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.

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(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

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(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).

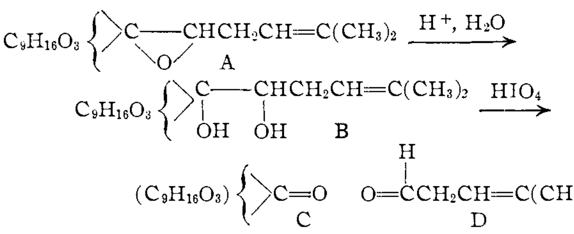
(4) J. M. Ross, D. S. Tarbell, W. E. Lovett and A. D. Cross, *ibid.*, **78**, 4675 (1956).

(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).

structure and perhaps to gain further information about the rest of the molecule by hydration of the epoxide to the diol B, followed by periodate cleavage to yield the methylpentenal D and the ten-carbon fragment C. Landquist[5] reported some success along these lines; the hydration was carried out by treating alcohol I with 0.02 *N* sulfuric acid followed by periodate oxidation of the products, when acetone and a small amount of a six-carbon aldehyde were isolated as their respective dinitrophenylhydrazones. He did not establish the structure of the aldehyde by synthesis, but from the analysis it seemed likely to be 4-methylpent-3-enal. However, Julia and Tchernoff[8a] have recently reported the synthesis of 4-methylpent-3-enal and the melting point of the dinitrophenylhydrazone differs from that of the degradation product obtained by Landquist. These workers proved the structure of their product by hydrogenation to the known 4-methylpentanal and also by isomerization to the known 4-methylpent-2-enal.[8b] The ultraviolet spectral data were also in accord with the assigned structures. Prior to the synthesis of this aldehyde we had investigated the action of acids on alcohol I in the hope of obtaining a glycol which could be cleaved by periodate.[9] In a previous paper we described an experiment using a catalytic quantity of perchloric acid in which the resulting product consumed 70% of the theoretical amount of periodate.[4] In a later experiment using 2% oxalic acid in aqueous dioxane, a triol was obtained, which was oxidized by periodate to give, in good yield, an aldehyde whose dinitrophenylhydrazone corresponded in properties to that described by Landquist.[5] This material was lost before it could be characterized, and repeated efforts to obtain it again, using a variety of acidic conditions for the hydration reactions, including those described by Landquist,[5] have been unsuccessful. A number of distinct hydration products of alcohol I with the composition $C_{16}H_{28}O_5$ have been obtained, but none of these is oxidized by periodate. One of them, alcohol-IV, $C_{16}H_{28}O_5$, is crystalline and readily available, so that its properties are of importance to the general structural problem. None of the hydration products shows any carbonyl absorption in its infrared spectrum.



We observed that, as in Landquist's experiments, the hydration product which can be cleaved by periodate to furnish the required aldehyde, gives a carbon analysis considerably lower than those obtained for the $C_{16}H_{28}O_5$ hydration products. Indeed, our triol has analysis in good agreement with the formula $C_{15}H_{28}O_5$.

One of the non-crystalline isomers of alcohol IV afforded both a mono- and a diacetate, neither being crystalline. Alcohol IV forms a crystalline monoacetate, m.p. 113°, and gives an oily diacetate under forcing conditions of acetylation. Saponification of the diacetate affords alcohol IV again. The diacetate shows an infrared band at 1727 cm.$^{-1}$ (shoulder at 1739 cm.$^{-1}$), frequencies incompatible with the existence of a hemiacetal link in alcohol IV.[3] Alcohol IV is recovered unchanged after treatment with hydrogen and platinum in ethanol or acetic acid, and hence has lost the double bond present in alcohol I, a conclusion supported by the complete transparency down to 200 mμ of the ultraviolet spectrum of alcohol IV. Since it has added the elements of water, as compared to alcohol I, and still contains only two hydroxyl groups, alcohol IV must possess an oxygen-containing ring, in whose formation the side-chain double bond has been involved. A strong band at 831 cm.$^{-1}$ in the infrared spectrum, at first thought to be due to a trisubstituted double bond, might well be assignable to the tertiary ether grouping,[10] $-\mathrm{CH}\underset{\displaystyle \mathrm{O}}{\underset{|}{\mathrm{C}}}(\mathrm{CH_3})_2$.

Alcohol IV shows no reaction with periodic acid, with Fehling and Tollens reagents, with lithium aluminum hydride in refluxing tetrahydrofuran or with refluxing 5% aqueous alkali. Marked stability toward vigorous reducing conditions is in strong contrast to the behavior of alcohol I, dihydroalcohol Ib and tetrahydroalcohol Iab.[4] It is concluded that the ether link common to these three alcohols is either non-existent in alcohol IV or its environment has changed sufficiently to confer upon it the observed inertness. The former conclusion infers formation of two, rather than one, new ether rings in the acid-catalyzed rearrangement of alcohol I. Alcohol IV therefore appears to be a very stable compound and hence resembles the basic hydration products[3] of alcohol I.

Oxidation of alcohol IV with chromic oxide–acetic acid gave a crystalline ketone, $C_{16}H_{26}O_5$, m.p. 114°, together with a non-crystalline isomeric ketone. The former was obtained in greater yield by chromic oxide–pyridine oxidation, when it was accompanied solely by a trace of a γ-lactone. A monofurfurylidene derivative, m.p. 157°, of alcohol IV ketone was prepared, showing the presence of the grouping $-CH_2CO-$ in the ketone. An infrared band at 1408 cm.$^{-1}$ for the ketone, which is absent in the spectrum of alcohol IV, is in agreement with an α-methylene ketone.[3] Hydrogenation of the ketone over platinum catalyst yielded solely alcohol IV.[11]

The first product, $[\alpha]_D$ 1.0°, from treatment of alcohol I with 0.5% oxalic acid, was subjected to chromic oxide–pyridine oxidation. A small amount of a crystalline isomer of alcohol I, m.p. 129.5°, was separated from the oxidation products, the main components being ketone and a γ-lactone.

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(8) (a) M. Julia and G. Tchernoff, *Compt. rend.*, **245**, 1248 (1957); (b) H. Schinz and A. Rossi, *Helv. Chim. Acta*, **31**, 1953 (1948).

(9) Continuing some unpublished experiments of Dr. J. M. Ross.

(10) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Methuen, London, 1954, pp. 100 and 106.

(11) This hydrogenation therefore resembles that of tetrahydroalcohol Iab ketone which affords solely tetrahydroalcohol Iab.[12] and differs from hydrogenation of the ketone of dihydrotriol E[3] which gives dihydrotriol E and its epimer.

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

These experiments on acid treatment of alcohol-I have not provided clear-cut support for the presence of the side-chain structure A, because of the great tendency of alcohol I to undergo rearrangement under hydrating conditions. However, we consider that A is a good working hypothesis for the side-chain structure.

The action of dilute sulfuric acid in aqueous dioxane on dihydroalcohol Ia, which contains the epoxide ring but not the side-chain double bond of alcohol I,[4] yielded two non-crystalline products whose analyses agreed with the composition $C_{16}H_{30}O_5$, and another product with a higher carbon content.

Dehydrogenation experiments on alcohol IV yielded materials which appeared, from their spectral properties, to be mixtures of various alkyl substituted benzenes. Gas phase chromatography showed the presence of six to eight materials, and the prospects of identifying the components of the mixture were not promising.

Experimental[13]

Action of Acids on Alcohol I. (a) 2% Oxalic Acid Solution.—A solution of alcohol I (6.83 g., $[\alpha]_D$ −56°) in purified dioxane (100 ml.) was boiled gently under reflux together with 5% aqueous oxalic acid (60 ml.) during 8 hours. The reaction solution was neutralized with sodium bicarbonate, diluted to double its volume, and the majority of the dioxane removed as a constant boiling mixture by distillation. Extraction of the aqueous oily suspension with four 100-ml. portions of chloroform gave, on evaporation of the dried extracts, a yellow oil (5.34 g.) which showed a negative reaction for epoxide.[14] The oil was adsorbed onto alumina (125 g.) and elution with 50:1 ether–methanol afforded a **C_{15}-diol** (2.10 g.), $[\alpha]_D$ −12.1°.

Anal. Calcd. for $C_{15}H_{28}O_5$: C, 62.47; H, 9.79; O, 27.74; OCH_3, 10.77; active hydrogen, 2.00. Found: C, 62.13; H, 9.65; O, 27.92; OCH_3, 10.05; active hydrogen, 1.91.

Further elution with 10:1 ether–methanol yielded a **C_{15}-triol** (2.11 g.), $[\alpha]_D$ −0.6°.

Anal. Calcd. for $C_{15}H_{28}O_5$ (see above): Found: C, 62.13; H, 9.21; O, 27.90; OCH_3, 9.84; active hydrogen, 2.83.

(b) 5% Sulfuric Acid.—Aqueous 10% sulfuric acid (200 ml.) was added to a solution of crystalline alcohol I (20.0 g.) in dioxane (200 ml.) and the mixture boiled under reflux with vigorous stirring in an atmosphere of nitrogen. A pink color developed immediately, but faded and the solution became yellow, finally changing to light brown. The solution was neutralized, diluted, concentrated and extracted as described above for the oxalic acid reaction. A yellow oil (17.73 g.) was obtained and chromatographed on alumina (350 g.). Oils eluted with ether and from earlier fractions in development with 200:1 ether–methanol were retained. Later, 200:1 and the 100:1 and 50:1 ether–methanol fractions eluted crystalline **alcohol IV**, recrystallized from *n*-heptane as prisms or swords, m.p. 122.9–123.5° (6.2 g.), $[\alpha]_D$ −18.6°.

Anal. Calcd. for $C_{16}H_{28}O_5$: C, 63.97; H, 9.40; O, 26.63; OCH_3, 10.33; active hydrogen, 2.0; 1 C–CH_3, 5.00. Found: C, 64.21; H, 9.47; O, 26.49; OCH_3, 10.35; active hydrogen, 1.96; C–CH_3, 10.91.

The mother liquors were combined with the oils retained earlier and rechromatographed on alumina (160 g.). Elution with ether gave a **diol**, $[\alpha]_D$ −22.3°, which was purified for analysis by high vacuum distillation.

Anal. Calcd. for $C_{16}H_{28}O_5$ (see above): Found: C, 64.03; H, 9.34; O, 26.57; active hydrogen, 2.17.

Another **diol**, $[\alpha]_D$ 41.4°, was eluted with 200:1 ether–methanol. The analytical sample was purified by distillation.

Anal. Calcd. for $C_{16}H_{28}O_5$ (see above): Found: C, 63.16; H, 9.62; O, 26.49; active hydrogen, 1.82.

Elution with more polar solvents removed a little more crystalline alcohol IV.

Rechromatography was necessary to obtain a complete separation of the two oily diols. Other oils with small positive or negative rotations were removed from the first column, after alcohol IV, as the percentage of methanol in the eluent increased, but no single component was isolable.

These experimental results were largely reproducible, the only variations being in the quantities of the levo- and dextrorotary oily diols obtained.

Alcohol IV gave negative reactions with periodate, and in Fehling and Tollens tests.

Oxidation of the C_{15}-Triol with Periodate.—The C_{15}-triol (1.206 g.) was dissolved in purified ethanol (50 ml., distilled from sodium ethoxide), potassium metaperiodate (1.92 g., 2 equiv. oxygen) and water (15 ml.) were added, and the whole was acidified with 2 *N* sulfuric acid. A stream of nitrogen was passed through the stirred, refluxing solution and into a saturated solution of 2,4-dinitrophenylhydrazine in 2 *N* hydrochloric acid. After 10 hours no further precipitation of hydrazones occurred on replacing the 2,4-dinitrophenylhydrazine hydrochloride solution with a fresh solution of the same reagent. The heavy precipitate was filtered off, washed several times with dilute hydrochloric acid and with water, and dried (665 mg.). Some purification of the material was achieved by chromatography on silica, eluting with various petroleum ether–ether mixtures. Once recrystallized from 95% ethanol as yellow needles (400 mg.) the 2,4-dinitrophenylhydrazone had m.p. 158–160° and ultraviolet spectrum 356 (4.40).[15] Concentration of the ethanolic mother liquors afforded orange crystals which showed signs of melting at 125° but melted largely at 156–159°. The existence of acetone 2,4-dinitrophenylhydrazone in the reaction products caught in the trap solution was demonstrated by extraction of that solution with benzene, and chromatography on paper using the heptane–methanol development system.[16] A known spot of acetone 2,4-dinitrophenylhydrazone was run parallel to establish the identity of the minor product.

The periodate oxidation reaction solution was treated with sodium arsenite (0.5 g.) and shaken; when the dark brown solution became pale yellow, water (50 ml.) was added, most of the ethanol removed by vacuum distillation and a pale yellow oil extracted from the aqueous solution with ether. The oil was purified by chromatography on alumina (10 g.), a pale yellow brown oil (120 mg.) being obtained which was insoluble in cold alkali. An ether solution of the oil was washed with thiosulfate solution and with water. The oil on recovery showed bands at 3509, 3356 (both hydroxyl), 1761 (γ-lactone) and 1721 cm.$^{-1}$ (carbonyl) among others in the infrared spectrum.

Attempted Reduction of Alcohol IV. (a).—A solution of alcohol IV in ethanol (or acetic acid) absorbed no hydrogen when shaken with the gas at room temperature and atmospheric pressure over pre-reduced Adams catalyst. Alcohol IV was recovered quantitatively from the solution.

(b).—Alcohol IV (0.6 g.) in freshly purified tetrahydrofuran (25 ml.) was run slowly into a boiling, stirred suspension of an excess of lithium aluminum hydride in tetrahydrofuran (25 ml.). The reaction mixture was boiled under reflux for 24 hours and then worked up in the normal manner. A pale yellow oil (0.4 g.) was obtained which crystallized from petroleum ether as prisms, m.p. 121.8–122°, undepressed on admixture with alcohol IV.

Alcohol IV Monoacetate.—Alcohol IV (0.6 g.) was warmed on the steam-bath for 4 hours with acetic anhydride (5 ml.) and pyridine (2 ml.), the cooled mixture then poured into water (60 ml.), and extracted with three 50-ml. portions of ether. The ether extracts were washed successively with dilute hydrochloric acid, sodium bicarbonate solution and saturated ammonium chloride solution, dried and evaporated. A pale yellow oil (315 mg.) was obtained which, after preliminary purification by chromatography on

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[13] See ref. 3, footnotes 13 and 14. Infrared spectra of oils were taken in chloroform solution and of solids as potassium bromide disks, except where stated otherwise.

[14] W. C. J. Ross, *J. Chem. Soc.*, 2257 (1950).

[15] Landquist gives ultraviolet spectrum 363 (4.34) and m.p. 159–160° for this derivative.

[16] F. E. Huelin and B. H. Kennett, *Chemistry & Industry*, 715 (1956).

Woelm neutral alumina (10 g.), crystallized from heptane as prisms of **alcohol IV monoacetate**, m.p. 112.8–113.0°. Infrared bands for acetate were observed at 1736 and 1235 cm.$^{-1}$, and for hydroxyl at 3356 cm.$^{-1}$.

Anal. Calcd. for $C_{18}H_{30}O_6$: C, 63.13; H, 8.83; O, 28.04; acetyl, 12.57. Found: C, 63.28; H, 8.84; O, 28.16; acetyl, 14.92.

Alcohol IV Diacetate.—A solution of alcohol IV (0.65 g.) in acetic anhydride (5 ml.) and pyridine (2 ml.) was heated under reflux during 48 hours, poured into water (50 ml.) and the product extracted with four 50-ml. portions of chloroform. The chloroform extracts, after being washed as described above for the monoacetate preparation, were evaporated to furnish a brown gum (0.70 g.). Chromatography on Woelm neutral alumina (22 g.) afforded **alcohol IV diacetate** as a colorless gum (0.55 g.), b.p. 133–142° (bath) (1 × 10^{-3} mm.), [α]D 29.9°. There was no band for hydroxyl in the infrared spectrum, but an acetate band at 1727 cm.$^{-1}$ (shoulder at 1739 cm.$^{-1}$).

Anal. Calcd. for $C_{20}H_{32}O_7$: C, 62.48; H, 8.39; O, 29.13; acetyl, 21.61; active hydrogen, nil (4 equiv. consumed). Found: C, 62.24; H, 8.56; O, 29.34; acetyl, 21.76; active hydrogen, 0.38 (4.07 equiv. consumed).

Saponification of Alcohol IV Diacetate.—Alcohol IV diacetate (150 mg.) was warmed on the steam-bath with 0.35 *N* sodium hydroxide (2 ml.) for 3 hours, diluted to 25 ml., and extracted with three 25-ml. portions of chloroform. Evaporation of the dried chloroform extracts gave a colorless gum (118 mg.) which crystallized from *n*-hexane in prisms, m.p. 120.8–121.3°, undepressed by an authentic sample of alcohol IV.

Alcohol IV itself was unchanged after being boiled with 5% aqueous sodium hydroxide for 5 hours.

Acetylation of a Dextrorotary Isomer of Alcohol IV.—The dextrorotary isomer of alcohol IV (0.55 g., [α]D 41°) from sulfuric acid treatment of alcohol I was treated with acetic anhydride (5 ml.) and pyridine (2 ml.) in exactly the same manner as described for the preparation of alcohol IV monoacetate. A pale yellow gum (0.61 g.) resulted, which was separated by chromatography on Woelm neutral alumina (18 g.) into two products. Elution with 2:1 petroleum ether–ether afforded a colorless gum (127 mg.), [α]D 74.0°, b.p. 125–131° (bath) (5 × 10^{-4} mm.) which, from the absence of hydroxyl bands in the infrared spectrum and bands for acetate at 1727 and 1742 cm.$^{-1}$ (shoulder), is the **alcohol diacetate**.

Anal. Calcd. for $C_{20}H_{32}O_7$ (see above): Found: C, 62.31; H, 8.44; O, 29.32; acetyl, 21.11.

The alcohol monoacetate (90 mg.) was removed from the column with ether as a colorless gum, [α]D 4.7°, b.p. 134–142° (bath) (1 × 10^{-3} mm.), showing infrared bands at 3390 (hydroxyl) and 1727 cm.$^{-1}$ (acetate).

Anal. Calcd. for $C_{18}H_{30}O_6$ (see above): Found: C, 63.37; H, 9.65.

Chromic Oxide Oxidation of Alcohol IV. (**a**).—Alcohol IV (1.8 g.) in chloroform (3 ml.) was poured into glacial acetic acid (10 ml.) at 40° with stirring. A solution of chromic oxide (1 g.) in acetic acid (5 ml.) and water (1 ml.) was added dropwise with the solution temperature maintained below 50° (5–6 minutes required). After the addition was completed, the mixture was warmed to 50° for 0.5 hour, cooled and the excess of chromic acid destroyed by cautious addition of methanol (1.5 ml.), the temperature again being kept below 50°. On evaporation to near dryness under vacuum a sticky residue remained which was triturated with ether and water simultaneously. Ether extracts of the aqueous phase afforded a pale yellow oil (1.59 g.) separated into its two principal components by chromatography on alumina (40 g.); 200:1 ether–methanol eluted crystalline **alcohol IV monoketone** (150 mg.), recrystallized from hexane as rods, m.p. 114.6–115.1°, [α]D −43.0°, showing infrared spectrum bands at 3424 and 1724 cm.$^{-1}$.

Anal. Calcd. for $C_{16}H_{26}O_5$: C, 64.40; H, 8.78; O, 26.81; active hydrogen, 1 (1 equiv. consumed). Found: C, 64.42; H, 8.99; O, 26.72; active hydrogen, 0.99 (0.81 equiv. consumed).

Elution of the column with 100:1 and 50:1 ether–methanol yielded an oily ketone (370 mg.) which, after distillation b.p. 126–133° (bath) (5 × 10^{-4} mm.), was a viscous, colorless gum, [α]D −37.9°. A strong infrared band appeared at 1721 cm.$^{-1}$.

Anal. Calcd. for $C_{16}H_{26}O_5$: see above. Found: C, 63.94, 64.09; H, 8.85, 8.91; O, 27.20; active hydrogen, 1.47 (1.17 equiv. consumed).

(**b**).—Alcohol IV (6.2 g.) was added to a cold mixture of chromium trioxide (4.0 g.) in dry pyridine (70 ml.) and allowed to stand at room temperature for 4 days before being poured into water (100 ml.). The product was extracted with five 100-ml. portions of chloroform, and the chloroform extracts were washed successively with dilute hydrochloric acid, dilute sodium bicarbonate solution and saturated ammonium chloride solution. Evaporation of the dried extracts furnished a gummy crystalline mass. This was crystallized twice from *n*-hexane to yield alcohol IV ketone (3.3 g.), m.p. 112–113° alone or mixed with the ketone from chromic oxide–acetic acid oxidation. The mother liquors were chromatographed over alumina when more alcohol IV ketone (0.97 g.) was obtained, together with unreacted alcohol IV (0.80 g.). An over-all yield of 69% of ketone was thus obtained.

In a similar experiment no alcohol IV was recovered, but later fractions from the column, on evaporation, afforded oils which showed a band for γ-lactone (1776 cm.$^{-1}$) in the infrared spectrum as well as the ketone band (1721 cm.$^{-1}$). Insufficient material was available for further investigation.

Catalytic Reduction of Alcohol IV Ketone to Alcohol IV.—A solution of alcohol IV ketone (0.40 g.) in ethanol (15 ml.) was shaken with hydrogen at room temperature and pressure over prereduced Adams catalyst until uptake ceased. Consumption of hydrogen proceeded very slowly and 3.5 days were necessary to approach the theoretical gas uptake. Evaporation of the filtered solution gave a colorless gum (372 mg.) which was separated chromatographically into unchanged alcohol IV ketone (87 mg.) and alcohol IV (220 mg.), m.p. and mixed m.p. 121.2–121.8°.

Condensation of Alcohol IV Ketone with Furfural.—To a solution of alcohol IV ketone (0.15 g.) in ethanol (1.5 ml.) were added furfural (0.1 g.) and 2% aqueous sodium hydroxide (1 ml.). After being warmed gently at 50–60° for 10 minutes the solution was allowed to stand overnight. A solid slowly separated which was collected and, after recrystallization from aqueous ethanol, furnished the **monofurfurylidene derivative of alcohol IV ketone** as pale yellow needles (47 mg.), m.p. 156.7–157.1°, with ultraviolet spectrum, 330 (4.36), in agreement with that expected for a monofurfurylidene derivative,[17] and showing clearly that it was not a bis-derivative.[18] The infrared spectrum showed bands, among others, at 3448 (hydroxyl), 1692 (conjugated carbonyl), 1613 and 1546 (double bond conjugated with furan ring[19]), and 831 cm.$^{-1}$ (trisubstituted double bond).

Anal. Calcd. for $C_{21}H_{28}O_6$: C, 67.00; H, 7.50; O, 25.50. Found: C, 66.89; H, 7.85; O, 25.33.

Chromic Oxide Oxidation of an Isomer of Alcohol IV.—The first product from treatment of alcohol I with 0.5% aqueous oxalic acid (1.43 g.), [α]D 1.0°, was added to a chromic oxide–pyridine slurry (0.8 g. in 10 ml.) and allowed to stand 5 days before working up as described for oxidation of alcohol IV. Chromatography of the oily products (0.8 g.) on alumina (24 g.) gave, first, a colorless crystalline compound (30 mg.), followed by oils which, from the infrared spectra (bands at 1730 and 1764 cm.$^{-1}$), consisted of a ketone and γ-lactone mixtures, inseparable by further chromatography. The crystalline compound was recrystallized from hexane to furnish an **isomer of alcohol I**, m.p. 129.5–129.6°.

Anal. Calcd. for $C_{16}H_{26}O_4$: C, 68.06; H, 9.28. Found: C, 68.08; H, 9.55.

Action of Selenium on Alcohol IV.—Selenium (6 g.) and alcohol IV (2 g.) were ground together and the mixture was maintained at 325–335° for 24 hours, with initial rapid heating to this temperature. The ether-soluble products were chromatographed on alumina, eluting with hexane and hexane–ether mixtures. Arbitrary combinations of contiguous chromatographic fractions were distilled in bulb-tubes under vacuum (water-pump), and each combination of

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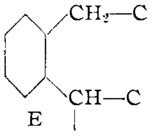
[17] E. C. Hughes and J. R. Johnson, This Journal, **53**, 737 (1931).

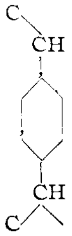
[18] H. Stobbe and R. Haertel, *Ann.*, **370**, 99 (1909).

[19] E. R. Blout, M. Fields and R. Karplus, This Journal, **70**, 194 (1948).

fractions split into a lower and higher boiling fraction again arbitrarily. Infrared spectral examination of the six distillation fractions revealed strong bands for three different types of benzene ring substitution. Bands for hydroxyl, carbonyl and other oxygen-containing groups were totally absent. No one distillation fraction appeared homogeneous on the basis of its spectrum. Comparisons of the spectra with many reference spectra[20] allowed allocation of minimum structural features to each of the three substituted benzenes, E-G.



E



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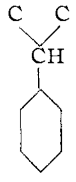

G

Separation of the selenium dehydrogenation products was effected by vapor phase chromatography,[21] which revealed the presence of no fewer than six, and probably eight, benzenoid compounds bearing C_4-, C_5-, C_7-, C_8- and C_9-alkyl groups (in the one or two side chains). In view of the observed complexity no further work was performed on these reaction products.

Action of Acid on Dihydroalcohol Ia.—Dihydroalcohol Ia (1.06 g.) was dissolved in dioxane (20 ml.), the stirred solution treated with sulfuric acid (20 ml. of 10%) and boiled under reflux for 3 hours in a nitrogen atmosphere. The cold reaction solution, after neutralization with bicarbonate, was diluted to 100 ml. and the majority of the dioxane removed by distillation, prior to extraction with three 50-ml. portions of ether. Evaporation of the dried ether extracts yielded a brown oil (0.90 g.), separated by chromatography on alumina (25 g.) into two components. Elution with 100:1 ether–methanol removed a pale yellow gum (0.16 g.), $[\alpha]_D$ 39.5°, showing hydroxyl but no carbonyl in the infrared. After distillation the gum was colorless, b.p. 119–126° (bath) (5×10^{-4} mm.).

Anal. Calcd. for $C_{15}H_{28}O_4$: C, 66.14; H, 10.36; O, 23.50. Found: C, 66.20; H, 10.03; O, 23.83; active hydrogen, 0.56.

A pale yellow gum was eluted with 30:1 and 20:1 ether–methanol which, on distillation, was separated into a lower and a higher boiling fraction. The fraction b.p. 128–136° (bath) (5×10^{-4} mm.) was a colorless gum.

Anal. Calcd. for $C_{16}H_{30}O_5$: C, 63.54; H, 10.00; O, 26.46; active hydrogen, 3. Found: C, 64.03; H, 9.97; O, 26.26; active hydrogen, 2.58.

The second fraction, b.p. 149–162° (bath) ($5 \times 10^{-}$ mm.), was also a colorless gum.

Anal. Calcd. for $C_{16}H_{30}O_5$ (see above): Found: C, 63.30; H, 10.01; O, 26.57.

ROCHESTER, N. Y.

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[20] American Petrolum Institute Infrared Tables.

[21] We are indebted to Prof. A. C. Cope of Massachusetts Institute of Technology for the separation. A silicone oil column was used at 265° with a preheater at 300°

[JOINT CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE STATE UNIVERSITY AND THE UNITED STATES DEPARTMENT OF AGRICULTURE FEDERAL EXPERIMENT STATION IN PUERTO RICO]

Naturally Occurring Oxygen Heterocyclics. II.[1] Characterization of an Insecticidal Principle from *Mammea americana* L.[2]

BY CARL DJERASSI, E. J. EISENBRAUN, B. GILBERT, A. J. LEMIN, S. P. MARFEY AND M. P. MORRIS

RECEIVED FEBRUARY 17, 1958

The crystalline insecticidal principle from the seeds of *Mammea americana* L. has been named mammein and found to possess the empirical formula $C_{22}H_{28}O_5$. Chemical and spectroscopic data are presented to support the characterization of the oxygen functions in terms of a lactone ring, a conjugated carbonyl moiety and two phenolic (or enolic) hydroxyl groups. The reactive double bond of mammein has been shown to be present in the system $(CH_3)_2C{=}CH{-}\overset{|}{\underset{|}{C}}{-}$.

The mamey tree, *Mammea americana* L., is indigenous to the West Indies and it has been known for some time that various parts of the plant possess insecticidal properties.[3] The seeds[4] of the fruit are particularly effective in this respect and while the latter is edible, reports of poisoning in humans are known. Recently,[5] one pure crystalline toxic constituent has been isolated from the seeds and assigned the empirical formula $C_{18}H_{22}O_4$. Earlier work[6] with crude seed extracts suggested a structural similarity to the pyrethrins, but the apparent empirical formula (for correction see below) and especially the reported[5] ultraviolet absorption maxima of the crystalline material clearly showed that this could not be the case.

In view of the fact that the important, naturally occurring insecticides[7] can be reduced to three distinct chemical types—rotenoids, pyrethrins and unsaturated isobutylamides—it was of obvious interest to determine whether the insecticidal activity of mamey was due to a different chemical type. If true, then this might offer a lead to the synthesis of new and possibly more effective insecticides. Our work has concentrated on the toxic crystalline constituent of the seeds isolated by Morris and Pagan[5] and we have coined the name "mammein" for it. The present paper is concerned with an improved isolation of mammein, the preparation of various derivatives and the tentative characterization of the functional groups.

The ground seed was extracted with petroleum ether, the resulting oil was treated with acetone to remove some insoluble material[5] and then was chromatographed on acetic acid–deactivated alumina.[8] Elution with petroleum ether and petroleum

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[1] The paper by W. B. Mors, O. R. Gottlieb and C. Djerassi, THIS JOURNAL, **79**, 4507 (1957), is considered Part I of this series.

[2] The work at Wayne State University was supported by a research grant from the National Science Foundation.

[3] See H. K. Plank, *J. Econ. Entom.*, **37**, 737 (1944).

[4] H. K. Plank, *Trop. Agric.*, **27**, 38 (1950).

[5] M. P. Morris and C. Pagan, THIS JOURNAL, **75**, 1489 (1953).

[6] M. A. Jones and H. K. Plank, *ibid.*, **67**, 2266 (1945).

[7] For review see L. Feinstein and M. Jacobson in L. Zechmeister's "Progress in the Chemistry of Organic Natural Products," Springer, Vienna, 1953, Vol. X, pp. 423–476.

[8] The lability of mammein toward alkali precluded the use of alkaline alumina as adsorbent.