6.21 and 6.30 μ in the double bond region. Two model benzofurans showed no band at 6.13.

Anal. Found: C, 84.03; H, 9.36. Calcd. for $C_{15}H_{20}O$: C, 83.28; H, 9.32. For $C_{15}H_{18}O$: C, 84.07; H, 8.47.

The second fraction showed only end absorption in the ultraviolet (down to 220 mμ). A similar one from Pd-charcoal dehydrogenation showed a peak at 218 mμ (a 38.0). The infrared spectrum showed carbonyl absorption (5.84 μ) and double bond absorption (6.24 and 6.31 μ). Benzaldehyde also shows these three peaks.

Anal. Found: C, 81.74; H, 10.05. Calcd. for $C_{18}H_{18}O$: C, 82.06; H, 9.54. For $C_{13}H_{20}O$: C, 81.20; H, 10.48.

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

The Chemistry of Fumagillin.[1a] III

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The alcohol moiety of fumagillin, alcohol-I ($C_{16}H_{26}O_4$), contains a secondary alcoholic hydroxyl group, a methoxyl group, and two non-carbonyl oxygen functions; it shows no absorption in the ultraviolet. Catalytic reduction of alcohol-I yields the crystalline tetrahydroalcohol-I, which contains two hydroxyl groups, one secondary and one tertiary. Permanganate oxidation of tetrahydroalcohol-I gives isocaproic acid; treatment with mineral acid isomerizes tetrahydroalcohol-I to carbonyl-containing products, and oxidation with chromic oxide–pyridine yields a saturated ketone. Numerous other transformations of fumagillin derivatives are described.

Earlier work[4–6] has shown that fumagillin has the empirical formula $C_{26}H_{34}O_7$, and this has been confirmed by an X-ray crystallographic study.[7] Alkaline hydrolysis of fumagillin yields decatetraenedioic acid and a neutral substance, $C_{16}H_{26}O_4$, which we have named alcohol-I.

This material is a viscous high boiling oil, which has not been obtained crystalline, and which, in spite of varied and sustained efforts, has not yielded any crystalline derivatives. It contains a secondary hydroxyl group, a methoxyl group, and two non-carbonyl oxygen atoms; it shows no absorption in the carbonyl region of the infrared, and no absorption in the ultraviolet. The carbon–oxygen linkages are subject to hydrogenolysis, and alcohol-I consumes one equivalent (*i.e.*, 0.25 mole) of lithium aluminum hydride, in addition to the equivalent which reacts with the hydroxyl group.

Treatment of alcohol-I with hydrogen and platinum catalyst in alcohol gives an uptake of almost two moles of hydrogen, and chromatography on alumina of the resulting products leads to isolation of the crystalline tetrahydroalcohol-I, $C_{16}H_{30}O_4$, m.p. 89–90°. The success of this reduction depends both on the quality of the alcohol-I and of the platinum catalyst. In the best cases, the yield of crystalline material reaches 70%, but in other runs, only slightly more than one mole of hydrogen is absorbed, and a viscous dihydroalcohol-I (see below) is obtained, with only traces of the crystalline tetrahydro compound.

The tetrahydroalcohol-I results from the addition of one mole of hydrogen to a carbon–carbon double bond, and from the hydrogenolysis of a carbon–oxygen linkage by the second mole of hydrogen. This is demonstrated by the presence of two active hydrogens in the compound, by the fact that, in contrast to alcohol-I, it is unaffected by lithium aluminum hydride, and by the oxidation to a hydroxyketone (below).

Oxidation of tetrahydroalcohol-I by permanganate in 10% sulfuric acid yielded isocaproic acid, which was identified (through the crystalline *p*-bromophenacyl ester) by mixed m.p. and by the correspondence of the infrared spectra with an authentic sample. This evidence shows the presence of the $>CCH_2CH_2CH(CH_3)_2$ grouping in the molecule, and, coupled with the isolation of acetone from ozonization,[6] indicates the presence of the $>CCH_2$-$CH{=}C(CH_3)_2$ group in alcohol-I and in fumagillin

The other product from the acid permanganate oxidation of tetrahydroalcohol-I was a neutral compound, showing strong absorption at 1706 cm.$^{-1}$, and of composition agreeing with the formula C_{16}-$H_{30}O_4$; it apparently was a ketonic isomerization product produced by action of the sulfuric acid on tetrahydroalcohol-I. Treatment of tetrahydroalcohol-I with aqueous alcoholic hydrogen chloride, or with Dowex-50, gave materials with strong absorption in the 1720–1706 cm.$^{-1}$ region; the hydrochloric acid appeared to introduce some chlorine into the molecule, and the product showed absorption in the ultraviolet[8]: 227 (3.4), 278 (3.8).

Treatment of tetrahydroalcohol-I with the elegant chromic oxide–pyridine reagent,[9] which, being

(1a) Part of this material was presented before the Division of Medicinal Chemistry at the American Chemical Society Meeting in New York, September, 1954; D. S. Tarbell, H. R. Al-Kazimi, P. Hoffman, G. A. Page, H. R. Vogt, J. R. Schenck, M. P. Hargie and A. Isarasena, Abstracts of New York Meeting, 1954, p. 17 N.

(1b) Abbott Laboratories Fellow, 1952–1953.

(2) Fellow of the Royal Iraqian Government, 1950–1954.

(3) Abbott Laboratories Fellow, 1953–1954.

(4) T. E. Eble and F. R. Hanson, *Antibiotics and Chemotherapy*, 1, 54 (1951).

(5) J. R. Schenck, M. P. Hargie, D. S. Tarbell and P. Hoffman, THIS JOURNAL, **75**, 2274 (1953).

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

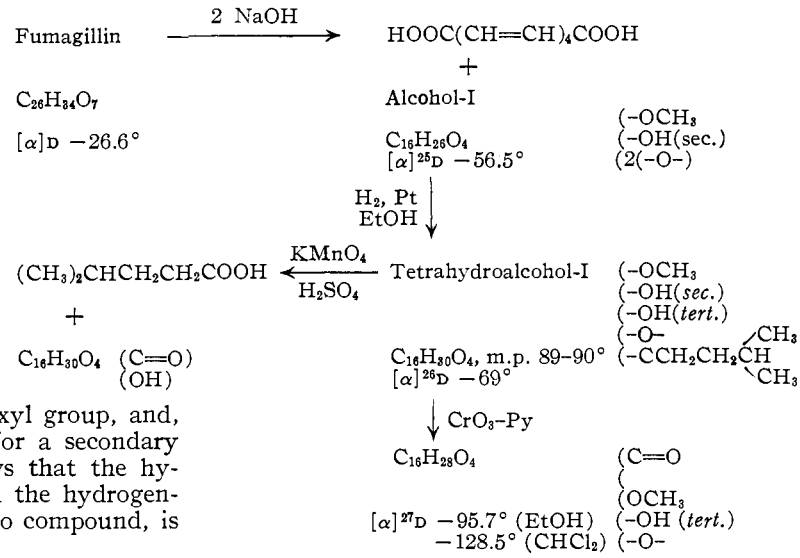
(7) C. J. Brown and J. K. Landquist, *Chemistry & Industry*, 973 (1953).

(8) Ultraviolet spectra are indicated throughout by giving λ_{max} in mμ, and log ϵ in parentheses.

(9) G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, THIS JOURNAL, **75**, 425 (1953).

non-acidic, would not affect the acid-sensitive oxygen functions in the molecule, gave a product showing a strong carbonyl band at 1724 cm.$^{-1}$, with a composition corresponding to $C_{16}H_{28}O_4$, and with strong hydroxyl absorption in the infrared. This compound did not give aldehyde reactions. The ultraviolet spectrum of this product, 279 (1.51), was also in agreement with the presence of an unconjugated carbonyl group. The strong hydroxyl absorption in the ketonic oxidation product shows that tetrahydroalcohol-I contains a secondary and a tertiary hydroxyl group, and, coupled with the evidence below for a secondary hydroxyl group in alcohol-I, shows that the hydroxyl group which is generated in the hydrogenolysis of alcohol-I to the tetrahydro compound, is tertiary.

CHART I



Tetrahydroalcohol-I was stable to boiling 10% aqueous alkali, to permanganate in sodium carbonate solution, to lithium aluminum hydride, and did not yield crystalline derivatives with numerous reagents which should react with hydroxyl groups. The only isolatable product after treatment with trityl chloride was triphenylcarbinol, which is in agreement with the absence of a primary hydroxyl group.[10] Treatment of tetrahydroalcohol-I with *p*-phenylazobenzoyl chloride in pyridine at 100° for 1 hour yielded only starting material; this would indicate a considerable degree of substitution around the secondary hydroxyl group, because these conditions esterify 3-hydroxy steroids.[11]

Treatment of alcohol-I with chromic oxide–pyridine yielded a carbonyl compound, $C_{16}H_{24}O_4$, which gave a positive test with Fehling and Tollens reagents, and was converted in part by silver ion to an amorphous sodium hydrogen carbonate-soluble material.[11a] Nevertheless, the hydroxyl group in alcohol-I is considered to be secondary rather than primary, for the following reasons: (1) The carbonyl compound showed a strong hydroxyl as well as carbonyl band in the infrared, and hence the oxidation apparently was accompanied by isomerization. (2) The carbonyl compound gave a negative Schiff test. (3) The hydroxyl group in tetrahydroalcohol-I is almost certainly secondary.

Some of the relationships developed so far are indicated in Chart I.

Treatment of alcohol-I with base changed the rotation from −56° to *ca.* +12°; this product was at first[1a] considered to be an isomer of alcohol-I and was designated isoalcohol-I. More detailed examination has shown that this change is not a simple isomerization; the elementary analysis and active hydrogen determination are in agreement with the idea that the material is a mixture composed of about one-third of a hydration product of alcohol-I, and two-thirds of an isomerization product of alcohol-I. It will be convenient to designate this mixture as "isoalcohol-I."

Catalytic reduction of "isoalcohol-I" with platinum and hydrogen gave an uptake of exactly 1 mole of hydrogen, even in the presence of a large excess of catalyst; none of the crystalline tetrahydroalcohol-I could be obtained. It thus appears that the basic treatment of alcohol-I results in some change which prevents the hydrogenolysis reaction, which occurs on catalytic reduction of alcohol-I. This "dihydroisoalcohol-I" had the same composition and infrared spectrum as a product obtained by base treatment of the alcohol obtained on saponification of decahydrofumagillin (below).

Oxidation of "isoalcohol-I" with chromic oxide–pyridine gave a product showing a strong carbonyl and a strong hydroxyl band in the infrared; the composition of this product was in agreement with the idea that "isoalcohol-I" was partially hydrated.

Reduction of fumagillin with hydrogen and platinum in ethanol gave an uptake of approximately five moles of hydrogen, yielding a non-crystalline decahydrofumagillin. Hydrolysis with two equivalents of base yielded sebacic acid,[5] and a neutral oil, "dihydroalcohol-II." This compound, like alcohol-I, showed a change in rotation when heated with alkali, and the product showed an infrared spectrum indistinguishable from that of "dihydroisoalcohol-I." The rotation of several samples of dihydroalcohol-II differed, and it appeared that partial hydration and isomerization had occurred in these runs, due to the action of the base on the initially formed product. This conclusion was supported by examination of the infrared spectra, which appeared to show that mixtures of the two compounds were present.

The action of dilute aqueous alcoholic sulfuric acid on decahydrofumagillin gave a good yield of diethyl sebacate, which was identified by analysis and hydrolysis to sebacic acid. The formation of this ester confirms the observation that transesterification reactions occur with fumagillin derivatives

(10) B. Helferich and J. Becker, *Ann.*, **440**, 1 (1924); R. C. Hockett and C. S. Hudson, THIS JOURNAL, **53**, 4456 (1931); **56**, 945 (1934).

(11) K. Ladenburg, E. Fernholz and E. S. Wallis, *J. Org. Chem.*, **3** 294 (1938).

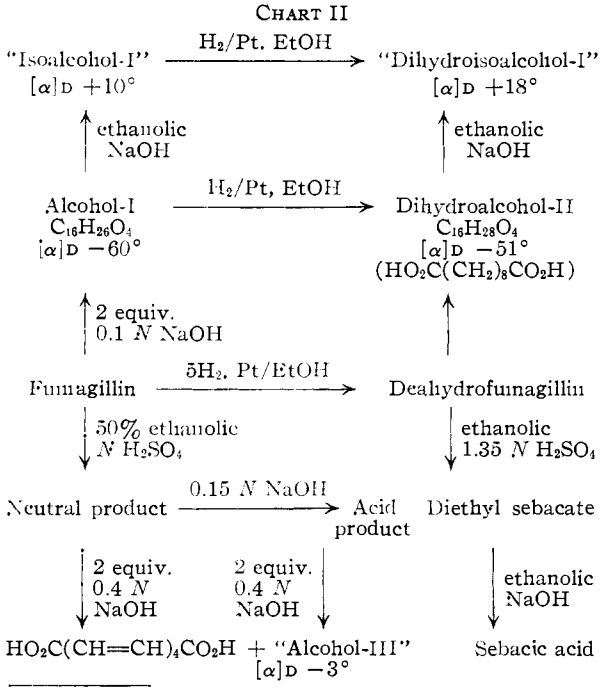
(11a) ADDED IN PROOF.—In recent work, this ketone has been obtained colorless; it gives no Fehling or Schiff test, and gives a slight Tollens reaction, as does alcohol-I.

with great ease under conditions which would be expected to lead instead to hydrolysis.[12]

Further evidence for the ester interchange reaction (Chart II) was obtained from the action of dilute aqueous alcoholic sulfuric acid on fumagillin itself. This yielded an acidic and a neutral product; the latter was saponified by alkali of not greater than 0.15 *N* strength to the yellow, ether-soluble, acid component, their identity being confirmed by infrared spectra. Both fractions were hydrolyzed by base of 0.4 *N*, or greater, strength to decatetraenedioic acid and a neutral oil, alcohol-III. This significantly lower rate of alkaline hydrolysis of these products from acid-treated fumagillin indicates that acid must alter the environment of the ester linkage in fumagillin. Similarly, when alcohol-I was heated with aqueous ethanolic sulfuric acid, the main product was a neutral oil having an infrared spectrum identical with that of the samples of alcohol-III.

The composition of alcohol-III is indefinite, apparently depending upon the degree of hydration achieved during the stage of acid treatment. Samples obtained from the saponification of both the neutral and the acidic products of the same acid hydrolysis were indistinguishable by optical rotation, infrared spectra and both had the same composition. Similar acid hydrolyses of fumagillin yielded the alcohol as oils having the same infrared spectrum, but differing in optical rotation by several degrees.

CHART II



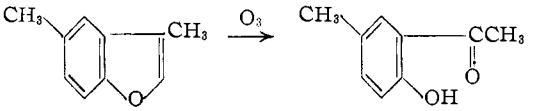
From analytical data it appears that alcohol-III consists of a mixture of hydrated derivative of alcohol-I, with a product formed by combination with ethanol. A sample of alcoholic material was also obtained by saponification of an ether soluble acidic fraction prepared by heating fumagillin with 1 *N* sulfuric acid in the absence of ethanol; this alcohol had an infrared spectrum indistinguishable from that of samples of alcohol-III, but differed in its optical rotation and did not show the abnormally high methoxyl value of alcohol-III samples.

The effect of this hydration is considerable, and is shown by the fact that alcohol-III absorbs an insignificant amount of hydrogen at room temperature and pressure, both in solution in ethanol and in acetic acid. There is also no apparent change in the composition of alcohol-III on treatment with hot alcoholic base, which indicates that any sensitive centers in the molecule have already undergone change under the acid conditions.

An extensive series of dehydrogenation experiments using sulfur, and better selenium, on crystalline tetrahydroalcohol-I and on the viscous oil which is formed as a by-product in the preparation of tetrahydroalchol-I (see Experimental), gave strong indications that phenolic compounds and a substituted benzofuran were formed; conclusive identifications were not obtained, although the formation of methanol was demonstrated. The presence of phenolic compounds was inferred from the fact that a few mg. of sodium hydroxide-soluble material was obtained in each run, which showed ultraviolet spectra characteristic of substituted phenols,[13] showing λ_{max} 280 (3.30), which compares well with reported values.[13] The phenolic fractions obtained in different runs had odors like cresols, xylenols and guaiacol.

The neutral fraction was separated by chromatography into several liquid fractions, whose ultraviolet spectra were almost identical with that of 3,5-dimethylbenzofuran,[14] which was used for comparison. This compound showed the following maxima: 250 (3.95), 273 (3.31), 279 (3.39), 282 (3.42), 289 (3.45). A fraction from the neutral oil from dehydrogenation showed the following spectrum (log ϵ values calculated assuming about twelve carbons): 253 (3.81), 278 (3.32), 286 (3.24). The shapes of the curves were strikingly similar.

Virtually the only way of characterizing benzofurans appears to be by ozonization,[15] which, with the model compound, takes the course



Ozonization of the supposed benzofuran from the dehydrogenation yielded a few mg. of alkali-soluble material, which showed the following ultraviolet absorption maxima (extinction coefficients not calculated): 252, 280 (shoulder), 323 mμ. Ozoniza-

(12) Brown and Landquist (ref. 7) noted that treatment of fumagillin or its methyl ester with aqueous methanolic alkali yielded the methyl or dimethyl ester of decatetraenedioic acid, respectively. P. Karrer and A. Helfenstein (*Helv. Chim. Acta*, **13**, 392 (1930)) noted that α-crocin also gave ester interchange reactions very rapidly under basic conditions. The results described above on decahydrofumagillin show that the rapid ester interchange reaction takes place under acidic conditions, and that it does not require a long conjugated unsaturated acid chain, which is present in α-crocin and in fumagillin itself. The ester interchange reaction must be a function of the alcohol part of the ester linkage in decahydrofumagillin.

(13) A. Burawoy and J. T. Chamberlain, *J. Chem. Soc.*, 2310 (1952), report the spectra of many substituted phenols.

(14) A. Hantzsch and E. Lang, *Ber.*, **19**, 1300 (1886).

(15) A. Wacek, H. O. Epinger and A. Bezard, *ibid.*, **73**, 521 (1940); A. Schönberg, N. Badran and N. A. Starkowsky, THIS JOURNAL, **75**, 1992 (1953).

tion of the model compound gave product with the following spectrum: 254 (3.80), 285 (3.10, a slight peak), 330 (3.44). The shapes of the two curves were very similar[16]; furthermore, infrared spectra of the two ozonization products in the hydroxyl and carbonyl regions were practically identical.

Experimental[17]

Purification of Fumagillin.—The fumagillin as supplied from Abbott Laboratories was sometimes in a high state of purity, and was sometimes crude.

The crude fumagillin is a mixture of about 42% fumagillin, 45% sucrose, 10% anti-foam agent and 3% of other impurities. It is powdery in appearance and possesses a moldy odor. Fumagillin is very soluble in chloroform, and insoluble in ether; its solubility in boiling methanol is approximately 3.6%, and is 0.6% in cold methanol.

A sample of 40 g. of crude fumagillin was digested with 150 ml. of chloroform; the insoluble sucrose was collected on a filter paper and washed several times with small amounts of chloroform. The dark brown solution was concentrated almost to dryness at room temperature and under reduced pressure. The residue was triturated with 20 ml. of methanol to remove some methanol-soluble impurities. The fumagillin was separated from the methanol solution by suction filtration, and was recrystallized twice from 500 ml. of hot methanol. The fumagillin crystallized slowly at room temperature, and for complete precipitation it required standing overnight in the refrigerator. The crystallized fumagillin was then digested six or more times with 100-ml. portions of ether on the steam-bath to remove about 4 g. of an amorphous white solid, which was found to be a long-chain fatty ester, presumably originating from an anti-foam agent added to the fumagillin culture. The above treatment gave 13.5 g. of relatively pure crystalline fumagillin which did not melt sharply, but instead decomposed at about 200° to a glass-like mass. This material was used in many of the experiments reported in this study.

Further purification of the crystalline fumagillin could be effected by dissolving a 10-g. sample in 150 ml. of 0.2 *N* ammonia. It was found necessary to keep the solution cold and to avoid excess base, to which fumagillin is sensitive. The insoluble material was filtered off and the ammonia solution, cooled with running cold water, was acidified carefully with constant shaking to *p*H 4 with 1 *N* hydrochloric acid in the presence of 150 ml. of chloroform to effect the immediate removal of the acid-labile fumagillin. The chloroform layer was washed several times with distilled water, dried over anhydrous sodium sulfate and evaporated under reduced pressure, to yield a light brown solid. This material was washed with 20 ml. of methanol to remove some methanol-soluble colored impurities. Fumagillin was separated from the methanol solution by suction filtration and was recrystallized from 200 ml. of hot methanol to afford 6.5 g. of white needle-like crystals which melted sharply at 194–195°, $[\alpha]^{25}D$ −26.2° (*c* 4.5, 95% ethanol).

It was found that the yield and properties of the tetrahydroalcohol-I were the same when the fumagillin was purified by the shorter procedure, and therefore the ammonia procedure, which is wasteful of material and time, was not used ordinarily.

Fumagillin Methyl Ester.—To 0.50 g. of fumagillin in 25 ml. of methylene chloride cooled in an ice-bath was added a cold ethereal solution of diazomethane and, after standing for 1 hr., the solvent was evaporated at the water-pump. The residue was taken up in dry benzene and chromatographed on a short neutral alumina column, yielding an almost colorless solid, m.p. 145.5–150°. Recrystallization from aqueous methanol yielded 0.44 g., m.p. 149–150°. The reported[4] m.p. is 145–147°.

Anal. Calcd. for $C_{27}H_{36}O_7$: C, 68.61; H, 7.68. Found: C, 68.74; H, 7.76.

Alcohol-I from Fumagillin.—Fumagillin was added to a 0.3 *N* solution containing 2.0 equivalents of sodium hydroxide under nitrogen. The 0.3 *N* alkali gives better yields than 0.1 *N* alkali. The resulting suspension was heated on the steam-bath for 1 hr. with mechanical stirring or occasional swirling. The fumagillin gradually went into solution and an oil settled out. The mixture was cooled and extracted with ether; the extracts were dried over anhydrous sodium sulfate and the ether was evaporated, leaving a viscous, pale amber oil. The oil was distilled in a short path still at a block temperature of 120–130° (approximately 10^{-2} mm.), with the distillate becoming progressively more viscous as the distillation proceeded. Various samples showed $[\alpha]^{25}D$ (all rotations in 95% alcohol, unless indicated) in 1–5% solution of −46 to −59°. Analyses on many samples were somewhat low for $C_{16}H_{26}O_4$, and the more viscous higher-boiling fractions showed a lower carbon content, indicating some hydration, probably. A typical analysis for the distilled material:

Anal. Calcd. for $C_{16}H_{26}O_4$: C, 68.06; H, 9.28; O, 22.67; OCH_3, 10.99; one C-methyl, 5.31. Found: C, 67.26; H, 9.13; O, 24.67; OCH_3, 11.22; C-methyl, 9.74; 1.104 active hydrogens; 1.105 equivalents of lithium aluminum hydride consumed. (The C-methyl determination was run on a different sample.) The reagents used and the results (in parentheses) in an attempt to prepare solid derivatives of alcohol-I were as follows: α-naphthyl isocyanate (oil); *p*-nitrobenzoyl chloride (oil); 3,5-dinitrobenzoyl chloride (oil); *p*-phenylazobenzoyl chloride (oil eluted from silica gel column with 5% methanol in benzene); 3-nitrophthalic anhydride (oil); 3,5-dinitrobenzazide (glassy, amorphous solid, m.p. 94–98°, eluted from a silica gel column with 2:1 ether–hexane; this could not be purified by further chromatography nor by crystallization); cyanic acid (oil); methanesulfonyl chloride (oil). The preparation of a derivative with trimethylsilyl chloride, which is reported[18] to yield distillable products with high-boiling alcohols, was tried, but the product was not stable to distillation; hydrolysis with moist acetone gave material containing silicon and chlorine.

"Isoalcohol-I."—A solution of alcohol-I (3.40 g., $[\alpha]^{23}D$ −55.4°) in 95% ethanol (30 ml.) was treated with 10% aqueous sodium hydroxide (30 ml.) in a stream of nitrogen, and heated on a steam-bath for 3 hr. The yellow reaction mixture was concentrated to half-volume, cooled, and extracted with ether (four 25-ml. portions). The combined ether extracts were washed with water and dried over sodium sulfate. The crude oil was evaporatively distilled at *ca.* 10^{-3} mm., the main fraction being collected at a block temperature of 135–145°, yielding a colorless, extremely viscous oil (2.37 g., 70%, $[\alpha]^{22}D$ 10.6° (0.98)).

Anal. Calcd. for $C_{16}H_{26}O_4$: C, 68.05; H, 9.28; O, 22.67; OCH_3, 10.99; active hydrogen, 1.00. Calcd. for $C_{16}H_{26}O_4 \cdot H_2O$: C, 63.97; H, 9.40; O, 26.63; OCH_3, 10.32; active hydrogen, 3.00 or 2.00. Found: C, 66.69; H, 9.24; O, 24.31; OCH_3, 12.20, 12.17; active hydrogen, 1.57.

In a repeat experiment under the same conditions as above, "isoalcohol-I" had $[\alpha]^{26}D$ 7.4° (0.45).

Anal. Found: C, 66.37; H, 9.51; O, 24.42; active hydrogen 1.61. These analyses agree reasonably well with $C_{16}H_{26}O_4 \cdot {}^1/_2H_2O$.

The reaction was repeated using 20% more sodium hydroxide and a reflux period of 8 hr.; the crude oil had $[\alpha]^{24}D$ 12.0° (3.4).

Repetition on crude alcohol-I and a reflux period of 4 hr. (exposed to the atmosphere), after a short path distillation in high vacuum, gave $[\alpha]^{27}D$ 12.50° (1.5).

"Dihydroisoalcohol-I."—"Isoalcohol-I" (2.12 g., $[\alpha]^{22}D$ 10.6°) in 95% ethanol (25 ml.) was added to pre-reduced platinum (950 mg.) and hydrogenated at normal temperature and pressure. The very rapid uptake of hydrogen (virtually complete in 15 min.) ceased after 4 hr., when the theoretical amount for one molar equivalent had been absorbed.

The colorless, viscous product (1.99 g.) was dissolved in petroleum ether (25 ml.) and adsorbed onto alumina (40 g., Brockmann grade III). Elution with petroleum ether–ether (5:1) removed some levorotary material (280 mg., $[\alpha]^{23}D$ −16.6°); elution with more polar mixtures, including methanol, yielded a total of 1.47 g. ($[\alpha]^{23}D$ 12.6 to 20.6°). The latter fractions were combined and evaporatively distilled at *ca.* 10^{-4} mm., yielding 1.18 g. of a colorless viscous oil, $[\alpha]D$ 18.4° (1.65).

(16) The curves agree with those given for *o*-acylphenols by R. A. Morton and A. L. Stubbs, *J. Chem. Soc.*, 1347 (1940).

(17) We are indebted to Mr. E. F. Shelberg and his associates of Abbott Laboratories for analyses, and to Carl Whiteman of this Laboratory for infrared spectra.

(18) R. W. Martin, THIS JOURNAL, **74**, 3024 (1952).

Anal. Calcd. for $C_{16}H_{28}O_4$: C, 67.57; H, 9.93; O, 22.49; active hydrogen, 1.00. Calcd. for $C_{16}H_{28}O_4 \cdot H_2O$: C, 63.54; H, 10.00; O, 26.46; active hydrogen, 2.00 or 3.00. Found: C, 66.06; H, 10.15; O, 23.72; active hydrogen, 1.55.

In a similar experiment "dihydroisoalcohol-I," $[\alpha]^{25}D$ 13.3° (1.66), was analyzed. Found: C, 65.93; H, 10.17; O, 23.84; active hydrogen, 1.64. These analyses agree well with $C_{16}H_{28}O_4 \cdot {}^1/_3H_2O$.

Oxidation of "Isoalcohol-I" with Chromium Trioxide in Pyridine.—"Isoalcohol-I" (0.86 g.) in dry pyridine (8 ml.) was added to a slurry of chromium trioxide (0.9 g.) in pyridine (10 ml.) prepared by the method of Sarett, *et al.*[9] After standing overnight the mixture was poured into water (75 ml.) and extracted three times with benzene (40 ml.—emulsions dispelled by centrifuging). The washed and dried benzene solution was evaporated yielding an oil which distilled at 180–185° at 1.5 mm. as a viscous yellow oil. Infrared absorption: strong bands at 2.94 and 5.81 μ.

Anal. Calcd. for $C_{16}H_{24}O_4$: C, 68.54; H, 8.63; O, 22.83. Calcd. for $C_{16}H_{24}O_4 \cdot H_2O$: C, 64.40; H, 8.78; O, 26.82. Found: C, 65.98; H, 8.94; O, 24.59.

Oxidation of Alcohol-I.—A solution of alcohol-I (5.4 g., $[\alpha]D$ −52°) in dry pyridine (50 ml.) was added to a slurry of chromic anhydride (5.0 g.) in pyridine (50 ml.), and the mixture was kept at room temperature for 24 hr. The reaction product was poured into ice-cold 3 *N* hydrochloric acid (250 ml.), filtered and the filtrate extracted with ether (five 75-ml. portions). The washed and dried ethereal extract yielded a crude oil which was evaporatively distilled at *ca.* 10^{-4} mm.; the fraction collected at a block temperature of 120–130° was a pale yellow, mobile oil (2.06 g., $[\alpha]^{23}D$ −53.9° (0.96)), a smaller quantity of viscous yellow oil (0.93 g., $[\alpha]D$ −38.3° (0.80)) was collected at a higher temperature (130–150°). Ultraviolet absorption: 283 mμ (1.10); infrared: very strong band at 5.81–5.83 μ; medium strong band at 2.91 μ.

Anal. Calcd. for $C_{16}H_{24}O_4$: C, 68.54; H, 8.63; O, 22.83; OCH_3, 11.07. Found: C, 68.50; H, 9.05; O, 22.98; OCH_3, 10.23.

The distilled ketone formed a distinct silver mirror with Tollens reagent, a red precipitate of cuprous oxide with Fehling solution, but gave a negative test with Schiff reagent.

Tetrahydroalcohol-I.—A solution of alcohol-I (8.24 g., $[\alpha]^{26}D$ −54°) in 95% ethanol (50 ml.) was hydrogenated at room temperature and pressure, in the presence of prereduced platinum (1.30 g.). Slightly more than one molar equivalent of hydrogen was absorbed in the first hour, and the total uptake was complete after 18 hr. when 1.9 moles of hydrogen had been absorbed. Removal of catalyst, and solvent under reduced pressure, yielded an opaque oil which crystallized on standing for a few hours.

The crude tetrahydroalcohol-I (6.8 g.) was dissolved in petroleum ether (40 ml.) and adsorbed on alumina (100 g., Brockmann grade III). Elution with petroleum ether (b.p. 30–60°) (200 ml.) removed traces of an oily wax (100 mg.). Elution with more polar mixtures, up to and including ether, yielded the pure crystalline alcohol, m.p. 89–90° (4.8 g., $[\alpha]^{24}D$ −68.9°). A pale yellow, viscous oil (1.1 g., $[\alpha]^{24}D$ −20.6°) was removed on elution with methanol. Yields varying from 40–70% were obtained in a total of 15 runs.

Anal. Calcd. for $C_{16}H_{30}O_4$: C, 67.09; H, 10.56; O, 22.35; OCH_3, 10.83. Found (for the crystalline material): C, 67.46, 67.45; H, 10.58, 10.53; O, 22.06; OCH_3, 10.53; active hydrogen, 2.04.

The viscous oil (obtained from a different run) was analyzed. *Anal.* Calcd. for $C_{16}H_{28}O_4 \cdot H_2O$: C, 63.54; H, 10.00; OCH_3, 10.26. Found: C, 65.26; H, 10.30; OCH_3, 10.66.

Oxidation of Tetrahydroalcohol-I with Chromic Oxide-Pyridine.—A solution of tetrahydroalcohol-I (3.64 g.) in dry pyridine (35 ml.) was added to a slurry of chromic oxide (1.5 g.) in pyridine (15 ml.) according to Sarett's procedure.[9] After standing at room temperature for 24 hr., the mixture was poured into water (100 ml.), extracted with ether (six 50-ml. portions) the combined ethereal extracts were washed three times with 3 *N* hydrochloric acid (80 ml.) and water, and were dried over sodium sulfate. The crude oil was evaporatively distilled at *ca.* 5×10^{-4} mm. at a block temperature of 81–84°, yielding a colorless, mobile oil (2.88 g., 80%); $[\alpha]^{24}D$ −95.7° (3.85), −128.5° ($CHCl_3$, 1.46); ultraviolet absorption, 279 mμ (1.51); infrared absorption: bands at 2.93, 5.83 μ and a weak band at 6.11 μ.

Anal. Calcd. for $C_{16}H_{28}O_4$: C, 67.57; H, 9.92; O, 22.51; OCH_3, 10.91. Found: C, 67.53; H, 10.20; O, 22.44; OCH_3, 10.53; active hydrogen, 1.5.

The distilled ketone gave negative tests with Fehling and Benedict solutions and Schiff reagent, and an indistinct reaction with Tollens reagent.

Oxidation of Tetrahydroalcohol-I with Potassium Permanganate. Isolation of Isocaproic Acid.—Tetrahydroalcohol-I (1.0 g.) was suspended in 25 ml. of water and 10 ml. of 10% sulfuric acid was added. The mixture was stirred and 1.0 g. of powdered potassium permanganate was added portionwise over the course of 1 hr. The stirring was continued for 0.5 hr. longer, then the manganese dioxide was dissolved by the addition of sodium bisulfite solution. An oil had separated from the aqueous phase. The mixture was extracted with ether, the ether extracts were washed with 10% sodium carbonate solution followed by water, and dried over anhydrous sodium sulfate. The dried ether solution was evaporated to yield a viscous, pale yellow oil with a trace of solid material suspended in it. The oil was distilled in an Emich-type still at 145–150° (1 mm.). The infrared spectrum of the distillate-showed a strong hydroxyl band at 2.96 μ and a strong carbonyl band at 5.85 μ.

Anal. Calcd. for $C_{16}H_{30}O_4$: C, 67.09; H, 10.56; O, 22.35; OCH_3, 10.83. Found: C, 66.55; H, 10.76; O, 22.72, 22.73; OCH_3, 10.89.

An attempt to obtain a 2,4-dinitrophenylhydrazone derivative resulted in a very small yield of an oily orange solid, in insufficient quantity to allow further purification.

The sodium carbonate wash of the ether solution, described above, was acidified with concentrated hydrochloric acid and extracted with chloroform. The chloroform extracts were washed with water, dried over anhydrous sodium sulfate and evaporated, to yield a pale yellow oil with a stench-like odor. The *p*-bromophenacyl ester was prepared to yield a white crystalline solid, m.p. 62.5–73.5°. Recrystallization from 95% ethanol yielded 20 mg., m.p. 74.5–76°. The authentic *p*-bromophenacyl ester of isobutyric acid was prepared, m.p. 76.5–77° (reported m.p. 77°),[19] and it was depressed by more than 20° in a mixed m.p. determination. The authentic *p*-bromophenacyl ester of isocaproic acid was prepared, m.p. 77–78° (reported[20] m.p. 77°), mixed m.p. 75.5–77.5°. The infrared spectra of the *p*-bromophenacyl esters of the permanganate oxidation product and of the authentic isocaproic acid were identical.

Dihydroalcohol-II, Sebacic Acid and "Dihydroisoalcohol-I" from Decahydrofumagillin.—Fumagillin (10.1 g., 0.0221 mole) was suspended in 250 ml. of 95% ethanol and reduced with Adams catalyst in a Parr shaker (room temperature, 45 lb. hydrogen pressure). The uptake of hydrogen stopped in 15 min., after slightly more than 5 moles had been absorbed. The mixture was filtered and concentrated to approximately 25 ml. in a nitrogen atmosphere. Water (100 ml.) was added and the solution was concentrated further to remove ethanol. A solution of 1.67 g. (0.0418 mole) of sodium hydroxide in 250 ml. of water was added and the mixture was heated on the steam-bath, with stirring, for 1 hr., under nitrogen. The cooled mixture was extracted with ether, concentrated to approximately 50 ml. and acidified with concentrated hydrochloric acid, to yield 3.32 g. of a white solid, m.p. 132–133°. There was no depression in a mixed melting point determination with authentic sebacic acid. The ether extracts were washed with water, dried over anhydrous sodium sulfate, and the ether was evaporated to yield 5.98 g. of a pale yellow, viscous oil. The oil was distilled in a short path still with the major fraction distilling at 125–130° (10^{-2} mm.) as a colorless, viscous oil, $[\alpha]D$ −24.1° (3.7).

Anal. Calcd. for $C_{16}H_{28}O_4$: C, 67.57; H, 9.93. Found: C, 68.08; H, 10.02.

The oil (1.32 g.) in 25 ml. of 95% ethanol was added to a solution of 10 g. of sodium hydroxide in 50 ml. of water (nitrogen atmosphere) and the resulting solution was refluxed on the steam-bath for 4 hr. The ethanol was distilled

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

(20) S. G. Powell, *ibid.*, **53**, 1172 (1931).

off on the steam-bath, causing an oil to separate. The mixture was extracted with ether, the ether extracts were washed with water, dried over anhydrous sodium sulfate, and the ether was evaporated, to yield 0.85 g. of a slightly discolored, viscous oil which gave an infrared spectrum identical with that of the oil which had beend esignated "dihydroisoalcohol-I" (above).

The successive hydrogenation and hydrolysis of fumagillin was repeated, carrying out the hydrogenation in aqueous solution containing one equivalent of sodium hydroxide, and hydrolyzing, after removal of the platinum catalyst, by heating on the steam-bath with a second equivalent of base. This yielded a colorless viscous oil, after distillation in the short-path still, $[\alpha]^{32}D$ −53.2° (1.5), and was designated dihydroalcohol-II. The infrared spectrum was somewhat different from that of the oil, $[\alpha]^{27}D$ −24.1°, described above; however, the bands in the spectrum of the −24.1° sample could be identified with those in the spectrum of the −53.2° sample, and in the spectrum of a sample of "dihydroisoalcohol-I" ($[\alpha]^{25}D$ +10.5°). This indicated that the −24.1° sample was a mixture of the other two.

To confirm this, 1.08 g. of the oil (specific rotation −53.2°) was dissolved in 25 ml. of 95% ethanol and was added to a solution of 5 g. of sodium hydroxide in 25 ml. and refluxed on the steam-bath for 4 hr. The ethanol was evaporated *in vacuo* on the steam-bath and the resulting mixture was extracted with ether. The ether extracts were washed with water, dried over anhydrous sodium sulfate and evaporated, to yield a slightly discolored, viscous oil: $[\alpha]^{29}D$ +13.2° (*c* 1.5). This was distilled in a short-path still at a block temperature of 130° (5×10^{-3} mm.), and an infrared spectrum was obtained which proved identical with that of "dihydroisoalcohol-I."

Diethyl Sebacate from Decahydrofumagillin.—A solution of 10 g. of decahydrofumagillin in a mixture of 280 ml. of alcohol, 450 ml. of water and 40 g. of concd. sulfuric acid (1.35 *N* acid) was heated for 5 hr. on the steam-bath. The reaction mixture was diluted with water, extracted with ether and the extracts were washed thoroughly with 5% sodium carbonate, were dried, and the oil remaining after evaporation of the solvent was distilled in the short-path still. The mobile fraction distilling at 90–100° (block temperature) at 0.05 mm. was redistilled in a micro fractionating column. The product was shown to be ethyl sebacate by elementary analysis and by alkaline hydrolysis to crystalline sebacic acid, identified by a mixed m.p.

Dihydroalcohol-I.—Alcohol-I (7.23 g., $[\alpha]D$ −49°) in ethanol (50 ml.) was hydrogenated at room temperature and pressure in the presence of pre-reduced platinum oxide of poor quality (0.9 g.). The initially rapid uptake was almost complete after one hour, and a total uptake of hydrogen equivalent to 1.10 molar equivalents did not increase after 33 hr. The crude product was dissolved in ether (25 ml.) and adsorbed onto a column of Brockmann grade II alumina (200 g.). Elution with ether (400 ml.) yielded traces of gum, followed by crystalline tetrahydroalcohol-I (425 mg., m.p. 88–89°, $[\alpha]^{27}D$ −66.6° (1.70)) eluted with 1.4 l. of ether. Elution with ethanol–ether (1:125; 1 l.) removed a colorless viscous oil (1.34 g., $[\alpha]^{27}D$ −24.5°) and elution with methanol yielded a light yellow viscous oil (4.82 g., $[\alpha]^{27}D$ −34.9°).

The oils were combined and evaporatively distilled at 10^{-2} mm. at a block temperature of 123–128°, yielding a colorless viscous oil (5.11 g.), $[\alpha]^{27}D$ −32.3° (2.29), having an infrared spectrum virtually identical to that of the alcohol obtained on saponification of decahydrofumagillin.

Anal. Calcd. for $C_{16}H_{28}O_4$: C, 67.57; H, 9.92; O, 22.51. Found: C, 67.30; H, 9.91; O, 22.91; active hydrogen, 1.31 (1.09 equivalents of lithium aluminum hydride was also consumed).

Oxidation of Dihydroalcohol-I with Chromium Trioxide–Pyridine.—Dihydroalcohol-I (1.84 g.) in dry pyridine (15 ml.) was added to chromium trioxide (1.0 g.) in dry pyridine (10 ml.) as described by Sarett, *et al.*[9] After 24 hr. at room temperature, the product was poured into water, extracted with ether, and the ethereal solution washed with 1 *N* hydrochloric acid, water and dried over sodium sulfate. The crude ketone was evaporatively distilled at 3×10^{-4} mm. at a block temperature of 137–143°, yielding a pale yellow, viscous oil (1.20 g., 65%, $[\alpha]^{24}D$ −19.1° (0.93)). The ketone showed a strong carbonyl absorption at 5.81 μ, but still had considerable absorption in the hydroxyl region at 2.94 μ. It showed the characteristic weak peak of a saturated ketone at 278 mμ (1.60).

Anal. Calcd. for $C_{16}H_{26}O_4$: C, 68.05; H, 9.28; O, 22.67. Found: C, 67.50; H, 9.82; O, 22.92.

Acid Hydrolysis of Fumagillin.—Fumagillin (20 g.) was added to a stirred mixture of ethanol (140 ml.) and 2 *N* sulfuric acid (140 ml.) and the suspension was refluxed under nitrogen for 4 hr. The crystalline fumagillin gradually dissolved and an oil separated as the reaction proceeded. The cold mixture was extracted with ether (two 200-ml. portions), diluted with water (250 ml.) and extracted with ether until no further color was removed. The combined ether extracts (*ca.* 1 l.) were separated into acidic and into neutral fractions with 5% sodium carbonate solution. Acidification of the alkaline extracts gave a yellow precipitate which was extracted with ether; a small quantity (0.6 g.) of the solid was ether-insoluble and was shown to be the decatetraenedioic acid.

Removal of solvent from the dried neutral extract left a dark brown viscous oil (7.92 g.) which was undistillable up to 160° at 10^{-4} mm., and which slowly solidified, on standing, to an amorphous powder, $[\alpha]^{26}D$ −26.5° (0.81). Ultraviolet absorption: 273 mμ (4.19); 281 mμ (4.19); infrared (nujol) showed bands, among others, at 2.99, 5.79–5.82 and 6.10 μ. The absence of ultraviolet absorption above 300 mμ is surprising because saponification liberates the decatetraenedioic acid (see below). Possibly lactonization has occurred in the unsaturated acid structure.

Anal. Calcd. for $C_{28}H_{40}O_8$ (the ethyl ester of fumagillin (plus 1 H_2O)): C, 66.64; H, 7.99. Calcd. for $C_{28}H_{40}O_8 \cdot H_2O$: C, 64.35; H, 8.10. Found: C, 65.41, 65.22; H, 7.92, 7.88. The found values agree closely with $C_{28}H_{40}O_8 \cdot {}^1/_2H_2O$.

The acid fraction was isolated as an amorphous yellow solid (11.0 g.), $[\alpha]^{26}D$ −38.4° (0.29); ultraviolet absorption: 334 mμ (4.43), 349 mμ (4.38). The infrared spectrum in nujol showed bands at 2.99, 5.87 and 6.18 μ.

Anal. Calcd. for $C_{26}H_{36}O_8$: C, 65.53; H, 7.61. Calcd. for $C_{26}H_{36}O_8 \cdot H_2O$; C, 63.14; H, 7.75. Found: C, 64.25; H, 7.82. Similar to the compound above, the analysis agrees well with $C_{26}H_{36}O_8 \cdot {}^1/_2H_2O$.

Saponification of the Neutral Fraction: "Alcohol-III."—The neutral compound (4.01 g.) in ethanol (10 ml.) was treated with warm 0.35 *N* sodium hydroxide (45 ml., two equivalents). The mixture became turbid and a sludge formed which was dissolved in ethanol (15 ml.) and dioxane (25 ml.); the final strength of alkali was 0.15 *N*. The dark red solution was refluxed under nitrogen for 3 hr. and the cooled mixture separated into neutral and into acidic fractions.

A small quantity of viscous, orange, neutral oil (520 mg., $[\alpha]^{26}D$ −2.6° (2.07)) was obtained, but the bulk of the reaction product was acidic. Some ether-insoluble decatetraenedioic acid was isolated, but most of the acid fraction was ether-soluble, and was shown to be identical with that obtained in the acidic fraction of the sulfuric acid hydrolysis, $[\alpha]^{26}D$ −27.0° (0.38); infrared absorption (nujol): 2.98, 5.88, 6.19 μ.

Anal. Calcd. for $C_{26}H_{36}O_8$: C, 65.53; H, 7.61. Calcd. for $C_{26}H_{36}O_8 \cdot H_2O$: C, 63.14; H, 7.75. Found: C, 64.66, 64.27; H, 7.51, 7.43. The analysis agrees well with $C_{26}H_{36}O_8 \cdot {}^1/_2H_2O$.

In a repeat experiment, the neutral fraction (4.17 g.) was dissolved in ethanolic sodium hydroxide (0.66 g. in 8 ml., two equivalents) and warmed in a nitrogen atmosphere. The ethanol-insoluble sodium salt was rapidly precipitated. After 0.5 hr. the solvent was removed *in vacuo*, water was added (40 ml., making the alkali strength *ca.* 0.41 *N*) and the solution was heated on a steam-bath for 2 hr. After working up in the usual way, the acid fraction was identified as decatetraenedioic acid (1.1 g. (69%), m.p. 292–294° dec. (uncor.)) and the neutral oil was evaporatively distilled (block temp. 130–135° at *ca.* 2×10^{-4} mm.), yielding a pale yellow, very viscous oil, designated alcohol-III; (1.08 g. (44%). $[\alpha]^{26}D$ −1.7° (4.34)). Infrared absorption: 2.95, 5.86 and 6.12 μ, the latter two bands being very weak.

Anal. Calcd. for $C_{16}H_{26}O_4 \cdot {}^2/_3H_2O$: C, 65.28; H, 9.36; O, 25.36; OCH_3, 10.54. Found: C, 65.79; H, 9.77; O, 24.98; OCH_3, 13.44; active hydrogen, 1.66.

Saponification of the Acidic Fraction.—The crude acid fraction (6.87 g.) was added to a stirred solution of 0.35 *N*

sodium hydroxide (82.8 ml., two equivalents) and heated on a steam-bath in a nitrogen atmosphere for 1 hr. The cold solution was extracted with ether, yielding a small quantity of neutral oil (880 mg., $[\alpha]^{26}D$ −2.6° (3.61)). Acidification of the aqueous layer gave a yellow, granular precipitate (5.0 g.) which was almost completely soluble in ether, and hence was not the decatetraenedioic acid.

The acid fraction (5.0 g.) in ethanol (5 ml.) was treated with ethanolic sodium hydroxide (0.84 g. in 5 ml., two equivalents), causing an immediate precipitate of the sodium salt. After refluxing under nitrogen for 0.5 hr., the solvent was removed under reduced pressure and water added (50 ml., alkali strength *ca.* 0.42 *N*). The clear solution was heated in a nitrogen atmosphere, on a steam-bath for 2.5 hr. On working up in the usual way, the ether-insoluble decatetraenedioic acid was obtained (1.72 g. (80%), m.p. 291–293° dec. (uncor.)) and the neutral fraction was evaporatively distilled at a block temperature of 128–136° at *ca.* 2×10^{-4} mm., yielding a pale yellow, very viscous oil (1.42 g. (45%), $[\alpha]^{26}D$ −5.4° (5.68)). The infrared spectrum was completely identical with that of the "alcohol-III" obtained by saponification of the neutral fraction above.

Anal. Calcd. for $C_{16}H_{26}O_4 \cdot {}^2/_3H_2O$: C, 65.28; H, 9.36; O, 25.36; OCH_3, 10.54. Found: C, 65.46; H, 9.89; O, 24.86; OCH_3, 13.08; active hydrogen, 1.60.

Hydrogenation of the Neutral Fraction.—The neutral compound from the acid treatment of fumagillin (2.11 g.) was dissolved in ethanol (20 ml.) and hydrogenated at room temperature and pressure in the presence of pre-reduced platinum (200 mg.). The initial fairly rapid uptake of three molar equivalents of hydrogen slowed down after 2 hr., and the total uptake after 23 hr. was slightly under four moles. The viscous product was dissolved in ether–methanol (1:1) and filtered through alumina (5 g.). The eluate yielded a pale yellow viscous oil (1.71 g.) which was heated for 2 hr. with 0.35 *N* sodium hydroxide (19 ml., two equivalents) in a nitrogen atmosphere. Saponification under these conditions was incomplete, but was accomplished successfully using two equivalents of 10% alcoholic sodium hydroxide.

The acidic fraction crystallized from aqueous ethanol in colorless leaflets, m.p. 132–133°, undepressed on admixture with an authentic sample of sebacic acid.

The neutral oil was evaporatively distilled (bath temp. 135–145° at *ca.* 10^{-4} mm.) yielding a pale yellow viscous oil, $[\alpha]^{25}D$ −1.4° (1.25), whose infrared spectrum was identical to those of the samples of "alcohol-III" obtained by direct saponification.

Hydrogenation of the Acidic Fraction.—The crude acid (3.0 g.) was dissolved in a mixture of ethanol (15 ml.) and 0.35 *N* sodium hydroxide (27 ml.) and hydrogenated at room temperature and pressure, with prereduced platinum (300 mg.). The slow uptake of hydrogen was complete after 24 hr., when four molar equivalents had been absorbed.

The filtered solution was treated with 0.35 *N* sodium hydroxide (7 ml., total strength 0.24 *N*, two equivalents) and heated under nitrogen for 1 hr. The incomplete saponification yielded a mixture of unchanged acid and sebacic acid; the latter (600 mg.) was recrystallized from aqueous ethanol in colorless leaflets, m.p. 131.5–132.5°, undepressed on admixture with an authentic sample.

The neutral fraction was evaporatively distilled (bath temp. 140–145° at *ca.* 10^{-4} mm.) yielding a pale yellow, viscous oil (315 mg., $[\alpha]^{25}D$ −4.1° (1.26)), whose infrared spectrum was identical with the other "alcohol-III" samples.

Action of Aqueous Ethanolic Sulfuric Acid on Alcohol-I.—Alcohol-I (2.53 g., $[\alpha]^{25}D$ −50°) in ethanol (25 ml.) was treated with 2 *N* sulfuric acid (25 ml.) in a nitrogen atmosphere, and heated on a steam-bath for 2 hr. The colorless solution gradually changed to dark brown; more prolonged heating appeared to lower the final yield. The reaction mixture was concentrated to half-volume, diluted with water and extracted with ether. The washed and dried ethereal solution gave a viscous oil (1.41 g.) which was evaporatively distilled at a bath temperature of *ca.* 150° at 10^{-3} mm. yielding a pale yellow, very viscous oil indistinguishable by infrared spectrum from the "alcohol-III" obtained on saponification of sulfuric acid-treated fumagillin; $[\alpha]^{24}D$ +1.9° (1.22).

Anal. Found: C, 65.03; H, 9.60; O, 25.19.

Action of Acetic Acid on Alcohol-I.—A solution of alcohol-I (2.30 g., $[\alpha]^{25}D$ −51°) in acetic acid (20 ml.) was kept at room temperature for 24 hr. in a nitrogen atmosphere. After removal of acetic acid at room temperature the viscous yellow residue was taken up in ether, washed thoroughly with saturated sodium bicarbonate and water, and dried over sodium sulfate. The product was evaporatively distilled at a block temperature of 120–124° at 3×10^{-4} mm. yielding a colorless, viscous oil, $[\alpha]^{25}D$ −50° (1.57) exhibiting an infrared spectrum identical to alcohol-I.

Attempted Base Isomerization of "Alcohol-III."—A solution of alcohol-III (760 mg., $[\alpha]^{26}D$ −1.7°) in ethanol (10 ml.) was treated with 10% sodium hydroxide (10 ml.) in a nitrogen atmosphere. After refluxing for 3 hr., the solution was concentrated to half volume and the cold mixture extracted with ether. The crude oil was evaporatively distilled (bath temp. 140–150° at 2×10^{-4} mm.) yielding a pale yellow, very viscous oil (490 mg., $[\alpha]^{25}D$ +1.0° (1.95)) having the same infrared spectrum as the starting material.

Attempted Hydrogenation of Alcohol-III.—"Alcohol-III" (1.09 g., $[\alpha]^{26}D$ −5.4°) in ethanol (20 ml.) was hydrogenated at room temperature and pressure with pre-reduced platinum (500 mg.). There was no significant uptake in 6 hr. The resultant oil had $[\alpha]^{25}D$ −3.8° (2.27) and its infrared spectrum was identical to that of the starting material.

"Alcohol-III" (0.99 g., $[\alpha]^{25}D$ +5.0°) in glacial acetic acid (20 ml.) was hydrogenated at room temperature and pressure in the presence of pre-reduced platinum oxide (0.5 g.). After a small uptake of hydrogen in the first hour, no further absorption occurred during 18 hr. The distilled product (690 mg. at a bath temp. of *ca.* 145° at 10^{-3} mm.) had $[\alpha]^{26}D$ +2.5° (2.74) and exhibited the same infrared spectrum as the starting material.

Dehydrogenation Experiments.—A total of six runs was carried out with selenium on amounts of 1–6 g. of the crystalline tetrahydroalcohol-I or the viscous product from the same reduction. The same general results were obtained from the two materials. The products distilling from the dehydrogenation mixture were collected in a small cup sealed to the bottom of a cold finger; the residue remaining in the flask was completely decomposed. The condensed product consisted of two liquid phases, one containing water and methanol, and the other containing water-insoluble material. The presence of methanol was demonstrated by oxidation with permanganate to formaldehyde and identification of this by color formation with chromatropic acid.[21]

The following procedure is representative. Selenium (11.0 g.) was heated with 6.1 g. of the viscous reduction product from alcohol-I. The temperature was raised slowly to 300° and kept at 320–330° for 8 hr.; the condensed product was removed periodically. The condensate consisted of two layers; the water-insoluble layer (1.73 g.) was taken up in ether and, by extraction with 2 *N* alkali, 80 mg. of alkali-soluble material was obtained. This showed the phenolic ultraviolet spectrum described above, and had a phenolic odor. Attempts to obtain solid derivatives and to get information by various color tests were not successful.

The neutral fraction amounted to 1.315 g., and as it had not been found practical in earlier runs to separate it by distillation, it was chromatographed on 30 g. of alumina. In some runs, a neutral material of b.p. about 95° was present, which appeared to be an aliphatic ether, but it could not be identified conclusively.

The crude product appeared to contain selenium, because a red product, probably selenium dioxide, was formed at once on the alumina. Elution of the column by hexane, then with hexane–ether, and finally with ether, gave a total of 10 fractions, whose ultraviolet spectra were determined. Fraction 4 was distilled, and the product showed $n^{27}D$ 1.5355; the value for 3,5-dimethylbenzofuran was $n^{23}D$ 1.5458. The third and fourth fractions, totaling 363 mg., showed the ultraviolet spectrum characteristic of 3,5-dimethylbenzofuran; this compound also gave an orange-yellow color in concd. sulfuric acid, very similar to that given by the dehydrogenation product. The latter would not form a picrate, a reaction which does occur with 3-methylbenzofuran, but not with the 3-ethyl compound.

Ozonization Experiments. A. 3,5-Dimethylbenzofuran.—This compound (300 mg.) in 2 ml. of carbon tetrachloride was ozonized for 1 hr. at 0°. The solvent was removed, the residue was heated with a little water for 30 min., the product was taken up in ether, and extracted with sodium

(21) F. Feigl, "Spot Tests," Nordemann, New York, N. Y., 1939, p. 329.

bicarbonate, which removed only a trace of material; sodium hydroxide extraction removed most of the product, which gave a ferric chloride test and the ultraviolet spectrum given above.

B. Of the Dehydrogenation Product.—Fraction 3 (183 mg.), which had the benzofuran spectrum, although it did not appear to be as pure as some other fractions, was ozonized as above; the sodium hydroxide-soluble fraction (2–4 mg.) gave the ultraviolet spectrum reported above, and showed infrared bands at 3.31, 3.41, 5.89 and 6.12 μ, identical with the model compound.

Hydrogenation Experiments. A. 3,5-Dimethylbenzofuran.[22]—Reduction of 5.7 g. of this material (n^{23}D 1.5458) in ethanol with Raney nickel and hydrogen at 2 atm. for 48 hr. gave 4.4 g. of product after distillation; b.p. 100–104° (24 mm.), n^{23}D 1.5269; ultraviolet absorption, 228 (3.64); 287 (3.48). This product is presumably 3,5-dimethyl-2,3-dihydrobenzofuran, which has not been described very thoroughly.[23]

B. Of the Dehydrogenation Product.—The product (50 mg.) was hydrogenated under the above conditions, and also at 100° and 40 atm. of hydrogen, but appeared from its ultraviolet spectrum and the color in concentrated sulfuric acid, to be unchanged. The reduction experiments appeared to remove some selenium-containing impurity, because the product after attempted reduction, smelled much more like 3,5-dimethylbenzofuran. The failure of the dehydrogenation product to reduce is perhaps to be expected if it has a large group in the 3-position.

Acknowledgment.—We are indebted to Dr. J. R. Schenck, Dr. R. D. Coghill and Dr. D. W. MacCorquodale of Abbott Laboratories for their interest and assistance in this problem.

(22) R. L. Shriner and J. Anderson, THIS JOURNAL, **61**, 2705 (1939), showed that 2-substituted benzofurans could be reduced catalytically with Raney nickel at low temperature and pressure.

(23) German Patent 501,723 (*C. A.*, **24**, 4793 (1930)); J. B. Niederl and E. A. Storch, THIS JOURNAL, **55**, 4549 (1933).

ROCHESTER, NEW YORK

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Quinol Imides and *o*-Quinone Imide Diacetates. I. Conversion of 4-Benzenesulfonamidotriphenylmethane to 4-Benzohydryl-*o*-quinonediacetate-1-benzenesulfonimide

BY ROGER ADAMS, E. J. AGNELLO AND RICHARD S. COLGROVE[1]

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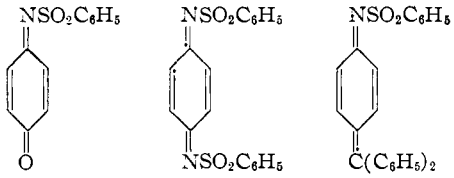
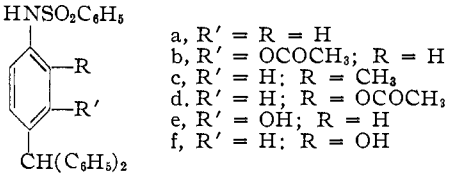
4-Benzenesulfonamidotriphenylmethane is oxidized by lead tetraacetate in glacial acetic acid to give two compounds, the chief one 4-benzohydryl-*o*-quinonediacetate-1-benzenesulfonimide and the secondary one 2-benzenesulfonamido-5-benzohydryl-*p*-benzoquinone. The structures, the addition reactions and the mechanism of formation and reactions of these two compounds are discussed. The 3-methyl derivative of 4-benzenesulfonamidotriphenylmethane gives upon oxidation an analogous compound which adds reagents; the entering groups are probably *para* to the methyl group in all cases.

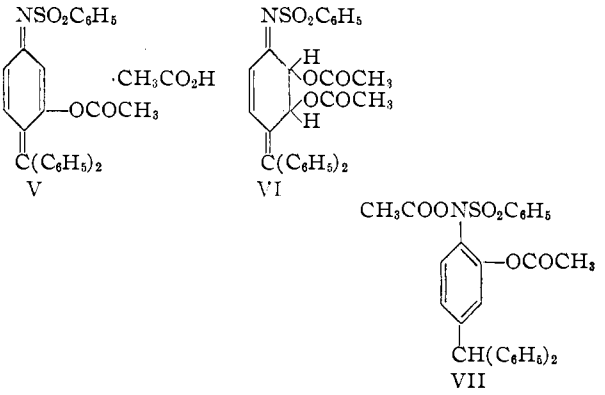
Previous studies have shown that *p*-quinonemonobenzenesulfonimide (I)[2] and *p*-quinonedibenzenesulfonimide (II)[3] are stable compounds which exhibit many of the reactions of *p*-quinones. Since fuchsonebenzenesulfonimide (III) is closely related structurally to I and II, it has been the subject of investigation in order to compare its properties with those of its oxygen congener, fuchsone.



4-Benzenesulfonamidotriphenylmethane (IVa) used as the raw material in attempts to synthesize III was prepared by the following sequence of reactions: condensation of benzohydrol and acetanilide in refluxing glacial acetic acid, hydrolysis of the acetylamino group with 30% sulfuric acid followed by benzene sulfonation of the amino group in pyridine solution. Quinone imides generally are prepared by oxidation of the corresponding amides with lead tetraacetate in either acidic or neutral solvents. Upon oxidation of IVa with two or more



mole equivalents of lead tetraacetate in glacial acetic acid the formation of III was anticipated. Instead, two compounds resulted, the chief one of which had the empirical structure of III with two moles of acetic acid added. Three possible formulas for this compound first were proposed as shown in V, VI and VII, but all proved to be untenable on various grounds.



Structure V could be formed by oxidation of IVa to III followed by 1,4-conjugate addition of acetic acid[4] to give structure IVb. Compound IVb,

(1) An abstract of a thesis submitted by Richard S. Colgrove to the Graduate College of the University of Illinois, 1954, in partial fulfillment of the requirements for the degree of Doctor of Philosophy; University of Illinois Fellow, 1950–1951; Minnesota Mining and Manufacturing Co. Fellow, 1951–1952; American Cyanamid Co. Fellow, 1952–1953.

(2) R. Adams and J. H. Looker, THIS JOURNAL, **73**, 1145 (1951).

(3) R. Adams and A. S. Nagarkatti, *ibid.*, **72**, 4601 (1950).

(4) R. Adams and D. S. Acker, *ibid.*, **74**, 3657 (1952).