[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER]

The Chemistry of Fumagillin. V. The Presence of a Carbocyclic Ring in Fumagillin[1]

BY JAMES G. MCNALLY, JR., AND D. STANLEY TARBELL[2]

RECEIVED DECEMBER 3, 1957

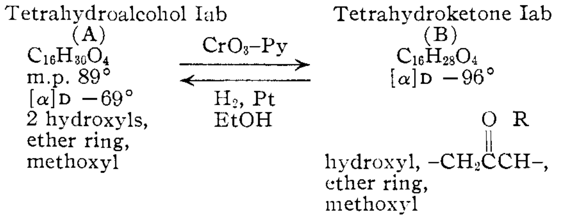
Tetrahydroketone I, $C_{16}H_{28}O_4$, obtained by chromic acid–pyridine oxidation of tetrahydroalcohol Iab, $C_{16}H_{30}O_4$, is converted by catalytic reduction to the alcohol from which it is prepared, proving that there has been no skeletal rearrangement during the oxidation. Ozonization of the furfurylidene derivative of tetrahydroketone I, and treatment of the ozonide with hydrogen peroxide, yields a carboxylic acid containing a γ-lactone group. This compound contains all of the carbon atoms originally present in the tetrahydroketone; this demonstrates that the carbonyl group in the ketone is contained on a ring (presumably a six-membered carbocyclic ring), and hence that the hydroxyl group in alcohol I itself is on a carbocyclic ring. The absence of a tetrasubstituted carbon-carbon double bond in alcohol I and its derivatives has been demonstrated by measurements of their ultraviolet spectra.

Degradative work in the antibiotic fumagillin is described in previous papers in this series[3–6] and in an important paper by Landquist.[7] The work reported in the present paper and those which accompany it[8] furnishes much new information about the chemistry of alcohol I[9] and its derivatives, and while it does not allow the formulation of a unique solution to the structural problem, it does allow a clearer definition of that problem.

Alcohol I, $C_{16}H_{26}O_4$, which is the neutral hydrolysis product of fumagillin,[3–7] contains a secondary hydroxyl, an epoxide group and a double bond,[6,7] as well as a methoxyl group and an ether ring. Reduction in one step with hydrogen–platinum, or in two stages, using lithium aluminum hydride and catalytic reduction,[5,6] yields tetrahydroalcohol Iab, m.p. 89° (A). Oxidation of A with chromic oxide–pyridine (the Sarett procedure) yields the corresponding ketone, $C_{16}H_{28}O_4$ (B). This ketone was shown to have the structural element $-CH_2\overset{\overset{O}{\|}}{C}\overset{R}{C}H-$, or less probably $-CH_2\overset{\overset{O}{\|}}{C}CR_2-$, by formation of a monofurfurylidene derivative and by bromination.

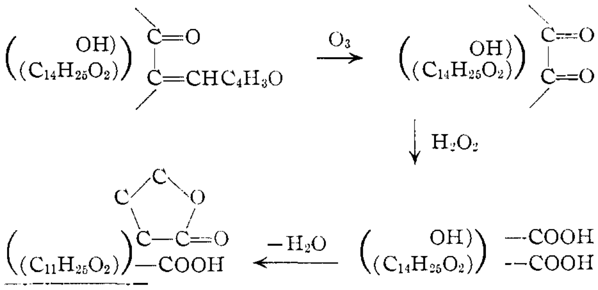
In view of the striking tendency of alcohol I and its derivatives to rearrange,[8] we have shown that the Sarett oxidation of A to B does not involve rearrangement, by catalytic reduction of the ketone, to regenerate the crystalline tetrahydroalcohol Iab. Since this compound in turn can be obtained from alcohol I by reduction with platinum and hydrogen in ethanol, it appears safe to conclude that there has been no rearrangement involved in the transformation of alcohol I to the ketone B. Hence, conclusions about the environment of the keto group in B may be applied to the secondary hydroxyl group in alcohol I.

It was obviously desirable to cleave the ketone B at the carbonyl group, to find out if the latter was present in a ring or in a straight chain, and this was carried out by ozonizing the crystalline furfurylidene derivative of B described previously.[6,10]



A series of ozonizations was carried out, mainly in ethyl acetate at −70°, and the ozonide was usually decomposed by 30% hydrogen peroxide. Neutral and acidic products were obtained in all cases; the acidic product in each case showed infrared absorption corresponding to a γ-lactone and a carboxyl group (bands at *ca.* 3450, 1767 and 1724 cm.$^{-1}$). The analyses of the lactonic acids corresponded to $C_{16}H_{26}O_6 \cdot H_2O$. Many attempts were made to remove the water of hydration from this acid, but with little success. Analysis of the product obtained by distilling the acid with toluene showed a higher carbon content than starting material, indicating at least partial dehydration. The methyl ester, prepared from the lactonic acid with diazomethane, had the proper analysis for $C_{17}H_{28}O_6$, thus supporting the $C_{16}H_{26}O_6$ formula. The lactone-*p*-bromoanilide was prepared through the reaction of the acid chloride on *p*-bromoaniline. This compound analyzed correctly for $C_{22}H_{30}O_5NBr$, thus offering further support for the $C_{16}H_{26}O_6$ formula.

These results indicate that the α-diketone formed by ozonization of the furfurylidene compound was cleaved by the peroxide to a dibasic acid, one of



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(1) Aided by a grant from the National Institutes of Health.

(2) Inquiries regarding these papers should be addressed to this author.

(3) J. R. Schenck, M. P. Hargie, D. S. Tarbell and P. Hoffman, THIS JOURNAL, **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**, 1675 (1956).

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

(8) (a) D. D. Chapman and D. S. Tarbell, THIS JOURNAL, **80**, 3679 (1958); (b) A. D. Cross and D. S. Tarbell, *ibid.*, **80**, 3682 (1958).

(9) The nomenclature of ref. 6 will be used in the present papers.

(10) Other methods of degradation, such as oxidation of an oxymethylene derivative (as used by L. Ruzicka, E. Rey and A. C. Muhr, *Helv. Chim. Acta*, **27**, 478 (1944), on lanosterol), which would have required treatment of B by base, were avoided, because B has been found to be isomerized by base.

whose carboxyls then lactonized with a hydroxyl group on the γ-carbon atom. This would correspond to the $C_{16}H_{26}O_6$ formula. The process corresponds to the transformations shown.

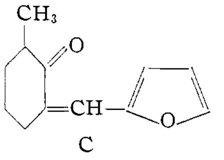
These results show that no carbon is lost from the C_{16} molecules during ozonization and cleavage, and hence the carbonyl group of the ketone B is present on a ring. It cannot be a four- or five-membered ring, because of the carbonyl frequency[5,6] (1720 cm.$^{-1}$), which is normal for a six- or seven-membered ring ketone. It is possible that the carbonyl group is present on a six-membered oxygen-containing ring, but this is not very likely, and it is much more probable that the ketone group is present on a cyclohexane ring. For reasons given above, the secondary hydroxyl group in alcohol I may thus be assigned to a cyclohexane ring.

In several, although not all, ozonolysis runs the neutral material could be converted to a crystalline solid, m.p. 132°, on treatment with base. Spectral evidence indicates that this compound could be the monoenolic form of an α-diketone. This would infer that the neutral material was the α-diketone, arising from the decomposition of the ozonide without cleavage. The crystalline material is described more fully in the Experimental section.

At one stage, the possibility was considered that alcohol I and its derivatives might contain a tetrasubstituted double bond instead of an additional ring. This possibility was ruled out by measurements of the ultraviolet absorption spectra of tetrahydroalcohol Iab in the 210–220 mμ region.[11]

Numerous attempts were made to isolate the α-diketone by reductively decomposing the ozonide of the furfurylidene compound. By reduction of the ozonide with hydrogen and palladium, an oil was obtained which had the expected properties of a cyclic α-diketone, and had the composition $C_{16}H_{28}O_6$, which corresponds to the expected diketone, $C_{16}H_{26}O_5$, plus the elements of water. The diketone could not be obtained crystalline, nor were solid derivatives obtained.

In this connection it is of significance that ozonization of the furfurylidene derivative of methylcyclohexanone (C)[12] and reduction of the ozonide by the same procedure yielded an oil showing the color tests for the diketone D, but the product was not obtained crystalline; D has been prepared by several methods,[13] and it melts at 64–65°.



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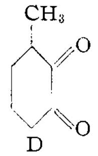

D

In one run, the ozonide from the furfurylidene derivative of B was decomposed by refluxing with zinc dust, and the product was chromatographed on alumina; a crystalline compound, m.p. 168–169°, was obtained, which contained aluminum, and whose analysis and molecular weight corresponded to the formula $(C_{16}H_{28}O_8Al)_{8-13}$. Treatment of this product with mineral acid gave an acidic oil of composition agreeing with $C_{16}H_{26}O_6$.

The possibility that the tetrahydroketone I contains the methoxyl group on the carbon adjacent to the carbonyl group, *e.g.*, that it contains the $-CH_2C{=}O-C-OCH_3H-$ group, was considered because the carbonyl frequency of the ketone (1720 cm.$^{-1}$) was slightly higher than the normal one for a cyclohexanone derivative; the increase might be due to the electron-attracting methoxyl group. However, the tetrahydroketone is not demethylated by boiling dilute mineral acid, in contrast to the behavior of 2-methoxycyclohexanone[14]; furthermore, the ketone gives negative Tollens and Fehling tests,[5] in contrast to open-chain α-methoxyketones.[15] It therefore is probably safe to conclude that the ketone does not contain an α-methoxyl group.

Experimental[16]

Catalytic Reduction of Tetrahydroketone Iab to Tetrahydroalcohol Iab.—The ketone (2.10 g., $[\alpha]^{25}D$ −94°) in 30 ml. of 95% ethanol was shaken for 12 hours with 250 mg. of prereduced platinum in a Parr shaker. Removal of the catalyst and solvent yielded 1.81 g. of crude product, which was taken up in 10 ml. of ligroin and chromatographed on 20 g. of alumina. Elution with ligroin, ligroin–ether and ether gave 864 mg. of crystalline material, m.p. 85–87°. Further elution of the column with ether–methanol mixtures yielded 777 mg. of a colorless oil which did not crystallize; this material showed a strong carbonyl band at 1712 cm.$^{-1}$. A sample of the crystalline product after two recrystallizations from ligroin melted at 87.2–88.5°, and gave no depression on mixed m.p. with an authentic sample of tetrahydroalcohol Iab.

Furfurylidene Derivative of Tetrahydroketone Iab.—The ketone[6] (6.833 g., $[\alpha]^{25}D$ −94.0°) in ethanol (30 ml.) was added to 15 ml. of 0.35 *N* sodium hydroxide containing 2.31 g. of furfural. The reaction flask was stoppered and kept in the dark for 67 hours, at the end of which time its contents were poured into water (100 ml.). The solution was reduced to half its original volume, saturated with sodium chloride and extracted with five 45-ml. portions of ether. The ether extracts were combined, washed with water, and dried; removal of the ether left a red oil which was chromatographed on 40 g. of alumina. A light yellow oil was eluted from the column with ether and 10:1 ether–methanol, which crystallized on scratching. The yield of the furfurylidene derivative of the tetrahydroketone was 5.74 g. (66%, m.p. 88–90°). Recrystallization from ligroin–ether mixtures afforded large colorless rhombic crystals, m.p. 96–97°.

The experimental conditions employed above differ from those of Lovett[6] in that the base concentration is lower and the reaction time longer. By changing these factors the yield has been doubled.

Ozonolysis of the Furfurylidene Ketone.—The following procedure is typical of many runs. The furfurylidene derivative (3.0 g.) in 40 ml. of ethyl acetate was ozonized at −70° for 1.8 hours, using a stream of ozonized oxygen containing about 1.5% ozone. At the end of this time the solution showed the characteristic blue ozone color. On completion of the ozonolysis, the solvent was removed on the steam-bath under a nitrogen stream, leaving the ozonide as a viscous red oil.

Reductive Decomposition of the Ozonide with Hydrogen–

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[11] *Cf.* P. Bladon, H. B. Henbest and G. W. Wood, *J. Chem. Soc.*, 2737 (1952). We are indebted to Dr. T. J. King of the University of Nottingham and Dr. A. D. Cross of this Laboratory for this measurement.

[12] N. Wolff, *Compt. rend.*, **174**, 1469 (1922).

[13] C. Harries, *Ber.*, **35**, 1178 (1902); O. Wallach, *Ann.*, **414**, 314 (1918); **437**, 180 (1924).

[14] M. Bergmann and M. Gierth, *ibid.*, **448**, 48 (1926).

[15] H. R. Henze and N. E. Rigler, THIS JOURNAL, **56**, 1350 (1934).

[16] All m.p.'s are corrected. Rotations and ultraviolet spectra are measured in 95% ethanol, unless otherwise stated. Chromatography was carried out using the general procedure described in ref. 6, footnote 19. Ultraviolet spectra are reported, as previously, with λmax in mμ, followed by log *E* in parentheses. We are indebted to Mr. D. C. Sievers for the microanalyses.

Palladium; Formation of the Diketone.—The ozonide from 1.52 g. of the furfurylidene compound was hydrogenated at atmospheric pressure over palladium-on-barium sulfate. The ozonide solution was kept at −70° by means of a Dry Ice–acetone-bath during the reduction. The solvent was removed under vacuum; the residue was shaken with 10 ml. of 10% sodium carbonate and was extracted with ether. The basic solution then was acidified and again extracted with ether. These ether extracts were washed with water and dried over Linde molecular sieve, type 4A. Removal of the ether left 501 mg. of a dark red oil which had infrared peaks at 3450, 1770 and 1724 cm.$^{-1}$. This material gave a blue-green ferric chloride test and formed an emerald green chelate with cupric acetate in chloroform.

Anal. Calcd. for $C_{16}H_{28}O_6$: C, 60.74; H, 8.92; O, 30.34. Found: C, 60.68; H, 8.57; O, 30.25.

The analysis corresponds to that of the expected diketone, $C_{16}H_{26}O_5$, plus the elements of water.

The diketone (150 mg.) was treated with 185 mg. of freshly prepared diazomethane in ether for 7 hours at 0°. The excess diazomethane was removed by evaporation of the ether solution to dryness. Ether (30 ml.) was added to dissolve the residue. After being washed with 10% sodium carbonate, the ether solution was dried. Removal of the solvent gave 112 mg. of crude product as a viscous oil. This oil was taken up in ligroin and chromatographed over neutral alumina. Elution with 10:1 ether–methanol gave 49 mg. of a light yellow oil which had infrared peaks at 3425, 1770 and 1736 cm.$^{-1}$.

Anal. Calcd. for $C_{17}H_{30}O_6$: C, 61.80; H, 9.79; O, 29.11. Found: C, 62.22; H, 8.75; O, 27.66.

Decomposition of the Ozonide with Hydrogen Peroxide; the Lactonic Acid.—The ozonide from 4.0 g. of the furfurylidene derivative was shaken for 1 hour with 45 ml. of 30% hydrogen peroxide; the excess peroxide was then decomposed with thiosulfate. The aqueous layer was saturated with sodium chloride and was extracted with ether; the ether extracts were washed with water. From the dried ether solution was obtained 669 mg. of a neutral viscous oil, whose further treatment is described below.

The combined carbonate and aqueous washes were acidified with hydrochloric acid and extracted with ether. From the ether solution was obtained 2.03 g. of colorless viscous lactonic acid, with infrared peaks at 3450, 1767 (γ-lactone) and 1724 cm.$^{-1}$ (carboxyl).

Anal. Calcd. for $C_{16}H_{26}O_6$: C, 61.13; H, 8.34; neut. equiv., 314. Found: C, 60.69; H, 8.42; neut. equiv., 299.

Attempts to prepare a phenylhydrazide and a benzylthiouronium salt from the lactonic acid did not yield crystalline products.

In another ozonization carried out under conditions similar to those described above, 4.44 g. of the furfurylidene derivative yielded 1.25 g. of neutral oil, and 2.23 g. of the lactonic acid, with infrared spectrum similar to the one above: bands at 3390, 1764 and 1715 cm.$^{-1}$. This material gave a good analysis for the lactonic acid plus the elements of water.

Anal. Calcd. for $C_{16}H_{26}O_6 \cdot H_2O$: C, 57.81; H, 8.49; O, 33.70; OCH_3, 9.05; neut. equiv., 166 (332 in hot). Found: C, 57.81, 57.41, 58.20; H, 8.09, 8.33, 8.13; O, 32.35, 32.87, 33.49; OCH_3, 8.59; neut. equiv., 243 (hot).

An attempt to prepare a crystalline anilide from the lactone acid by mixed carbonic–carboxylic anhydride procedure[17] yielded only benzanilide as a crystalline product.

The methyl ester of the above lactone acid was prepared by treatment with dimethyl sulfate and potassium carbonate in dry acetone. The neutral product was chromatographed on alumina, and showed infrared bands at 1770 (γ-lactone) and 1733 cm.$^{-1}$ (ester).

Anal. Calcd. for $C_{17}H_{28}O_6$: C, 62.17; H, 8.59; O, 29.23. Found: C, 61.90; H, 8.96; O, 28.64.

A sample of the **methyl ester** of the lactone acid was prepared in another run as follows: the ozonide from 4 g. of the furfurylidene compound was decomposed with hydrogen and palladium–barium sulfate at −70°, and the solvent was removed under nitrogen on the steam-bath; the crude product (presumably the diketone) was taken up in ether, extracted with sodium carbonate, and the red carbonate solution was heated 1 hour on the steam-bath. The solution was then acidified with dilute hydrochloric acid; ether extraction yielded 2.60 g. of dark red oil. This material was dissolved in 20 ml. of 3 *N* sodium hydroxide, and 20 ml. of 30% hydrogen peroxide was added in 5-ml. portions over a period of 20 min. The mixture was heated on the steam-bath for 2 hours, which caused the color to change from red to yellow. The mixture yielded, on cooling, acidification and extraction, 2.40 g. of product, which was methylated with an excess of diazomethane at 0° for 12 hours. After removing the excess diazomethane on the steam-bath, the residue was taken up in ether and washed four times with sodium carbonate to remove any acidic material. The ether solution yielded 2.06 g. of neutral material, which was distilled in a short-path still at 120–130° (5×10^{-5} mm.); the distillate weighed 1.5 g. and showed infrared bands characteristic of an ester containing a γ-lactone group (1770 and 1736 cm.$^{-1}$). The product was chromatographed on alumina, and 569 mg. of colorless oil was obtained by elution with 3:1 ligroin–ether.

Anal. Calcd. for $C_{17}H_{28}O_6$: C, 62.17; H, 8.59; O, 29.23; OCH_3, 18.91. Found: C, 62.17; H, 8.47; O, 29.03; OCH_3, 19.08, 19.28.

Preparation of the *p*-Bromoanilide of the Lactone-acid.—Two hundred milligrams of lactone-acid was refluxed for 45 min. with an excess of thionyl chloride. After removal of the unreacted thionyl chloride the residue was treated with 1.0 g. of *p*-bromoaniline in 30 ml. of benzene. The reaction mixture was warmed on the steam-bath for 2 min., then washed with water, dilute hydrochloric acid, sodium hydroxide and water again. The benzene solution was then dried and evaporated to dryness leaving 204 mg. of a dark oil. Chromatography of this oil over 5.0 g. of grade III alumina afforded 134 mg. of a pale yellow oil which was eluted with 1:1 ligroin–ether. The infrared spectrum of this substance was consistent with that of a lactone anilide, with principal absorption maxima at 3270 (secondary amide hydrogen), 1767 (γ-lactone) and 1685 cm.$^{-1}$ (anilide carbonyl).

Anal. Calcd. for $C_{22}H_{30}BrNO_5$: C, 56.41; H, 6.46. Found: C, 56.10; H, 6.56.

Product from Alkali Treatment of Ozonide.—Part of the neutral material (300 mg.) described in the first paragraph of the preceding section was heated for 1.5 hours in 15 ml. of 6 *N* sodium hydroxide. On cooling and acidification a yellow solid precipitated, which, after purification by sublimation at 100°, formed long colorless needles melting at 132.5–133° (in a sealed tube). The product showed infrared peaks at 3390, 1684 and 1613 cm.$^{-1}$; the ultraviolet absorption showed 215 (3.88) and 275 (3.81), which is in fair agreement with the reported spectral properties of monoenolic 1,2-cyclohexanediones.[18]

Anal. Calcd. for $C_{16}H_{26}O_5$: C, 64.40; H, 8.78; OCH_3, 11.4. Found: C, 64.28; H, 8.48; OCH_3, 11.7.

The preparation of this compound was not always reproducible, although it was obtained in several runs. Some samples had a composition agreeing better with $C_{16}H_{24}O_4$ or $C_{15}H_{22}O_4$.

Decomposition of the Ozonide with Zinc Dust.—The ozonide from the ozonolysis of 3.0 g. of the furfurylidene derivative was refluxed for 2 hours with 2.0 g. of zinc dust in 30 ml. of water under nitrogen. The aqueous solution was extracted with ethyl acetate, the extract was washed with dilute hydrochloric acid and was dried. The crude product obtained by evaporation of the solvent was taken up in 1:1 ligroin–ether and was chromatographed on alumina. Elution with ether–methanol mixtures and with methanol gave a reddish glass, which crystallized when triturated with ligroin. Recrystallization from ligroin–ether yielded 400 mg. of a white solid, m.p. 168–169°, with infrared absorption at 3390, 1748 and 1587 cm.$^{-1}$.

Anal. Calcd. for $C_{16}H_{28}O_8Al$: C, 51.2; H, 7.47; O, 34.16; Al, 7.2; mol. wt., (375)*n*. Found: C, 50.98; H, 7.6; O, 34.16; Al, 7.26; mol. wt., 3000-5000 (ebullioscopic, in benzene).

The above compound (380 mg.) was refluxed for 4 hours with 7.5 ml. of 6 *N* hydrochloric acid. Ether extraction yielded 235 mg. of red acidic oil.

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(17) J. R. Vaughan, Jr., and R. Osato, THIS JOURNAL, **74**, 676 (1952).

(18) E. G. Meek, J. H. Turnbull and W. Wilson, *J. Chem. Soc.*, 2891 (1953) (ultraviolet); R. W. LeFevre, F. Maramba and R. L. Werver, *ibid.*, 2496 (1953) (infrared).

Anal. Calcd. for $C_{16}H_{26}O_6$: C, 61.13; H, 8.34; mol. wt., 314. Found: C, 60.69; H, 7.54; mol. wt., 390 (in benzene).

Treatment of Tetrahydroketone I with Hydrochloric Acid.—The tetrahydroketone I (1.14 g.; $[\alpha]^{25}D$ $-94°$) in 40 ml. of 50–50 water–dioxane, which was 0.1 *N* in hydrochloric acid, was refluxed for 1.5 hours. The mixture was then poured into 75 ml. of water, extracted with ether three times and the extracts were dried. The crude product showed a band at 1730 cm.$^{-1}$. Chromatography of the product on alumina gave 530 mg. of yellow oil, which was eluted with 20:1 ether–methanol. No significant amount of material was eluted by less polar solvents. The undistilled product showed $[\alpha]^{25}D$ $-2.3°$; distillation in a short-path still did not remove the yellow color.

Anal. Calcd. for $C_{16}H_{28}O_4$: C, 67.57; H, 9.93; O, 22.49; OCH_3, 10.91. Found: C, 67.54; H, 9.63; O, 22.63; OCH_3, 9.34.

ROCHESTER, NEW YORK

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER]

The Chemistry of Fumagillin. VI. The Action of Aqueous Base on Alcohol I[1]

BY DEREK D. CHAPMAN AND D. STANLEY TARBELL

RECEIVED DECEMBER 3, 1957

Alcohol I, $C_{16}H_{26}O_4$, on being heated with sodium hydroxide in aqueous dioxane yields two monoöls which are isomeric with it, and a triol, $C_{16}H_{28}O_5$. Catalytic reduction of each of these leads to the corresponding dihydro compounds. The monools are regarded as being formed by attack of the hydroxyl group on the epoxide linkage of alcohol I, with formation of a new oxygen-containing ring and generation of a new hydroxyl group. The triol contains one ether ring which may be the original one present in alcohol I and a secondary hydroxyl group. The dihydromonoöls and the dihydrotriol are found to be stable to further rearrangement and numerous transformation products have been prepared and characterized.

The action of aqueous alcoholic sodium hydroxide on alcohol I, $C_{16}H_{26}O_4$, was found[2] to yield a product with an unsatisfactory analysis; when the presence of an epoxide ring in alcohol I was recognized[3,4] it was realized that aqueous ethanolic base might cause simultaneous hydrolysis and ethanolysis of the epoxide ring, with the formation of mixtures. In order to gain information about the action of base on alcohol I under conditions likely to lead to more homogeneous products, alcohol I has been refluxed with 5% sodium hydroxide in 50% aqueous dioxane. Separation of the resulting mixture by chromatography has yielded three products: two monoöls, A and C, $C_{16}H_{26}O_4$, which are isomers of alcohol I, and a triol, B, $C_{16}H_{28}O_5$, in a total yield of about 60%. A and B are crystalline, and all three products, A, B and C, no longer contain the epoxide ring which was present in their precursor, alcohol I, as shown by the thiosulfate test.[3,5] Each of these three products is reduced catalytically to form a crystalline dihydro derivative: monoöls A and C to form isomeric dihydromonoöls D and F, $C_{16}H_{28}O_4$, and triol B to the dihydrotriol E, $C_{16}H_{30}O_5$. Monoöl A was obtained in less than 5% yield.

The dihydrotriol E and the dihydromonoöl F were examined in detail to see what useful information could be gained about the structure of alcohol I.

Difficulty was experienced in obtaining consistent active hydrogen analyses on the triol B and its dihydro derivative E. In fact, several determinations indicated a value closer to four than three. However, acetylation of the dihydrotriol E under forcing conditions using isopropenyl acetate effected complete acetylation as demonstrated by the absence of hydroxyl absorption in the infrared spectrum of the product. An acetyl determination showed the presence of three acetyl groups. The dihydrotriol E could be regenerated by saponification with aqueous alcoholic potassium hydroxide solution.

Acetylation by heating with acetic anhydride and pyridine on the steam-bath afforded a crystalline monoacetate. This indicated a difference in reactivity between the hydroxyl groups in the dihydrotriol and further evidence of this was obtained by oxidation to a crystalline monoketone G using the chromic oxide–pyridine reagent. Catalytic reduction of this ketone regenerated the dihydrotriol E along with a crystalline isomer H, m.p. 160°, which is presumably an epimer of E. This proves that no rearrangement has occurred during the oxidation of the secondary hydroxyl group with the chromic oxide–pyridine reagent; another example proving the same thing is given in an accompanying paper[6] dealing with the oxidation of tetrahydroalcohol Iab.

The ketone G forms a crystalline monofurfurylidene derivative, showing the presence of a $-\overset{\overset{\displaystyle O}{\|}}{C}CH_2-$ grouping. The presence of this group is also supported by a band at 1410 cm.$^{-1}$ in the infrared spectrum[7]; G is not oxidized by selenium dioxide in refluxing dioxane.

The dihydrotriol E is unaffected by boiling 5% sulfuric acid, and hence it contains no readily dehydrated hydroxyl groups; it has lost the striking tendency for rearrangement and hydration shown by alcohol I under acidic conditions.[8] Oxidation of E with acid permanganate yielded a neutral ketonic fraction, which could not be characterized further, and isocaproic acid, which was identified by vapor phase chromatography and by a solid derivative. The dihydrotriol E thus contains the

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[1] Aided by a grant from the National Institutes of Health.

[2] D. S. Tarbell, *et al.*, THIS JOURNAL, **77**, 5610 (1955).

[3] J. M. Ross, D. S. Tarbell, W. C. Lovett and A. D. Cross, *ibid.*, **78**, 4675 (1956).

[4] J. K. Landquist, *J. Chem. Soc.*, 4237 (1956).

[5] W. C. J. Ross, *ibid.*, 2257 (1950).

[6] J. G. McNally, Jr., and D. S. Tarbell, THIS JOURNAL, **80**, 3676 (1958).

[7] R. J. Jones and A. R. H. Cole, *ibid.*, **74**, 5648 (1952).

[8] A. D. Cross and D. S. Tarbell, *ibid.*, **80**, 3682 (1958).