts, of the methyls at C-7 and C-8 in **5** preclude the epoxy group in **5** from being anti to the benzene ring.

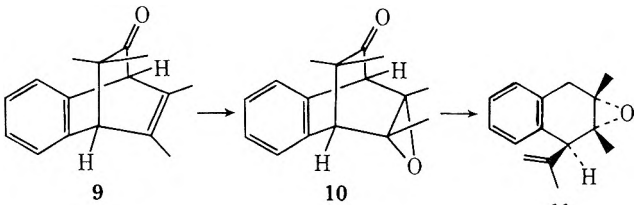
Irradiation of an ether solution of **5** through a Corex filter with a Hanovia L 450-W lamp affords unsaturated



8

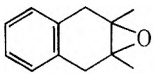
epoxide **8** in *ca.* 95% yield. The photoproduct (parent peak at *m/e* 242) is an oil which lacks carbonyl absorption in the infrared region and has an ultraviolet maximum (C_6H_{12}) at 285 nm (ϵ 149). The pmr ($CDCl_3$) spectrum of **8** consists of three-proton singlets at τ 8.75, 8.71, 8.56, and 8.44, a three-proton doublet (J = 7 Hz) at τ 8.50, a one-proton quartet (J = 7 Hz) at τ 6.94, a one-proton multiplet at τ 5.17, a broad one-proton singlet at τ 4.85, and a four-proton aromatic multiplet centered at τ 2.94. In the pmr spectra of the corresponding unsaturated epoxides obtained from the photodecarbonylations of **6** and **7**, the three-proton singlets are absent at τ 8.44 and 8.56, respectively. Consequently, the signals in the pmr spectrum of **8** are assigned as indicated in the figure. The stereochemical assignments of the substituent groups in **8** follow from the mode of formation of **8** (*cf.* ref 6).

An analogous photodecarbonylation occurs with the tetramethylepoxy ketone **10**: mp 85–86°; pmr ($CDCl_3$) aliphatic methyls at τ 9.27, 8.73, 8.49, and 8.39, bridgehead protons at τ 6.82 and 6.21, and an aromatic multiplet, τ 3.0–2.6, which is readily obtained by treatment of **9**[8] with *m*-chloroperbenzoic acid. Comparable irradiation of **10** gives **11** in *ca.* 75% yield.[9] The pmr



9 10 11

($CDCl_3$) spectrum of **11** consists of three-proton singlets at τ 8.57, 8.49, and 8.48, a broad two-proton singlet at τ 6.81, a one-proton singlet at τ 6.15, a one-proton multiplet at τ 5.20, a broad one-proton singlet at τ 4.92, and a four-proton aromatic multiplet centered at τ 2.87. The pmr ($CDCl_3$) spectrum of the model epoxide **12**, prepared from 2,3-dimethyl-1,4-dihydronaph-

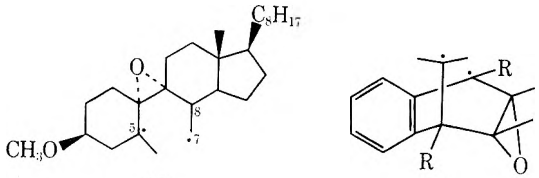


12

thalene,[10] contains a six-proton singlet at τ 8.56, a broad four-proton singlet at τ 6.89, and an aromatic multiplet centered at τ 2.93.

Irradiation of acetone solutions of epoxy ketones **5** or **10** through Pyrex results in a much slower rate of disappearance of the epoxy ketones, and the formation of complex reaction mixtures.

Chambers and Marples have concluded from labeling studies that diradical **13** provides **2** by two hydrogen migrations, C-7 → C-5 and C-8 → C-7 (overall a formal 1,4-hydrogen shift), which may be consecutive in this order or synchronous.[6] However, this mechanism does not account for the formation of **8** from **5** and **11** from **10**. Ostensibly, **8** and **11** result from diradical **14**



13 14

following formal 1,6-hydrogen shifts. Thus, it is apparent that the Chambers and Marples mechanism is not an exclusive route for the photodecarbonylation of β,γ-epoxy ketones.

Experimental Section

syn-7,8-Epoxy-1,3,3,4,7,8-hexamethyl-5,6-benzobicyclo[2.2.2]-oct-5-en-2-one (**5**).—A solution of 0.790 g (3.89 mmol) of 85%

(8) Ketone **9** was first prepared by T. Kakihana (M.S. Thesis, Michigan State University, 1966); experimental details are presented here.

(9) Monitoring the photoreaction by glpc indicated the formation of a minor photoproduct, which proved to be photolabile under the reaction conditions, and was not identified.

(10) G. Arich and S. Volpe, *J. Gas Chromatogr.*, **6**, 384 (1968).

m-chloroperbenzoic acid in 15 ml of methylene chloride was added during 15 min to an ice-cold stirred solution of 0.900 g (3.54 mmol) of 4[7] in 30 ml of methylene chloride. Stirring was continued in an ice bath for 1 hr and at room temperature for an additional 24 hr. Excess peracid was destroyed by the addition of 10% sodium sulfite until a test with starch–iodide paper was negative. The reaction mixture was washed with 5% sodium bicarbonate solution (3 × 50 ml), water (2 × 50 ml), and saturated sodium chloride solution (2 × 50 ml), and dried over anhydrous magnesium sulfate. Evaporation of the solvent provided an oil which was exhaustively evaporated of solvent at reduced pressure to give 0.900 g (89%) of **5**, which was recrystallized from pentane, mp 83–85°. The pmr spectrum is discussed in the text; ir (CCl_4) 2980, 1720, 1480, 1460, 1390, 1380, 1370, 1280, 1175, 1090, 1030, 1010, and 870 cm^{-1}; $\lambda_{max}^{C_6H_{12}}$ 316 nm (ϵ 200), 305 (340), 295 (330), 282 (260), 271 (465), 264 (510), 258 (300), 227 (5000).

Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 79.89; H, 8.15.

Similarly, ***syn*-7,8-epoxy-1,3,3,7,8-pentamethyl-4-methyl-d_3-5,6-benzobicyclo[2.2.2]oct-5-en-2-one** (**6**) was prepared by epoxidation of 1,3,3,7,8-pentamethyl-4-methyl-d_3-5,6-benzobicyclo[2.2.2]octa-5,7-dien-2-one[7] and ***syn*-7,8-epoxy-1,3,3,4,8-pentamethyl-7-methyl-d_3-5,6-benzobicyclo[2.2.2]oct-5-en-2-one** (**7**) was obtained from 1,3,3,4,8-pentamethyl-7-methyl-d_3-5,6-benzobicyclo[2.2.2]octa-5,7-dien-2-one.[7]

General Photolysis Procedure.—All irradiations were carried out with a 450-W Hanovia Type L mercury lamp with the light filtered through a Corex glass sleeve. The solution to be irradiated was placed in a quartz test tube, sealed with a serum cap, and attached to the outside of a water-cooled immersion well, 2–3 cm from the center of the mercury lamp. This apparatus was then placed in a water bath, which maintained the temperature of the solution between 15 and 20° during irradiation.

For each of the irradiations reported, a control experiment showed that no reaction occurred under comparable conditions in the dark.

Irradiation of Epoxy Ketone 5.—A solution of 100 mg of **5** in 10 ml of diethyl ether was irradiated through a Corex filter. The photolysis was monitored by glpc (10 ft × 0.25 in. FFAP column; 215°; 60 ml/min of helium). Irradiation led to a progressive decrease in the concentration of **5** (retention time 22.6 min) and an increase in the concentration of a photoproduct with a retention time of 10.2 min. This photoproduct reached a maximum concentration after 225-min irradiation, and further irradiation for 75 min produced only a slight decrease in its concentration. After 5-hr irradiation, no more starting material remained. Glpc and pmr analysis with internal standards indicated that the photoproduct was obtained in *ca.* 95% yield. Purification of the photoproduct by glpc (above conditions) provided a colorless oil, epoxide **8**. The pmr spectrum is discussed in the text; ir (CCl_4) 2980, 2940, 1640, 1495, 1450, 1370, 1175, 1150, 1120, 1100, 1060, 1040, 900, and 870 cm^{-1}. The major peaks in the mass spectrum [*m/e* 242 (M^+)] are at 199 and 157.

Anal. Calcd for $C_{17}H_{22}O$: C, 84.25; H, 9.15. Found: C, 84.37; H, 9.17.

3,3,7,8-Tetramethyl-5,6-benzobicyclo[2.2.2]octa-5,7-dien-2-one (**9**).[8]—A solution of anthranilic acid (4.5 g, 33 mmol) in acetone (40 ml) was added during 1 hr to a solution of 3,4,6,6-tetramethyl-2,4-cyclohexadienone[11] (3.28 g, 21.8 mmol) and isoamyl nitrite (3.87 g, 33 mmol) in methylene chloride (80 ml). After an additional 1 hr at reflux, the solvent was evaporated and the residual brown oil was dissolved in ether (70 ml) and washed with 10% sodium hydroxide, then water, and finally dried over anhydrous sodium sulfate. Evaporation of the solvent provided an oil which was distilled to give 3.18 g (63%) of **9**, a pale yellow oil: bp 104–105° (0.5 Torr); pmr (CCl_4) three-proton singlets at τ 9.42, 8.86, 8.23, and 8.16, one-proton singlets at τ 6.60 and 5.98, and a four-proton aromatic multiplet centered at τ 2.88; ir (CCl_4) 1720, 1675, 1600, and 710 cm^{-1}; λ_{max}^{EtOH} 300 nm (ϵ 389), 273 (1100), 268 (1200), and 216 (8130). Treatment of **9** with hydroxylamine hydrochloride in ethanol–pyridine gave a crystalline oxime, mp 175–176° (from ethanol).

Anal. Calcd for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80. Found: C, 79.90; H, 7.94; N, 5.80.

***syn*-7,8-Epoxy-3,3,7,8-tetramethyl-5,6-benzobicyclo[2.2.2]octa-5-en-2-one** (**10**).—Epoxidation of **9** with *m*-chloroperbenzoic acid, according to the procedure described in detail for **4** → **5**, gave epoxy ketone **10**, mp 85–86° (from pentane). The pmr spectrum is discussed in the text; ir (CCl_4) 2975, 2925, 1725, 1475, 1455, 1380, 1195, 1165, 1130, 1095, and 875 cm^{-1}.

Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.39; H, 7.44.

Irradiation of Epoxy Ketone 10.—A solution of 100 mg of **10** in 10 ml of diethyl ether was irradiated through a Corex filter. The photolysis was monitored by glpc (10 ft × 0.25 in. FFAP column; 210°; 60 ml/min of helium). Examination of the solution after 30-min irradiation showed a significant decrease in the concentration of **10** (retention time 25.9 min), the appearance of a main photoproduct (retention time 11.8 min), and a trace of another photoproduct (retention time 8.2 min). Continued irradiation led to a progressive decrease in the concentration of **10** and a progressive increase in the concentration of the photoproduct with retention time 11.8 min. A new photoproduct with retention time 6.2 min also appeared and further irradiation led to an increase in the concentration of this product at the expense of the compound with retention time 8.2 min. After 5-hr irradiation, no more starting material remained, and integration of the peak areas of the photoproducts showed their relative concentrations to be retention time 6.2 min (4.6%), 8.2 min (2.1%), and 11.8 min (93.3%). Pmr analysis with an internal standard of the photolysate indicated that the photoproduct with a retention time of 11.8 min was obtained in *ca.* 75% yield. This photoproduct was purified by glpc (above conditions) to provide a colorless oil, epoxide **11**. The pmr spectrum is discussed in the text; ir (CCl_4) 3075, 3010, 2970, 1640, 1495, 1450, 1385, 1245, 1170, 1145, 1080, 1010, 900, and 875 cm^{-1}.

Anal. Calcd for $C_{15}H_{18}O$: C, 84.07; H, 8.47. Found: C, 84.27; H, 8.49.

2,3-Epoxy-2,3-dimethyl-1,4-dihydronaphthalene (**12**).—Epoxidation of 2,3-dimethyl-1,4-dihydronaphthalene[10] with *m*-chloroperbenzoic acid, according to the procedure described in detail for **4** → **5**, gave **12**. The pmr spectrum is discussed in the text.

Anal. Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.84; H, 8.07.

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Registry No.—**4**, 17384-73-5; **5**, 41498-90-2; **8**, 41498-91-3; **9**, 22686-90-4; **9** oxime, 41498-21-9; **10**, 41498-92-4; **11**, 41498-93-5; **12**, 41498-22-0; 3,4,6,6-tetramethyl-2,4-cyclohexadienone, 14069-95-5; 2,3-dimethyl-1,4-dihydronaphthalene, 21564-72-7.

(11) H. Hart and R. M. Lange, *J. Org. Chem.*, **31**, 3776 (1966).

Photosensitized Oxygenations of Some Derivatives of Kaurenes

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The dye-sensitized photooxygenation of organic compounds, which has been studied extensively by many workers,[2] provides a smooth method for the specific

(1) Correspondence should be directed to this author.

(2) K. Gollnick and G. O. Schenck in "1,4 Cycloaddition Reactions," J. Hamer, Ed., Academic Press, New York, N. Y., 1967, p 255; K. Gollnick and G. O. Schenck, *Pure Appl. Chem.*, **9**, 507 (1964); E. J. Bowen, *Advan. Photochem.*, **1**, 23 (1963); G. O. Schenck, *Angew. Chem.*, **69**, 579 (1957); C. S. Foote, *Accounts Chem. Res.*, **1**, 104 (1968).

introduction of oxygen into their molecules. It has been elegantly employed in the synthesis, interconversion, and rearrangement of a number of natural products related to diterpenoids[3] and steroids[4] as a means of establishing their structural interrelationship and also as a model experiment for their biosynthetic pathways.

The oxygenation of olefins containing allylic hydrogen atoms in the presence of a suitable sensitizer and with visible light gives allylic hydroperoxides which are invariably accompanied by a shift of the double bond, a reaction analogous to the "ene" reaction. During the course of the isolation and structure determination[5] of the constituents of several species *Espeletia* (family *Compositae*), a fairly large amount of kaurene derivatives has been available. Thus photooxygenation of (−)-kaur-15-en-19-oic acid (**1a**),[6] (−)-kaur-16-en-19-oic

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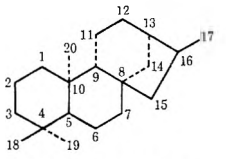
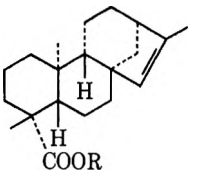


(−)-kaurane

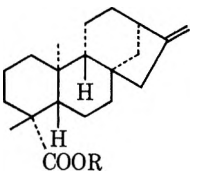
acid (**2a**), and (−)-kaur-9(11)-en-19-oic acid (**3a**) appeared to offer an interesting problem, since thy may be the precursors of 15α-hydroxy-(−)-kaur-16-en-19-oic acid (**5a**),[5b] (−)-kaur-15-ene-17,19-diol (**6b**),[7] and methyl 9-hydroxykaur-19-oate (**4**),[8] respectively, and their conversion might occur *in vivo* by a process analogous to this sensitized photooxygenation.

Methyl (−)-kaur-15-en-19-oate (**1b**) in pyridine was irradiated with fluorescent tubes using haematoporphorin as a sensitizer. The resulting hydroperoxide was not isolated and was directly reduced in ethanol solution with sodium iodide and acetic acid. Chromatography of the product over silica gel afforded in 42% yield an allylic alcohol **5b**: *m/e* 332 (M^+); ir 3540 (OH) and 1727 cm^{-1} (ester C=O); nmr δ 0.85 (s, 3, tertiary methyl), 1.20 (s, 3, tertiary methyl), 3.66 (s, 3, carbomethoxy), 5.13 and 5.26[9] (broad m, 2, terminal methylene), and 3.83 (broad s, 1, proton[10] at C-15). Oxidation of **5b** with Jones reagent[11] at 0° afforded a keto methyl ester **5c**, which exhibited the characteristic absorption

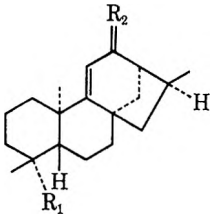
CHART II



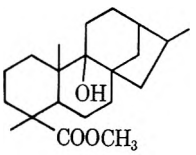
1a, R = H
b, R = CH_3



2a, R = H
b, R = CH_3

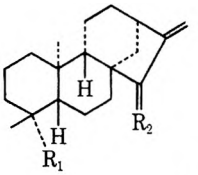


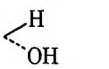
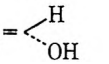
3a, R_1 = COOH; R_2 = H_2
b, R_1 = $COOCH_3$; R_2 = H_2
c, R_1 = $COOCH_3$; R_2 = 
d, R_1 = $COOCH_3$; R_2 = O
e, R_1 = CH_2OH; R_2 = 
f, R_1 = CH_2OH; R_2 = H_2
g, R_1 = CH_2OH; R_2 = 
h, R_1 = $COOCH_3$; R_2 = 

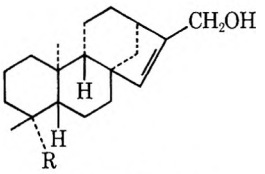


4

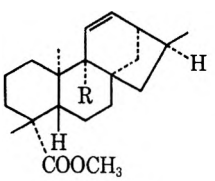
CHART III



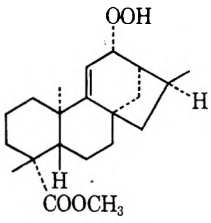
5a, R_1 = COOH; R_2 = 
b, R_1 = $COOCH_3$; R_2 = 
c, R_1 = $COOCH_3$; R_2 = O



6a, R = $COOCH_3$
b, R = CH_2OH



7a, R = OOH
b, R = OH



8

of α,β-unsaturated ketones [uv max (MeOH) 234 nm (ε 7500) and ir 1700 (broad, unresolved ester and α,β-unsaturated C=O) and 1620 cm^{-1} (CH_2=C<)]. The identity of **5b** with methyl 15α-hydroxy-(−)-kaur-16-en-19-oate[12] was established by direct comparison

(3) M. F. Barnes, R. C. Durley, and J. MacMillan, *J. Chem. Soc. C*, 1341 (1970); R. A. Bell and R. E. Ireland, *Tetrahedron Lett.*, 269 (1963); M. F. Barnes and J. MacMillan, *J. Chem. Soc. C*, 361 (1967).

(4) (a) A. Nickon and J. F. Bagli, *J. Amer. Chem. Soc.*, **83**, 1498 (1961); A. Nickon, N. Schwartz, J. B. DiGiorgio, and D. A. Widdowson, *J. Org. Chem.*, **30**, 1711 (1965); (b) J. E. Fox, A. I. Scott, and D. W. Young, *J. Chem. Soc., Perkin Trans. 1*, 799 (1972).

(5) (a) A. Usubillaga and A. Morales Méndez, *Rev. Latinoamer. Quím.*, **1**, 128 (1970); (b) A. Morales Méndez, A. Usubillaga, A. K. Banerjee, and T. Nakano, *Planta Med.*, in press.

(6) The numbering and nomenclature of these diterpenoids follows a system recommended by R. McCrindle and K. H. Overton in "Advances in Organic Chemistry, Methods and Results," Vol. 5, R. A. Raphael, E. C. Taylor, and H. Wynberg, Ed., Interscience, New York, N. Y., 1965, p 47.

(7) H. A. Lloyd and H. M. Fales, *Tetrahedron Lett.*, 4891 (1967).

(8) L. A. Cuevas, F. García Jiménez, and A. Romo de Vivar, *Rev. Latinoamer. Quím.*, **3**, 22 (1972).

(9) These protons give broadened signals at about δ 4.70–4.80. See L. H. Briggs, B. F. Cain, R. C. Cambie, B. R. Davis, P. S. Rutledge, and J. K. Wilmskurst, *J. Chem. Soc.*, 1345 (1963), and G. Hugel, L. Lods, J. M. Mellor, D. W. Theobald, and G. Ourisson, *Bull. Soc. Chim. Fr.*, 2882, 2888 (1965).

(10) The β configuration of this hydrogen (hence the α configuration of the hydroxyl group) may be expected on the basis of attack of oxygen from the less hindered α side of the 15,16 double bond.

(11) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).

(12) Reference 5b; C. H. Brieskorn and E. Pöhlmann, *Tetrahedron Lett.*, 5661 (1968); C. H. Brieskorn and E. Pöhlmann, *Chem. Ber.*, **102**, 2621 (1969). For the corresponding compound with the 15β-hydroxy group, see D. E. U. Ekong and A. U. Ogan, *J. Chem. Soc. C*, 311 (1968).

(melting point, mixture melting point, and ir spectrum) of both specimens.

Methyl (−)-kaur-16-en-19-oate (**2b**) was also photooxygenated under a similar condition and the resulting hydroperoxide, without isolation, was treated in the same way as above. Chromatography of the product over silica gel afforded in 30% yield an allylic alcohol **6a**: *m/e* 332 (M^+); ir 3300 (OH), 1730 (ester C=O), and 1680 cm^{-1} (C=C); nmr δ 0.85 (s, 3, tertiary methyl), 1.15 (s, 3, tertiary methyl), 3.63 (s, 3, carbomethoxy), 4.16 (s, 2, 17-allylic hydroxymethyl), and 5.35 (broad m, 1, 15-vinyl proton). Reduction of **6a** with lithium aluminum hydride in tetrahydrofuran gave a diol **6b**: mp 193–194°; $[\alpha]_D$ −11° (*c* 1.0, $CHCl_3$); *m/e* 304 (M^+); nmr δ 0.93 (s, 3, tertiary methyl), 1.00 (s, 3, tertiary methyl), 3.39 and 3.73 (AB q, 2, J = 12 Hz, 19α-hydroxymethyl), 4.16 (broad s, 2, allylic 17-hydroxymethyl), and 5.33 (broad m, 1, 15-vinyl proton). The spectroscopic as well as physical properties of this compound were completely consistent with those reported for (−)-kaur-15-ene-17,19-diol (**6b**).[13]

Methyl (−)-kaur-9(11)-en-19-oate (**3b**) was rather resistant to photooxygenation. When it was irradiated for 120 hr and the resulting hydroperoxide was treated as before, there was isolated in 10% yield[14] an allylic alcohol, $C_{21}H_{32}O_3$, *m/e* 332 (M^+). At first it was assumed that this alcohol must be **7b**, derived from the attack of oxygen from the less hindered α side of the 9,11 double bond accompanied by an allylic shift of the double bond to the 11,12 position. However, the nmr spectrum of this alcohol did not exhibit signals corresponding to two olefinic protons, but instead one proton signal at δ 4.10 (multiplet), which could be assigned to the proton attached to the carbon bearing an allylic hydroxyl group, and one vinyl proton signal at δ 5.36 (doublet, J = 4.5 Hz), besides signals of two tertiary methyls at δ 0.95 (singlet) and 1.16 (singlet), one secondary methyl at δ 0.95 (doublet, J = 6 Hz), and one carbomethoxy group at δ 3.61 (singlet). This indicated that the original 9,11 double bond still exists at the same position. Furthermore, the fact that the 11-vinyl proton which appeared at δ 5.18 as a triplet (J = 3 Hz) in **3b** now resonates as a doublet (J = 4.5 Hz) suggested that substitution of one of the hydrogens at C-12, possibly with the hydroxyl group, had taken place. Therefore, this allylic alcohol must be **3c** and its mode of formation may be envisaged as follows. Photooxygenation of **3b** would first yield the unstable intermediate 9α hydroperoxide **7a**,[15] which would then undergo an allylic rearrangement of the type observed in analogous systems[16] to the 12α hydroperoxide **8**. Subsequent reduction of **8** with potassium iodide would give rise to the allylic alcohol **3c**. The presence of the allylic hydroxyl function in **3c** was further verified by its oxidation with Jones reagent[11] at 0° to **3d**. The ketone **3d** displayed the characteristic α,β-unsaturated carbonyl absorption [ir 1722 (ester C=O) and 1666 cm^{-1} (α,β-unsaturated C=O); uv max (95% ethanol) 245 nm (ϵ 9734)].

Reduction of **3c** with lithium aluminum hydride in tetrahydrofuran afforded a diol **3e**. Its nmr spectrum revealed an AB quartet (δ 3.53 and 3.83, J = 11 Hz) that could be assigned to an axial 19α-hydroxymethyl group, a 12β-proton multiplet at δ 4.08, and an 11-vinyl proton at δ 5.30 (doublet, J = 4.5 Hz), in addition to two tertiary methyls at δ 0.93 (singlet) and 1.05 (singlet) and one secondary methyl at α 0.95 (doublet, J = 6.5 Hz).

Prolonged irradiation of **3b** did not improve the yield of the allylic alcohol **3c**. After photooxygenation for 15 days, followed by reduction of the resulting hydroperoxide with lithium aluminum hydride, the alcohol **3e** was obtained in 6% yield.[17]

In order to confirm the structure of **3c**, we then attempted to prepare it from **3b** *via* a different route. The allylic oxidation[18] of olefins with uv light in the presence of mercuric bromide or *N*-bromosuccinimide, or direct oxidation[19] of allylic methylene with *N*-bromosuccinimide to carbonyl with visible light, was recently reported. However, **3b** was found to be totally resistant to the oxidation of this type, and only starting material was recovered unchanged. Therefore, we turned to the usual chromic acid oxidation.[20] When **3b** was treated with chromium trioxide in acetic acid at room temperature for 2 days, the desired ketone **3d** was obtained in good yield. This ketone proved to be identical (ir, uv, nmr, and mass spectra) with the ketone obtained from the photooxygenation of **3b** followed by oxidation of the resulting allylic alcohol **3c**.

Reduction of **3d** with lithium aluminum hydride in tetrahydrofuran yielded a diol. The ir spectrum of this diol was very similar to, but not identical with, that of **3e**. Its nmr spectrum showed an AB quartet (δ 3.45 and 3.73, J = 10 Hz) attributable to the axial 19α-hydroxymethyl group. However, in comparison with the spectrum of the allylic alcohol **3e**, the corresponding 11-vinyl proton resonated as a doublet (J = 1.5 Hz) at δ 5.05 (0.25 ppm upfield) and the 12 proton as a multiplet at δ 4.51 (0.43 ppm downfield). The 12-hydroxyl group of this allylic alcohol must have the β configuration, since the attack of the hydride is expected from the less hindered α side[21] of the molecule. This alcohol is thus formulated as **3g**. Reduction of **3d** with sodium borohydride in 2-propanol also yielded from the same stereochemical grounds the 12β alcohol, which is formulated as **3h**. In its nmr spectrum, the 11-vinyl proton resonated as a doublet (J = 1.5 Hz) at δ 5.22 (0.14 ppm upfield) and the 12α proton as a multiplet at δ 4.62 (0.52 ppm downfield), as compared with those corresponding protons in **3c**.

Experimental Section

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Ir spectra were run on a Perkin-Elmer 337

(13) See ref 7. Direct comparison was not achieved because a comparison sample could not be obtained.

(14) Approximately 90% of the starting material was recovered unchanged.

(15) The attack of oxygen is expected from the less hindered α side of the 9,11 double bond of **3b**. For a similar case, see the hydroboration of **3b**: F. Piozzi, S. Passannanti, M. L. Marino, and V. Spiro, *Can. J. Chem.*, **50**, 109 (1972).

(16) G. O. Schenck, O.-A. Neumüller, and W. Eisfeld, *Justus Liebigs Ann. Chem.*, **618**, 202 (1958); ref 4b.

(17) After chromatography over silica gel, there was obtained the alcohol **3f** in 50% yield, besides **3e**.

(18) N. Friedman, M. Gorodetsky, and Y. Mazur, *Chem. Commun.*, 874 (1971).

(19) B. W. Finucane and J. B. Thomson, *Chem. Commun.*, 1220 (1969).

(20) **3b** was resistant to the selenium dioxide oxidation. Under varying conditions only starting material was recovered unchanged.

(21) Note that no epimeric 12α alcohol was obtained. Inspection of the molecular model indicated that the β side of the 12 carbonyl is severely sterically hindred by the β bridging of ring D as well as the β-methyl group at C-16.

spectrometer in KBr disks and uv spectra were measured with a Cary Model 15 spectrometer. Nmr spectra were obtained on a Varian A-60 instrument in deuteriochloroform and chemical shifts are reported in parts per million downfield from internal TMS (δ scale). Rotations were measured at 23° in chloroform with a Zeiss polarimeter (0.01°). Mass spectra were recorded on a Hitachi Perkin-Elmer RMU-6H at 70 eV using a direct inlet system. For column chromatography Merck standardized alumina, activity II-III, and Merck silica gel were used. For tlc Merck silica gel G was used and the spots were identified by exposure to iodine vapor. All organic extracts were dried over anhydrous magnesium sulfate and evaporated under reduced pressure below 40°. Microanalyses were carried out by A. Bernhardt Microanalytical Laboratory, 5521 Elbach über Engelskirchen, West Germany.

Photooxygenations were conducted in a vertical Pyrex tube irradiated externally along its length by two 33-W fluorescent bulbs mounted about 10 cm away. A fritted glass plate was near the bottom of the tube to disperse the oxygen, which was admitted at the bottom at a convenient rate and without interruption.

Photooxygenation of Methyl (−)-Kaur-15-en-19-oate (1b).[6a]—The methyl ester **1b** (0.28 g) and haematoporphorin (10 mg) were dissolved in dry pyridine (25 ml) and the deep brown solution was irradiated for 96 hr until no starting material had remained. The progress of the reaction was monitored by tlc. The solution was evaporated *in vacuo* and the resultant hydroperoxide (0.34 g) was treated at room temperature overnight with a solution of ethanol (30 ml) containing acetic acid (1 ml) and sodium iodide (2 g). The dark brown oil left after concentration of the solution *in vacuo* was taken up in ether and the ether solution was washed with aqueous sodium thiosulfate, then water, dried, and evaporated. The crude product (0.31 g) thus obtained was chromatographed over silica gel (30 g), and elution with hexane–ether (8:2) yielded methyl 15α-hydroxy-(−)-kaur-16-en-19-oate (**5b**) (0.12 g) which on recrystallization from ether–hexane showed mp 114–116°, $[\alpha]_D$ −95° (c 0.1). Direct comparison of this compound with an authentic sample[12] established its identity (melting point, mixture melting point, and ir spectrum).

Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.91; H, 9.85.

Oxidation of Methyl 15α-Hydroxy-(−)-kaur-16-en-19-oate (5b) with Jones Reagent.—The alcohol **5b** (40 mg) in acetone (10 ml) was oxidized at 0° with Jones reagent.[11] After usual work-up a gummy mass was obtained, which was purified in ether through alumina. The α,β-unsaturated ketone **5c** was crystallized from ether–hexane, mp 147–148°, $[\alpha]_D$ −92° (c 1.0). This ketone was identical (uv, melting point, mixture melting points, and ir spectrum) with an authentic sample.[12]

Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.22; H, 8.96.

Photooxygenation of Methyl (−)-Kaur-16-en-19-oate (2b).[22]—The methyl ester **2b** (0.35 g) and haematoporphorin (10 mg) in dry pyridine (25 ml) were irradiated for 120 hr. The solution was then evaporated *in vacuo* and the crude hydroperoxide, without isolation, was reduced, as before, in a solution of ethanol (35 ml) containing acetic acid (1 ml) and sodium iodide (2 g). The dark brown residue obtained after removal of the solvent was taken up in ether. The ether solution was washed with aqueous sodium thiosulfate, then water, dried, and evaporated. The residue (0.32 g) was chromatographed over silica gel (30 g), and elution with hexane–benzene (1:1) yielded the unchanged methyl ester **2b** (0.13 g). Further elution with hexane–ether (1:9) afforded methyl 17-hydroxy-(−)-kaur-15-en-19-oate (**6a**) (100 mg), which on recrystallization from ether–hexane had mp 125–126°, $[\alpha]_D$ −15° (c 1.0).

Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.67; H, 9.54.

Reduction of Methyl 17-Hydroxy-(−)-kaur-15-en-19-oate (6a) with Lithium Aluminum Hydride.—The methyl ester **6a** (80 mg) in dry tetrahydrofuran (20 ml) was reduced under reflux with lithium aluminum hydride (100 mg) for 4 hr. The complex was decomposed with alkali and the product was isolated in the usual way. (−)-Kaur-15-ene-17,19-diol (**6b**) (30 mg) was obtained and crystallized from chloroform to show mp 193–194°, ir 3250 cm^{-1} (OH). The physical constants (rotation, melting point, and nmr spectrum) were in perfect agreement with those reported in the reference.[7]

(22) The isolation and characterization of these related known diterpenoids are to be published somewhere.

Anal. Calcd for $C_{20}H_{32}O_2$: C, 78.89; H, 10.59. Found: C, 78.64; H, 10.33.

Photooxygenation of Methyl (−)-Kaur-9(11)-en-19-oate (3b).[22]

A.—The methyl ester **3b** (1.587 g) and haematoporphorin (25 mg) were dissolved in dry pyridine (25 ml) and the solution was irradiated for 120 hr. The solvent was then removed *in vacuo* and the resultant crude hydroperoxide was treated with a solution of ethanol (50 ml) containing potassium iodide (2.5 g) and acetic acid (0.75 ml) at room temperature for 24 hr. Water was added, the product was extracted with chloroform, and the chloroform extract was washed with aqueous sodium thiosulfate, then water, and dried. Evaporation of the chloroform left a dark brown residue which was chromatographed over silica gel (20 g). The methyl ester **3b** (1.25 g) was recovered unchanged from hexane–benzene and benzene fractions. Elution with chloroform containing methanol (1–5%) yielded methyl 12α-hydroxy-(−)-kaur-9(11)-en-19-oate (**3c**) as an amorphous powder (0.166 g) which could not be induced to crystallize: ir 3400 (OH) and 1730 cm^{-1} (ester C=O). The ir spectrum of this alcohol was different from that of the alcohol **3h** (see below) obtained by the reduction of **3d** with sodium borohydride.

Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.54; H, 9.46.

B.—The methyl ester **3b** (1.25 g) and haematoporphorin (25 mg) in dry pyridine (25 ml) was photooxygenated for 15 days. The solvent was removed *in vacuo* and the crude hydroperoxide was reduced in dry tetrahydrofuran (40 ml) under reflux with lithium aluminum hydride (3 g) for 4 hr. The complex was decomposed with alkali and the product (1.15 g) was isolated in the usual way and chromatographed over silica gel (30 g). Elution with benzene–chloroform yielded (−)-kaur-9(11)-en-19-ol (**3f**)[22] (0.6 g), mp 97–100° (from chloroform–hexane). Elution with chloroform afforded (−)-kaur-9(11)-ene-12α,19-diol (**3e**) (70 mg), mp 171–175° (from ether–hexane; see below).

C.—The methyl ester **3b** (0.963 g) and haematoporphorin (26 mg) in dry pyridine (30 ml) were irradiated for 20 days. The crude hydroperoxide was reduced with potassium iodide as before and the product (0.95 g) was obtained. Chromatography over silica gel (20 g) and elution with benzene yielded recovered methyl ester **3b** (0.698 g). Further elution with chloroform containing methanol (1–10%) yielded methyl 12α-hydroxy-(−)-kaur-9(11)-en-19-oate (**3c**) (46 mg).

Reduction of Methyl 12α-Hydroxy-(−)-kaur-9(11)-en-19-oate (3c) with Lithium Aluminum Hydride.—The methyl ester **3c** (0.107 g) in dry tetrahydrofuran (40 ml) was refluxed with lithium aluminum hydride (0.5 g) for 4 hr. Water was added to decompose the excess reagent and the complex was treated with 5% aqueous sodium hydroxide (5 ml). The product was isolated in the usual way and purified through silica gel (10 g). Elution with chloroform yielded (−)-kaur-9(11)-ene-12α,19-diol (**3e**) (60 mg), which after recrystallization from ether–hexane showed mp 170–175°; *m/e* 304 (M^+); ir 3340 cm^{-1} (OH).

Anal. Calcd for $C_{20}H_{32}O_2$: C, 78.89; H, 10.59. Found: C, 78.61; H, 10.33.

Oxidation of Methyl 12α-Hydroxy-(−)-kaur-9(11)-en-19-oate (3c) with Jones Reagent.—The methyl ester **3c** (60 mg) in acetone (10 ml) was treated with Jones reagent[11] at 0°. The product was isolated by extraction with chloroform in the usual way, and methyl 12-oxo-(−)-kaur-9(11)-en-19-oate (**3d**) (55 mg) was obtained as a semisolid, *m/e* 330 (M^+).

Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.61; H, 8.93.

Oxidation of Methyl (−)-Kaur-9(11)-en-19-oate (3b) with Chromium Trioxide in Acetic Acid.—The methyl ester **3b** (0.203 g) in acetic acid (10 ml) was treated with chromium trioxide (0.12 g) and the solution was stirred at room temperature for 4 hr. An additional amount (0.13 g) of chromium trioxide was then added and the solution was stirred at room temperature for 2 days. After addition of water the product was extracted with chloroform and the chloroform extract was washed with water, dried, and evaporated to afford a crude product (0.19 g). This oxidation was repeated using the methyl ester **3b** (0.4 g), chromium trioxide (0.3 g), and acetic acid (15 ml), and the combined products (0.58 g) were chromatographed over alumina (20 g), and methyl 12-oxo-(−)-kaur-9(11)-en-19-oate (**3d**) (0.26 g) was obtained by elution with hexane–benzene (1:1): $[\alpha]_D$ +121° (c 1.1). This ketone was identical (ir, uv, nmr, and mass spectra) with the ketone obtained by the oxidation of **3c** with Jones reagent.

Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.11; H, 8.82.

Reduction of Methyl 12-Oxo-(−)-kaur-9(11)-en-19-oate (3d) with Lithium Aluminum Hydride.—The ketone **3d** (0.107 g) in dry tetrahydrofuran (40 ml) was treated with lithium aluminum hydride (0.4 g) and the solution was refluxed for 2 hr. The excess reagent was decomposed with water and the complex was treated with 5% aqueous sodium hydroxide (5 ml). After addition of anhydrous magnesium sulfate, the solution was filtered and evaporated. The crude product was chromatographed over silica gel (20 g) and elution with benzene–chloroform (1:1) and chloroform afforded (−)-kaur-9(11)-ene-12β,19-diol (**3g**) (50 mg), mp 160–165° (from ether-hexane), $[\alpha]_D$ +48° (*c* 0.9), *m/e* 304 (M^+). The ir spectrum of this diol was very similar to, but different from, that of the diol **3e**.

Anal. Calcd for $C_{20}H_{32}O_2$: C, 78.89; H, 10.59. Found: C, 78.61; H, 10.31.

Reduction of Methyl 12-Oxo-(−)-kaur-9(11)-en-19-oate (3d) with Sodium Borohydride.—The ketone **3d** (80 mg) in 2-propanol (10 ml) was treated with sodium borohydride (90 mg) and the solution was left under stirring at room temperature for 4 days. Water was then added and the product (92 mg) was isolated by extraction with chloroform. This reduction was repeated using the ketone **3d** (80 mg) and the combined products (0.15 g) were chromatographed over silica gel (20 g). Elution with benzene yielded methyl 12β-hydroxy-(−)-kaur-9(11)-en-19-oate (**3h**) (0.14 g) as an amorphous powder, *m/e* 332 (M^+), $[\alpha]_D$ +46° (*c* 1.3). The ir spectrum of this alcohol was different from that of the alcohol **3c** obtained from the photooxygenation of **3b**.

Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.55; H, 9.46.

Acknowledgment.—We wish to thank Mrs. M. Cerhalmi de Hazos for the determination of the ir, uv, nmr, and mass spectra.

Registry No.—**1b**, 18671-79-9; **2b**, 41473-15-8; **3b**, 41473-16-9; **3c**, 41473-17-0; **3d**, 41473-18-1; **3e**, 41473-19-2; **3f**, 41473-20-5; **3g**, 41473-21-6; **3h**, 41473-22-7; **5b**, 22343-41-5; **5c**, 22376-47-2; **6a**, 35030-39-8; **6b**, 41473-26-1.

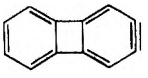
Communications

See Editorial, *J. Org. Chem.*, **37**, No. 13, 4A (1972).

2,3-Dehydrobiphenylene

Summary: Thermal decomposition of 2-biphenylenediazonium 3-carboxylate affords 2,3-dehydrobiphenylene which forms 2-chlorobiphenylene with 1,2-dichloroethane, biphenylenebicyclo[2.2.2]octatriene with benzene, and 1,2,3,4-tetraphenylbenzo[*b*]biphenylene with tetraphenylcyclopentadienone.

Sir: As part of our program to synthesize the higher homologs of biphenylene which incorporate four-membered rings into an annellated system, we have been able to generate and trap the novel aryne, 2,3-dehydrobiphenylene (**1**). The precursor[1] of **1**, 2-biphenylene-



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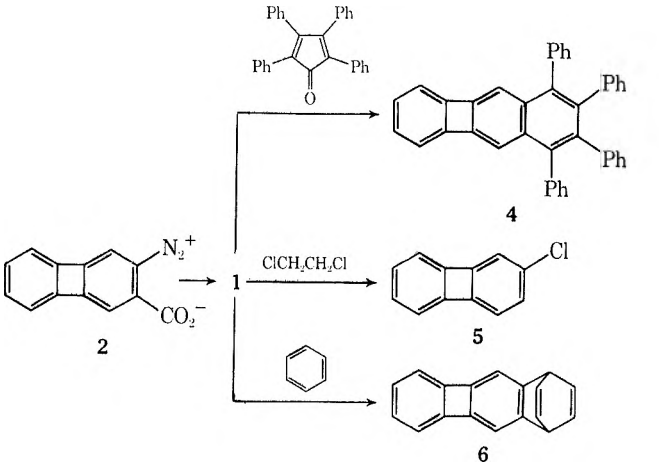
diazonium 3-carboxylate (**2**), was prepared starting with 2-acetamido-3-bromobiphenylene[2] which on treatment with cuprous cyanide in dimethylformamide gave 2-acetamido-3-cyanobiphenylene. Hydrolysis of the cyano group with hot concentrated hydrochloric acid afforded 2-acetamidobiphenylene-3-carboxylic acid which on treatment with sodium hydroxide in aqueous ethanol gave 2-aminobiphenylene-3-carboxylic acid (**3**). Diazotization of **3** with isoamyl nitrite in tetrahydrofuran containing a trace of trichloroacetic acid gave **2**. Thermal decomposition of **2** in the presence of tetraphenylcyclopentadienone yielded the adduct **4** isolated *via* chromatography (neutral alumina–pentane) in 10% yield: white needles; mp 316–317.5°; uv max (cyclohexane) 251 nm (ε 27,500), 274 (50,700), 282 (66,700), 296 (42,800), 309 (55,100), 341 (7250), 353 (5070), 373 (6520), 394 (6520); nmr ($CDCl_3$) δ 7.15 (s, 10, C-1 and C-4 phenyls), 6.80 (s) and 6.76 (s) (16, C-2 and C-3 phenyls + biphenylene); mass spectrum *m/e* 506 (parent).



(1) See paragraph at end of table regarding supplementary material.

(2) W. Baker, J. F. W. McOmie, D. R. Preston, and V. Rogers, *J. Chem. Soc.*, 414 (1960).

Attempts to isolate the dimer of **1** have thus far been unsuccessful. Thus, the thermal decomposition of **2** in refluxing 1,2-dichloroethane affords as the main product (9% yield) 2-chlorobiphenylene **5**.[3] In refluxing benzene **2** affords mostly polymeric material accompanied by a small amount (1%) of biphenylenebicyclo[2.2.2]-octatriene (**6**): a yellow solid; mp 156–158°; nmr ($CDCl_3$) δ 7.2-6.3 (m, 10, aromatic plus olefinic), 5.0–4.7 (m, 2, bridgehead); mass spectrum *m/e* 228 (parent) 202 (P − C_2H_2).

Attempts at crossing 2,3-dehydrobiphenylene with benzyne resulted primarily in the independent dimerization of benzyne to yield biphenylene.

It is evident from the trapping experiments that 2,3-dehydrobiphenylene generated from the diazonium carboxylate **2** is a true aryne, undergoing cycloaddition reactions typical of the highly reactive intermediates. However, under conditions generally favorable for aryne dimerization, **1** either does not undergo aryne coupling (*i.e.*, dimerization or crossing) or does so in such a myriad of concomitant reactions that the expected products are not isolable.

Regardless of this, 2,3-dehydrobiphenylene is in itself an interesting intermediate warranting further synthetic and theoretical investigation.[4]

Supplementary Material Available.—Details of the syntheses of the compounds reported here along with spectral information will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 20 × reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-1973-3812.

(3) W. Baker, J. W. Barton, and J. F. W. McOmie, *J. Chem. Soc.*, 2666 (1958).

(4) This investigation was assisted financially by a grant from the National Science Foundation.

(5) Taken in part from the thesis of E. N. Losey, submitted in partial fulfillment of the requirement for the Ph.D. degree at Michigan State University, 1973.

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Three-Electron Oxidations. V. The Rapid Reaction of Chromic Acid with Two-Component Substrate System[1,2]

Summary: The chromic acid oxidation of binary systems containing isopropyl alcohol and bifunctional compounds such as dicarboxylic acids, hydroxy acids, and aldehydo or keto acids can be much faster than

(1) Part IV: F. Hasan and J. Roček, *J. Amer. Chem. Soc.*, **95**, 5421 (1973).

(2) This investigation was supported by the National Science Foundation.

that of either of the two substrates; hydroxy acids and picolinic acid are most effective in accelerating the oxidation.

Sir: We have recently reported[3] a dramatic rate acceleration of two to three orders of magnitude observed in the chromic acid oxidation of a two-substrate system of isopropyl alcohol and oxalic acid. The results lead us to propose a mechanism consisting of the formation of a termolecular complex and its decomposition in a single-step three-electron oxidation reaction.

We now wish to report that the ability to accelerate the chromic acid oxidation of isopropyl alcohol is not restricted to oxalic acid, but is shared by a large number of other substrates, particularly by those which could be expected to form relatively stable (usually bidentate) complexes with chromic acid.

The results are summarized in Table I. The first column shows the experimental pseudo-first-order rate constant for the oxidation of the given substrate in the absence of isopropyl alcohol. The next gives the sum of this value and of the pseudo-first-order rate constant for the oxidation of isopropyl alcohol and represents the oxidation rate for the mixture of the two substrates in the absence of any rate acceleration. The next column gives the observed oxidation rate for the mixture of isopropyl alcohol and the substrate. With the exception of succinic acid, ethylene glycol, and diethylene glycol the observed rate constant is always higher than that calculated in the preceding column. The last two columns represent two different quantitative measures of the rate accelerating effect. Column five gives the ratio of the observed to the calculated rate constant. The last column gives a rate constant computed on the assumption that a third-order term (first order in the substrate, in isopropyl alcohol, and in chromic acid) is responsible for the observed rate acceleration.[3]

Among the group of simple dicarboxylic acids, the previously investigated oxalic acid is by far the most effective participant in cooxidation reactions. Succinic acid is entirely unreactive. Malonic acid shows only a small rate-accelerating effect, whereas mono- and, particularly, dialkylmalonic acids are much more effective. This trend would be expected if the observed acceleration was due to a three-electron oxidation leading to $\cdot CH_2CO_2^-$, $R\dot{C}HCO_2^-$, and $R_2\dot{C}CO_2^-$, respectively, in analogy to the mechanism proposed for the cooxidation of oxalic acid.[3] In fact, the acceleration for disubstituted malonic acids is quite impressive considering the very low oxidation rates of these acids in the absence of the alcohol.

While we anticipated the possible rate-acclerating effect for maleic acid, the observed rate acceleration for fumaric acid and particularly for crotonic acid was entirely unexpected.

TABLE I

EFFECTIVENESS OF SOME SUBSTRATES IN COOXIDATION REACTIONS WITH CHROMIC ACID AND ISOPROPYL ALCOHOL[a]

Substrate (M)	10^3k, sec^{-1}	$10^3\Sigma k$,[b] sec^{-1}	10^3k_{obsd}, sec^{-1}	$\frac{k_{obsd}}{\Sigma k}$	$\frac{10^3(k_{obsd} - \Sigma k)}{[substrate][i\text{-PrOH}]}$
$(COOH)_2$ (0.254)	51.3	52.5	151	2.9	9940
$CH_2(COOH)_2$ (0.101)	0.126	1.29	1.31	1.02	6.09
$MeCH(COOH)_2$ (0.268)	0.277	1.44	1.61	1.12	16.6
$Me_2C(COOH)_2$ (0.203)	0.0009	1.16	1.41	1.22	31.6
$EtCH(COOH)_2$ (0.363)	0.231	1.39	1.61	1.15	15.5
$Et_2C(COOH)_2$ (0.179)	0.009	1.17	1.39	1.18	31.5
$(CH_2)_2(COOH)_2$ (0.158)	0.0022	1.16	1.16	1.00	0
MeCH=CHCOOH (0.191)	0.126	1.29	1.51	1.17	30.1
Fumaric acid (0.076)	0.120	1.28	1.61	1.26	111
Maleic acid (0.189)	0.533	1.69	2.57	1.52	119
Citraconic acid (0.231)	1.98	3.14	3.65	1.16	56.6
Mesaconic acid (0.073)	0.478	1.64	1.93	1.17	103
$O(CH_2COOH)_2$ (0.241)	0.026	1.19	1.65	1.38	48.9
$HOCH_2CO_2H$ (0.237)	1.73	2.89	6.93	2.40	437
MeCH(OH)COOH (0.134)	10.8	12.0	13.9	1.16	360
$Me_2C(OH)COOH$ (0.156)	0.116	1.28	5.78	4.52	740
MeEtC(OH)COOH (0.170)	0.165	1.33	8.25	6.20	1040
Malic acid (0.267)	4.47	5.63	13.3	2.36	737
meso-Tartaric acid (0.205)	10.8	12.0	69.3	5.78	7170
d-Tartaric acid (0.198)	11.6	12.8	46.4	3.63	4370
Citric acid (0.232)	0.087	1.25	9.60	7.68	923
OCHCOOH (0.065)	96.2	97.4	116	1.19	733
EtCOCOOH (0.173)	131	132	151	1.14	282
$HOOCCH_2CH_2COCOOH$ (0.232)	21.0	22.2	31.5	1.42	1030
$HOOCC(OH)_2C(OH)_2COOH$ (0.034)	7.22	8.38	28.9	3.45	15460
$HOCH_2CH_2OH$ (0.359)	2.89	4.05	4.08	1.01	2.14
$(HOCH_2CH_2)_2O$ (0.191)	1.24	2.40	2.41	1.00	1.34
$H_2NCH_2CO_2H$ (0.687)	0.0071	0.0187[c]	0.0201[c]	1.07[c]	5[c]
		1.17	1.31	1.12	5
Picolinic acid (0.264)	0.116	0.232[d]	8.06[d]	35[d]	7600[d]
		1.27	119	93	11800

[a] t = 60°, $HClO_4$ 0.628 M, i-PrOH 0.039 M, $k_{i\text{-PrOH}} = 1.16 \times 10^{-3}$ sec^{-1}. [b] $\Sigma k = k_{substrate} + k_{i\text{-PrOH}}$. [c] [$i$-PrOH] = 3.9×10^{-4} M. [d] [i-PrOH] = 3.9×10^{-3} M.

(3) F. Hasan and J. Roček, *J. Amer. Chem. Soc.*, **94**, 3181 (1972).

One of the most interesting classes of compounds included in Table I are the hydroxy acids which proved extremely effective in accelerating the oxidation of isopropyl alcohol. Aldehydo acids, keto acids, and diglycolic acid (containing an ether function) show less impressive but still quite substantial rate accelerations.

Another very high rate acceleration was observed for picolinic acid. The change in the value in the last column indicates that the reaction probably follows a different rate law than observed previously for oxalic acid.[3] Glycine affects the rate of the oxidation of isopropyl alcohol only to a very small extent.

Detailed investigations of several of the reactions reported in this communication are in progress.

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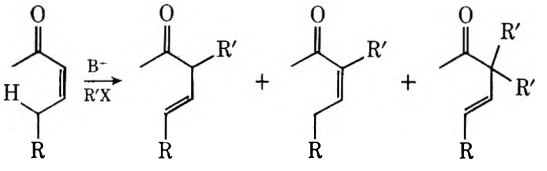
Regioselective Methylations of 2-Thioalkoxyenones

Summary: Methylation (methyl iodide) of the kinetic enolate generated from 2-thio-*n*-propyl-5,5-dimethyl-2-cyclohexen-1-one and lithium hexamethyldisilazide in tetrahydrofuran takes place at C_6, whereas methylation of the potassium enolate in *tert*-butyl alcohol occurs at C_2.

Sir: Alkylation of an α,β-unsaturated ketone having γ-hydrogen atoms under enolate equilibrating conditions usually results in formation of an α-alkyl-β,γ-unsaturated ketone (Scheme I). A major problem,

SCHEME I

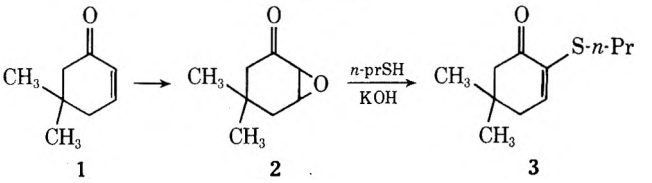


however, is that this initial product may be isomerized to an α-alkyl-α,β-unsaturated ketone or may undergo further alkylation.[1] This problem could not arise during alkylation of 2-thioalkoxyenones, in which the enone α-hydrogen atom is replaced by a potentially removable thioalkoxy group (*e.g.*, **3**).

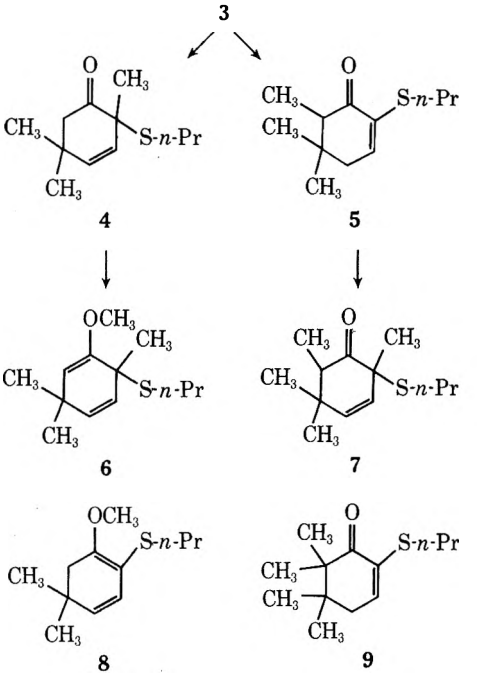
We wish to report some preliminary alkylation studies of thioalkoxyenones, here represented by 2-thio-*n*-propyl-5,5-dimethyl-2-cyclohexen-1-one (**3**). By simply varying the reaction conditions, we have been able to effect nearly quantitative carbon alkylation at either the 2 position in **3** to give enone **4** or at the 6 position to give enone **5** (Scheme III).

Cyclic 2-thioalkoxyenones may be efficiently prepared from the corresponding enone *via* an epoxy ketone.[2] In the present case (Scheme II), potassium

SCHEME II



SCHEME III



hydroxide catalyzed reaction of epoxide **2**[3] with *n*-propyl mercaptan in ethanol gave 2-thioalkoxycyclohexenone **3** in 94% isolated yield [bp 94–96° (~0.3 Torr), *m/e* 198].

Methylation of the potassium enolate of **3** generated by addition of **3** (10 g) to a solution of 1.1 equiv of potassium *tert*-butoxide in dry *tert*-butyl alcohol followed by addition of 2 equiv of methyl iodide gave predominately the 2-alkylated enone **4** (95%), some dialkylated enone **7** (4%), and a trace of enol ether **6** (Scheme III).[4] Enone **4** [80% isolated yield, bp 90° (~0.4 Torr), *m/e* 212] displayed olefinic proton resonance centered at δ 5.43 and 5.72 (J_{AB} = 10 Hz) and ir absorption at 5.87 μ (film).

It is noteworthy that oxygen alkylation of **3** to give **8** did not occur under these conditions. Indeed, even when the potassium enolate[5] of **3** was methylated in tetrahydrofuran (THF) solution (conditions known to facilitate oxygen alkylation), no oxygen alkylation of **3** could be detected. Under these conditions, **4** (75% yield), **5** (14%), **6** (6%), and recovered **3** (3%) were obtained. This result is to be contrasted with methylation of the potassium enolate of ketone **4** in THF–hexamethylphosphoramide (HMPA) solution to give predominately oxygen-alkylated **6** (90%), along with **7** (10%).

(1) H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972, Chapter 9.

(2) M. A. Tobias, J. G. Strong, and R. P. Napier, *J. Org. Chem.*, **35**, 1709 (1970).

(3) R. L. Wasson and H. O. House, *Org. Syn.*, **37**, 58 (1957).

(4) An F & M Model 700 gas chromatograph fitted with a thermal conductivity detector and a 6 ft × 1/8 in. stainless steel column filled with 10% UC-W98 on Chromosorb W, 80–100 mesh size, at 170° was used.

(5) Generated by addition of **3** to a suspension of potassium hydride in THF. This base–solvent combination has been used to generate ketone enolates in their equilibrium ratios: C. A. Brown, private communication; C. A. Brown, *J. Amer. Chem. Soc.*, **95**, 982 (1973).

Lithium secondary amide bases have been used to generate kinetic enolates from α,β-unsaturated ketones[6] and 3-alkoxycyclohexenones.[7] However, we have found that lithium hexamethyldisilazide (LHDS) is clearly superior to diisopropylamide or isopropylcyclohexylamide in methylation studies with 2-thioalkoxyenones.[8]

The following procedure is typical. A solution of **3** (10 g) in THF was added over 15 min at −78° to 1.1 equiv of LHDS (generated *in situ* from hexamethyldisilazane and *n*-butyllithium at ice bath temperature) in THF. HMPA (1.5 equiv), followed by methyl iodide (2 equiv), was added and the resulting solution was allowed to warm to room temperature and, after 1.2 hr, water was added. Analysis[4] revealed that 2-thio-*n*-propyl-5,5,6-trimethyl-2-cyclohexen-1-one (**5**, 92% yield) and enone **4** (0.3%), along with dialkylated compounds **9** (2.7%) and **7** (1.6%), as well as recovered **3** (4.1%), were present. Thioalkoxyenone **5** [88% isolated yield, bp 120° (~0.3 Torr), *m/e* 212] displayed olefinic proton resonance centered at δ 6.58 (J = 4.5 Hz) and ir absorption at 5.96 μ (film).

The ratio of α' to α alkylation using LHDS is vitally dependent upon the order in which HMPA and **3** are added to the base. Using conditions identical with those already described (in which **5** and **4** formed in a ratio of 300:1), except that HMPA was added to LHDS before **3**, resulted in a ratio **5**:**4** of 6:1. These results suggest that the basic properties of LHDS are modified in the presence of HMPA. Recently, a lithium diisopropylamide–HMPA complex has been reported to exhibit markedly reduced nucleophilicity when compared to lithium diisopropylamide alone.[9]

Construction of a wide variety of 2,6-dialkylated cyclohexenone derivatives should be possible by consecutive alkylation of 2-thioalkoxyenones. For example, methylation of enone **5** (methyl iodide, potassium *tert*-butoxide in *tert*-butyl alcohol) gave dialkylated enone **7** [88% yield, bp 100° (~0.3 Torr), *m/e* 226].

Acknowledgment.—This work was supported by an E. I. du Pont de Nemours and Co. Young Faculty Grant.

(6) R. A. Lee, C. McAndrews, K. M. Patel, and W. Reusch, *Tetrahedron Lett.*, 965 (1973).

(7) G. Stork and R. L. Danheiser, *J. Org. Chem.*, **38**, 1775 (1973).

(8) Methylation studies with **3** and analogs using secondary amide bases under a variety of conditions always resulted in recovery of 15–30% thioalkoxyenone.

(9) J. L. Herrmann, G. R. Kieczykowski, and R. H. Schlessinger, *Tetrahedron Lett.*, 2433 (1973).

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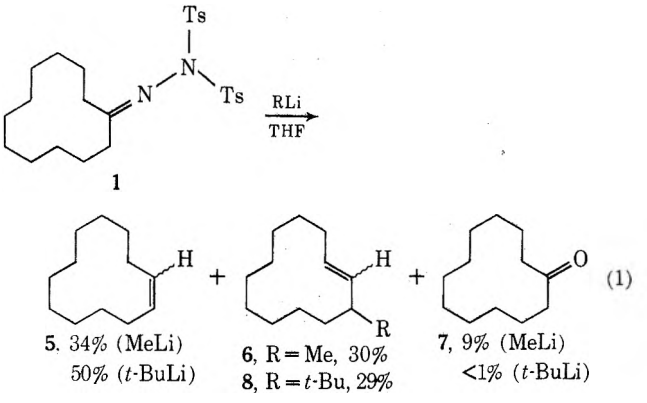
N,N-Ditosylhydrazones. Synthesis and Some Unique Reactions with Alkyllithium Reagents

Summary: Several *N,N*-ditosylhydrazones have been synthesized and converted into either 3-alkyl olefins or simple alkylated hydrocarbons by reaction with methyl- and *tert*-butyllithium.

Sir: The reactions of tosylhydrazones with alkyllithium reagents and other bases are well known, providing useful synthetic routes from ketones to a variety of compounds including olefins, allenes, acetylenes, diazo compounds, and carbenes.[1] This paper describes the preparation of several members of a new class of compounds, the *N,N*-ditosylhydrazones, and the reaction of representative members with methyl- and *tert*-butyllithium. While yields have not been optimized in any of the experiments described below, we consider the transformations sufficiently novel to report them at this time.[2]

Using Baumgarten's[3] procedure for the preparation of *N,N*-ditosylamines, a dry DMF solution of cyclododecanone monotosylhydrazone, mp 154–156°, prepared by the method of Bamford and Stevens,[4] was treated at 25° (N_2) with 1.2 equiv of sodium hydride followed by 1.0 equiv of toluenesulfonyl chloride. After water work-up cyclododecanone *N,N*-ditosylhydrazone (**1**), mp 152–153°, was obtained in 49% yield. The *N,N*-ditosylhydrazones listed in Table I were similarly prepared.

Reaction of ditosylhydrazone **1** with 2.5 equiv of methyllithium (2.0 *M* in hexane) in THF at 0° (N_2) followed by a water quench and ether extraction led to the mixture of products shown in eq 1 which was separated by preparative vpc.



The products were identified by direct comparison with authentic samples. Cyclododecene[5,6] (**5**) was prepared by reaction[1] of cyclododecanone monotosylhydrazone with methyllithium. Authentic 3-methylcyclododecene[5,7] (**6**) was prepared by treating 2-methylcyclododecanone monotosylhydrazone[7] with methyllithium.

The formation of 3-methylcyclododecene (**6**) in this reaction was quite unexpected, suggesting that the reaction of ditosylhydrazones with other alkyllithium reagents might constitute a new 3-alkyl olefin synthesis. We were particularly intrigued by the use of *tert*-butyllithium since few examples of the direct introduction of a *tert*-butyl group into a molecule are known.[8]

(1) See, *inter alia*, L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley-Interscience, New York, N.Y., Vol. 2, 1969, pp 417–423, and Vol. 3, 1972, p 293; A. M. Foster and W. C. Agosta, *J. Org. Chem.*, **37**, 61 (1972).

(2) See paragraph at end of paper regarding supplementary material.

(3) P. J. DeChristopher, J. P. Adamek, G. D. Lyon, J. J. Galante, H. E. Haffner, R. J. Boggio, and R. J. Baumgarten, *J. Amer. Chem. Soc.*, **91**, 2384 (1969).

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

(5) A mixture of cis and trans isomers.

(6) V. Prelog and M. Speck, *Helv. Chim. Acta.*, **38**, 1786 (1955).

(7) J. Casanova and B. Waegell, *Bull. Soc. Chim. Fr.*, 1289 (1971).

(8) See, for example, G. H. Posner and J. J. Sterling, *J. Amer. Chem. Soc.*, **95**, 3076 (1973).

TABLE I

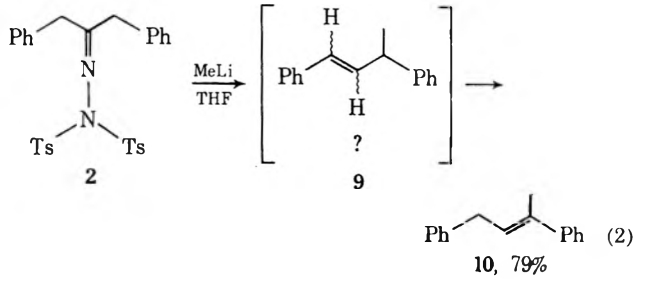
MELTING POINT AND YIELD DATA FOR REPRESENTATIVE MONO- AND DITOSYLHYDRAZONES

Parent ketone	Monotosylhydrazone Mp, °C	Monotosylhydrazone Yield,[a,b] %	Ditosylhydrazone Mp, °C	Ditosylhydrazone Yield,[b,c] %	Compd no.
Cyclododecanone	154–156	75	152–153	49	1
Dibenzyl ketone	180–181	86	159–160	26	2
Cyclohexanone	152–153[d]	81	149–150	50	3
4-*tert*-Butylcyclohexanone	144–145	62	169–170	36	4
Pentan-3-one	104–106	61	149–150	42	
Pinacolone	152–154[e]	69	155–156	41	
Cholestan-3-one	171–173[f]	44	171–172	19	

[a] Based on starting ketone. [b] Satisfactory analytical data (±0.4% for C, H, and N, the latter when determined) were reported for all new compounds listed in the table. [c] Based on starting monotosylhydrazone. [d] Lit.[4] mp 156°. [e] Lit.[4] mp 155°. [f] C. W. Shoppe, D. N. Jones, and G. H. R. Summer, *J. Chem. Soc.*, 3100 (1957), reported mp 172–174°.

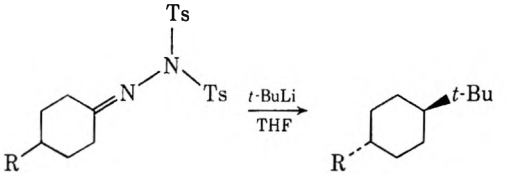
Treatment of ditosylhydrazone **1** with 3.5 equiv of *tert*-butyllithium (2.54 *M* in pentane) in THF at −78° (N_2) followed by slow warm up to 25°, water quench, ether extraction, and preparative vpc led in 29% yield to *trans*-3-*tert*-butylcyclododecene (**8**). The position of the *tert*-butyl group was assigned by analogy to methyl olefin **6** and the trans isomer was indicated[9] by the presence of strong absorption at 968 cm^{-1} and the lack of pronounced absorption in the region of 690 cm^{-1}. Also produced in this experiment in 50% yield was a mixture of *cis*- and *trans*-cyclododecene in a ratio of 41:59. The major component was identified as *trans*-cyclododecene by comparison with an authentic sample prepared by the method of Smith and Mennon.[10]

The reaction of methyllithium with dibenzyl ketone *N,N*-ditosylhydrazone (**2**) gave predominantly *cis*-1,3-diphenylbutene-2 (**10**) in 79% crude yield (eq 2), the spectral properties of which corresponded to those reported for the substance by Cram.[11] Olefin **10** was probably produced by base-catalyzed isomerization[11] of the initially formed 1,3-diphenylbutene **9** and likely contained some of the other olefin isomers. Cram[11] has shown that olefin **10** is the most stable isomer in an equilibrium established through catalysis by *tert*-butyl alcohol–potassium *tert*-butoxide.



2 9 10, 79% (2)

We next examined the reaction of *tert*-butyllithium with the *N,N*-ditosylhydrazones **3** and **4** of cyclohexanone and 4-*tert*-butylcyclohexanone, expecting to obtain, respectively, 3-*tert*-butylcyclohexene and 3,5-di-*tert*-butylcyclohexene. We were surprised to observe formation of *tert*-butylcyclohexane (**11**) in 35% yield from the first reaction and the analogous product, *trans*-1,4-di-*tert*-butylcyclohexane (**12**), in 56% yield from the second reaction (eq 3). The *tert*-butylcyclohexane (preparative vpc) was identified by direct comparison with a commercially available sample, while the *trans*-1,4-di-*tert*-butylcyclohexane (preparative vpc) showed physical and spectral properties identical with those reported for the substance by Kuss.[12]



(3)

3, R = H
4, R = *t*-Bu

11, R = H, 35%
12, R = *t*-Bu, 56%

Acknowledgment.—We thank the National Science Foundation (GP 27367) for generous financial support and Professor Jerome E. Gurst, University of West Florida, for the preparation of cholestan-3-one *N,N*-ditosylhydrazone.

Supplementary Material Available.—Mechanistic rationalizations, together with experimental details, will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 20 × reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-1973-3815.

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(12) E. Kuss, P. Pollsman, and H. Stegemeyer, *J. Mol. Structure*, **1**, 61 (1967).

(13) Alfred P. Sloan Fellow, 1972–1974; John Simon Guggenheim Fellow, 1972–1973; recipient of an NIH Research Career Development Award, 1972–1977.

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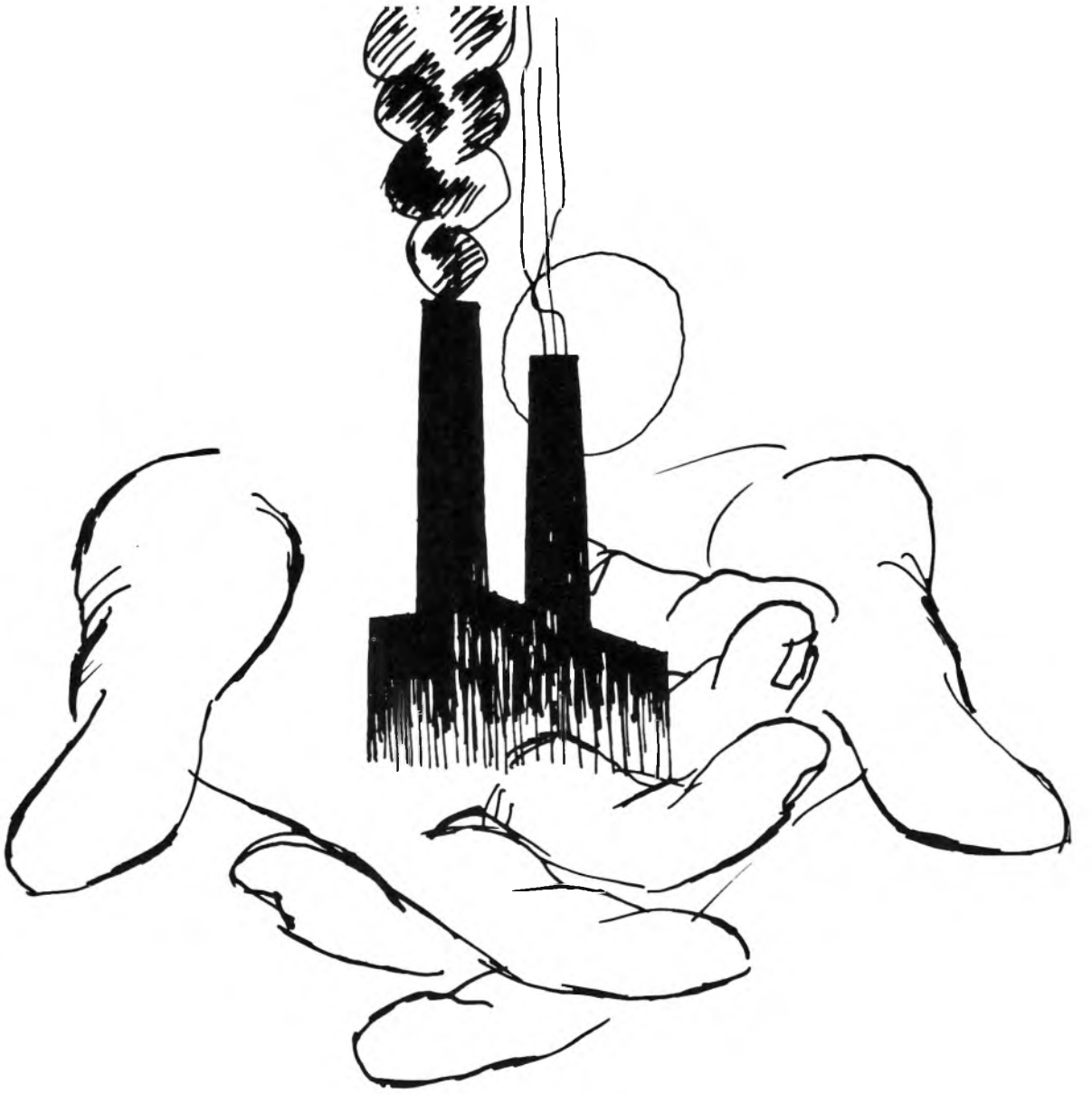

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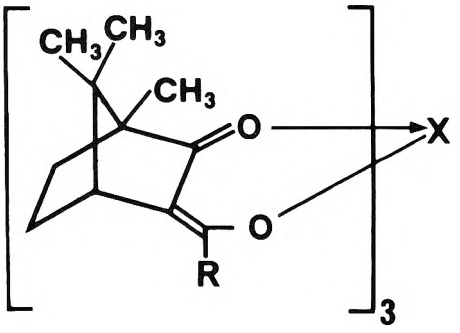
NMR Shift Reagents

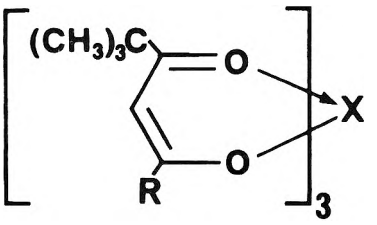
Polarimetry by NMR

The determination of enantiomeric or optical purity by classical methods is difficult and time-consuming.[1] Recently, rare-earth chelates of chiral β-diketones[2] have been used to determine enantiomeric purity simply and conveniently by nmr. The nmr spectra of chiral alcohols, amines, esters, ketones, sulfoxides and epoxides observed in the presence of TFMC-Eu, TFMC-Pr or THFC-Eu generally show such large chemical shift differences for the enantiotopic nuclei that the proportions of enantiomers can be measured directly by integration.[2] Consequently, these reagents provide a simple and convenient spectroscopic alternative to classical methods.



R = CF_3, X = Eu	**Tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorato]-europium (TFMC-Eu)**
R = CF_3, X = Pr	**Tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorato]-praseodymium (TFMC-Pr)**
R = *n*-C_3F_7, X=Eu	**Tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]-europium (THFC-Eu)**

Stretch Your NMR



R = $C(CH_3)_3$; X = Eu, Pr

R = *n*-C_3F_7; X = Eu, Pr

In the short period since their discovery[3] rare-earth chelates of β-diketones have become extremely important to all users of nmr because of their ability to simplify complex spectra by causing spectacular changes in the chemical shifts of nuclei adjacent to an electronegative substituent. The Resolve-Al* reagents produce large changes in chemical shift for protons adjacent to hydroxyl, amino, oxime, aldehyde, ketone, ester, ether, sulfoxide, nitrile, phosphonate and phosphate substituents with little line broadening. The addition of Resolve-Al* or Resolve-Al EuFOD* as either a solid or a solution to an nmr sample generally shifts resonances downfield while Resolve-Al Pr* or Resolve-Al PrFOD* shifts resonances upfield. In addition, correlation of observed shift with the geometry of the substrate-shift reagent complex facilitates configurational assignments.

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