converted into the hydrazone[16] XXX and 39 g. (0.11 mole) of this material was dissolved in 250 ml. of warm absolute ethanol. To this was added 250 ml. of ethanol saturated with HCl. The red solution, on boiling for 1 hour, turned yellow and a precipitate formed. On dilution with water, the product was obtained as an insoluble, yellow solid. One recrystallization from ethanol gave white product, m.p. 149–150.5°, 17.5 g. (47%) being obtained. The ultraviolet spectrum had λ_{max} 235 mμ, ε 30,000, and 294 mμ, ε 17,600. The carbonyl absorption occurred at 5.92 μ in the infrared.

Anal. Calcd. for $C_{23}H_{19}NO_2$: C, 80.91; H, 5.61; N, 4.10. Found: C, 81.03; H, 5.64; N, 4.09.

1,2-Diphenyl-3-indolecarboxylic Acid (XXXIII).—A mixture of 3 g. of ethyl ester XXXII, 25 ml. of 35% aqueous sodium hydroxide, 15 ml. of water and 50 ml. of methanol was refluxed for 18 hours. The mixture then was cooled and solid filtered; this was the sodium salt of the product. When dissolved in hot water and treated with excess hydrochloric acid, this furnished XXXIII as a white solid. The analytical sample was obtained by recrystallizing twice from acetone to give material with m.p. 244–245° dec. Ultraviolet maxima occurred at 234 mμ, ε 29,000, and 294 mμ, ε 16,800. The infrared spectrum had a band at 6.05 μ.

Anal. Calcd. for $C_{21}H_{15}NO_2$: C, 80.49; H, 4.83; N, 4.47. Found: C, 80.42; H, 4.67; N, 4.40.

A portion of the **sodium salt** was recrystallized from water to give white needles, m.p. > 300°.

Anal. Calcd. for $C_{21}H_{14}NO_2Na$: C, 75.21; H, 4.21; N, 4.18. Found: C, 75.26; H, 4.34; N, 3.99.

In a similar run with 10.2 g. (0.03 mole) of ester, 6.5 g. (69%) of acid was obtained.

(16) A. Hantzsch and E. v. Hornbostel, *Ber.*, **30**, 3009 (1897).

Methyl 1,2-Diphenyl-3-indolecarboxylate (XXXI).—Since an attempt to prepare this compound by transesterification of XXXII with sodium methoxide in methanol gave only a very impure product, the route *via* the acid chloride was chosen. This was prepared from 1 g. of acid XXXIII and 10 ml. of thionyl chloride, the solution being refluxed for 45 minutes after the initial reaction had stopped. The excess reagent was then removed *in vacuo*, 10 ml. of methanol added, and the mixture refluxed for 45 minutes. After cooling, the insoluble product was separated and recrystallized from methanol (charcoal) to yield white needles, m.p. 195–196°. The product was essentially the same as the by-product from the cyclization of XXVIII, above. The carbonyl group absorbed at 5.93 μ in the infrared. The ultraviolet spectrum had λ_{max} 235 mμ, ε 29,800, and 294 mμ, ε 17,600.

Anal. Calcd. for $C_{22}H_{17}NO_2$: C, 80.71; H, 5.23; N, 4.28. Found: C, 80.67; H, 5.01; N, 4.25.

Attempted Conversions of XXIX into Indoles.—A mixture of 1 g. of XXIX, 1 g. of sodium methoxide and 15 ml. of dry xylene was refluxed for 5 hours. Only a trace of neutral material resulted. The acidic fraction yielded unreacted XXIX.

A solution of 0.8 g. of XXIX and 20 ml. of ethanolic HCl was refluxed for 3 hours to give a light red solution which gave a negative ferric chloride test. On dilution with water a tan solid resulted. This, on recrystallization from 95% ethanol, furnished a white solid, m.p. 121–123°, mixed m.p. with 1-phenyloxindole[15] 122–123.5°. Since the hoped-for indoles XXXII or XXXIII are less soluble than 1-phenyloxindole, little or any could have been formed.

When a solution of 0.5 g. of XXIX, 30 ml. of ethanol, 10 ml. of concentrated aqueous HCl and 10 ml. of water was refluxed for 5 hours, 1-phenyloxindole was again the only product isolated.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER, ROCHESTER 20, N. Y.]

The Chemistry of Fumagillin[1]

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Experimental evidence is presented and discussed which allows the assignment of structures to fumagillin and its transformation products.

The chemistry of fumagillin has been intensively investigated[3–11] since its isolation.[12] Its antiparasitic properties[13] and its carcinolytic activity against some experimental tumors[14] have stimulated studies of the biological properties of compounds in this series.

Fumagillin was early[3,4] shown to be an acid ester, yielding on mild saponification decatetraenedioic acid, and a neutral fragment, $C_{16}H_{26}O_4$, called[15] alcohol-I. The present paper discusses the experimental evidence, mainly published only in preliminary form,[11,16,17] which allows the assign-

(1) Supported in part by Grant E-1138 of the U. S. Public Health Service.

(2) (a) Abbott Laboratories Fellow, 1960–1961; (b) 1957–1958; (c) Esso Fellow, 1960–1961; (d) Abbott Laboratories Fellow, 1959–1960; (e) 1956–1957; (f) 1958–1959.

(3) J. R. Schenck, M. P. Hargie, D. S. Tarbell and P. Hoffman, *J. Am. Chem. Soc.*, **75**, 2274 (1953).

(4) J. R. Schenck, M. P. Hargie and A. Isarasena, *ibid.*, **77**, 5606 (1955).

(5) D. S. Tarbell, P. Hoffman, H. R. Al-Kazimi, G. A. Page, J. M. Ross, H. R. Vogt and B. Wargotz, *ibid.*, **77**, 5610 (1955).

(6) J. M. Ross, D. S. Tarbell, W. E. Lovett and A. D. Cross, *ibid.*, **78**, 4675 (1956).

(7) J. K. Landquist, *J. Chem. Soc.*, 4237 (1956).

(8) J. G. McNally, Jr., and D. S. Tarbell, *J. Am. Chem. Soc.*, **80**, 3676 (1958).

(9) D. D. Chapman and D. S. Tarbell, *ibid.*, **80**, 3679 (1958).

(10) A. D. Cross and D. S. Tarbell, *ibid.*, **80**, 3682 (1958).

(11) R. M. Carman, D. D. Chapman, N. J. McCorkindale, D. S. Tarbell, F. H. L. Varino, R. L. West and D. J. Wilson, *ibid.*, **81**, 3151 (1959).

(12) T. E. Eble and F. R. Hanson, *Antibiotics and Chemotherapy*, **1**, 54 (1951); *cf.* I. N. Asheshov, F. Strelitz and E. A. Hall, *ibid.*, **2**, 361 (1952).

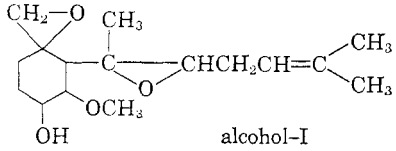
(13) (a) Amoebacidal activity: M. C. McCowen, M. E. Callender and J. F. Lawlis, Jr., *Science*, **113**, 202 (1951); H. H. Anderson, *et al.*, *Am. J. Trop. Med. Hyg.*, **1**, 552 (1952); J. H. Killough, G. B. Magill and R. C. Smith, *Science*, **115**, 71 (1952); (b) activity against *Nosema apis*, H. Katznelson and C. A. Jamieson, *ibid.*, **115**, 70 (1952).

(14) J. A. DiPaolo, D. S. Tarbell and G. E. Moore, *Antibiotics Annual*, 1958–1959, p. 541.

(15) The systematic nomenclature for these compounds is so cumbersome—alcohol-I has been called oxiranspiro-[2-(3-isopent-2'-enyl-1'-methoxyloxiranyl)-3-methoxycyclohexan-4-ol] (*Current Chem. Papers*, 290 (1960))—that some trivial nomenclature is necessary. The use of a name such as fumagillane for the parent hydrocarbon, with the indication of the oxygen functions by numbers, has little to recommend it. The use of "fumagillol"[7] for alcohol-I requires special indications for the diols and triols obtained by reductive opening of the epoxide groups. We have therefore retained the trivial names used in earlier papers of this series, when the complete structures were not known, in order to show the structures of the compounds discussed in the earlier papers. The suffix "a" refers to reduction of the side chain double bond, and "b" to the reductive opening of the spiroepoxide.

ment of structures to alcohol-I and its transformation products. Because of the complicated and interlocking nature of the structural arguments.

$$\underset{\text{fumagillin}}{HOOC(CH{=}CH)_4COOC_{16}H_{25}O_3} + H_2O \xrightarrow{NaOH} HOOC(CH{=}CH)_4COOH + \underset{\text{alcohol-I}}{C_{16}H_{26}O_4}$$



alcohol-I
A, $C_{16}H_{26}O_4$

it will be desirable to discuss the most important transformation products in turn, starting with a brief account of the evidence for the various functional groups in alcohol-I itself.

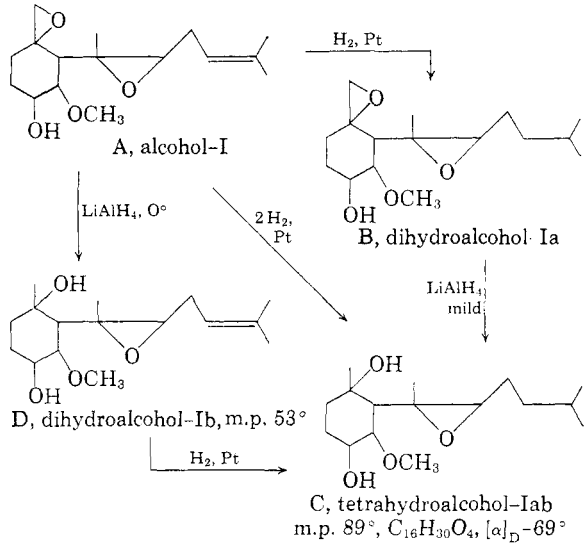
Chemical Properties of Alcohol-I.—This substance, $C_{16}H_{26}O_4$, m.p. 55–56°, $[\alpha]_D$ −68°,[18] shows no carbonyl absorption in the infrared, and hence none of its four oxygens is doubly bonded to carbon.[5-7] One is a secondary hydroxyl (see below), and one is a methoxyl group, as shown by analysis and by a singlet due to three protons at a value of about 6.6 in the n.m.r. spectra of alcohol-I and its derivatives; the other two oxygens are present in ring structures, because they can be opened reductively to lead in turn to diols and triols[4,6,7] (see below).

The presence of the double bond is demonstrated by the uptake of 1 mole of hydrogen to yield dihydroalcohol-Ia,[6] by the presence of a single vinyl proton at 4.9 in the n.m.r. and by ozonization to yield acetone.[3,7] The n.m.r. spectrum confirms the presence of the isopropylidene grouping (six protons at τ 8.26, 8.35) and it also shows that *one* additional methyl group is present with methyl beta to oxygen (CH_3–C–O, τ 8.88). This methyl group is unsplit, and hence there are no hydrogens on the carbon which carries it.[19]

The fact that one of the ring oxygens in alcohol-I is an epoxide is shown by the positive thiosulfate test[6,7,20] and by the very rapid reduction of the epoxide by lithium aluminum hydride or sodium borohydride to form a new hydroxyl group, as well as by some quantitative procedures for epoxides.[6] Epoxides show a band in the C–H stretching region between 2990–3050 cm.$^{-1}$ [21]; alcohol-I shows a band at 3026 cm.$^{-1}$, probably due to the combined effect of vinyl and epoxide hydrogens.[22] Dihydroalcohol-Ia (B) in which the double bond is reduced, shows a strong peak at 3016 cm.$^{-1}$; the presence of at least one epoxidic hydrogen is therefore indicated.

From the empirical formula of alcohol-I, it must contain a carbocyclic ring or a second double bond; its behavior on catalytic reduction indicates that it does not contain a second easily reducible double bond. Alcohol-I is sensitive to both acid and alkali, yielding a whole series of rearrangement and hydration products.[9,10] Chemical and spectroscopic evidence for a second inert epoxide ring is described later. The presence of the two epoxide groups, one of them very reactive, the double bond and the hydroxyl group offer ample scope for rearrangement reactions.

Tetrahydroalcohol-Iab (C).—This key intermediate in the structural work can be made by several reduction procedures *via* dihydroalcohols-Ia and Ib or, most conveniently, by reduction with two moles of hydrogen and active Adams platinum.[6] The structures are



Dihydroalcohol-Ia gives a thiosulfate test for epoxide, but dihydroalcohol-Ib and the tetrahydroalcohol do not. The empirical formula of the tetrahydroalcohol allows two rings, one oxygen containing and the other carbocyclic. The possible existence of a second double bond, necessarily tetrasubstituted (no olefinic proton absorption in the n.m.r. spectrum of the tetrahydroalcohol), instead of a carbocyclic ring is excluded[8] by the absence of characteristic ultraviolet end absorption[23] in the region 210–220 mμ.

The tetrahydroalcohol forms only a monoacetate, m.p. 63°, by treatment with acetic anhydride–pyridine in the cold, and is readily oxidized to a ketone which still has hydroxyl absorption in the infrared. That the secondary hydroxyl is the one which is present in alcohol-I is clear from the fact that dihydroalcohol-Ia, which still contains the epoxide group, forms a monoacetate under mild

(16) D. S. Tarbell, R. M. Carman, D. D. Chapman, K. R. Huffman and N. J. McCorkindale, *J. Am. Chem. Soc.*, **82**, 1005 (1960).

(17) D. D. Chapman, S. E. Cremer, R. M. Carman, M. Kunstmann, J. G. McNally, Jr., A. Rosowsky and D. S. Tarbell, *ibid.*, **82**, 1009 (1960).

(18) Rotations and ultraviolet absorption spectra are taken in 95% ethanol unless otherwise specified. Ultraviolet spectra are reported as follows: ϵ_{22} 1500, meaning that an absorption maximum at 220 mμ has ϵ = 1500. Nuclear magnetic resonance values (n.m.r.) are reported in τ-values relative to tetramethylsilane (G. Van Dyke Tiers, *J. Phys. Chem.*, **62**, 1151 (1958)), and were taken with a Varian 60 mc. machine. To minimize the complexity of the n.m.r. spectra, the hydrogen on oxygen was replaced by deuterium by exchange in heavy water. Infrared spectra were taken in potassium bromide disks or, for oils, without diluents.

(19) The Kuhn–Roth C-methyl determinations[3] show C-methyl found, 10.43; calcd. for one C-methyl, 5.31.

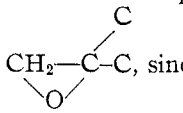
(20) W. C. J. Ross, *J. Chem. Soc.*, 2257 (1950).

(21) H. B. Henbest, *et al.*, *ibid.*, 1459 (1957).

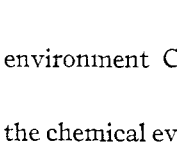
(22) H. B. Henbest, *et al.*, *ibid.*, 997 (1957); A. R. H. Cole and R. L. S. Willix, *ibid.*, 1215 (1959).

(23) P. Bladon, H. B. Henbest and G. W. Wood, *ibid.*, 2737 (1952).

conditions. Therefore the hydroxyl group generated by reductive cleavage of the epoxide group is tertiary. The n.m.r. data show conclusively that the reactive epoxide grouping has the structure

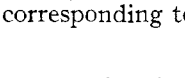


of tetrahydroalcohol at τ 8.78, which is absent in A and B, assignable to three methyl protons in the



the chemical evidence.[11]

Treatment of the crystalline monoacetate E with thionyl chloride–pyridine at 0° gives a mixture, which consists mainly of two unsaturated compounds, separable by column chromatography. These are assigned structures F and G, respectively; they show no hydroxyl in the infrared, G shows terminal methylene absorption at 895 cm.$^{-1}$ and yields formaldehyde on ozonization (62% yield as the methone derivative). Compound F shows a trisubstituted double bond in the infrared (813 cm.$^{-1}$), and shows three protons in the n.m.r. corresponding to



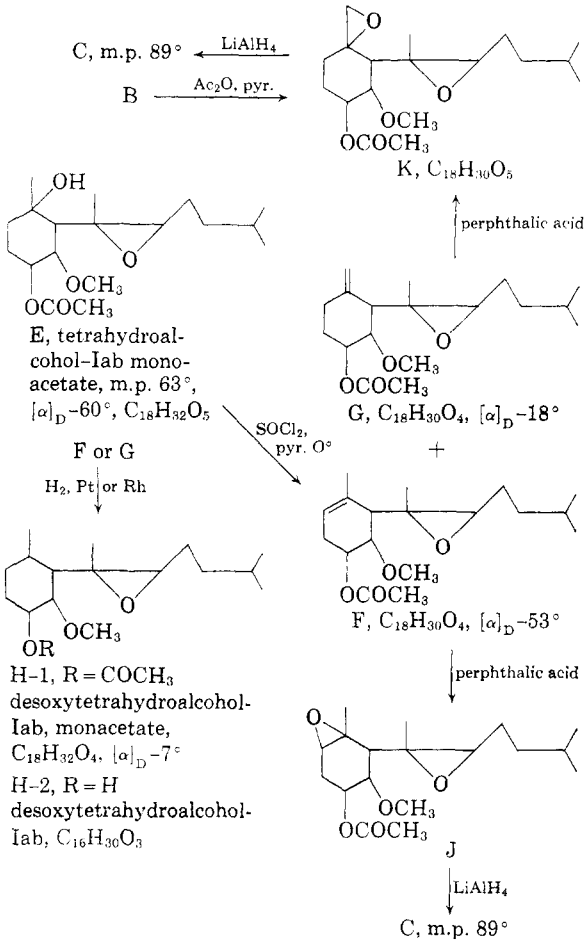
(τ 8.30) which is not present in the tetrahydroalcohol. Both F and G are reduced catalytically, best by hydrogen with rhodium-on-alumina,[24] to yield the same saturated compound, desoxytetrahydroalcohol acetate (H). When the catalytic reduction of F and G is carried out with platinum, there is a considerable amount of hydrogenolysis of the second epoxide ring in addition to saturation of the double bond; this hydrogenolysis product turns out to be an important link in the structural argument, and will be discussed below (α- and β-hexahydroalcohols).

Although the thionyl chloride–pyridine dehydration procedure is not known to be accompanied by rearrangement, we felt impelled, in view of the many rearrangements in the fumagillin series,[9,10] to prove that the dehydration was straightforward. Compounds F and G were oxidized separately with monoperphthalic acid, giving epoxides J and K; each of these was converted by lithium aluminum hydride to the crystalline tetrahydroalcohol-Iab, as shown by m.p. and mixed m.p. The hydride removes the acetyl group in addition to opening the epoxide group. Further, the epoxide from the terminally unsaturated compound G was identical, on the basis of the infrared spectrum, with the acetate derived from dihydroalcohol-Ia (B). This confirms the presence of the terminal epoxide grouping in alcohol-I.

Oxidation of the tetrahydroalcohol (C) with acid permanganate gives isocaproic acid[5]; many other attempts to oxidize the compound by a variety of reagents, and to identify the products by a variety of partition procedures, led to no illuminating results; isocaproic acid, sometimes accompanied by its two lower homologs, usually was found.

(24) W. E. Cohn and D. G. Doherty, *J. Am. Chem. Soc.*, **78**, 2863 (1956).

CHART I



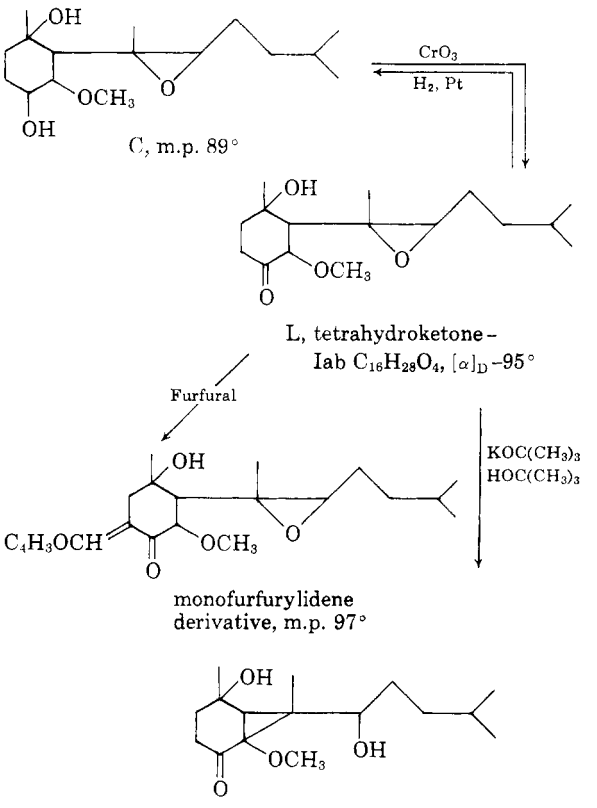
Extensive attempts to dehydrogenate the tetrahydroalcohol C have not given identifiable aromatic compounds, although mixtures of aromatic ketones and phenols are apparently formed, judging from ultraviolet and infrared spectra. Base-soluble phenolic fractions are obtained, which can be converted by methyl sulfate and alkali to neutral materials. A small amount of material with the spectral properties of a benzofuran is obtained.[4,5] Ethyl isoamyl ketone is formed by dehydrogenation,[4] and is identified through solid derivatives; this can arise plausibly by cleavage of the side chain with accompanying isomerization of the epoxide to a carbonyl group.

The action of strong bases (sodium hydride, potassium *t*-butoxide) on the tetrahydroalcohol leads to carbonyl compounds, with a band near 1710 cm.$^{-1}$; the best characterized of these, obtained by butoxide treatment, is probably due to isomerization of the epoxide group to a carbonyl.[25] Mineral acid isomerizes the tetrahydroalcohol, but the products have not been thoroughly characterized.

Tetrahydroketone (L) (Chart 2).—The tetrahydroalcohol C is oxidized by chromic oxide–pyridine or, preferably, by chromic oxide–acetone–

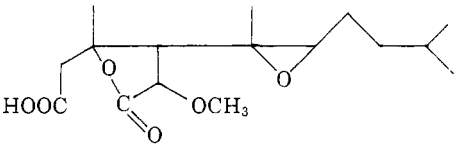
(25) A. C. Cope and B. D. Tiffany, *ibid.*, **73**, 4158 (1951); A. C. Cope, P. A. Trumbull and E. R. Trumbull, *ibid.*, **80**, 2844 (1958), and following papers, have shown that strong bases can isomerize epoxides to carbonyl compounds.

CHART 2



sulfuric acid[26] to the liquid tetrahydroketone $C_{16}H_{28}O_4$, $[\alpha]_D$ $-95°$,[5,6] and the ketone can be reduced back to the crystalline alcohol,[8] showing that there is no rearrangement during oxidation. The ketone contains one free methylene adjacent to the carbonyl group, because it forms a crystalline monofurfurylidene derivative,[6] and it contains one free hydrogen on the other α carbon. This is suggested by bromination experiments on the ketone,[6] which yields an unstable bromo compound, containing between two and three bromines per molecule, and more conclusively by deuterium exchange experiments on the furfurylidene derivative of L, in which 42% of one atom of deuterium is taken up in dioxane–deuterium oxide with potassium carbonate as the catalyst.[27] The position of the methoxyl group on the carbon α to the carbonyl is indicated by arguments based on the structure of β-hexahydroalcohol (see below), and by the infrared frequency of the carbonyl group (1724 cm.$^{-1}$) which is higher than normal for cyclohexanones, and is in agreement with the presence of an electron-attracting group on the α-carbon,[28,29] in the equatorial position. Furthermore, neither the methoxyl nor the hydroxyl is eliminated by treatment with strong base, and hence neither group is on either of the carbon atoms beta to the carbonyl group.

The formulation of L as a ring ketone is based on the results of ozonization followed by peroxide oxidation of the furfurylidene ketone; the product is a lactonic acid, $C_{16}H_{26}O_6$, which must have been formed by ring cleavage to a dibasic acid, followed by lactonization[8]; a possible structure is



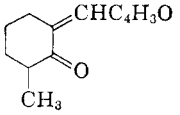
Since the side chain requires eight carbon atoms (formation of isocaproic acid, isocapraldehyde and the methyl protons β to oxygen, as below), and the methyl and methoxyl groups on the nucleus account for two more carbons, there are only six carbons remaining. The presence of a four- or five-membered ring is most unlikely, because the carbonyl frequency of L is too low, and also a smaller ring would not allow for placement of the oxygen functions, without putting one of them on the carbons beta to the carbonyl.

The carbonyl group in the ketone L is unreactive; no crystalline carbonyl derivatives have been obtained from it, and it reacts with the methyl Grignard and methyllithium only slowly, giving ill-defined products. The ketone is isomerized by both acids and bases; the action of potassium *t*-butoxide in boiling *t*-butyl alcohol for 1 hr. leads to a crystalline isotetrahydroketone, M, $C_{16}H_{28}O_4$, $[\alpha]_D$ 18.5°, which has not lost methanol or water, and hence the starting ketone L cannot have hydroxyl or methoxyl on the carbons beta to the carbonyl group. The evidence for structure M is presented in a later section; the isoketone itself is isomerized by further treatment with acid or base to mixtures of products. Treatment of the ketone L with potassium *t*-butoxide for 8 hr. leads apparently to a mixture of four ketones, and also gives a small amount of phthalic acid.

Hydride Reduction of Tetrahydroalcohol C: Structure of the Triol, α-Hexahydroalcohol N (Charts 3 and 4).—Reduction of the tetrahydroalcohol C with lithium aluminum hydride in boiling tetrahydrofuran opens the oxygen-containing ring with formation of a new hydroxyl group; previously[6] a single dextrorotatory hexahydroalcohol was described,[30] but further work has shown that

(26) K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(27) The ketone L and its furfurylidene derivative are sensitive to strong acid and strong base, so that these conditions cannot be used for the exchange. As a control in the exchange experiments, the furfurylidene derivative of 2-methylcyclohexanone,



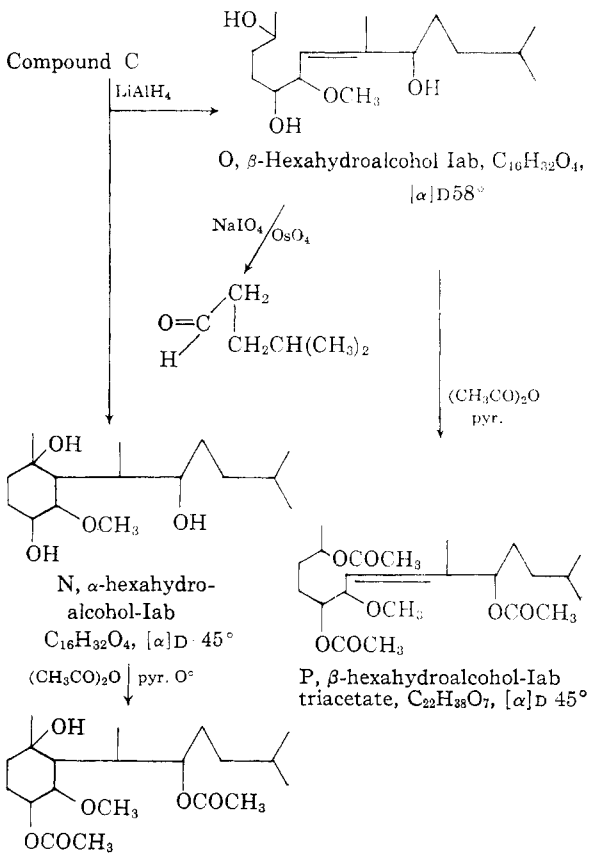
was used, and showed an uptake of 86% of one atom of deuterium.

(28) R. N. Jones, *et al.*, *J. Am. Chem. Soc.*, **70**, 2024 (1948); C. Sandris and G. Ourisson, *Bull. soc. chim.*, [5] **23**, 958 (1956); R. N. Jones, *et al.*, *J. Am. Chem. Soc.*, **74**, 2828 (1952); E. J. Corey, *ibid.*, **75**, 2301 (1953); H. P. Sigg and C. Tamm, *Helv. Chim. Acta*, **43**, 1402 (1960); *cf.* M. Uskokovic, M. Gut and R. I. Dorfman, *J. Am. Chem. Soc.*, **82**, 958 (1960).

(29) The earlier conclusion[8] that the methoxyl group was not on the α-carbon was based on the observations that the methoxyl group was not hydrolyzed by dilute aqueous acid, and did not react with Tollens or Fehling reagents; positive tests are characteristic of simple α-methoxyketones. The high degree of substitution around the methoxyl group apparently makes it unreactive to these reagents.

two triols, the α- and β-hexahydroalcohols, $C_{16}H_{32}O_4$ (N and O), are actually formed, and can be separated by column chromatography of the free triols or, better, of their acetates. The β-hexahydroalcohol is an open chain compound formed by ring cleavage (see below), and hence its structure, while interesting in itself, is not compelling evidence for the structure of the tetrahydroalcohol C.

CHART 3

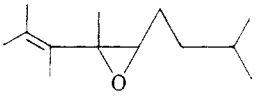


The α-hexahydroalcohol contains two secondary and one tertiary hydroxyl groups, because it forms a crystalline diacetate (Q) after acetylation under mild conditions. Thus, the new hydroxyl, generated by reductive opening of the ether ring in the tetrahydroalcohol C, is secondary because the tetrahydroalcohol contains one secondary and one tertiary hydroxyl.

The more important point, that the α-hexahydroalcohol, unlike the β-compound, is formed from the tetrahydroalcohol by hydride reduction *without rearrangement*, rests on the following reaction sequence. The crystalline α-hexahydroacetate Q is dehydrated with thionyl chloride-pyridine at 0°, giving a mixture of unsaturated compounds, which is reduced catalytically to the desoxy-α-hexahydroalcohol diacetate S-1. This yields, after removal of the ester group with lithium aluminum hydride, the crystalline desoxy-α-hexahydroalcohol S-2.

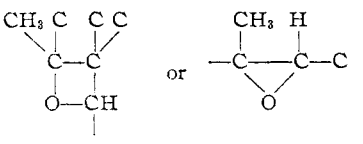
The same crystalline compound S-2 is related to the tetrahydroalcohol monoacetate E as follows. Dehydration of E with thionyl chloride-pyridine gives the mixture of anhydro compounds F and G, which, when reduced with hydrogen and Adams catalyst, yields a mixture of the hydrogenolysis product T, desoxy-α-hexahydroalcohol monoacetate T, and the desoxytetrahydroalcohol mono acetate H-1. Compound T contains no double bond, has an additional hydroxyl group, and forms the diacetate S-1 on acetylation, which is identical, from infrared spectra, with the compound obtained from Q by dehydration and catalytic reduction; saponification of S-1, prepared by both routes, yields the same crystalline desoxy compound S-2 (as shown by mixed m.p.'s and infrared spectra). A secondary hydroxyl is present in T, as shown by oxidation to a ketone of carbonyl frequency 1705 cm.$^{-1}$. Since dehydration of the tetrahydroalcohol monoacetate E has been demonstrated above to occur without rearrangement, and since catalytic hydrogenation may be safely assumed to occur without rearrangement, this demonstrates that lithium aluminum hydride reduction of the tetrahydroalcohol to α-hexahydroalcohol occurs without rearrangement.

The mechanism of the hydrogenolysis reaction, in going from F and G to T, is not clear; it might be expected that it would involve a double bond shift so that the carbon–oxygen linkage, which is hydrogenolyzed, is allylic, *i.e.*



This would require that the tetrasubstituted double bond in this partial structure should reduce readily, or be readily isomerized to another position.

The tetrahydroalcohol-Iab (C), as already mentioned, shows two unsplit CH_3–C–O in its n.m.r. spectrum; the α-hexahydroalcohol diacetate shows only one CH_3–C–O, and four peaks are observed in the C–CH_3 region with an area equal to nine protons. This corresponds to the *gem*-dimethyl group with a new CH_3–C superimposed. The splitting into two indicates a CH_3–CH group. This shows that the ether ring system of the tetrahydroalcohol contains either



Further evidence for the structure of α-hexahydroalcohol N is obtained by oxidation of desoxy-α-hexahydroalcohol (S-2) to the diketone U; this shows two carbonyl peaks, at 1725 and 1705 cm.$^{-1}$, and is a stable compound. This proves, obviously, that the two hydroxyl groups are secondary, and also that the new carbonyl group is a normal one, lacking adjacent groups which affect its frequency. The spectral properties and lack of

(30) The "nor" series, to which was attributed[3] a C_{15}-formula, we now believe to have been an error; much further work has failed to yield a single crystalline member of the C_{15}-series from the hydride reductions, and the "C_{15}"-compounds were probably impure samples of C_{16}-hexahydroalcohols.

CHART 4

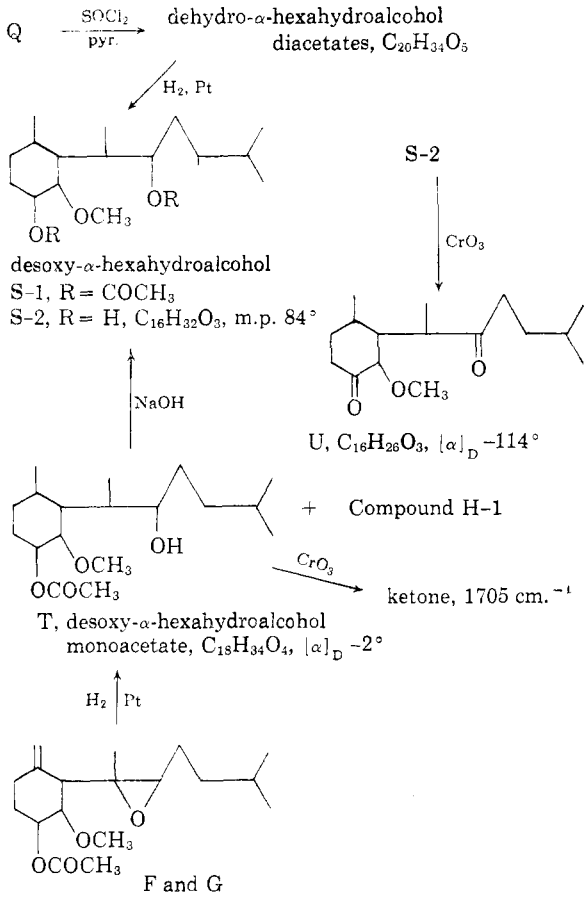
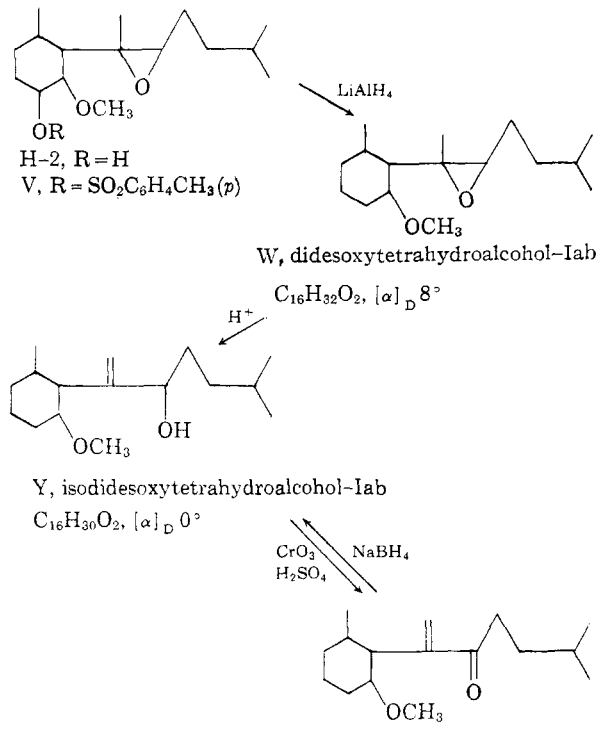


CHART 5

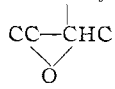


enolic properties indicate that this compound is not an α- or a β-diketone.

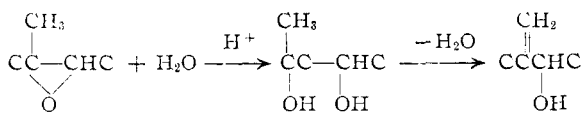
The Nature of the Ether Ring in Tetrahydroalcohol-Iab (C) (Chart 5).—As shown above, the ether ring in tetrahydroalcohol-Iab (C) is hydrogenolyzed by lithium aluminum hydride to form the α- and β-hexahydroalcohols (N and O). This suggests that the ether ring is either three or four-membered, since these are the only rings which are hydrogenolyzed by lithium aluminum hydride[31]; however, highly substituted trimethylene oxides[32] and even highly substituted epoxides[33] may not be attacked by this reagent.

The presence of the epoxide ring is supported by the following chemical evidence, in addition to the lithium aluminum hydride reduction reaction. The desoxytetrahydroalcohol H-2 is converted into the tosylate V, which is reduced with lithium aluminum hydride in ether to the didesoxytetrahydroalcohol-Iab (W), along with some by-product which appears to be the enol ether, formed by elimination of tosylate. Treatment of the didesoxyalcohol W with dilute mineral acid gives an isomeric compound, the allylic alcohol Y, which is converted by oxidation with chromic oxide to a ketone Z; this is shown by its ultraviolet absorption (ϵ_{220} 7000) and its carbonyl frequency (1680 cm.$^{-1}$) to be an α,β-unsaturated ketone. Reduction of the ketone with sodium borohydride regenerates the allylic alcohol Y; the presence of the terminal methylene group in Y is shown by infrared, and the assignment of this group to the side chain is supported by the fact that oxidation to the conjugated ketone Z, followed by reduction of the carbonyl to the alcohol, leaves the terminal methylene group unaffected. If, in Y, the terminal methylene was attached to a carbocyclic ring, the double bond should be isomerized to the endocyclic position, because methylenecyclohexane is much less stable than 1-methylcyclohexene.[34]

The formation of the secondary allylic alcohol Y from W is support for the presence of the CH_3 group in W; the epoxide could hydrate



to the 1,2-diol, which on dehydration would form the allylic alcohol[35]



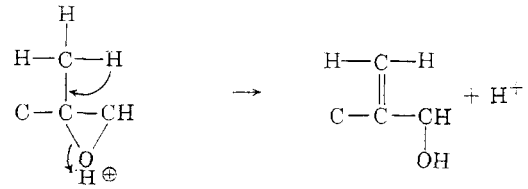
(31) N. G. Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publishers, Inc., New York, N. Y., 1956, pp. 646 ff, 711 ff. Reductive cleavage of tetrahydrofuran by lithium aluminum hydride and aluminum chloride or benzyl halides is reported by W. J. Bailey and F. Marktscheffel, *J. Org. Chem.*, **25**, 1797 (1960).

(32) G. Büchi, C. G. Inman and E. S. Lipinsky, *J. Am. Chem. Soc.*, **76**, 4327 (1954).

(33) N. G. Gaylord, ref. 31, pp. 663 ff.; G. D. Meakins and J. S. Stephenson, *J. Chem. Soc.*, 526 (1958).

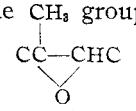
(34) R. B. Turner and R. H. Garner, *J. Am. Chem. Soc.*, **79**, 253 (1957); **80**, 1424 (1958); A. C. Cope, D. Ambros, E. Ciganek, C. F. Howell and Z. Jacura, *ibid.*, **81**, 3153 (1959).

(35) A concerted process is possible here but the periodate cleavage evidence below indicates that the 1,2-glycol can be formed.



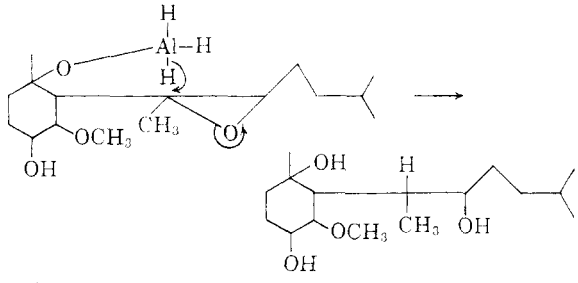
There is ample precedent for the isomerization of epoxides to allylic alcohols.[36]

The n.m.r. spectra of W and Y agree with this formulation; W shows the unsplit methyl protons beta to oxygen for the CH_3 group at τ 8.90, and



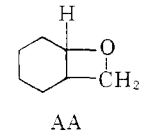
this group has disappeared in Y, with the appearance of two vinyl protons.

The failure of tetrahydroalcohol-Iab to give an epoxide test with thiosulfate, even under extreme conditions, is not conclusive evidence against it, because this test is not given by highly blocked epoxides.[37] The unreactive nature of the epoxide group in compound W is shown by its recovery unchanged after long refluxing with lithium aluminum hydride in tetrahydrofuran, in marked contrast to the tetrahydroalcohol itself, in which the ring is readily reduced open in refluxing ether. This suggests that the reduction in the latter case involves a ring opening by internal hydride ion transfer from a hydroxyl complex with the hydride reagent. This idea also explains why the



hydroxyl group generated in the reduction is secondary rather than tertiary[37a]; the tertiary alcohol would be expected normally in an epoxide reduction, and this is, of course, observed in the reduction of alcohol-I and dihydroalcohol-Ia (A → D and B → C).

Simple trimethylene oxides give strong infrared C–O stretching absorption[38] at 970–980 cm.$^{-1}$; the fused trimethylene oxide AA[39] shows a strong broad band at 950–970 cm.$^{-1}$. Epoxides in open chain compounds give a C–O frequency[40] around

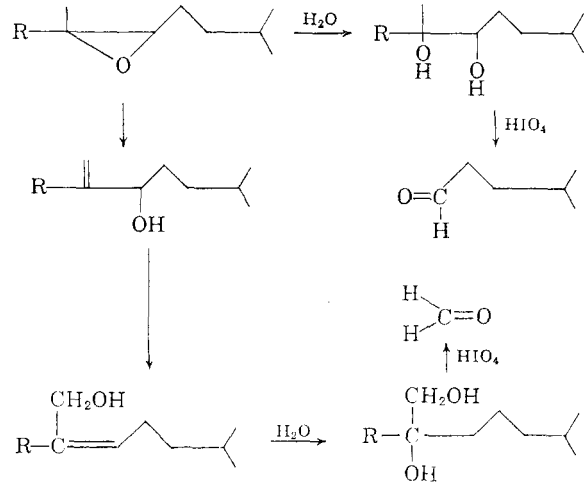


AA

900 cm.$^{-1}$; tetrahydroalcohol-Iab (C) shows medium bands at 920 and 963 cm.$^{-1}$, and the didesoxy compound W shows weak absorption at 935–955 cm.$^{-1}$. While these bands are in the correct region for both epoxides and trimethylene oxides, they do not seem to be intense enough for this latter function.

The n.m.r. evidence is more conclusively in favor of the epoxide group. Protons on an epoxide ring are reported to absorb at τ 7.34–7.71[41a] and 7.05–7.20.[41b] The $-CH_2OCH_2-$ protons in 3,3-bis-chloromethyltrimethylene oxide absorb[41a] at τ 5.64, and the $-CHO-$ proton in a trimethylene oxide, which has an α-carboxyl group, appears at τ 5.3.[42] The $-CH_2-O$ protons in compound AA show two quartets, at τ 5.41 and 5.1; the tertiary $-CHO-$ proton in AA shows a multiplet at 6.10.[39] A tabulation of the n.m.r. data for alcohol-I and fourteen derivatives shows clearly the presence of *three* epoxide protons in alcohol-I (A) and dihydroalcohol-Ia (B), of a single epoxide proton, at 7.20–7.65 in all of the other compounds in which the second ether ring is intact, and its absence in the hexahydroalcohols, in which the epoxide ring has been opened.

Further chemical support for the second epoxide ring is found in the action of periodic acid and of sodium periodate on the anhydro compounds F and G, to yield both formaldehyde and isocapraldehyde as the dinitrophenylhydrazones. The formation of isocapraldehyde is obvious, but the formation of the formaldehyde must involve some such sequence as



Apparently sodium periodate solution is acidic enough to catalyze the hydration and rearrangement of the epoxide group.

In an earlier publication,[11] it was postulated that the side chain in alcohol-I had the structure

(36) E. P. Kohler, M. Tishler, H. Potter and H. T. Thompson, *J. Am. Chem. Soc.*, **61**, 1057 (1939); W. J. Hickinbottom, *J. Chem. Soc.*, 1331 (1948); L. F. Fieser and T. Goto, *J. Am. Chem. Soc.*, **82**, 1693 (1960); W. Kirchhof, *Chem. Ber.*, **93**, 2712 (1960).

(37) G. G. Freeman, J. E. Gill and W. S. Waring, *J. Chem. Soc.*, 1128 (1959).

(37a) A similar process must occur in the opening of the epoxide in the drimenol derivative: H. H. Appel, C. J. W. Brooks and K. H. Overton, *ibid.*, 3322 (1959).

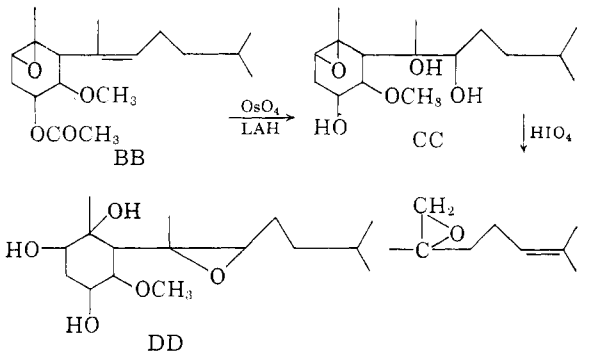
(38) G. M. Barrow and S. Searles, *J. Am. Chem. Soc.*, **75**, 1175 (1953).

(39) A. Rosowsky and D. S. Tarbell, *J. Org. Chem.*, **26**, in press; *cf.* also J. Fishman, E. R. H. Jones, G. Lowe and M. C. Whiting, *J. Chem. Soc.*, 3948 (1960).

(40) O. D. Shreve, M. R. Heether, H. B. Knight and D. Swern, *Anal. Chem.*, **23**, 277 (1951).

(41) (a) G. Van Dyke Tiers, Tables of Tau Values; (b) C. Y. Hopkins and H. J. Bernstein, *Can. J. Chem.*, **37**, 775 (1959).

(42) K. B. Wiberg and H. W. Holmquist, *J. Org. Chem.*, **24**, 578 (1959).



with the reactive epoxide group in the side chain and the unreactive one in the nucleus. This was based on the following sequence, in which the anhydro compound now shown to have structure G, was regarded as BB. As shown above, isocapraldehyde can be formed by periodate cleavage from compounds in which the reactive terminal epoxide has been removed, and hence the second epoxide must be assigned to the side chain. The glycol from the anhydro compound G is therefore assigned structure DD, instead of CC, and the isocapraldehyde comes from hydration and cleavage of the side chain epoxide group.

CHART 6

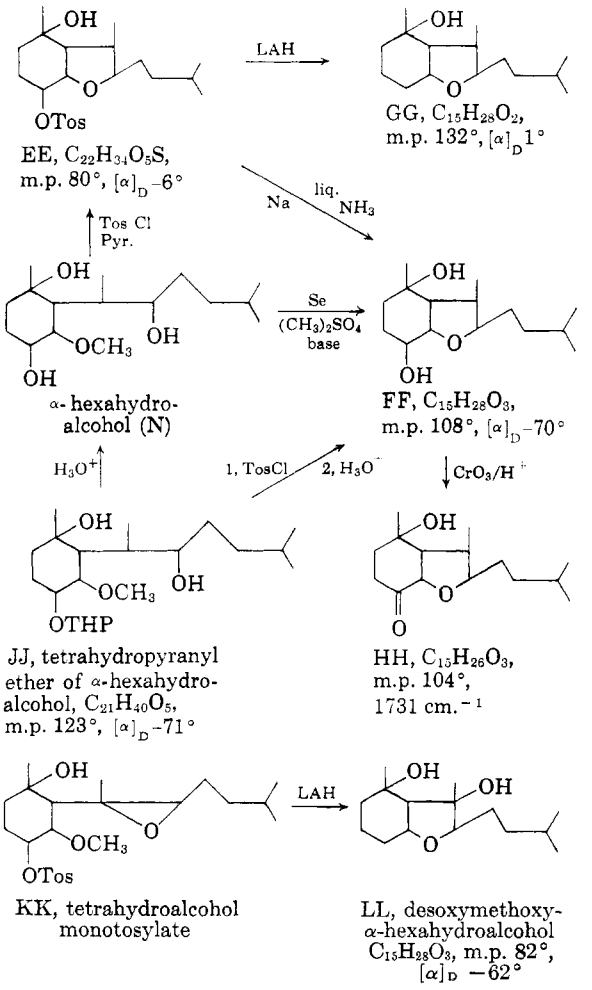
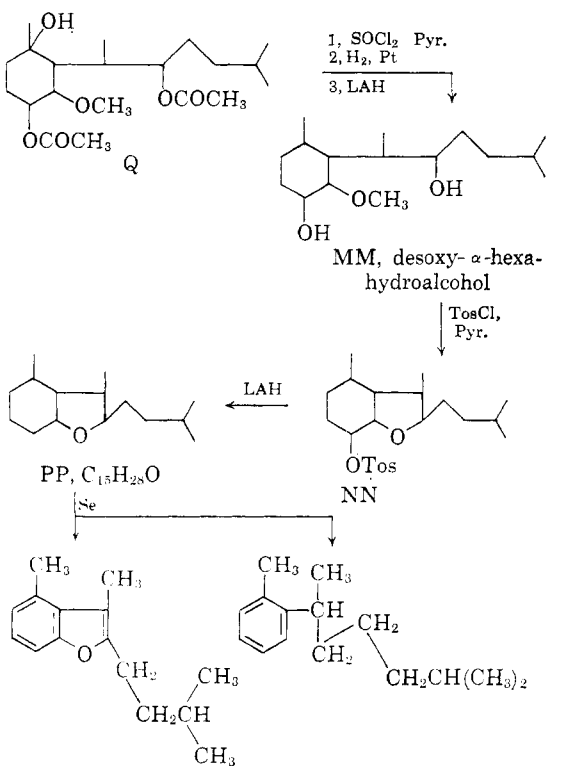


CHART 7



Reactions Involving Loss of the Methoxy Group with Formation of Perhydrobenzofurans (Charts 6 and 7).—A number of reactions has been observed in which the methoxyl group is eliminated, with the formation of a new tetrahydrofuran ring; these can occur under mild conditions, and have structural significance because they involve the oxygen of the second (side chain) epoxide and the methoxyl group.

Treatment of α-hexahydroalcohol (N) with tosyl chloride–pyridine at room temperature gives a crystalline tosylate (EE) which contains no methoxyl and has lost the elements of methanol. Cleavage of the tosylate with sodium–liquid ammonia generates the crystalline diol FF, the desmethoxy-α-hexahydroalcohol (2-isoamyl-3,4-dimethyl-4,7-dihydroxyperhydrobenzofuran); the same compound is obtained as one product from the action of selenium on the α-hexahydroalcohol, and also by the action of methyl sulfate–aqueous alkali (but not by aqueous alkali alone) on the α-hexahydroalcohol. Compound FF contains one secondary and one tertiary hydroxyl, because it is oxidized to the crystalline ketone HH, which shows carbonyl absorption at 1731 cm.$^{-1}$; this high value may be attributed to the effect of the oxygen adjacent to the carbonyl group.[28]

The secondary hydroxyl group on the ring is not involved in the loss of the methoxyl group; this is shown by the monotetrahydropyranyl ether of α-hexahydroalcohol (JJ), whose structure is certain from its mode of synthesis, and which yields the α-hexahydroalcohol on mild acid hydrolysis. Treat-

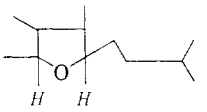
ment of JJ with tosyl chloride–pyridine, followed by acid hydrolysis, yields the crystalline desmethoxy compound FF.

Reductive removal of the tosylate group in EE with lithium aluminum hydride yields the crystalline desmethoxydesoxy compound GG; this contains only the tertiary hydroxyl group, as expected because it is not oxidized to a ketone.

The loss of methoxyl is also observed on lithium aluminum hydride treatment of the crystalline tosylate of tetrahydroalcohol-Iab (KK), which yields the dihydroxyperhydrobenzofuran LL. In this reduction, there is some cleavage of the carbocyclic ring, to form a desoxy-β-hexahydroalcohol (2,9 - dihydroxy - 6 - methoxy - 8,12 - dimethyl-7-tridecene), in addition to LL.

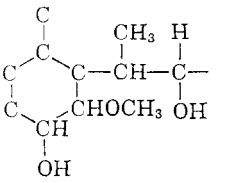
Another desmethoxy compound, which is of key importance in the structure proof of this series, is obtained from desoxy-α-hexahydroalcohol (MM); tosyl chloride–pyridine gives the desmethoxydesoxy tosylate NN, which with lithium aluminum hydride yields the hydroxyl-free perhydrobenzofuran PP, $C_{15}H_{28}O$. Selenium dehydrogenation of PP gives a good yield of a mixture of the benzofuran QQ and the hydrocarbon OO, whose structures are established by consideration of their physical properties and by synthesis (see below).

The basis for the formulation of the desmethoxy compounds as perhydrobenzofurans is: They lack the methoxyl group, as shown by Zeisel analyses and disappearance of the methoxyl protons in the n.m.r. A new ether ring is formed, as shown by analysis, active hydrogen determinations and infrared spectra. The n.m.r. spectrum of FF shows one proton under hydroxyl at 6.00, and two additional ones on carbon attached to oxygen at 6.26 and 6.52. Compounds GG and LL both show two protons at 6.41 and 6.46. The ketone HH shows two protons, one at 5.68 and one at 6.55. These n.m.r. signals are attributed to the underlined protons; the shift of one proton in the ketone



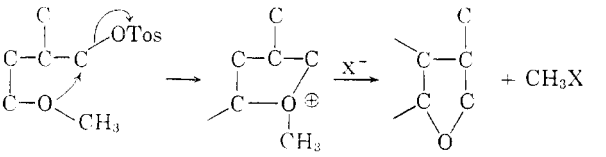
HH indicates that the carbonyl group is adjacent to this proton, $-\overset{\overset{O}{\|}}{C}-\overset{\overset{H}{|}}{C}-O-$. Since there are *two* protons in the $-O-C-\underline{H}$ positions, this means that the *secondary*, not the tertiary carbon in the side chain is involved. The formation of the desmethoxy compounds from MM, which lacks the nuclear tertiary hydroxyl group, and from the ether JJ, where the secondary hydroxyl is protected, shows that *only* the side chain oxygen and the methoxyl group are involved.

The formation of QQ, and the analogy below, makes it appear that the new ether ring is 5-membered. It seems unlikely that rearrangements would occur under the mild and varied reaction conditions involved. This indicates that the relationship of the side chain hydroxyl to methoxyl in the α-hexahydroalcohol is



Hence the position of the side chain epoxide with relation to the methoxyl and secondary hydroxyl on the ring is established in the tetrahydroalcohol-I (C) and in alcohol-I (A).

The loss of methoxyl is regarded as displacement, by the methoxyl oxygen, on the hydroxyl function (probably as the tosylate) to form a methoxonium ion, with subsequent loss of methyl. The loss of methoxyl upon treatment of N with methyl sulfate must involve formation of an oxonium salt



of a dimethoxy compound followed by elimination of methyl ether. Analogous reactions can be written for the cyclization[43] of KK to LL.

Displacements leading to loss of methoxyl and closure of a tetrahydrofuran ring have been observed by Winstein, in the treatment of $CH_3O(CH_2)_3CH(OBs)CH_3$ and $CH_3CH(OCH_3)(CH_2)_3OCH_3$ with lithium aluminum hydride.[44]

Properties and Synthesis of 2-Isoamyl-3,4-dimethylbenzofuran (QQ).—The ultraviolet spectrum of QQ resembles that of 3,5-dimethylbenzofuran,[5] and the analysis and infrared spectrum are in agreement with structure QQ. The n.m.r. spectrum shows a multiplet corresponding to three aromatic protons at τ 3.08, with the coupling constants those to be expected for three aromatic protons on adjacent carbons.[45] Five protons overlap at τ 7.37 and 7.42, due to the methyl group and the methylene group at the 2- and 3-positions, and three protons at τ 7.70 are assigned to the aromatic methyl. Six protons as a doublet at τ 9.00 and 9.08 are due to the isopropyl group, and the three remaining side chain protons appear at 8.40.

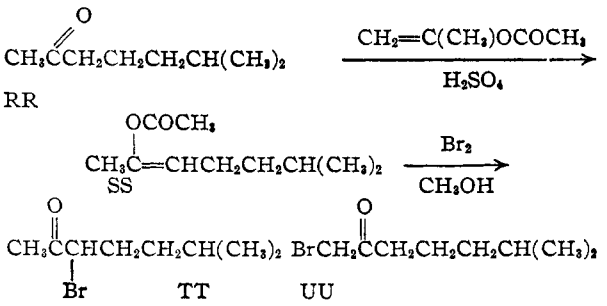
Compound QQ was synthesized by the following sequence: 6-methyl-2-heptanone (RR)[46] was converted into the enol acetate SS with isopropenyl acetate and sulfuric acid, and the enol acetate was brominated in methanol, forming 3-bromo-6-methyl-2-heptanone (TT). Compounds SS and TT were new compounds, and although it appeared

(43) For elegant studies on methoxonium intermediates in displacement reactions, see D. S. Noyce and B. N. Bastian, *J. Am. Chem. Soc.*, **82**, 1246 (1960), and earlier papers by Noyce.

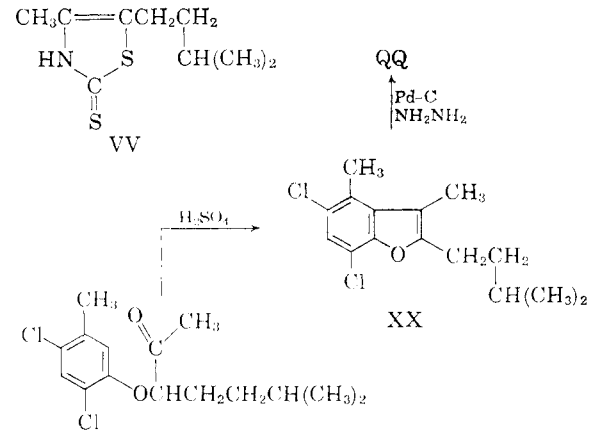
(44) E. L. Allred, Ph.D. Dissertation, University of California, Los Angeles, Calif., 1959, pp. 146–160. We are indebted to Professor Winstein for communicating these results prior to publication. *Cf.* also S. Winstein, E. Allred, R. Heck and R. Glick, *Tetrahedron*, **3**, 1 (1958). Studies in this Laboratory by Mr. Stephen Cantor show that a simple perhydrobenzofuran is formed in high yield under mild conditions with loss of methoxyl.

(45) S. Goodwin, J. N. Shoolery and L. F. Johnson, *J. Am. Chem. Soc.*, **81**, 3065 (1959).

(46) Prepared from citral (D. H. Hey and D. S. Morris, *J. Chem. Soc.*, 48 (1948)), and also purchased from K and K Laboratories.

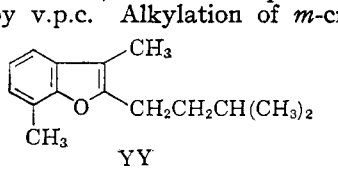


from analogous cases[47] that they had the structures assigned, instead of the alternative ones such as UU, the question required definitive proof. This was done by converting TT to the crystalline thiazole VV by condensation with ammonium dithiocarbamate; this product showed three unsplit methyl allylic protons in the n.m.r. spectrum, at τ 7.85. The n.m.r. spectrum (see Experimental) indicates that the thiazole has the thione structure shown, rather than the tautomeric mercaptothiazole constitution. The isomeric bromoketone UU would not furnish a thiazole with this spectral feature.



Alkylation of 3-methyl-4,6-dichlorophenol with the bromoketone TT yielded the ether WW, which was readily cyclized to the crystalline dichlorobenzofuran XX with cold concentrated sulfuric acid. Removal of the chlorines in XX was accomplished in nearly quantitative yield by refluxing in methyl Cellosolve with hydrazine and palladium charcoal.[48] The sample of QQ obtained in this way was identical with the product from dehydrogenation, in elementary analysis, ultraviolet, infrared and n.m.r. spectra and in retention time in vapor phase chromatography (v.p.c.).

A similar synthesis carried out on *o*-cresol yielded 2-isoamyl-4,7-dimethylbenzofuran (YY), which differed markedly from QQ in the three spectra and in v.p.c. retention time; the two compounds could be separated by v.p.c. Alkylation of *m*-cresol with

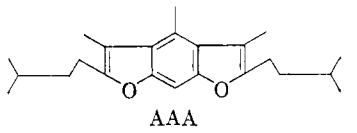


YY

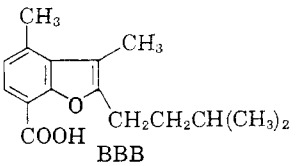
TT followed by cyclization gave a mixture of QQ (40%) and the 6-methyl isomer (60%), which was analyzed by v.p.c.

Initial attempts to synthesize QQ were directed toward condensations of orcinol to form benzofuran derivatives of type ZZ; it was hoped that the phenolic hydroxyl could be removed by sodium–liquid ammonia reduction of the phosphate[49] or Raney nickel desulfuration of the tosylate.[50] Preliminary experiments on these methods were unpromising.

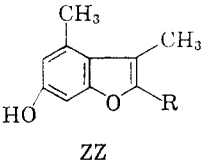
Orcinol yielded a mixture of products when refluxed with the bromoketone TT in alcoholic sodium ethoxide; one of the products was crystalline and had the composition of AAA or an isomer.



AAA



BBB



ZZ

An alternative synthesis started from ethyl 2-hydroxy-4-methylbenzoate, which was alkylated in poor yield with TT, and was then cyclized to the corresponding ester and the acid BBB. The poor yield in the alkylation stage, undoubtedly due to chelation of the phenolic group with the ester group, made this procedure unattractive.

Synthesis of the Hydrocarbon OO.—This was synthesized by preparation of the corresponding carbinol by addition of *o*-tolymagnesium bromide to 6-methyl-2-heptanone, followed by catalytic hydrogenolysis of the benzylic hydroxyl group with palladium–charcoal in acetic acid. This product was identical in analysis, spectra and v.p.c. retention time with the hydrocarbon from the dehydrogenation.

The Structure of β-Hexahydroalcohol (0:2, 5-Dihydroxy-6-methoxy-8,12-dimethyl-7-tridecene).—The β-hexahydroalcohol is isomeric with the α-compound N, and is formed from the tetrahydroalcohol-I by hydride reduction along with the α-compound. The β-compound has a methoxyl group (analysis and a three proton peak at τ 6.81), has three secondary (or primary) hydroxyl groups (formation of a triacetate P with acetic anhydride–pyridine at room temperature) and contains a trisubstituted double bond. The latter is indicated by the ultraviolet absorption spectrum (ϵ_{210} 1100–1400, ϵ_{220} 113–240), and by the n.m.r. spectrum, which shows a single vinyl proton at τ 4.94; this appears to be split into a doublet, indicating the structural element $RC(CH_3)=CHCHR'R''$. The presence of the double bond is indicated also by hydrogenation with platinum to an octahydro compound. The position of a methyl group on the double bond is indicated by the presence of an unsplit band (three protons) at τ 8.23 (allylic methyl region). That the three hydroxyl

(47) E. H. Man, F. C. Frostick, Jr., and C. R. Hauser, *J. Am. Chem. Soc.*, **74**, 3228 (1952).

(48) W. L. Mosby, *Chemistry & Industry*, 1348 (1959).

(49) S. W. Pelletier and D. M. Locke, *J. Org. Chem.*, **23**, 131 (1958).

(50) G. W. Kenner and M. A. Murray, *J. Chem. Soc.*, S-178 (1949).

groups are secondary is indicated by the n.m.r. spectrum, where there are at least four protons, excluding the methoxyl group, alpha to oxygen (5.85–6.63 τ). If one of these is due to the proton under the methoxyl, the other three must be under hydroxyl groups.

In addition to the allylic methyl group, the β-hexahydroalcohol shows four other methyl groups in the n.m.r. A six-proton doublet (at τ 9.05, 9.16) indicates the isopropyl group $(CH_3)_2CH-$. A three-proton group at τ 8.85, split into a doublet, indicates a secondary methyl group beta to oxygen, CH_3CHOH-, and this is confirmed chemically by the isolation of CHI_3 in 5% yield by the iodoform reaction on O. A positive iodoform test is also given by the dihydro-β-hexahydroalcohol and by the tetrahydropyranyl acetal of the β-hexahydroalcohol. The CH_3CHOH-group is thus not the secondary alcohol group present in the tetrahydroalcohol-I (C).

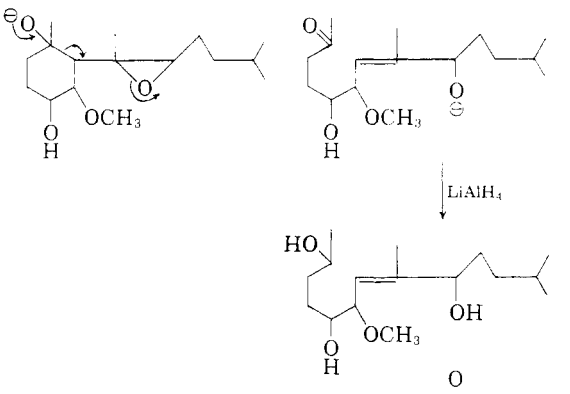
Consideration of the above facts shows that the β-hexahydroalcohol must have the structure $CH_3CHOHC_nC(CH_3)=CHC_{(7-n)}CH(CH_3)_2$, where n = 0–7.

The β-hexahydroalcohol like the α-isomer does not react with periodic acid, but treatment with osmium tetroxide, followed by periodate, does give a 24% yield of isocapraldehyde (as the dinitrophenylhydrazone). The same result is obtained with the tetrahydropyranyl acetal of the β-hexahydroalcohol, and this demonstrates the partial structure $C=C(CH_3)CHOHCH_2CH_2CH(CH_3)_2$ in these compounds.

The proton under the methoxyl in all of the fumagillin compounds occurs in the normal position for a proton alpha to an ether linkage (τ 6.40–7.25). If this proton were allylic, it would be expected to appear at a lowered τ value. The region 5.85–6.63 τ in deuterated β-hexahydroalcohol is complex, due the presence of the other protons under hydroxyl groups. However, acetylation lowers these latter protons to the τ 4.6–5.1 region, and the n.m.r. spectrum of the β-hexahydroalcohol triacetate P shows only one proton, a quartet at τ 5.93. This can be attributed to splitting of the proton under the methoxyl group, by the allylic proton at C-7, and by the proton under the secondary hydroxyl at C-5. The combined evidence is thus conclusive for structure O for the β-hexahydroalcohol.[51]

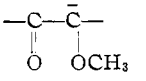
The β-hexahydroalcohol is thus seen to be a ring opened isomer of the α-hexahydroalcohol. It is probably formed by a "fragmentation reaction," involving ring opening,[52] as shown in sequence O.

Structure of the Isoketone M.—The isoketone M, m.p. 77–78°, obtained in good yield by the action of *t*-butoxide on the ketone L, shows absorption at 1692 cm.$^{-1}$ in chloroform solution, but no absorption in this region when the spectrum is taken in a potassium bromide disk, indicating that a hemiketal form is present in the solid. This

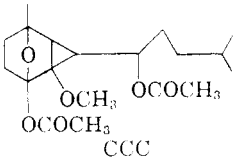


is confirmed by vigorous acetylation of M, which gives a diacetate, with strong absorption at 1730 cm.$^{-1}$ (normal acetate) and 1751 cm.$^{-1}$, a value in good agreement with the reported absorption[53] of hemiketal acetates. Since M has two hydroxyl groups, while its precursor L has only one, the epoxide ring in L must have been cleaved with the formation of a new hydroxyl. The carbonyl frequency[54] of M, its ultraviolet absorption,[55] ϵ_{214} 1455, ϵ_{291} 25, and the fact that it is not reduced with hydrogen and platinum are in agreement with the cyclopropyl ketone structure M; this is also in agreement with the fact that infrared measurements in the 1–3 micron region show that M does not contain an *unsubstituted* methylene group on the cyclopropane ring.[56]

The formation of M can be attributed to attack by the carbanion



on the epoxide group, giving the secondary hydroxyl group and the cyclopropane ring. The diacetate from M would have structure CCC.



CCC

Structures Derived from Acidic and Basic Treatment of Alcohol-I.—The action of 10% aqueous sulfuric acid on alcohol-I gives a crystalline hydration product,[10] $C_{16}H_{28}O_5$, called alcohol-IV. This compound is stable to hydrogen and platinum in ethanol or acetic acid, is unaffected by lithium aluminum hydride, has two hydroxyl groups, one secondary and one tertiary, gives no reaction with per-

(51) Products obtained by oxidative cleavage of P also furnish evidence for the structures O and P (Dr. A. K. Barua, unpublished work in these laboratories).

(52) For a summary of the fragmentation reaction, see C. A. Grob, "Theoretical Organic Chemistry, The Kekulé Symposium," Butterworth, London, 1959, p. 114.

(53) N. J. Leonard, J. C. Little and A. J. Kresge, *J. Am. Chem. Soc.*, **79**, 2642 (1957).

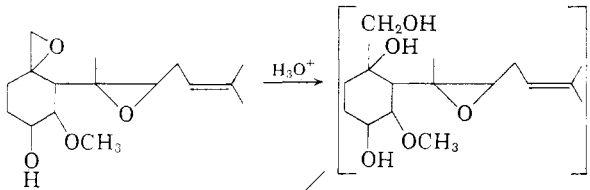
(54) E. J. Corey and H. J. Burke, *ibid.*, **78**, 174 (1956); G. Büchi and D. M. White, *ibid.*, **79**, 750 (1957).

(55) R. H. Eastman and S. K. Freeman, *ibid.*, **77**, 6642 (1955): the positions of the absorption maxima correspond to those expected for a cyclopropyl ketone, but the extinction coefficients are low. This may be due to the low percentage of the keto form relative to that of the hemiketal form in ethanol solution (*cf.* C. D. Hurd and W. H. Saunders, Jr., *ibid.*, **74**, 5324 (1952)).

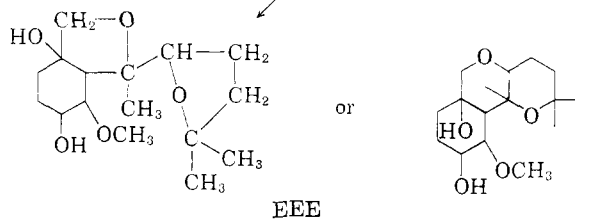
(56) W. H. Washburn and M. J. Mahoney, *ibid.*, **80**, 504 (1958); we are indebted to Mr. Washburn of Abbott Laboratories for the measurements.

iodate and contains the $-CH_2CH(OH)-CH(OCH_3)-$, because it forms a crystalline ketone (1724 cm.$^{-1}$) which forms a crystalline monofurfurylidene derivative. From its analysis, it must have a new oxygen-containing ring.

These observations can be accommodated by structures formed from alcohol-I by hydration of the reactive epoxide, followed by attack on the second epoxide and cyclization with the double bond. These structures, DDD or EEE, while in agreement with the observations, are not uniquely defined by them, and alcohol-IV may be the result of a more deep-seated rearrangement for which ample opportunity exists.



A, alcohol-I, $C_{16}H_{26}O_4$



EEE

DDD, alcohol-IV, $C_{16}H_{28}O_5$, m.p. 123°, $[\alpha]_D$ −18.6°

Sodium hydroxide in aqueous dioxane converts alcohol-I into a mixture[9] of two isomers, $C_{16}H_{26}O_4$ ("monoöls A and C"), and a triol ("triol B"), which is a hydration product, $C_{16}H_{28}O_5$. All of these contain a double bond, and can be reduced catalytically to the corresponding crystalline dihydro compounds. The "dihydromonoöl F," derived from "monoöl C" shows a tertiary hydroxyl, yields isocaproic acid with acid permanganate, and is unaffected by lithium aluminum hydride in refluxing tetrahydrofuran. The "monoöls A" (formed in only 5% yield) and "C" must be formed by attack of a hydroxyl group on the reactive epoxide, because none of them gives an epoxide test with thiosulfate, as alcohol-I does.

Plausible structures can be proposed for these products involving attack of the secondary hydroxyl group on the reactive epoxide function.

Experimental

Tetrahydroalcohol-I Monoacetate (E).—Tetrahydroalcohol-I (C) (19 g.) was dissolved in pyridine (100 ml.) and allowed to stand with acetic anhydride (40 ml.) for 2 days at room temperature. The reaction mixture was poured onto ice and the crystals filtered off after 12 hr. The yield of crystalline material was 18.5 g. An additional 1.1 g. of acetate was obtained by extracting the filtrate with ether after acidification.

After recrystallization from petroleum ether, **tetrahydroalcohol monoacetate (E)** had m.p. 61–63° and $[\alpha]_D$ −60°.

Anal. Calcd. for $C_{18}H_{32}O_5$: C, 65.82; H, 9.82. Found: C, 66.08; H, 10.03.

Tetrahydroalcohol-I Monotosylate (KK).—The tetrahydroalcohol C (4.42 g.) was allowed to stand 4 days at room temperature with 4.42 g. of tosyl chloride in 50 ml. of pyridine, and then was poured on ice; the crystalline product isolated (63%) was purified by chromatography and crystallization from petroleum ether; m.p. 62–64°. The product decomposed on standing, unless it was highly pure and kept cool in a sealed vessel.

Anal. Calcd. for $C_{23}H_{36}O_6S$: C, 62.70; H, 8.24; O, 21.79; S, 7.29; OCH_3, 7.04. Found: C, 62.83; H, 8.57; O, 21.51; S, 6.54; OCH_3, 6.74.

Dehydration of Tetrahydroalcohol Monoacetate E with Thionyl Chloride-Pyridine.—Tetrahydroalcohol monoacetate (10.5 g.) dissolved in dry pyridine (50 ml.) was added slowly to a mixture of thionyl chloride (30 ml.) and pyridine (50 ml.) at 0°. After 40 min. the reaction mixture was poured onto ice. After 2 hr. the solution was cautiously acidified with dilute hydrochloric acid and rapidly extracted with chloroform. The extracts were washed with bicarbonate solution, sodium sulfate solution and then dried over magnesium sulfate. Removal of the chloroform afforded a pale yellow oil (8.5 g.) which was dissolved in petroleum ether and chromatographed on neutral alumina, activity II (300 g.). Elution with mixtures of petroleum ether and ether of gradually increasing polarity allowed separation into two main products. The major product, **anhydrotetrahydroalcohol acetate F** (3.52 g.), showed infrared absorption characteristic of a trisubstituted double bond (813 cm.$^{-1}$) and had $[\alpha]_D$ −53°. The analytical sample was purified by distillation, b.p. 70–80° (3×10^{-3} mm.).

Anal. Calcd. for $C_{18}H_{30}O_4$: C, 69.64; H, 9.74; O, 20.62; OCH_3, 10.00; acetyl, 13.90. Found: C, 69.47; H, 9.88; O, 20.65; OCH_3, 9.77; acetyl, 13.59.

The other main product, the isomeric **anhydrotetrahydroalcohol acetate G** (1.12 g.), exhibited terminal methylene absorption at 1640 and 895 cm.$^{-1}$; b.p. 70–80° (10^{-4} mm.), $[\alpha]_D$ −18°.

Anal. Found: C, 68.66; H, 9.70; O, 20.51; OCH_3, 9.64; acetyl, 12.37.

Elution of the column with more polar solvents gave 576 mg. of material which showed hydroxyl absorption in the infrared. Elution with methanol yielded a viscous oil (1.5 g.) which appeared to have lost the acetate group.

Ozonization of G gave formaldehyde, isolated and identified as the methone derivative (62% yield).

Periodate Oxidation of the Anhydro Compound F.—Treatment of 100 mg. of F in aqueous dioxane with 147 mg. of periodic acid, with nitrogen bubbling through the solution and into a dinitrophenylhydrazine solution gave a precipitate of derivative after a 3-day period. Chromatography of the product on Bentonite–Celite yielded 6 mg. of isocapraldehyde dinitrophenylhydrazone, identified by mixed m.p., and 20 mg. of formaldehyde dinitrophenyl-hydrazone, also identified by mixed m.p.

Repetition of the experiment using 100 mg. of F and 138 mg. of sodium periodate likewise yielded isocapraldehyde and formaldehyde, identified as above. Evidently both periodic acid and sodium periodate can hydrate the side-chain epoxide and cleave the glycol.

Catalytic Reduction of Anhydrotetrahydroalcohol Acetate (G).—Anhydrotetrahydroalcohol acetate (1.2 g.) in ethanol was hydrogenated over rhodium-on-alumina (300 mg.) at atmospheric pressure. After absorption of 1 mole of hydrogen, the catalyst was removed by filtration and after removal of solvent, the product was chromatographed on alumina. All the fractions had identical infrared spectra, and the double bond absorption had disappeared. Distillation at 80° (10^{-3} mm.) gave the analytical sample of **desoxytetrahydroalcohol acetate (H–1)**, $[\alpha]_D$ −7°.

Anal. Calcd. for $C_{18}H_{32}O_4$: C, 69.19; H, 10.32; O, 20.48. Found: C, 69.14; H, 10.28; O, 20.81.

The reduction of anhydrotetrahydroalcohol acetate F over rhodium yielded the same desoxytetrahydroalcohol acetate as above, based on a comparison of infrared spectra and optical rotation.

Saponification of Desoxytetrahydroalcohol Acetate.—Desoxytetrahydroalcohol acetate (3 g.) was dissolved in methanol (35 ml.), and potassium hydroxide (535 mg.) in water (50 ml.) added. After refluxing for 3 hr., the product was isolated by dilution with water and extraction with chloroform. **Desoxytetrahydroalcohol** (2.2 g.) (H-2) was obtained as a colorless oil, $[\alpha]_D$ −3° after chromatography and distillation.

Anal. Calcd. for $C_{16}H_{30}O_3$: C, 71.07; H, 11.18. Found: C, 71.09; H, 10.87.

Epoxidation of Anhydrotetrahydroalcohol Acetate (F) using Monoperphthalic Acid.—Anhydrotetrahydroalcohol acetate F (540 mg.) was treated with an excess of an ether solution of monoperphthalic acid. The solvent was removed *in vacuo* at room temperature, chloroform (20 ml.) was added and the solution was refluxed for 8 hr. The reaction mixture was cooled to 0°, the phthalic acid was filtered and washed with chloroform. The chloroform was evaporated and the residual oil (615 mg.) chromatographed on alumina. Petroleum ether–ether (9:1) eluted 310 mg. of an oil (55% yield, $[\alpha]D$ −36° to −30°). Ether eluted 156 mg. of a second oil (27% yield, $[\alpha]D$ −3°). The more negatively rotating oil was considered more closely related to alcohol-I and was designated epoxyanhydro acetate J.

Reduction of Epoxyanhydro Acetate J to Tetrahydroalcohol-I.—The epoxyanhydro acetate J (290 mg.) was dissolved in dry ether and cooled to about −10° in a salt–ice mixture. Lithium aluminum hydride (50 mg.) in ether was added with stirring and cooling over a period of an hour. The mixture was stirred for an additional hour at −10° to −5°. The reaction was quenched by adding wet ether. The product was isolated in the usual way and chromatographed on alumina. Petroleum ether–ether (9:1) eluted 76 mg. (33%) of crystalline product, m.p. 60–72°, which after rechromatography gave material of m.p. 82–84°, $[\alpha]D$ −57°, whose infrared spectrum was identical with that of tetrahydroalcohol-I. Recrystallization from petroleum ether gave crystals of m.p. 87–88.5°, undepressed on mixed m.p. with authentic tetrahydroalcohol-I.

Epoxidation of Anhydrotetrahydroalcohol Acetate G.—The anhydro compound G (the terminal methylene isomer, 1.00 g.) was treated wih monoperphthalic acid as described above. Chromatography of the product on alumina gave an oil (570 mg., $[\alpha]D$ −35°) whose infrared spectrum was identical with that of dihydroalcohol-Ia acetate (B-2). The material was distilled for analysis, b.p. 80–90° (10^{-3} mm.).

Anal. Calcd. for $C_{18}H_{30}O_5$: C, 66.23; H, 9.26; acetyl, 13.19. Found: C, 66.01; H, 9.05; acetyl, 12.91.

Reduction of Epoxyanhydrotetrahydroalcohol Acetate K with Lithium Aluminum Hydride.—The epoxyacetate K (359 mg.) was reduced with lithium aluminum hydride (70 mg.) as described for the epoxyacetate J. Chromatography of the product on alumina yielded tetrahydroalcohol (80 mg.), m.p. 88–89°.

Acetylation of Dihydroalcohol-Ia (B).—Dihydroalcohol Ia (340 mg.) in pyridine (5 ml.) was treated with acetic anhydride (0.6 ml.) at 0°. After 36 hr. at room temperature, the reaction mixture was poured onto ice and the product isolated by ether extraction. After chromatography on alumina, dihydroalcohol-Ia acetate (97 mg.) was obtained as a colorless oil, $[\alpha]D$ −31°. The infrared spectrum was identical with that of epoxyanhydrotetrahydroalcohol acetate (K).

Dehydrogenation of Tetrahydroalcohol-I.—Crystalline tetrahydroalcohol-I (7.2 g.) and 13 g. of selenium were ground intimately, placed in the dehydrogenation flask and heated to 260–285° for 4 hr. The temperature was then raised to 310–340° where it was maintained for 24 hr. The distillate (4.14 g.) was separated into the usual water and oily layers, the latter being further separated into base-soluble (194 mg.) and base-insoluble (1.703 g.) fractions by means of Claisen alkali extraction. The infrared spectrum of the base-soluble material showed it to be a ketophenol with peaks at 3200, 1707, 1600 and 1512 cm.$^{-1}$. No further characterization of this material was possible.

The base-insoluble oil (1.70 g.), whose infrared spectrum showed diminished hydroxyl, no double bond or aromatic peaks and a strong carbonyl peak at 1700 cm.$^{-1}$, was shaken for 1 hr. with 5 ml. of 30% hydrogen peroxide and 3 ml. of 10% sodium hydroxide. The excess hydrogen peroxide was reduced with ferrous sulfate and the aqueous solution extracted with ether. The ether extracts were evaporated to dryness leaving 1.128 g. of a mobile yellow oil which was completely free of selenium. Distillation of this oil gave 554 mg. of a colorless oil (pot temperature 120–180°)

Identification of Ethyl Isoamyl Ketone.—To a solution of 380 mg. of this oil in 5 ml. of 95% ethanol was added a slight excess of 2,4-dinitrophenylhydrazine sulfate in ethanol. After the solution had stood for 12 hr., an orange precipitate had formed. This solid (83 mg.) was collected, taken up in ether and dried over magnesium sulfate, then chromatographed on a 10.-g. column of Bentonite–Kieselguhr. Elution with 30 ml. of chloroform gave 43 mg. of a yellow-orange solid, m.p. 59–64°. Recrystallization from ether–hexane afforded shiny yellow-orange platelets, m.p. 59–64°. The reported[4] m.p. of ethyl isoamyl ketone 2,4-dinitrophenylhydrazone is 59–64°.

Anal. Calcd. for $C_{14}H_{20}O_4N_4$ (ethyl isoamyl ketone dinitrophenylhydrazone): C, 54.53; H, 6.54; N, 18.17. Found: C, 55.34; H, 6.48; N, 17.76.

Oxidation of Tetrahydroalcohol-I to the Ketone L.—The following method is preferable to that used earlier.[8] The tetrahydroalcohol-I (200 mg.) in 5 ml. of acetone at 0° was titrated with chromic acid reagent (66.7 g. of chromic oxide in 40 ml. of sulfuric acid and 200 ml. of water) until an orange color remained after shaking for 5 min. The solution was allowed to stand for 15 min. more, and was worked up in the normal manner to give 140 mg. of the ketone, identified by its infrared spectrum and by the preparation of the crystalline furfurylidene derivative.

Deuterium Exchange Experiments on 6-Furfurylidene-2-2-methylcyclohexanone.—A solution of 1.00 g. of 6-furfurylidene-2-methylcyclohexanone,[57] 0.72 g. of anhydrous potassium carbonate and 5.0 ml. of 99.5% deuterium oxide in 10 ml. of purified dioxane was refluxed under nitrogen for 24 hr. The dioxane and deuterium oxide were removed *in vacuo* and the residue was extracted with dry ether. The product was isolated and recrystallized from methanol; its m.p. was unchanged but the infrared spectrum was markedly different. Analysis for deuterium by the falling drop method[58] showed 0.86 atom of deuterium per molecule.

Deuterium Exchange Experiments on the Furfurylidene Derivative of the Tetrahydroketone.—The above exchange procedure was applied to 250 mg. of the crystalline furfurylidene[8] derivative of the ketone and yielded 90 mg. (36%) of crystalline material, m.p. 93.5–95°, after crystallization from petroleum ether–ether. The infrared spectrum and m.p. were unchanged by the exchange; analysis showed the presence of 0.42 atom of deuterium per molecule.

Isomerization of the Tetrahydroketone L by *t*-Butoxide.—To 25 ml. of a 0.36 *M* *t*-butyl alcohol solution of potassium *t*-butoxide was added 2.50 g. of the tetrahydroketone L, and the solution was refluxed under nitrogen for 1 hr. Most of the solvent was removed under reduced pressure, 100 ml. of water was added, the solution was saturated with sodium chloride and was extracted five times with ether. The ether extracts were washed with water, dried and yielded, after removal of solvent, 2.0 g. of orange oil, which was chromatographed. Elution with petroleum ether–ether (1:4) gave traces of yellow oil; elution with ether and ether–methanol (100:1) afforded 1.40 g. of pale yellow oil. This yielded, after crystallization from petroleum ether–ether, 1.13 g. (45%) of the isoketone; the analytical sample, after another crystallization, had m.p. 77–78°, $[\alpha]D$ 18.5°.

Anal. Calcd. for $C_{16}H_{28}O_4$: C, 67.57; H, 9.93; OCH_3, 10.91; active H, 2.00. Found: C, 67.93; H, 9.90; OCH_3, 10.47; active H, 1.99 (none consumed).

The infrared spectrum in chloroform showed bands of medium intensity at 3356 and 1692 cm.$^{-1}$, while in the solid state (potassium bromide disk) a strong band appeared at 3344 cm.$^{-1}$ with no absorption in the carbonyl region. The ultraviolet spectrum showed maxima at 214 (log ϵ 2.66) and 291 mμ (log ϵ 1.45).

The tetrahydroketone L was converted by refluxing for 8 hr. under the above conditions into a mixture which appeared to contain four carbonyl compounds, and from which 1% of crystalline phthalic acid was obtained. The crystalline isoketone above was converted into mixtures of carbonyl compounds by further refluxing with butoxide, and was also isomerized or altered by heating 1 hr. on the steam-bath with aqueous dioxane containing dilute hydrochloric acid.

Acetylation of the Isoketone.—A solution of 250 mg. of the isoketone, m.p. 77–78°, and 1 ml. of acetic anhydride in 5 ml. of dry pyridine was refluxed for 24 hr., and poured over crushed ice. The aqueous mixture was extracted

(57) N. Wolff, *Compt. rend.*, **174**, 1469 (1922); A. M. Islam and M. T. Zemaity, *J. Am. Chem. Soc.*, **79**, 6023 (1957).

(58) A. S. Keston, *et al.*, *J. Biol. Chem.*, **122**, 227 (1937); W. von E. Doering and A. K. Hoffman, *J. Am. Chem. Soc.*, **77**, 521 (1955).

with ether, and the product obtained from the ether extracts was dissolved in petroleum ether and chromatographed on alumina. Elution with petroleum ether–ether (9:1) gave 50 mg. (15%) of a **diacetate** as a colorless oil. The infrared spectrum showed bands at 1751 (hemiketal acetate) and 1730 cm.$^{-1}$ (normal acetate), with no absorption in the hydroxyl region.

Anal. Calcd. for $C_{20}H_{32}O_6$: C, 65.19; H, 8.75; acetyl, 23.36. Found: C, 64.93; H, 8.69; acetyl, 22.62.

Reduction of Tetrahydroalcohol-I with Lithium Aluminum Hydride in Tetrahydrofuran; Formation of α-Hexahydroalcohol (N) and β-Hexahydroalcohol (O).—The tetrahydroalcohol (C, 13 g.) in 200 ml. of tetrahydrofuran was added to a suspension of 6 g. of lithium aluminum hydride in 200 ml. of the same solvent. After refluxing for 20 hr., the product was isolated in the usual way and was chromatographed on alumina. Elution with 100:1 ether–methanol gave α-hexahydroalcohol (7.2 g.) as a viscous oil. The analytical sample, $[\alpha]D$ −47°, was obtained by distillation, b.p. 120° (10^{-3} mm.).

Anal. Calcd. for $C_{16}H_{32}O_4$: C, 66.63; H, 11.18; O, 22.19; active H, 3.00. Found: C, 66.63; H, 11.06; O, 22.21; active H, 2.99. The ultraviolet spectrum showed no absorption down to 210 mμ.

Elution of the chromatographic column with 20:1 ether–methanol yielded the β-hexahydroalcohol (O), $[\alpha]D$ 58°, identical with the triol ("hexahydroalcohol-Iab") described previously.[8] This compound showed end absorption in the ultraviolet, ϵ_{210} 1100, ϵ_{220} 250.

It was later found simpler to acetylate the mixture of α- and β-hexahydroalcohols and to separate the α-hexahydroalcohol diacetate (Q) from the β-hexahydroalcohol triacetate[8] (P) by chromatography. Thus acetylation of 32.0 g. of a mixture of the two triols N and O (from a lithium aluminum hydride reduction as above) with acetic anhydride–pyridine at room temperature for 4 days yielded, after chromatography on 800 g. of alumina, 22.3 g. of the α-hexahydroalcohol diacetate Q (described below) and 19.8 g. of the β-hexahydroalcohol triacetate P (see below).

Acetylation of α-Hexahydroalcohol to the Diacetate Q.—α-Hexahydroalcohol (N, 2.6 g.) was dissolved in pyridine (15 ml.) and acetic anhydride (15 ml.) and left at room temperature for 3 days. The reaction mixture was poured onto ice, acidified and extracted with ether. The crude product (3.4 g.) obtained by removal of the ether, was dissolved in petroleum ether and chromatographed on neutral alumina (100 g., activity II). Elution with mixtures up to and including 1:1 petroleum ether–ether removed traces of non-crystalline oils. Elution with ether gave a fairly viscous oil (2.7 g.) which crystallized after 2 days. Recrystallization from hexane yielded **α-hexahydroalcohol diacetate** (Q) as large rhombs, m.p. 68.5–69.5°, $[\alpha]D$ −24° (1.48 g.).

Anal. Calcd. for $C_{20}H_{36}O_6$: C, 64.49; H, 9.74. Found: C, 64.53; H, 9.64.

Dehydration of α-Hexahydroalcohol Diacetate (Q) with Thionyl Chloride–Pyridine.—α-Hexahydroalcohol diacetate (1.65 g.) in dry pyridine (10 ml.) was added slowly to a mixture of thionyl chloride (6 ml.) and pyridine (10 ml.) at 0°. The reaction was allowed to proceed for 40 min. and then worked up by pouring the mixture onto ice, followed by acidification and extraction with chloroform. The chloroform extract was washed with sodium bicarbonate and with sodium sulfate solution. Evaporation yielded an oil (1.4 g.) which was chromatographed on activity II neutral alumina (40 g.). Elution of the column with petroleum ether and 9:1 petroleum ether–ether gave a series of oily fractions whose infrared spectra were almost identical except for a trace of terminal methylene absorption in some of the earlier ones.

These fractions were combined and reduced with hydrogen and platinum in ethanol until one mole of hydrogen had been taken up. The desoxy-α-hexahydroalcohol diacetate S-1 was not purified further and was characterized as the free alcohol S-2.

Deacetylation of Desoxy-α-hexahydroalcohol Diacetate.—The diacetate (S-1, 190 mg.) in ether was treated with lithium aluminum hydride (90 mg.) at room temperature. The free alcohol was isolated in the usual way and, after passage through a small alumina column, was obtained as an oil (130 mg.) which crystallized on scratching. Recrystallization from petroleum ether at low temperature gave **desoxy-α-hexahydroalcohol S-2** as needles, m.p. 83–84.5°, $[\alpha]D$ −8°.

Anal. Calcd. for $C_{16}H_{32}O_3$: C, 70.54; H, 11.84. Found: C, 70.57; H, 11.76.

Catalytic Reduction of the Anhydrotetrahydroalcohol Acetates F and G with Platinum; Formation of a Hydrogenolysis Product.—A mixture of the anhydro acetates F and G (5 g.) in ethanol was hydrogenated over platinum at low pressure until the uptake of hydrogen ceased (1.6 moles). The infrared spectrum of the crude product showed hydroxyl absorption and the disappearance of the double bond bands at 895 and 815 cm.$^{-1}$. The product was dissolved in petroleum ether and chromatographed on 170 g. of activity II neutral alumina. Elution with petroleum ether yielded the desoxytetrahydroalcohol acetate (2 g.) identical with that (H-1) obtained by reduction (see above) of the **anhydrotetrahydroalcohol acetates F and G** with rhodium–hydrogen. Elution with more polar solvents gave the **hydroxyacetate T** (2.3 g.), the hydrogenolysis product in which the epoxide ring was reduced open. This compound was purified for analysis by rechromatography and distillation, b.p. 80–90° (10^{-3} mm.), $[\alpha]D$ −2°.

Anal. Calcd. for $C_{18}H_{34}O_4$: C, 68.75; H, 10.90. Found: C, 68.71; H, 10.65.

The oily **hydroxyacetate T** was acetylated with acetic anhydride–pyridine at room temperature to obtain the **diacetate S-1**, purified by chromatography and distillation.

Anal. Calcd. for $C_{20}H_{36}O_5$: C, 67.38; H, 10.18. Found: C, 67.50; H, 9.95.

Saponification of the Hydroxyacetate T to the Diol, Desoxy-α-hexahydroalcohol S-1.—The hydroxyacetate T (2 g.) was refluxed with 700 mg. of potassium hydroxide in 50% aqueous methanol for 3 hr. The reaction mixture was diluted with water and extracted with chloroform. The dried extracts afforded an oil which was chromatographed on alumina. Elution with 5:2 petroleum ether–ether gave an oil (980 mg.) which crystallized on scratching. Recrystallization from petroleum ether at −70° gave **desoxy-α-hexahydroalcohol S-2**, m.p. 83–84°, which gave no depression on mixed m.p. with a sample of S-2 prepared as above by dehydration of α-hexahydroalcohol diacetate, followed by catalytic reduction and saponification.

Oxidation of the Hydroxyacetate T.—The hydroxyacetate T (52 mg.) was oxidized in acetone with the chromic acid–sulfuric acid reagent. When the reaction was complete (persistence of the orange color) the mixture was diluted with water and extracted with ether. The ether solution was passed through a small column of alumina; infrared examination of the product without further purification showed bands at 1730 (acetate) and 1706 cm.$^{-1}$ (ketone).

Oxidation of Desoxy-α-hexahydroalcohol S-2 to the Diketone U.—The desoxy compound S-2 (790 mg.) in acetone was treated with the chromic oxide–sulfuric acid reagent until the orange color persisted. Dilution with water and extraction with ether gave an oil, which was dissolved in petroleum ether and chromatographed on alumina. **The diketone U** (420 mg.), the sole product, was purified by distillation, b.p. 85° (10^{-4} mm.), $[\alpha]D$ −114°. The infrared showeb two carbonyl peaks at 1705 and 1725 cm.$^{-1}$.

Anal. Calcd. for $C_{16}H_{28}O_3$: C, 71.60; H, 10.52. Found: C, 71.53; H, 10.22.

Desoxytetrahydroalcohol Tosylate V.—Desoxytetrahydroalcohol (1.3 g.) was dissolved in pyridine (5 ml.) and treated with tosyl chloride (1.3 g.). After 4 days at room temperature, the reaction mixture was poured onto ice, acidified with hydrochloric acid and extracted with ether. The tosylate was obtained as a colorless oil (1.82 g.) which was not purified but used directly in the next experiment.

Reduction of Desoxytetrahydroalcohol Tosylate with Lithium Aluminum Hydride.—The above tosylate (1.82 g.) was refluxed in ether with 1.8 g. of lithium aluminum hydride for 20 hr. The usual work-up gave 1.1 g. of a mobile oil which was chromatographed on alumina. The first fraction eluted with petroleum ether had strong end absorption in the ultraviolet and a strong band in the infrared at 1250 cm.$^{-1}$, suggesting the presence of a vinyl ether. The latter fractions were transparent in the ultraviolet and were purified by rechromatography and distillation to give the didesoxy compound W, 1-methoxy-2-2′-(2′, 3′-epoxy-6′-methylheptyl)-3-methylcyclohexane, as a colorless mobile oil, b.p. 70–75° (10^{-3} mm.), $[\alpha]D$ 8°.

Anal. Calcd. for $C_{16}H_{30}O_2$: C, 75.53; H, 11.89. Found: C, 76.09; H, 11.78.

Isomerization of the Didesoxy Compound W.—Didesoxytetrahydroalcohol (1.15 g.), 5% sulfuric acid (4 ml.) and sufficient dioxane to give a homogeneous solution were allowed to stand at room temperature for 2 days. Isolation of the product by ether extraction gave 1.05 g. of colorless oil. Chromatography on alumina removed first some ketonic material followed by the major product, the isomeric allylic alcohol (Y, 620 mg.). This was purified by rechromatography and distillation, b.p. 80–85° (10^{-3} mm.), $[\alpha]D$ 0°. The infrared spectrum showed bands at 3395 (hydroxyl), 1640 (carbon–carbon double bond) and 900 cm.$^{-1}$ (terminal double bond).

Anal. Calcd. for $C_{16}H_{30}O_2$: C, 75.53; H, 11.89. Found: C, 75.51; H, 12.09.

Oxidation of Isodidesoxytetrahydroalcohol Y with Chromic Acid in Acetone.—The above alcohol Y (180 mg.) was dissolved in acetone (2 ml.) and treated with the chromic oxide–sulfuric acid reagent. The product was isolated in the usual manner and chromatographed on alumina to give the **unsaturated ketone Z** (155 mg.). The purified material was distilled for analysis, b.p. 80° (10^{-5} mm.). Infrared bands appeared at 1680, 1628, 930 cm.$^{-1}$, and ultraviolet absorption at ϵ_{222} 7600.

Anal. Calcd. for $C_{16}H_{28}O_2$: C, 76.14; H, 11.18. Found: C, 76.22; H, 11.16.

Treatment of the conjugated ketone Z with sodium borohydride regenerated the allylic alcohol Y, with the terminal double bond.

Hydroxylation of Isodidesoxytetrahydroalcohol Y with Osmium Tetroxide followed by Periodate Cleavage.—Isodidesoxytetrahydroalcohol (Y, 180 mg.) in ether (30 ml.) and pyridine (2 ml.) was left with osmium tetroxide (150 mg.) at room temperature for 6 days. Lithium aluminum hydride work-up gave a brown oil which was chromatographed on alumina. The later fractions (35 mg.) gave a positive test with periodate for a 1,2-diol grouping. These fractions were dissolved in dioxane and sodium periodate (200 mg.) in water (3 ml.) was added. Nitrogen was blown through the solution and thence through dinitrophenylhydrazine reagent. The precipitated derivative (13 mg.) was separated by chromatography on 4:1 Bentonite–Celite. The first fraction yielded isocapraldehyde dinitrophenylhydrazone (9 mg.), m.p. 92–95°, after recrystallization from methanol. The mixed melting point with an authentic sample melting at 97–98° was 93–97° and the infrared spectra were identical.

The second fraction yielded formaldehyde dinitrophenylhydrazone, m.p. 155–160°. After recrystallization the melting point was raised to 160–163°. The mixed m.p. with the formaldehyde derivative was not depressed and the infrared spectra were identical.

Reaction of α-Hexahydroalcohol N with Tosyl Chloride; Formation of 3,4-Dimethyl-2-isoamyl-4-hydroxy-7-tosyl-oxyperhydrobenzofuran (EE).—Compound N (921 mg.) was allowed to stand with freshly crystallized tosyl chloride in 5 ml. of pyridine. After 5 days at room temperature the reaction mixture was poured onto ice, acidified and extracted with ether. The ether extract yielded the crude tosylate (1 g.) which was dissolved in petroleum ether and chromatographed on activity III neutral alumina. Some yellow noncrystalline material (140 mg.) was removed by elution with 9:1 petroleum ether–ether. Further elution with 4:1 petroleum ether–ether through ether yielded a crystalline tosylate. Recrystallization from petroleum ether afforded the perhydrobenzofuran EE as needles, m.p. 79.5–80.5°, $[\alpha]D$ −6°.

Anal. Calcd. for $C_{22}H_{34}O_5S$: C, 64.37; H, 8.35. Found: C, 64.08; H, 8.07.

3,4-Dimethyl-2-isoamyl-4-hydroxyperhydrobenzofuran (GG) from Tosylate EE.—The crystalline tosylate EE (450 mg.) in dry ether was added to a solution of lithium aluminum hydride (400 mg.) in ether and then heated under reflux for 19 hr. Work-up in the usual manner gave oily crystals (195 mg.) which were purified by chromatography and recrystallization. The perhydrobenzofuran GG (90 mg.) had m.p. 130–132°, $[\alpha]D$ 1°.

Anal. Calcd. for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74; OCH_3, 0.0; active H, 1.00. Found: C, 74.88; H, 11.76; OCH_3, 0.2; active H, 1.04.

Cleavage of Tosylate EE to 3,4-Dimethyl-2-isoamyl-4,7-dihydroxyperhydrobenzofuran (FF).—The tosylate EE (500 mg.) was cleaved[59] with sodium in liquid ammonia. The product (172 mg.) crystallized immediately, and after recrystallization from petroleum ether melted at 107–108°, $[\alpha]D$ −70°.

Anal. Calcd. for $C_{15}H_{28}O_3$: C, 70.27; H, 11.01; OCH_3, 0.0; active H, 2.00. Found: C, 70.26; H, 11.11; OCH_3, 0.26; active H, 2.04.

Treatment of FF with tosyl chloride–pyridine, followed by chromatography on alumina, regenerated the crystalline tosylate EE, m.p. and mixed m.p. 79.5–80.5°. This proved that the sodium–liquid ammonia treatment had not caused any change other than cleavage of the tosylate group.

Oxidation of FF to 3,4-Dimethyl-2-isoamyl-4-hydroxy-7-ketoperhydrobenzofuran (HH).—The diol FF (260 mg.) in acetone was treated with chromic acid solution at 0° until an orange color persisted. Work-up gave the **ketone HH** (255 mg.) which, when recrystallized from petroleum ether, had m.p. 102–103°, $[\alpha]D$ −58°. It showed a carbonyl band at 1731 cm.$^{-1}$, and in the ultraviolet, ϵ_{277} 90.

Anal. Calcd. for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 70.80; H, 10.53.

Formation of FF by Action of Dimethyl Sulfate on α-Hexahydroalcohol.—α-Hexahydroalcohol (1.1 g.) was refluxed with potassium carbonate in aqueous acetone, while dimethyl sulfate was added dropwise during 40 hr., and reflux was continued another 14 hr. Work-up in the usual manner, chromatography and elution with petroleum ether–ether, 9:1, gave a non-hydroxylated oil (0.3 g.). Further chromatography gave hydroxy-containing oils, and elution with petroleum ether–ether, 1:1, gave the perhydrobenzofuran FF (15% yield) showing no depression on mixed m.p. with an authentic sample. No FF was formed when dimethyl sulfate was absent.

Crystalline FF was also isolated in very small amounts from the selenium dehydrogenation of α-hexahydroalcohol.

Tetrahydropyranyl Ether of Tetrahydroalcohol-I.—Tetrahydroalcohol-I (C, 3.73 g.) was allowed to stand 48 hr. at 20° in 5 ml. of dihydropyran containing one drop of concd. hydrochloric acid. Addition of water and ether extraction gave on chromatography a hydroxyl-free material (0.3 g.), probably a ditetrahydropyranyl ether derived from an acid isomerization product of the tetrahydroalcohol (analysis was satisfactory), and the monotetrahydropyranyl ether (4.3 g.), a mobile oil, $[\alpha]D$ −57°, which was rechromatographed for analysis.

Anal. Calcd. for $C_{21}H_{38}O_5$: C, 68.06; H, 10.34; O, 21.59; OCH_3, 8.37. Found: C, 68.05; H, 10.15; O, 21.75; OCH_3, 7.85.

Hydrolysis of the ether with a trace of mineral acid in aqueous methanol at room temperature regenerated 50% of crystalline tetrahydroalcohol-I, identified by mixed m.p., along with some product formed from the tetrahydro-alcohol by acid-catalyzed isomerization.

Lithium Aluminum Hydride Reduction of Monotetrahydropyranyl Derivative of Tetrahydroalcohol.—A mixture of the mono- and ditetrahydropyranyl derivatives of C (9.8 g.) was reduced with 1 g. of lithium aluminum hydride in refluxing ether for 24 hr. Hydrolysis with saturated sodium sulfate gave a pale oil (9.8 g.) which on chromatography yielded four compounds: (1) the reduction product of the ditetrahydropyranyl ether (1.16 g.); (2) the tetrahydropyranyl ether of α-hexahydroalcohol (JJ, 4.8 g.); (3) the tetrahydropyranyl ether of β-hexahydroalcohol; (4) a methoxy-free compound, m.p. 139–140°, with composition corresponding to a tetrahydropyranyl derivative of FF or LL. Compounds 1 and 4 are not pertinent to the structural argument, and will not be described further, although they were completely characterized.

The tetrahydropyranyl ether of α-hexahydroalcohol JJ was recrystallized from petroleum ether and sublimed, m.p. 121–123°, $[\alpha]D$ −71°, ϵ_{210} 100.

Anal. Calcd. for $C_{21}H_{40}O_5$: C, 67.70; H, 10.82; O, 21.47; OCH_3, 8.33. Found: C, 67.92; H, 10.92; O, 21.68; OCH_3, 8.32.

It formed a **monoacetate** with pyridine–acetic anhydride at room temperature, $[\alpha]D$ −64°.

(59) D. B. Denney and B. Goldstein, *J. Org. Chem.*, **21**, 479 (1956).

Anal. Calcd. for $C_{23}H_{42}O_6$: C, 66.63; H, 10.21; O, 23.16; OCH_3, 7.48; acetyl, 10.38. Found: C, 66.84; H, 9.91; O, 23.23; OCH_3, 7.65; acetyl, 10.81.

The parent compound JJ was converted by standing in methanol, containing 1 drop of 6 *N* hydrochloric acid, for 1 hr. at 20°, to α-hexahydroalcohol, in high yield; identification was based on the infrared spectrum.

The tetrahydropyranyl derivative of β-hexahydroalcohol was obtained by distillation as a viscous oil, $[\alpha]_D$ 63°. The compound showed a peak at 1655 $cm.^{-1}$, and ultraviolet absorption ϵ_{210} 1260, ϵ_{220} 105.

Anal. Calcd. as above for JJ. Found: C, 67.09; H, 10.83; O, 22.42; OCH_3, 7.69.

Acidic hydrolysis in methanolic solution regenerated β-hexahydroalcohol, identified by infrared.

Conversion of the Tetrahydropyranyl Ether of α-Hexahydroalcohol JJ to the Perhydrobenzofuran FF.—Compound JJ (300 mg.) and tosyl chloride (330 mg.) were allowed to stay in pyridine solution for 48 hr. at 20°. Conventional work-up followed by chromatography yielded 94 mg. of product, which after crystallization from petroleum ether melted at 104–107°, and was shown to be identical with FF by mixed m.p.

Conversion of Tetrahydroalcohol Monotosylate KK to 3,4-Dimethyl-2-isoamyl-3,4-dihydroxyperhydrobenzofuran (LL).—The tosylate (22.4 g.) was heated under reflux with lithium aluminum hydride (8.2 g.) in ether for 16 hr. The usual work-up with saturated sodium sulfate solution yielded 11.5 g. of oil. Chromatography on activity II neutral alumina allowed some separation of a complex mixture of products. Oily material (3.2 g.) was removed by mixtures of petroleum ether and ether up to and including 2:1. Elution with 1:1 petroleum ether–ether gave a crystalline diol (1.425 g.) which was purified by recrystallization from petroleum ether; m.p. 81.2–82.0°. This perhydrobenzofuran derivative showed no absorption down to 210 mμ in the ultraviolet and had $[\alpha]_D$ −62°.

Anal. Calcd. for $C_{15}H_{28}O_3$: C, 70.27; H, 11.01; O, 18.72; OCH_3, 0.0; active H, 2.00. Found: C, 70.34; H, 11.11; O, 18.54; OCH_3, 0.0; active H, 1.96.

Further elution with ether and 200:1 ether–methanol yielded a **desoxy-β-hexahydroalcohol** (2.01 g.), m.p. 69–72°, raised to 74.1–75.2° on recrystallization from petroleum ether; $[\alpha]_D$ −20°. The product exhibited high end absorption in the ultraviolet and gave a yellow color with tetranitromethane.

Anal. Calcd. for $C_{16}H_{32}O_3$: C, 70.54; H, 11.84; O, 17.62; CH_3O, 11.39. Found: C, 70.34; H, 11.90; O, 17.49; CH_3O, 11.53.

Desoxy-β-hexahydroalcohol gave a positive iodoform test for the presence of a CH_3–CH–OH grouping.

Conversion of Desoxy-α-hexahydroalcohol MM to 3,4-Dimethyl-2-isoamyl-4-tosyloxyperhydrobenzofuran (NN).—Desoxy-α-hexahydroalcohol (MM, 6.00 g.) was allowed to stand at 20° for 5 days in 85 cc. of pyridine containing 13.0 g. of tosyl chloride. The solution was poured onto ice, and work-up yielded 8.5 g. of crude product. Chromatography on 200 g. of alumina yielded 3.8 g. (44%) of the perhydrobenzofuran tosylate (NN), with about 3.5 g. of following fractions. The tosylate was not analyzed, but was reduced immediately.

Lithium Aluminum Hydride Reduction of the Tosyloxyperhydrobenzofuran NN to 3,4-Dimethyl-2-isoamylperhydrobenzofuran (PP).—The tosylate NN (3.80 g.) was refluxed with 2.1 g. of lithium aluminum hydride in ether for 8 hr. The crude yellow oil obtained (2.8 g.) was separated by chromatography on alumina into 1.00 g. of the detosylated benzofuran PP (46%), along with 0.43 g. of some unsaturated material and 1.20 g. of hydroxyl-containing material. The infrared and n.m.r. spectra confirmed the absence of a methoxyl group, and the presence of a tetrahydrofuran ring.

Anal. Calcd. for $C_{15}H_{28}O$: C, 80.29; H, 12.58. Found: C, 80.01; H, 12.19.

Formation of 2-Isoamyl-3,4-dimethylbenzofuran (QQ) and Methyloctylbenzene (OO) by Dehydrogenation of the Perhydrobenzofuran PP.—The perhydro compound PP (640 mg.) was heated with 1.0 g. of powdered selenium metal for 42 hr. at 270–320°, in a bulb fitted with a long air condenser. The product was dissolved in petroleum ether and chromatographed on 20 g. of alumina, eluting solely with petroleum ether. The first fraction (76 mg.) was the hydrocarbon OO, $n^{25}D$ 1.4860, ultraviolet absorption ϵ_{263} 275, optically inactive.

Anal. Calcd. for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 88.00; H, 11.95.

The second fraction (160 mg.) was the benzofuran QQ. (The remainder of the material eluted from the column with more polar solvents (*ca.* 200 mg.) did not appear to be aromatic in character.) The ultraviolet and n.m.r. spectra of QQ are discussed above. The analytical sample of QQ was obtained from an earlier run and was purified by vapor phase chromatography and distillation.

Anal. Calcd. for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 83.11; H, 9.55.

Synthesis of Methyloctylbenzene (OO).—*o*-Tolylmagnesium bromide, prepared from 1.05 g. of magnesium and 7.18 g. of *o*-bromotoluene in 50 cc. of ether, was treated with 5.0 g. of 6-methyl-2-heptanone[46] in 100 ml. of ether, and the solution was refluxed for several hours. The solution was hydrolyzed with 10% sodium sulfate solution, and the mixture after the usual work-up yielded 7.0 g. of crude product, which was chromatographed on alumina. The hydroxyl-containing fractions were evaporatively distilled, yielding 5.3 g. of 2-(2′-methylphenyl)-6-methyl-2-heptanol, $n^{25}D$ 1.5082.

Anal. Calcd. for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.76; H, 10.86.

The carbinol (1.1 g.) was stirred with 0.4 g. of 5% palladium–charcoal in acetic acid[60] under a hydrogen atmosphere at room temperature for 6 hr., at which time the theoretical amount of hydrogen had been absorbed and the uptake stopped. The solution was filtered, water was added, the product was extracted with petroleum ether, and the extract yielded, after chromatography on activity I alumina, 800 mg. of hydrocarbon. After distillation, 730 mg. of pure hydrocarbon was obtained, which had the proper analysis and was indistinguishable in its infrared and ultraviolet spectra and its behavior on vapor phase chromatography from the hydrocarbon obtained by dehydrogenation.

6-Methyl-2-heptene-2-ol Acetate (SS).—To 96 g. of 6-methyl-2-heptanone (b.p. 164–165°, $n^{25}D$ 1.4120) in a 3-neck, 500-ml. flask, equipped with a stirrer and Vigreux column, 150 g. of isopropenyl acetate was added, followed by 5 ml. of concentrated sulfuric acid. The mixture (which turned dark brown) was heated with stirring on a steam-bath, while the acetone formed was distilled off until nearly a quantitative amount was obtained. The reaction was cooled, and triethylamine was added to neutralize the solution. The mixture was then distilled (Vigreux column), and the fraction with b.p. 78–82° (*ca.* 12 mm.), was collected. The clear, white liquid weighed 94 g. (74% yield). The analytical sample was prepared by redistillation of the product several times to give a substance which had $n^{24}D$ 1.4255.

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66. Found: C, 70.85; H, 10.66.

3-Bromo-6-methyl-2-heptanone[61] (TT).—A solution of 62.8 g. of the enol acetate SS in 170 ml. of carbon tetrachloride was cooled to 0° in a 500-ml. 3-neck flask equipped with a stirrer, dropping funnel and drying tube (calcium chloride). Bromine (59 g.) in 50 ml. of carbon tetrachloride was added slowly, and the temperature maintained from −10° to 0°. The bromine color was discharged immediately upon reaction with the enol acetate. The brominated solution was poured into 300 ml. of methanol with cooling to 0°. After the mixture had stood for 36 hr. at room temperature, 500 ml. of water was added and the carbon tetrachloride layer separated. The organic portion was extracted several times with 10% sodium carbonate and then once with water. After drying over sodium sulfate, the carbon tetrachloride was distilled off under reduced pressure. The product distilled from 96–98° at approximately 16 mm. The first cut (96–97°, $n^{25}D$ 1.4592) and the second cut (97–98°, $n^{25}D$ 1.4609) together weighed 50 g. (65% yield). Because the infrared showed the presence of some of the elimination product, $CH_3COCH=CHCH_2CH(CH_3)_2$, an analysis was not carried out.

4-Methyl-5-isoamyl-2-mercaptothiazole (VV).—To 2.0 g. of 3-bromo-6-methyl-2-heptanone dissolved in 10 ml. of abso-

(60) E. C. Horning and D. B. Reisner, *J. Am. Chem. Soc.*, **71**, 1036 (1949).

(61) *Cf.* P. Z. Bedoukian, *ibid.*, **67**, 1430 (1945).

lute methanol, 3 g. of freshly prepared ammonium dithiocarbamate[62] was added, and the mixture was allowed to reflux for 1 hr. An additional 2 g. of ammonium dithiocarbamate was then added and refluxing continued for 30 min. The mixture was poured over 75 g. of ice and the resulting precipitate was filtered. Recrystallization from heptane gave 1 g. (52% yield) of white needles, m.p. 130–132°.

Anal. Calcd. for $C_9H_{15}NS_2$: C, 53.72; H, 7.51; N, 6.96. Found: C, 53.91; H, 7.34; N, 7.07.

The n.m.r. spectrum (in CCl_4) showed six isopropyl protons (τ 9.03 and 9.12), three saturated aliphatic protons (8.56), three allylic methyl protons (7.85), two allylic protons (7.50), and one N–H proton (−2.4).

3-(2,4-Dichloro-5-methylphenoxy)-6-methyl-2-heptanone (WW).—To a stirred solution of 1.77 g. of sodium dissolved in 100 ml. of absolute ethanol, 13.6 g. of 3-methyl-4,6-dichlorophenol[63] was added followed by 15.6 g. of the α-bromoketone TT. The mixture was refluxed on a steam-bath for 3 hr., at which time the *p*H was 8–9. An additional 1–2 g. of α-bromoketone was added and the mixture refluxed 12 hr. more (until neutral to moist litmus). The reaction was cooled in an ice-bath, and the sodium bromide was filtered. The filtrate was evaporated on the steam-bath under reduced pressure, the residue was taken up in ether, and the ether was washed with 10% sodium hydroxide and water. The ether was dried, filtered, and evaporated. The residual liquid was distilled; the fraction boiling at 128–130° (0.5 mm.) was collected ($n^{25}D$ 1.5135, 13.6 g. or 58% yield). Another run gave a 61% yield.

An analytical sample was prepared by dissolving the product in petroleum ether (30–60°) and passing this over Woelm neutral alumina, activity I. The column was eluted with ether, the ether evaporated, and the residue distilled (molecular still) at 10^{-4} mm. (bath temperature 90°).

Anal. Calcd. for $C_{15}H_{20}O_2Cl_2$: C, 59.43; H, 6.65. Found; C, 59.73; H, 6.98.

A semicarbazone derivative of WW was made by heating an aqueous ethanolic solution of WW with semicarbazide hydrochloride and sodium acetate on a steam-bath for 12 hr. Evaporation of the alcohol–yielded a solid which was recrystallized from ethanol–water to give white needles, m.p. 111–113°.

Anal. Calcd. for $C_{16}H_{23}O_2N_3Cl_2$: C, 53.33; H, 6.43; N. 11.67. Found: C, 53.35; H, 6.45; N, 11.88.

2-Isoamyl-3,4-dimethyl-5,7-dichlorobenzofuran (XX).—To 15 ml. of concentrated sulfuric acid cooled in an ice-bath, 7.55 g. of the ketone WW was added. The reaction was stirred and cooled for about 5 min. or until a thick, orange mass was formed. This was poured over 200 g. of ice to produce a precipitate which was extracted into ether. The ether was dried over magnesium sulfate, filtered, and evaporated to a crude, crystalline solid. Recrystallization of this product several times from ethanol–water gave 5.55 g. (78% yield) of white, silky needles of XX, m.p. 52–53°.

Anal. Calcd. for $C_{15}H_{18}OCl_2$: C, 63.16; H, 6.36. Found: C, 63.42; H, 6.49.

2-Isoamyl-3,4-dimethylbenzofuran (QQ).—A mixture of 5.55 g. of the dichloro compound XX in 135 ml. of methyl Cellosolve, 10 ml. of 95% hydrazine and 1.5 g. of 5% palladium-on-carbon was allowed to reflux for 24 hr. The reaction was filtered and the solvent distilled off under reduced pressure on the steam-bath. The residue was taken up in ether, which was washed with water and dried. Evaporation of the ether gave 3.94 g. (94% yield) of the desired 2-isoamyl-3,4-dimethylbenzofuran (QQ).

The analytical sample was prepared by dissolving a small amount in petroleum ether (30–60°) and passing this solution over a column of neutral Woelm alumina (activity I). The column was eluted with petroleum ether and the eluents were combined and evaporated to a colorless, mobile liquid. This was distilled (molecular still) at 90° (10^{-4} mm.).

Anal. Calcd. for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 83.18; H, 9.17.

The benzofuran gave the following color changes on standing with concentrated sulfuric acid: yellow → orange → red → violet.

When passed through the v.p.c. using a 6.5-ft. Apiezon-Chromosorb column at 218–220° (flow rate 65 cc. He/min.), QQ had a retention time of 27 min. A mixture of synthesized and "natural" material gave this same retention time. The synthetic material showed only a single peak in the v.p.c.; however, the "natural" compound showed minor impurities. The synthetic compound showed the same ultraviolet spectrum as the "natural" material from dehydrogenation. Its infrared and n.m.r. spectra were also identical.

3-(2-Methylphenoxy)-6-methyl-2-heptanone and 2-Isoamyl-3,7-dimethylbenzofuran (YY).—To 3.45 g. of sodium dissolved in 100 ml. of ethanol 16.2 g. of *o*-cresol was added followed by 31 g. of the α-bromoketone TT. The mixture was stirred and allowed to reflux for 20 hr.; at this time an additional 2 g. of TT was added, and the mixture allowed to reflux 20 hr. longer. The reaction was cooled and filtered; the ethanol was removed by distillation under reduced pressure at steam-bath temperature. The residue was taken up in ether, and was extracted with 10% sodium hydroxide and water. The ether was dried, filtered, and evaporated. The residual liquid was subjected to distillation: fraction 1, 40–84° (approx. 0.1 mm.); fraction 2, 84–86° (approx. 0.1 mm.), 9.0 g. (26% yield), $n^{25}D$ 1.4920.

The analytical sample of the ketone was prepared by redistillation through a spinning band column, passing the distillate (in ether) over Woelm neutral alumina activity I, evaporation of the ether, and distillation of the residue in a molecular still.

Anal. Calcd. for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 77.30; H, 9.48.

A hydantoin derivative from the ketone was prepared following Henze,[64] and was recrystallized from absolute ethanol; m.p. 215–216.5°.

Anal. Calcd. for $C_{17}H_{24}O_3N_2$: C, 67.08; H, 7.95; N, 9.20. Found: C, 67.29; H, 8.00; N, 9.16.

Cyclization of the phenoxyketone to the benzofuran was accomplished by adding 3.5 g. of the ketone to 30 g. of polyphosphoric acid. The mixture turned light orange on standing at room temperature for 2 hr. The viscous reaction was heated further on a steam-bath (10.15 min.) until a deep orange-red color was present. The reaction mixture was poured over ice-water and then extracted with ether. The ether was washed with sodium bicarbonate, dried, and evaporated. The residue gave the characteristic color sequence on standing with sulfuric acid: yellow → orange → red → violet.

An analytical sample was prepared by dissolving the product (YY) in petroleum ether (30–60°) and passing the solution over a column of neutral alumina activity I. Subsequent distillation at 90° (10^{-4} mm.) gave a colorless oil.

Anal. Calcd. for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 83.45; H, 9.43.

Vapor phase chromatography of YY under the identical conditions as described for QQ gave a single peak with a retention time of 20.0 min. Moreover, a mixture of QQ and YY was separated under these same conditions; two peaks were observed with retention times of 26.3 and 20.0 min., respectively.

2,6-Diisoamyl-3,4,5-trimethylbenzo(1,2-b,5,4-b′)-difuran (AAA) (or the (1,2-b,3,4-b′)-Isomer.—To 2.3 g. of sodium dissolved in 50 ml. of ethanol, 12.4 g. of orcinol was added. The mixture was stirred while 20.7 g. of 3-bromo-6-methyl-2-heptanone was added in one lot. After several hr. at reflux temperature, sodium bromide precipitated from the solution, and within 40 hr. the reaction mixture was neutral to litmus. The contents of the flask were filtered and the filtrate evaporated under reduced pressure to an oil. The oil was taken up in ether which was then washed with water, dried, and evaporated. The residue was subjected to distillation under vacuum to remove unreacted α-bromoketone and comparatively low molecular weight compounds. The viscous residue was dissolved in ether and passed over a column of neutral alumina activity I. The column was eluted with ether and the first fractions were evaporated to give a semi-solid product. This material was recrystallized from ethanol to give white needles, m.p. 82–89°. After three recrystallizations from alcohol, the melting point was 93–94.5°. This substance (AAA) was insoluble in sodium hydroxide and gave a red-purple color with concentrated sulfuric acid.

(62) L. P. Miller, *Contrib. Boyce Thompson Inst.*, **5**, 31 (1933).

(63) M. p. 73.5°; obtained from Aldrich Chemical Co.

(64) H. R. Henze and R. J. Speer, *J. Am. Chem. Soc.*, **64**, 522 (1942).

Anal. Calcd. for $C_{28}H_{32}O_2$: C, 81.13; H, 9.47. Found: C, 81.25; H, 9.46.

On further elution of the column with ether containing 1% methanol, an orange-red oil was obtained which was soluble in warm 5% sodium hydroxide. The infrared indicated the presence of –O–H; however, attempts to induce crystallization failed.

2-Isoamyl-3,4-dimethylbenzofuran-7-carboxylic Acid (BBB).—To a solution of 2.7 g. of sodium methoxide (found to be only 85% pure) in 50 ml. of methanol was added 8.3 g. of methyl 2-hydroxy-4-methylbenzoate and the alcohol was evaporated *in vacuo*. Ether was added to the residue to give 6.1 g. of white solid. The salt was refluxed with 6.7 g. of 3-bromo-6-methyl-2-heptanone in ethanol for 9 hr. Nearly the theoretical amount of sodium bromide was collected, the alcohol was evaporated, and the residue dissolved in ether. The ether layer was extracted with sodium hydroxide, dried, and evaporated. The remaining oil was distilled in a molecular still; the last fraction (about 1 g.) was a viscous orange-red oil ($n^{24}D$ 1.4780) whose infrared spectrum indicated it was the phenoxy compound corresponding to WW. This material was treated with 10 g. of polyphosphoric acid at room temperature for about 15 min. The thick mixture was poured over ice, and the whole extracted with ether. The ether was dried and passed over a column of neutral alumina activity I. After elution and evaporation of the ether, an oil was obtained which was dissolved in methanol containing 20% aqueous sodium hydroxide. The solution was heated on a steam-bath for 1 hr. and the methanol evaporated to a white solid (the sodium salt of the acid) suspended in a small amount of water. Upon acidification with hydrochloric acid in the cold, a precipitate formed which was recrystallized from methanol–water. This material (about 200 mg.) had m.p. of 163–165°, gave the following color changes in cond. sulfuric acid, yellow → red → violet, and exhibited the presence of a carboxyl group in the infrared. The analytical sample was prepared by sublimation at 0.1 mm. and 160° bath temperature.

Anal. Calcd. for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 74.11; H, 7.62.

β-Hexahydroalcohol Triacetate (P).—The β-hexahydroalcohol can be converted to the triacetate with acetic anhydride–pyridine. The analytical sample was prepared as follows.

The β-hexahydroalcohol (16.46 g., $[\alpha]^{25}D$ 48.4°) was heated on the steam-bath for 2 hr. with 50 ml. of acetic anhydride and 165 ml. of pyridine. The mixture was dissolved in 2 l. of ether, washed with water, 3% aqueous hydrochloric acid, saturated bicarbonate solution, again with water and was dried and the solvent was removed. The product, 22.15 g., $[\alpha]^{25}D$ 44.90°, showed an infrared spectrum essentially identical with that of a distilled analytical sample of the triacetate prepared on a smaller scale; there was no hydroxyl band, and were strong ester bands.

Anal. Calcd. for $C_{22}H_{38}O_7$: C, 63.74; H, 9.24; O, 27.02; active H, 0.0 (6 equiv. consumed). Found: C, 63.65; H, 9.31; O, 26.79; active H, 0.68; (5.50 equiv. consumed).

Tetrahydropyranyl Ether of β-Hexahydroalcohol Diacetate.—The tetrahydropyranyl ether of β-hexahydroalcohol above (0.60 g.) was acetylated with acetic anhydride (3 ml.) in pyridine (5 ml.) for 48 hr. at 0°. Normal work-up and chromatography gave the diacetate (644 mg.). The analytical sample, obtained by distillation, had $[\alpha]D$ 58.6°, and the following ultraviolet absorption: ϵ_{220} 190, ϵ_{210} 1370. There was no hydroxyl absorption in the infrared, but strong acetate absorption at 1735 and 1236 $cm.^{-1}$.

Anal. Calcd. for $C_{25}H_{44}O_7$: C, 65.76; H, 9.71; O, 24.53; OCH_3, 6.80. Found: C, 65.62; H, 9.60; O, 24.44; OCH_3, 6.44.

Hydrolysis of this acetal in aqueous methanol with dilute hydrochloric acid gave the **β-hexahydroalcohol diacetate,** $[\alpha]D$ 44°, ϵ_{220} 210, ϵ_{210} 1152, and infrared bands at 3400, 1730, 1665 and 1231 $cm.^{-1}$, among others.

Anal. Calcd. for $C_{20}H_{36}O_6$: C, 64.49; H, 9.74; O, 25.77; OCH_3, 8.31. Found: C, 64.66; H, 10.01; O, 25.73; OCH_3, 8.59.

Treatment of this diacetate with lithium aluminum hydride gave a good yield of authentic β-hexahydroalcohol, $[\alpha]D$ 42.3°, as shown by its infrared spectrum.

Iodoform Reaction on β-Hexahydroalcohol and its Tetrahydropyranyl Ether.—β-Hexahydroalcohol (38 mg.) in 1 ml. of water was treated with aqueous alkali and iodine–potassium iodide solution at 80° for 40 min. Decolorization with sodium hydroxide and dilution with water gave 4 mg. of iodoform, m.p. 119–122°, with characteristic odor. The tetrahydropyranyl ether also gave iodoform under the same conditions.

Hydroxylation and Periodate Cleavage of the β-Hexahydroalcohol.—β-Hexahydroalcohol (850 mg.) in dioxane (5 ml.) and 5 ml. of water was treated with 15 mg. of osmium tetroxide and 3 g. of sodium periodate[65] overnight. A copious white precipitate was formed; nitrogen was passed passed through the solution and into a saturated aqueous solution of dinitrophenylhydrazine for 6 days. The precipitate was recrystallized and chromatographed, and was shown to be the dinitrophenylhydrazone (195 mg.) of isocapraldehyde by m.p. 94–95° and mixed m.p.; a mixed m.p. with the derivative (m.p. 95°) of methyl isoamyl ketone was strongly depressed.

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