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 monoöls 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 $-\overset{\overset{O}{\|}}{C}CH_2-$ 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

(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).

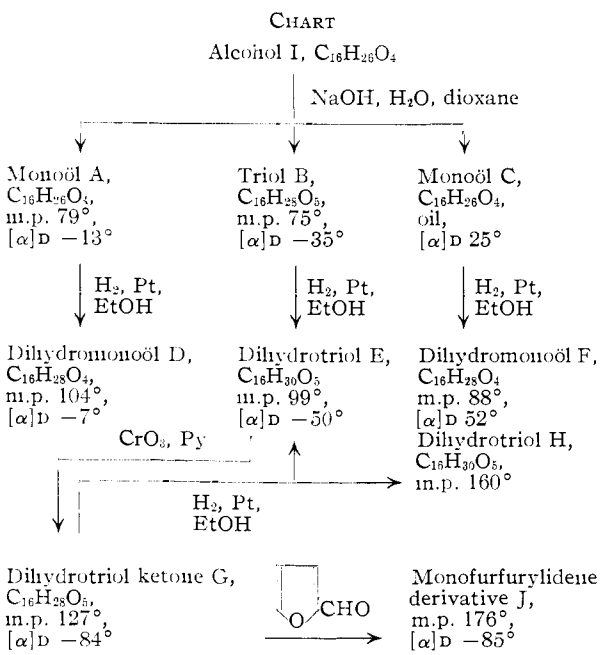
(6) J. G. McNally, Jr., and D. S. Tarbell, THIS JOURNAL, **80**, 3676 (1958).

(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).

side chain $-CHCH_2CH_2CH(CH_3)_2$ known to be present in tetrahydroalcohol Iab.

The empirical formula of the triol B and the fact that it contains a carbon–carbon double bond, require that it must contain an ether ring. If this is the original ether present in alchol I, then hydration of the epoxide must have been followed by some rearrangement stage because the dihydrotriol E is not oxidized by periodate and hence probably does not contain a 1,2-glycol function.[9]



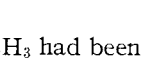
The double bond in alcohol I appears to play some part in the formation of the triol B; this was shown by treating dihydroalcohol Ia, which contains the epoxide but not the double bond, with base under the same conditions as for alcohol I. No dihydrotriol E was formed and the only product apart from some non-crystalline material was the dihydromonoöl F.

Turning now to the monoöls A and C, $C_{16}H_{26}O_4$, the information about them rests mainly on studies on the dihydro compound F, derived from C, because of the limited quantity of A available.

Compound F shows one active hydrogen, and forms a liquid monoacetate; it is recovered unchanged after treatment with the chromic oxide–pyridine reagent, and hence the hydroxyl group is considered to be tertiary. It yields isocaproic acid on oxidation with acid permanganate, as does the dihydrotriol E, and hence contains the same side-chain. In contrast to tetrahydroalcohol Iab,[3] it is unaffected by lithium aluminum hydride in refluxing tetrahydrofuran, and hence the oxygen-containing rings are not hydrogenolyzed.

Compound F is not a hemiacetal or hemiketal, because its distribution ratio between ether and aqueous buffers was unchanged by varying the *p*H of the buffers from 4 to 12; a hemiacetal would be appreciably acidic, and should be more soluble in the buffers of higher *p*H.[10]

Additional evidence for the absence of a hemiketal grouping in the dihydromonoöl F was obtained by an examination of the infrared spectrum of its monoacetate. The carbonyl frequency occurred at 1736 cm.$^{-1}$ whereas if the grouping



had been present, the frequency would have been raised to 1760–1770 cm.$^{-1}$.[11] The infrared spectrum of the acetate of dihydromonoöl D was also incompatible with the presence of this grouping.

The isomerization of alcohol I to the two monoöls by aqueous base is most simply regarded as involving attack by the alkoxide ion, derived from the secondary hydroxyl group of alcohol I, on the epoxide ring, to form a new oxygen-containing ring, presumably 5- or 6-membered, with the concomitant generation of a new hydroxyl group. The two monoöls may be position isomers or stereoisomers.

A close analogy to the process postulated here for the isomerization of alcohol I is the isomerization of scopine to scopoline by aqueous base[12]

In view of the susceptibility of alcohol I to basic rearrangement and hydration, it might be considered that alcohol I itself represents an isomerization product of the original alcohol moiety of fumagillin formed during the basic hydrolysis of fumagillin. This possibility cannot be ruled out completely, but it is rendered highly unlikely by an experiment in which fumagillin was hydrolyzed at room temperature in an aqueous borate buffer of *p*H 10; crystalline alcohol I was isolated in good yield, and was the same as the material obtained by the usual hydrolysis procedure at higher *p*H.

Experimental[13,14]

Action of Alkali on Alcohol I.—Alcohol I (11 g.) was heated under gentle reflux with dioxane (80 ml.) and 10% sodium hydroxide solution (80 ml.) in an atmosphere of nitrogen for 4 hours. Water (150 ml.) was added and the solution concentrated to 100 ml. After being cooled, the solution was extracted with three 200-ml. portions of ether. The extract was washed with water and dried; removal of the ether gave a yellow oil (9.4 g.) which was dissolved in ether and adsorbed on alumina (250 g.). Elution with ether–methanol (200:1) gave levorotatory material (1.12 g.), $[\alpha]_D$ −13°. These first fractions were rechromatographed on alumina (24 g.). Elution with ether–methanol (200:1) yielded 0.46 g. of crystalline material. Recrystallization from petroleum ether gave the **monoöl A** as colorless prisms, m.p. 78.9–79.6°.

(9) Examples of 1,2-glycols are known, usually in bridged ring systems, not oxidized by periodate or lead tetraacetate: R. J. Dimler, H. A. Davis and G. E. Hilbert, THIS JOURNAL, **68**, 1377 (1946); B. H. Alexander, R. J. Dimler and C. L. Mehltretter, *ibid.*, **73**, 4658 (1951).

(10) We are indebted to Professor Henry Rapoport for suggesting this procedure to us.

(11) N. J. Leonard, *et al.*, THIS JOURNAL, **79**, 2642 (1957).

(12) R. Willstätter and E. Berner, *Ber.*, **56**, 1079 (1923).

(13) All m.p.'s are corrected. Rotations and ultraviolet spectra are measured in 95% ethanol. Chromatograms were carried out as indicated in ref. 3, footnote 19. Mr. Harold Shaub rendered valuable technical assistance.

(14) We are greatly indebted to Mr. E. F. Shelberg and his staff, of Abbott Laboratories, for all of the microanalyses reported here.

Anal. Calcd. for $C_{16}H_{26}O_4$: C, 68.06; H, 9.28; O, 22.67; OCH_3, 10.99; active hydrogen, 1.00. Found: C, 68.04; H, 9.25; O, 22.90; OCH_3, 11.03; active hydrogen, 0.95.

Further elution of the main column with the same solvent mixture yielded the **triol B** (1.3 g.) as a viscous oil, $[\alpha]D$ −34.9° (0.70). Crystallization from petroleum ether afforded needles, m.p. 74.2–75.1°.

Anal. Calcd. for $C_{16}H_{28}O_5$: C, 63.97; H, 9.40; O, 26.63; OCH_3, 10.30; active hydrogen, 3.00. Found: C, 63.96; H, 9.37; O, 26.68; OCH_3 10.41; active hydrogen, 3.96.

Elution with more polar solvent mixtures gave fractions containing the **monoöl C**, totaling 5.4 g., $[\alpha]D$ −7.1 to 25°. A fraction (0.84 g.) $[\alpha]D$ 25° (0.65) was distilled for analysis, b.p. 130–140° (10^{-4} mm.).

Anal. Calcd. for $C_{16}H_{26}O_4$: C, 68.06; H, 9.28; O, 22.67; OCH_3, 10.99; active hydrogen, 1.00 Found: C, 67.53; H, 9.51; O, 23.56; OCH_3, 10.97; active hydrogen, 1.32.

The three products from the alkali reaction gave negative tests for the presence of an epoxide grouping.[5]

The Dihydromonoöl D.—Monoöl A (0.25 g.) in ethanol was shaken over pre-reduced platinum until the theoretical amount of hydrogen for one molar equivalent had been absorbed. The product was crystallized from petroleum ether to give D as colorless prisms, m.p. 104.0–104.2°, $[\alpha]D$ −7.3° (0.68).

Anal. Calcd. for $C_{16}H_{28}O_4$: C, 67.57; H, 9.93; O, 22.49; OCH_3, 10.90; active hydrogen, 1.00. Found: C, 67.53; H, 9.73; O, 22.25; OCH_3, 10.15; active hydrogen, 1.05.

The Dihydrotriol E.—Triol B (1.1 g.) was reduced as in the previous experiment. The product, a viscous oil (1.1 g.), was adsorbed on alumina (30 g.). Elution with ether–methanol (200:1) afforded the **dihydro compound E** (0.74 g.) as needles, m.p. 98.4–99.2°. Recrystallization from petroleum ether raised the m.p. to 98.9–99.5°, $[\alpha]D$ −50.0° (0.81). The dihydrotriol E was unaffected by boiling 5% sulfuric acid.

Anal. Calcd. for $C_{16}H_{30}O_5$: C, 63.54; H, 10.00; O, 26.46; OCH_3, 10.2; active hydrogen, 3.00. Found: C, 63.54; H, 9.99; O, 26.33; OCH_3, 9.57; active hydrogen, 3.0, 3.2.

The Dihydromonoöl F.—The dextrorotatory fractions $[\alpha]D$ >15° from the alcohol I–sodium hydroxide reaction (2.79 g.) were shaken with prereduced platinum until one equivalent of hydrogen had been absorbed. The viscous oil (2.76 g.) was dissolved in ether and chromatographed on alumina (52 g.). Elution with ether–methanol (200:1 and 100:1) afforded fractions which slowly crystallized. Recrystallization from petroleum ether gave the **dihydromonoöl F** (1.40 g.) as colorless prisms, m.p. 87.4–88.0°, $[\alpha]D$ 51.7°.

Anal. Calcd. for $C_{16}H_{28}O_4$: C, 67.57; H, 9.93; O, 22.49; OCH_3, 10.90; active hydrogen, 1.00. Found: C, 67.61; H, 9.94; O, 22.57; OCH_3, 11.02; active hydrogen, 0.97.

In later preparations of the dihydro compounds, it was found to be more convenient to reduce the crude product from the alcohol I–sodium hydroxide reaction and then to carry out a chromatographic separation, as it was easier to follow the course of the separation of the dihydro compounds because all three were crystalline. Even so, the separation of the dihydrotriol E from the dihydromonoöl F was not too efficient, and rechromatography of the intermediate fractions was often necessary. Further chromatography was also necessary to obtain dihydromonoöl F free from an oil with which it was contaminated.

Action of Alkali on Dihydroalcohol Ia.—Dihydroalcohol Ia[3] (3.58 g.) in dioxane (25 ml.) was heated under gentle reflux with 10% aqueous sodium hydroxide (25 ml.) under nitrogen for 4 hours. The product (3.4 g.) was isolated as described for the corresponding reaction of alcohol I, and adsorbed on alumina (70 g.). Elution with ether–methanol (200:1) yielded an oil (2.8 g.) from which the crude dihydromonoöl F (1.5 g.) gradually crystallized. Recrystallization from petroleum ether afforded pure dihydromonoöl F, m.p. and mixed m.p. 87.2–88.0°.

Oxidation of the Dihydrotriol E with Chromium Trioxide in Pyridine.[15]—Dihydrotriol E (1.5 g.) dissolved in pyridine (15 ml.) was added to a slurry of chromium trioxide (1.0 g.) in pyridine and the mixture allowed to stand at room temperature for 2.5 days with occasional shaking. The reaction mixture was then poured into water and extracted with four 300-ml. portions of ether. The ethereal solution was washed thoroughly with dilute hydrochloric acid to remove pyridine, followed by saturated sodium bicarbonate solution. Concentration of the dried ethereal solution afforded a yellow oil (1.4 g.) which on crystallization from hexane yielded colorless prisms of the **ketone G** (0.75 g.), m.p. 126.2–127.1°, $[\alpha]D$ −83° (0.72). The infrared spectrum (potassium bromide disk) showed bands at 3390, 3356 (hydroxyl), 1730 (carbonyl), 1410 cm.$^{-1}$ ($-CH_2CO$); the ultraviolet spectrum showed λ_{max} 289 mμ, ε 34.

Anal. Calcd. for $C_{16}H_{28}O_5$: C, 63.97; H, 9.40; O, 26.63; OCH_3, 10.30; active hydrogen, 2.00 (1.0 consumed). Found: C, 63.99; H, 9.37; O, 26.52; OCH_3, 10.35; active hydrogen, 2.96 (0.99 consumed).

Catalytic Reduction of the $C_{16}H_{28}O_5$ Ketone G.—Ketone G (0.19 g.) was hydrogenated over platinum in the normal manner. The uptake of hydrogen was approximately the theoretical. Crystallization of the product from hexane yielded a crop of crystals melting over the range 148–153°. Repeated recrystallization from hexane gave the **dihydrotriol H** as needles, m.p. 159.4–160.2° with softening at 156°.

Anal. Calcd. for $C_{16}H_{30}O_5$: C, 63.54; H, 10.00; O, 26.46; active hydrogen, 3.00. Found: C, 63.44; H, 10.03; O, 26.26; active hydrogen, 3.50.

Recrystallization from petroleum ether of the material obtained from the mother liquors yielded the dihydrotriol E, m.p. and mixed m.p. 97–99°.

The Monofurfurylidene Derivative of the Ketone G.—The ketone G (0.9 g.) was dissolved in ethanol (2 ml.), treated with furfural (0.6 g.) and 2% sodium hydroxide (3.5 ml.). After standing for 10 minutes the solution became cloudy and crystals separated. When separation was complete the product was filtered off and washed with aqueous ethanol. Crystallization from ethanol yielded the **monofurfurylidene derivative** (0.85 g.) as pale yellow prisms, m.p. 179.4–179.8°, $[\alpha]D$ −85° (0.60). The infrared spectrum (potassium bromide disk) showed bands at 1688, 1602, 1540, 1469 and 838 cm.$^{-1}$; the ultraviolet spectrum showed λ_{max} 222 mμ, ε 18,676 and 320 mμ, ε 12,726.

Anal. Calcd. for $C_{21}H_{30}O_6$: C, 66.64; H, 8.00; O, 25.36; OCH_3, 8.20; active hydrogen, 2.00 (1 consumed). Found: C, 66.54; H, 8.15; O, 25.24; OCH_3, 8.61; active hydrogen, 1.45 (0.88 consumed).

Acetylation of the Dihydrotriol E.—Dihydrotriol E (1.0 g.) was heated on the steam-bath with acetic anhydride (10 ml.) and pyridine (4 ml.) for 4 hours. The reaction mixture was cooled, poured into water and allowed to stand overnight. The resulting solution was extracted with ether and the ethereal extract washed with dilute hydrochloric acid, sodium bicarbonate solution and finally with water. Evaporation of the dried ethereal solution yielded a yellow oil (1.2 g.) which was chromatographed on neutral alumina (30 g.). Elution with mixtures of petroleum ether–ether up to and including 1:6 afforded the **monoacetate** (0.75 g.) as long needles, m.p. 112.2–112.8°, which was raised to 114.2–114.7° on recrystallization from petroleum ether. The infrared spectrum (potassium bromide disk) showed bands at 3367 (hydroxyl), 1733 (ester carbonyl) and 1254 cm.$^{-1}$ (C–O of acetate).

Anal. Calcd. for $C_{18}H_{32}O_6$: C, 62.76; H, 9.36; O, 27.87; OCH_3, 9.01; Ac, 12.48; active hydrogen, 2.00 (2 consumed). Found: C, 62.87; H, 9.29; O, 27.87; OCH_3, 9.14; Ac, 12.72; active hydrogen, 2.11 (2.1 consumed).

Saponification of the acetate yielded the crystalline dihydrotriol E, identified by mixed m.p.

Vigorous Acetylation of the Dihydrotriol E.—Dihydrotriol E (1.0 g.) was heated under reflux with isopropenyl acetate (2.5 g.) and *p*-toluenesulfonic acid (catalytic quantity) in dry benzene (25 ml.) for 65 hours. The solvent was removed and the residue was dissolved in petroleum ether and chromatographed on neutral alumina (20 g.). Elution with petroleum ether yielded the **triacetate** (480 mg.) which on recrystallization from aqueous ethanol melted at 113.0–113.9°. The infrared spectrum showed bands at 1740–1710 cm.$^{-1}$ (broad) and 1235 cm.$^{-1}$. There was no band attributable to hydroxyl.

(15) G. I. Poos, L. H. Sarett, *et al.*, THIS JOURNAL, **75**, 425 (1953).

Anal. Calcd. for $C_{22}H_{36}O_8$: C, 61.66; H, 8.47; O, 29.87; OCH_3, 7.24; Ac, 30.1; active hydrogen, 0 (6 consumed). Found: C, 61.33; H, 8.32; O, 30.62; OCH_3, 6.96; Ac, 29.1; active hydrogen, 0.9 (5.8 consumed).

Further elution of the column with mixtures of petroleum ether and ether gave incompletely acetylated material.

Oxidation of the Dihydrotriol E by Acid Potassium Permanganate.—Dihydrotriol E (1.0 g.) was suspended in 10% sulfuric acid (20 ml.) and heated on a steam-bath. Potassium permanganate solution (3%) was added slowly and with stirring until a pink color remained. The reaction mixture was treated with sodium bisulfite to dissolve the manganese dioxide, and was then continuously extracted with ether for two days. The ether extract was washed with sodium bicarbonate solution and then dried. Removal of the ether afforded a colorless oil (0.04 g.) which showed the following bands in its infrared spectrum: 3521, 3413, 1724 and 1695 cm.$^{-1}$.

The sodium bicarbonate extract was neutralized with hydrochloric acid and extracted with ether. The acidic fraction obtained from the dried ether extract was examined by means of vapor phase chromatography and shown to consist largely of a component which had the same retention time as isocaproic acid. The *p*-bromphenacyl ester was prepared in the usual manner and its m.p. was undepressed on admixture with an authentic sample of the *p*-bromophenacyl ester of isocaproic acid.[16]

Oxidation of the Dihydromonoöl F with Acid Potassium Permanganate.—Dihydromonoöl F (2 g.), dissolved in 10% sulfuric acid (40 ml.) and acetone (20 ml.), was treated with potassium permanganate solution (3%) at room temperature with stirring, until the solution remained pink. The reaction mixture was worked up as described for the oxidation of the dihydrotriol. The neutral product consisted of a yellow mobile oil (1.05 g.), which was chromatographed on neutral alumina (25 g.) Elution with mixtures of petroleum ether and ether yielded a colorless oil which showed these bands in its infrared spectrum: 3546, 3401, 1733, 1712 and 1656 cm.$^{-1}$.

The acidic fraction was examined by vapor phase chromatography and the results indicated that the main product was again isocaproic acid. Confirmation was obtained by comparing the *p*-bromophenacyl ester with an authentic sample.

Both the dihydromonoöl D and the dihydromonoöl F were unaffected by chromium trioxide under the Sarett conditions. The dihydromonoöl F was recovered unchanged after boiling with 20% sulfuric acid for 4 hours, and also after refluxing with lithium aluminum hydride for 24 hours in tetrahydrofuran.

Acetylation of Dihydromonoöl D.—Dihydromonoöl D (0.46 g.) was heated with acetic anhydride (6 ml.) and pyridine (2 ml.) on the steam-bath for 10 hours. The product was worked up as described for the acetylation of the dihydrotriol E. The yield of crude material was 0.45 g. which was dissolved in petroleum ether and chromatographed on neutral alumina (10 g.). Elution with petroleum ether afforded the **monoacetate** (0.12 g.) as a colorless oil. The analytical sample was purified by distillation, b.p. 100–110° (10^{-3} mm.). The infrared spectrum (in chloroform) showed a strong band at 1740 cm.$^{-1}$ (carbonyl).

Anal. Calcd. for $C_{18}H_{30}O_5$: C, 66.23; H, 9.27; O, 24.51; OCH_3, 9.51; active hydrogen, 0 (2 consumed). Found: C, 66.58; H, 9.59; O, 24.40; OCH_3, 9.23; active hydrogen, 0 (2.4 consumed).

Further elution of the column with mixtures of petroleum ether–ether and finally with ether yielded dihydromonoöl D (0.21 g.), m.p. and mixed m.p. 103–104°.

Acetylation of Dihydromonoöl F.—Dihydromonoöl F (0.5 g.) was acetylated as described in the previous experiment. The yield was 0.47 g. of pale yellow oil which was dissolved in petroleum ether and adsorbed onto neutral alumina (10 g.). Elution with petroleum ether–ether (1:1) gave the **monoacetate** (0.23 g.). Distillation under reduced pressure yielded the analytical sample as an oil, b.p. 100–110° (10^{-3} mm.).

Anal. Found: C, 65.99; H, 9.22; O, 24.42; OCH_3, 9.48; active hydrogen, 0 (2.2 consumed).

Further elution with ether–methanol (100:1) afforded dihydromonoöl F, m.p. and mixed m.p. 87.5–88.0°.

Saponification of the acetate with dilute sodium hydroxide solution regenerated the dihydromonoöl F.

The infrared spectrum (in chloroform) showed a band at 1736 cm.$^{-1}$ (ester).

Saponification of Fumagillin in Borate Buffer.—Fumagillin (7 g.) was stirred under nitrogen with 0.1 *M* boric acid (500 ml.) and 0.2 *N* sodium hydroxide (500 ml.) for 6 hours. The reaction mixture was extracted with ether. Evaporation of the dried ether extract yielded a pale yellow oil (2 g.) which was dissolved in a small volume of petroleum ether. Alcohol I crystallized as clumps of prisms, m.p. and mixed m.p. 55.0–56.0°.

ROCHESTER, N. Y.

(16) W. L. Judefind and E. E. Reid, THIS JOURNAL, **42**, 1048 (1920).

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

The Chemistry of Fumagillin. VII. Transformation Products Derived from Alcohol I by Action of Acids[1]

BY ALEXANDER D. CROSS AND D. STANLEY TARBELL[2]

RECEIVED DECEMBER 3, 1957

Alcohol I ($C_{16}H_{26}O_4$) is hydrated by dilute oxalic or sulfuric acid to yield several products, all diols or triols with no carbonyl groups. Other hydration products include a crystalline diol, alcohol IV, $C_{16}H_{28}O_5$, which contains two inert oxygen rings. Acetylation, oxidation and reduction experiments on alcohol-IV are described which illustrate the nature of the oxygen functions. A crystalline ketone, $C_{16}H_{26}O_5$, one of two obtained from alcohol-IV by chromic acid oxidation, was shown to contain one free methylene group adjacent to the carbonyl, by preparation of a monofurfurylidene derivative. The action of selenium on alcohol IV and of acid on dihydroalcohol Ia are also reported.

The preceding paper[3] describes the products obtained by the action of aqueous alkali on alcohol I, the alcohol moiety of fumagillin. The present paper shows that aqueous acids, particularly oxalic acid and sulfuric acid, convert alcohol I into a complicated mixture of isomerization and hydration products.

The demonstration of the presence of an epoxide group in alcohol I[4,5] and of an isohexenyl side-chain with an ether linkage on the fifth carbon suggested that the element A was present in alcohol I.[4–7] It should be possible to confirm this partial

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

(2) To whom inquiries regarding this paper should be addressed.

(3) D. D. Chapman and D. S. Tarbell, THIS JOURNAL, **80**, 3679 (1958).

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

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

(6) J. R. Schenck, M. P. Hargie and A. Isarasena, THIS JOURNAL, **77**, 5606 (1955).

(7) D. S. Tarbell, *et al.*, *ibid.*, **77**, 5610 (1955).