of AMP, and the latter group is then displaced by the thiol group of CoA in reaction (3′). The acyl CoA derivative is readily decomposed by H_2NOH. Thus, the increasing order of affinity for the acyl group is $-PO_3OH$, $-SH$ and $-NHOH$, *i.e.*, in order of increased basicity.

Acknowledgment.—The authors are indebted to Mrs. Enid Vercamer for her assistance in carrying out the enzymatic assays, and to Dr. Gordon Kilgour for helpful discussions regarding the chemical synthesis of BuAMP.

SEATTLE, WASHINGTON

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

The Chemistry of Fumagillin. IV. The Presence of an Epoxide Grouping and Other Observations on the Nature of the Oxygen Functions[1]

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The alcohol moiety of fumagillin, alcohol-I ($C_{16}H_{26}O_4$), has been obtained crystalline and has been shown to contain an epoxide grouping. Reduction of alcohol-I with lithium aluminum hydride under mild conditions opens the epoxide ring to give a crystalline diol, dihydroalcohol-Ib ($C_{16}H_{28}O_4$), which can be reduced catalytically to give the previously described crystalline tetrahydroalcohol-Iab. Also formed in this reduction are tetrahydroalcohol-Ib, a triol ($C_{16}H_{30}O_4$), in which both the epoxide ring and another cyclic ether grouping have been opened and tetrahydronoralcohol-I ($C_{15}H_{28}O_4$), a triol which has lost one carbon. Reduction of alcohol-I, dihydroalcohol-Ib and tetrahydroalcohol-Iab by lithium aluminum hydride in refluxing tetrahydrofuran gives as main products the C_{16} triols formed by reductive cleavage of the second cyclic ether group, as well as the C_{15} "nor" triols. The ketone ($C_{16}H_{28}O_4$) obtained by oxidizing tetrahydroalcohol-Iab with chromium trioxide–pyridine has been shown to contain one free methylene adjacent to the carbonyl group, by the preparation of a crystalline monofurfurylidene derivative.

Alcohol-I ($C_{16}H_{26}O_4$), which, along with decatetraenedioic acid, is obtained by the alkaline hydrolysis of the antibiotic fumagillin,[3–5] has now been obtained crystalline, $[\alpha]^{23}D$ -68.0, m.p. 55.5–56°. Earlier studies[5] showed that catalytic reduction of alcohol-I with hydrogen and platinum in ethanol yielded a crystalline diol, tetrahydroalcohol-Iab[6] ($C_{16}H_{30}O_4$), in which the double bond in the side chain had been reduced, and a cyclic ether linkage had been hydrogenolyzed to generate a new hydroxyl group. Alcohol-I also consumed one equivalent of lithium aluminum hydride, in addition to the equivalent which reacted with the hydroxyl group. This behavior suggested the presence of an epoxide group in alcohol-I; we have been able to establish the presence of an epoxide group in alcohol-I, and its absence in tetrahydroalcohol-Iab, by the following quantitative methods: the thiosulfate method,[7] the ethereal hydrogen chloride procedure[8] and the periodate–perchloric acid method.[9] The quantitative results showed 70–95% of the theoretical amount of epoxide in alcohol-I; however, the epoxide function in alcohol-I must be fairly highly substituted,[5] and it has been shown that these methods do not yield the theoretical values when applied to highly substituted ethylene oxides.[10] These results, in conjunction with those below, effectively rule out other possible cyclic ether groupings, such as a trimethylene oxide ring.[11]

Treatment of alcohol-I with lithium aluminum hydride in ether at 0° for 24 hr. gave a 66% yield of the crystalline diol, dihydroalcohol-Ib ($C_{16}H_{28}O_4$), m.p. 53°, in addition to the triols, tetrahydroalcohol-Ib ($C_{16}H_{30}O_4$), and tetrahydronoralcohol-I ($C_{15}H_{28}O_4$) discussed below. One of the two hydroxyl groups in dihydroalcohol-Ib must have resulted from hydrogenolysis of the epoxide group. Crystalline dihydroalcohol-Ib and tetrahydronoralcohol-I were obtained in 41 and 33% yield, respectively, by the action of sodium borohydride on alcohol-I in boiling methanol; no dextrorotatory material (*i.e.*, no tetrahydroalcohol-Ib) was obtained. Sodium borohydride thus can open the epoxide ring but not the second ether linkage. Catalytic reduction of the double bond in the side chain of dihydroalcohol-Ib yielded the same crystalline tetrahydroalcohol-Iab, m.p. 89°, which was previously[5] obtained by catalytic reduction of alcohol-I. This proves that the opening of the epoxide ring catalytically, to form tetrahydroalcohol-Iab, and by lithium aluminum hydride to form dihydroalcohol-Ib takes place in the same direction.[12]

The same reactions can be run in the reverse order. Alcohol-I, reduced catalytically with one

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[2] Inquiries regarding this paper should be addressed to this author.

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

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

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

[6] It has seemed advisable, in the interests of brevity and clarity, to adopt the naming system employing letters. The material now designated tetrahydroalcohol-Iab was previously[5] called tetrahydroalcohol-I.

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

[8] D. Swern, T. W. Findley, G. N. Billen and J. T. Scanlan, *Anal. Chem.*, **19**, 414 (1947).

[9] A. M. Eastham and G. A. Latremouille, *Can. J. Research*, **28B**, 264 (1950).

[10] W. J. Hickinbottom and D. G. M. Wood, *J. Chem. Soc.*, 1600 (1951); A. F. Millidge, D. P. Young and co-workers, *ibid.*, 2161, 2170, 2180 (1954).

[11] For recent observations on the trimethylene oxide system, *cf.* S. Searles, THIS JOURNAL, **73**, 124, 4515 (1951); **76**, 56, 2789 (1954); G. Büchi, C. G. Inman and E. S. Lipinsky, *ibid.*, **76**, 4327 (1954).

[12] This two-step procedure is a better preparative method for tetrahydroalcohol-Iab than the one-step catalytic reduction because many samples of platinum catalyst are not effective[5] in producing the crystalline tetrahydroalcohol-Iab.

mole of hydrogen, gave dihydroalcohol-Ia, in which the double-bond was reduced, but the epoxide ring was intact; treatment of this compound with lithium aluminum hydride in ether for a short time gave the crystalline tetrahydroalcohol-Iab.

Treatment of alcohol-I with lithium aluminum hydride in boiling tetrahydrofuran yielded two products, tetrahydronoralcohol-I ($C_{15}H_{28}O_4$), which will be discussed later, and tetrahydroalcohol-Ib ($C_{16}H_{30}O_4$). The significant point about this latter product is that it is a triol, and hence the more vigorous reducing conditions have split both the epoxide ring and a second cyclic ether group. Since the methoxyl group present[4,5] in alcohol-I is still intact, all of the four oxygen atoms are accounted for. The triol nature of the product was established by preparation of a triacetate, which had the proper composition and acetyl number, as well as by active hydrogen determinations.

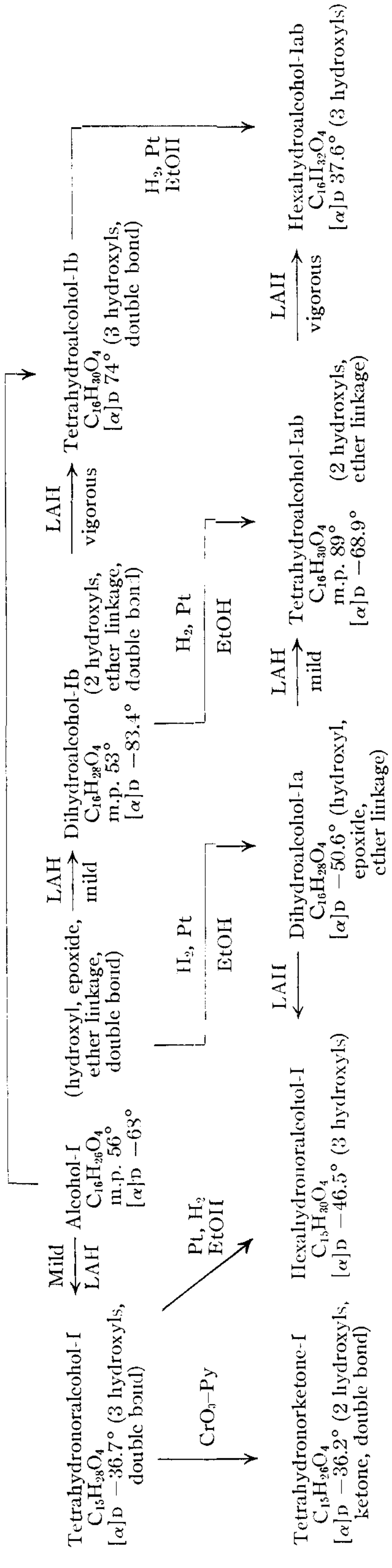
The side chain double bond in tetrahydroalcohol-Ib was readily reduced by platinum and hydrogen, giving the triol, hexahydroalcohol-Iab ($C_{16}H_{32}O_4$). This latter compound was also obtained by vigorous lithium aluminum hydride reduction of dihydroalcohol-Ia, in which the side chain is already reduced, and by the same procedure from tetrahydroalcohol-Iab.[13] The relationships between these compounds are set out in Chart I; it is seen that the complete set of compounds has been prepared, in which the side chain double bond, the epoxide group and the other cyclic ether have been reduced.

Reduction of alcohol-I and of dihydroalcohol-Ia with lithium aluminum hydride in boiling tetrahydrofuran yielded, in addition to the C_{16} triols, as has been mentioned, compounds whose composition agreed well for C_{15} formulas. The relationships are shown on the chart, and the carbon atom which has been lost is not the methoxyl carbon, since that is still present in the *nor* compounds. Active hydrogen determinations show that the *nor* series are triols, in which both the epoxide and the other cyclic ether group have been reductively cleaved. Tetrahydronoralcohol-I was reduced catalytically to the hexahydronoralcohol-I, a compound also obtainable by treatment of dihydroalcohol-Ia with lithium aluminum hydride. If these C_{15} formulas are correct, the most reasonable explanation for the loss of a carbon would be a reverse aldol reaction involving the loss of a molecule of formaldehyde or its equivalent.[14]

The composition of the ketone obtained by Sarett oxidation of tetrahydronoralcohol-I provides further evidence for the C_{15} formula.

Some information was gained about the structure of the tetrahydroketone, obtained[5] by Sarett oxidation of tetrahydroalcohol-Iab. This ketone formed a crystalline furfurylidene derivative, m.p.

Chart I[a]



[a] A methoxyl group is present in all compounds.

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[13] The previous statement[5] that this alcohol was unaffected by lithium aluminum hydride was based on a run in ether at room temperature and on an analytical active hydrogen determination.

[14] Alcohol-I and tetrahydroalcohol-Iab gave negative Labat tests for the methylenedioxy group (*Bull. soc. chim.*, **5**, 745 (1909)). A cleavage reaction involving a reverse aldol condensation, caused by an organometallic compound, which is somewhat analogous to the one suggested above, is reported by E. P. Kohler, N. K. Richtmyer and W. F. Hester, This Journal, **53**, 205 (1931).

96–96.7°, when treated with furfural and aqueous alkali. The ultraviolet absorption spectrum[15] of this compound, 229 (3.87), 339 (4.29), agreed with that expected for a monofurfurylidene derivative[16] and showed clearly that it was not a bis-derivative[17]; this was confirmed by the analytical data, including the methoxyl value. The infrared spectrum showed bands (among others) at 3322 cm.$^{-1}$ (hydroxyl), 1661 cm.$^{-1}$ (conjugated carbonyl) and 1577 cm.$^{-1}$ (double bond conjugated with furan ring).[18]

Bromination of the tetrahydroketone yielded a rather unstable product whose bromine content was between that of a dibromo and tribromo derivative. This is in agreement with the presence of three alpha hydrogens, adjacent to the carbonyl group.

It has not been demonstrated that the carbonyl oxygen in the tetrahydroketone corresponds to the hydroxyl group of alcohol-I which is esterified in fumagillin; the possibility of rearrangement during the Sarett oxidation has not been ruled out. However, the above observations do show that the tetrahydroketone contains one (and presumably only one) methylene group adjacent to the carbonyl group.

A number of oxidations of dihydroalcohol-Ia were investigated, using permanganate in acetone; careful paper chromatography of the acidic products indicated the presence of isocaproic, isovaleric and isobutyric acids. No evidence was obtained for the presence of other acids, monobasic or dibasic.

Discussion of the bearing of the observations reported in this paper on the structural problem posed by alcohol-I will be deferred.

Experimental[19]

Crystalline Alcohol-I.—Fumagillin (20 g.) was saponified and distilled[5]; the product (53%) crystallized after standing a week at room temperature. The crude crystalline product (7.9 g., m.p. 37–43°) was chromatographed on 160 g. of acid-washed alumina, using petroleum ether–ether (20:1). The main fraction (4.8 g., m.p. 40–47°, $[\alpha]_D$ −55 to −58°) was rechromatographed on 100 g. of alumina. The fraction eluted with petroleum ether–ether (15:1) was crystallized from petroleum ether at 0°, giving a 93% recovery of colorless crystals, m.p. 54.5–55.5°; $[\alpha]^{23}_D$ −68.0° (1.73). A purer sample melted at 55.5–56°.

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; active hydrogen, 1. Found: C, 68.22; H, 9.60; O, 22.91; OCH_3, 10.68; C-methyl, 10.43; active hydrogen, 1.06 (1.29 eq. consumed).

In later runs, fumagillin (20 g., twice recrystallized from methanol) was saponified by adding to hot aqueous sodium hydroxide (242 ml., 0.35 *N*). The reaction yielded, when worked up in the usual way, 9.62 g. (72%) of distilled alcohol-I, which was collected in 4 fractions. All 4 fractions crystallized spontaneously after standing several days at 0° and showed $[\alpha]_D$ 63.6° to −53.5°.

Ketone-1.—A sample of oily alcohol-I ($[\alpha]_D$ −54°) was oxidized to the ketone with chromic oxide–pyridine, as previously described.[5] The crude ketone was chromatographed, and the fractions eluted with petroleum ether–ether 10:1 and 5:1 were combined and evaporatively distilled at 10^{-4} mm. (block temperature 113–125°). The colorless mobile ketone (main fraction, $[\alpha]^{27}_D$ −49.7° (1.03)) gave negative results in the iodoform reaction, the Fehling test and the Schiff test; it did, however, cause blackening of Tollens reagent, as did samples of the oily alcohol-I; the crystalline alcohol-I gave a negative Tollens reaction. Unlike the tetrahydroketone-I (see below), ketone-I did not form a furfurylidene derivative in good yield; a trace of crystalline material was obtained, which showed the spectral properties expected; ultraviolet, 222 (3.19); 320 (4.04); infrared bands (among others) at 3367, 1675 and 1595 cm.$^{-1}$. The main product of the attempted furfurylidene derivative preparation was a levorotatory oil.

Qualitative Determination of Epoxide in Alcohol-I and Related Compounds.—The compounds mentioned below were tested[6] for epoxide content by treating the alcohol (20–50 mg.) in 15 ml. of pure acetone with 5 ml. of 0.1 *N* sodium thiosulfate and one drop of phenolphthalein indicator, followed by warming on the steam-bath. The development of a strong permanent (at least 1 hr.) red color was considered a positive test. The following gave positive tests: alcohol-1, dihydroalcohol-Ia, the viscous oil[5] formed along with tetrahydroalcohol-Iab in catalytic reduction of alcohol-I. Negative results were given by dihydroalcohol-Ib and tetrahydroalcohol-Iab. Alcohol-III[5] and tetrahydronoralcohol-I gave a faint permanent color.

Quantitative Determination of Epoxide in Alcohol-I. I. Thiosulfate Method of Ross.[7]—Alcohol-I (269 mg., $[\alpha]_D$ −57°) in pure acetone (2 ml.) was treated with 0.2 *M* sodium thiosulfate in 50% aqueous acetone (40 ml.) containing phenolphthalein indicator (3 drops). The mixture was heated under gentle reflux in an apparatus arranged so that the tip of a 10-ml. buret was directly above the surface of the boiling solution. Standardized 0.2 *N* acetic acid was added dropwise from the buret so as to maintain only a faint pink color in the reaction mixture. The reaction was initially fairly rapid, an amount of acetic acid equivalent to 0.5 mole of hydroxyl ion being added in 15 min.; the reaction was virtually complete after 45 min., and the final value after 2 hr. corresponded to the presence of 83% epoxide oxygen. In a similar experiment, using a less pure sample of alcohol-I ($[\alpha]_D$ −51°), the final value was equivalent to 72% epoxide oxygen.

II. **Chlorohydrin Method of Swern, *et al.***[8] **(a).**—Alcohol-I (937 mg., $[\alpha]_D$ −51°) in absolute ether (5 ml.) was treated with 0.2 *N* anhydrous hydrochloric acid in absolute ether (25 ml.) and kept at room temperature (29°) for 3 hr. Three blanks were run concurrently. The reaction mixtures were treated with 95% ethanol (50 ml.) and phenolphthalein indicator (1 ml., 2% solution) and titrated with standard 0.1 *N* sodium hydroxide. Whereas the blanks were readily titratable to a sharp end-point, the chlorohydrin gave a very unsatisfactory end-point, the red color due to the indicator near the end-point gradually fading until the base added was virtually the same as for the blanks (the value obtained corresponded to 9% epoxide present).

(b).—Alcohol-I (887 mg., $[\alpha]_D$ −55°) was treated as above and kept at room temperature for 3 hr.; three blanks were run concurrently. The HCl-ether mixture was then removed from the alcohol-I solution by distillation under reduced pressure, in a closed system. Titration of the distillate with standard alkali gave a value corresponding to a maximum of 95% reaction with the epoxide. The crude residue from the distillation was dissolved in 95% ethanol (50 ml.) and titrated with base with some difficulty; the reaction with sodium hydroxide gradually slowed up, and when the pink color of the indicator remained permanent for 15 min. at 70°, the amount of chlorohydrin, and therefore of epoxide, was equivalent to a minimum of 68%.

III. **Periodate Method of Eastham and Latremouille.**[9] **(a).**—Samples of alcohol-I (*ca.* 350 mg., $[\alpha]_D$ −55°) in absolute methanol (10 ml.) were treated with 60% perchloric acid (1 ml.) and 0.527 *M* periodic acid (5 ml.), and made up

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

(16) E. C. Hughes and J. R. Johnson, THIS JOURNAL, **53**, 737 (1931).

(17) H. Stobbe and R. Haertel, *Ann.*, **370**, 99 (1909).

(18) E. R. Blout, M. Fields and R. Karplus, THIS JOURNAL, **70**, 194 (1948).

(19) We are indebted to Mr. E. F. Shelberg and his associates of Abbott Laboratories for the microanalyses and to Mr. Carl Whiteman of these laboratories for infrared spectra; these were determined using Nujol mulls for solids and no solvent for oils. Rotations and ultraviolet spectra were all taken in 95% ethanol; chromatograms were carried out using Fisher alumina of grade III (Brockmann and Schodder, *Ber.*, **74**, 73 (1941)). It is essential to develop chromatograms slowly, changing the polarity of the solvents gradually, to get the separations described; several liters of solvents were used on most chromatograms. Purified solvents were used for all chromatograms; petroleum ether refers to material of b.p. 30–60°; m.p.'s are uncorrected.

to 25-ml. volume with water. Addition of the peracids to the blanks, run concurrently, caused heat to be evolved but no color change; the alcohol-I samples become warm, turned yellow with perchloric acid, then violet with periodic acid, which faded to yellow in a few minutes. Aliquots (5 ml.) were removed at intervals, neutralized with solid sodium hydrogen carbonate and titrated in the usual manner by the arsenite method.

The percentage of epoxide determined was 50 after 2 hr. reaction and increased to 70–78% after 20 hr.; it was no greater after 48 hr.

Reduction of Alcohol-I with Lithium Aluminum Hydride; Formation of Dihydroalcohol-Ib, Tetrahydronoralcohol and Tetrahydroalcohol-Ib.—Alcohol-I (10.35 g., $[\alpha]_D$ −58°) in 250 ml. of dry ether was added slowly to a vigorously stirred suspension of an excess (*ca.* 12 g.) of lithium aluminum hydride in 350 ml. of dry ether, the reaction being kept below 0° in an ice–salt bath. After addition of the alcohol-I was completed (2 hr.), the stirring was continued for 6 hr., and the reaction mixture was kept below 0° for a further 18 hr. The excess of reducing agent was destroyed by cautious addition of wet ether to the cold mixture, water (200 ml.) was added and the resulting mixture was extracted with four 100-ml. portions of ether. Evaporation of the dried ether extracts gave 10.16 g. of colorless oil, which was dissolved in petroleum ether–ether (6:1) and chromatographed on 180 g. of alumina. Elution with 5:1 and 3:1 petroleum ether–ether gave **dihydroalcohol-Ib**, as a crystalline solid, m.p. 51–52° (6.82 g., 66%). The analytical sample (prepared in another run) formed fine needles, after recrystallization from petroleum ether; m.p. 53–53.5°, $[\alpha]^{24}_D$ −83.4° (1.03).

Anal. Calcd. for $C_{16}H_{28}O_4$: C, 67.57; H, 9.92; O, 22.51; OCH_3, 10.83; active hydrogen, 2.00. Found: C, 67.42; H, 9.95; O, 22.96; OCH_3, 10.47; active hydrogen, 2.07.

Elution of the column with 1:1 and 1:2 petroleum ether–ether gave 1.69 g. (17%) of **tetrahydronoralcohol-I**, $[\alpha]^{24}_D$ −36.7° (0.78). The rotation and infrared spectrum of this sample were identical with those of a sample prepared in an earlier run, which was analyzed.

Anal. Calcd. for $C_{15}H_{28}O_4$: C, 66.14; H, 10.36; O, 23.50; active hydrogen, 3.00; OCH_3, 11.39. Found: C, 66.15; H, 10.33; O, 23.46; active hydrogen, 2.75; OCH_3, 10.29.

Elution of the column with ether gave **tetrahydroalcohol-Ib** (1.56 g. 15%) as a colorless viscous oil, $[\alpha]^{25}_D$ 56.5° (0.43). This had the same infrared spectrum as the sample described below.

Sodium Borohydride Reduction of Alcohol-I.—Sodium borohydride (*ca.* 3 g.) in 100 ml. of absolute methanol was added slowly (3 hr.) to a boiling solution of alcohol-I (1.76 g., $[\alpha]_D$ −51°) in 30 ml. of the same solvent. The mixture was refluxed for 3 hr., more borohydride (*ca.* 3 g.) in methanol was added slowly, and the solution was refluxed for 3 hr. more. The volume of the solution was reduced to about 50 cc., water was added and most of the methanol was removed *in vacuo*. The resulting oil was extracted with ether, the solution was dried and the solvent was removed. Chromatography of the product, essentially as described above, yielded 0.73 g. (41%) of crystalline dihydroalcohol-Ib, m.p. 52.5–53°, undepressed upon admixture with an authentic sample. Further elution gave 0.57 g. (34%) of tetrahydronoralcohol-I, $[\alpha]_D$ −26.7 to −30°, with the same infrared spectrum as an authentic sample. No dextrorotatory material was obtained by elution of the column with ether or methanol; hence tetrahydroalcohol-Ib appeared to be absent.

Lithium Aluminum Hydride Reduction of Alcohol-I in Refluxing Tetrahydrofuran: Tetrahydronoralcohol-I and Tetrahydroalcohol-Ib.—Alcohol-I (5.91 g., $[\alpha]_D$ −55°) was refluxed with lithium aluminum hydride in tetrahydrofuran for 24 hr. The product was chromatographed in the usual way, which yielded 1.52 g. of crude tetrahydronoralcohol-I, $[\alpha]_D$ −21 to −36°. Elution with petroleum ether–ether (1:3) gave 1.83 g. of slightly colored viscous product, $[\alpha]_D$ 54 to 71°. Distillation at 10^{-4} mm. yielded tetrahydroalcohol-Ib as a colorless viscous oil, $[\alpha]^{24}_D$ 73.5° (1.29).

Anal. Calcd. for $C_{16}H_{30}O_4$: C, 67.09; H, 10.56; O, 22.35; OCH_3, 10.83; active hydrogen, 3.00. Found: C, 67.12; H, 11.21; O, 22.30; OCH_3, 10,41; active hydrogen, 3.00 (no reagent consumed).

Triacetyltetrahydroalcohol-Ib.—The undistilled alcohol (510 mg., $[\alpha]_D$ 52°) was heated on the steam-bath for 2 hr. in a mixture of 2 ml. of pyridine and 5 ml. of acetic anhydride. After working up in the usual way, the crude product was distilled at 5 × 10^{-4} mm. (bath temperature 120°); the triacetate (200 mg., $[\alpha]_D$ 36.6° (0.42)) was obtained as a colorless mobile oil.

Anal. Calcd. for $C_{22}H_{36}O_7$: C, 64.05; H, 8.80; O, 27.25; active hydrogen, 0.0; acetyl, 31.30. Found: C, 63.63; H, 8.90; O, 27.57; active hydrogen, trace; acetyl, 33.33.

Catalytic Hydrogenation of Dihydroalcohol-Ib to Tetrahydroalcohol-Iab.—The dihydroalcohol-Ib (570 mg., m.p. 51.5–52.5°, ($[\alpha]^{24}_D$ −84°)) in 25 ml. of ethanol was hydrogenated at room temperature and pressure with prereduced platinum; the rapid uptake of hydrogen was virtually complete in 20 min., when 1 mole had been absorbed. After removal of catalyst and solvent, the partially crystalline product was dissolved in 15 ml. of petroleum ether and allowed to stand at room temperature for 16 hr. The resulting crystals were recrystallized from petroleum ether at 0°, and 300 mg. (53%) of tetrahydroalcohol-Iab (colorless octahedra, m.p. 88–88.4°) was obtained, which showed no depression on mixed m.p. with an authentic sample.

Lithium Aluminum Hydride Reduction of Dihydroalcohol-Ia to Tetrahydroalcohol-Iab.—Dihydroalcohol-Ia[20] (4.17 g., $[\alpha]_D$ −45°) in 50 ml. of ether was added during 2 min. to a rapidly stirred solution of lithium aluminum hydride (2 g.) in 150 ml. of ether, the mixture was refluxed vigorously with stirring for 10 min., and the excess hydride was decomposed by addition of ethyl acetate. The reaction yielded, when worked up in the usual way, 3.43 g. (82%) of colorless viscous oil. A solution of 2.80 g. of the crude product in 25 ml. of petroleum ether was chromatographed on 60 g. of alumina; no material was eluted with petroleum ether or petroleum ether–ether (10:1). Elution with petroleum ether–ether (4:1) gave crystalline tetrahydroalcohol-Iab (1.56 g., 56% of material put on column). The main fractions had m.p. 86.5–87.5° and showed no depression on mixed m.p. with an authentic sample. Elution of the column with ether, and with methanol, gave oils (1.05 g., 37%) whose rotations varied between −42 and +20°. The fractions with rotations of *ca.* −40° yielded, when rechromatographed, a product with an infrared spectrum identical with that of authentic hexahydronoralcohol-I.

Catalytic Hydrogenation of Tetrahydronoralcohol-I to Hexahydronoralcohol-I.—The pure alcohol (1.20 g., $[\alpha]_D$ −36.6°) in 20 cc. of ethanol was hydrogenated in the usual way at room temperature and pressure with 250 mg. of prereduced platinum. The uptake of hydrogen had ceased after 18 hr., at which time 95% of 1 mole had been absorbed. The product was worked up in the usual way and was purified by distillation in the short path still at 10^{-4} mm. (bath temperature 140°); the product (895 mg.) was a colorless, very viscous oil (almost a glass), $[\alpha]^{26}_D$ −38.4° (3.54).

Anal. Calcd. for $C_{15}H_{30}O_4$: C, 65.65; H, 11.02; O, 23.32; OCH_3, 11.31; active hydrogen, 3.00. Found: C, 65.78; H, 10.78; O, 23.82; OCH_3,[21] 9.70; active hydrogen, 2.96.

Lithium Aluminum Hydride Reduction of Tetrahydroalcohol-Iab to Hexahydroalcohol-Iab.—The alcohol (1.59 g., m.p. 83–84°) in 30 ml. of tetrahydrofuran was added to a stirred solution of 1.0 g. of lithium aluminum hydride in 25 ml. of the same solvent, and the mixture was refluxed gently for 24 hr. The pale yellow viscous oil (1.08 g., 68%) which was obtained by working up in the usual way, was chromatographed on 20 g. of alumina, using petroleum ether–ether (7:1). Elution with petroleum ether–ether (6:1 and 4:1) removed levorotatory material (660 mg., $[\alpha]_D$ −7° to −30°). Elution with the same solvents (2:1) and with ether gave dextrorotatory material (447 mg., $[\alpha]_D$ 47 to 48°); short path distillation of this at 5 × 10^{-4} mm. gave the product, $[\alpha]^{24}_D$ 54.1° (1.58). Comparison of the infrared spectra showed it to be identical with the two

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(20) Prepared by catalytic reduction of alcohol-I at room temperature and pressure with platinum and alcohol, with an uptake of 1 mole of hydrogen; $[\alpha]_D$ −51 to −47°, after purification by chromatography followed by short path distillation; the analysis agreed with $C_{16}H_{28}O_4$. This material was reported previously[5] to have $[\alpha]_D$ −32.3°.

(21) This methoxyl determination was run on a sample prepared by lithium aluminum hydride reduction of dihydroalcohol-Ia (below).

samples of hexahydroalcohol-Iab prepared by lithium aluminum hydride reduction of dihydroalcohol-Ia and by catalytic reduction of tetrahydroalcohol-Ib,

Anal. Calcd. for $C_{16}H_{32}O_4$: C, 66.63; H, 11.18; O, 22.19; active hydrogen, 3.00. Found: C, 66.50; H, 11.61; O, 22.43; active hydrogen, 3.04.

Lithium Aluminum Hydride Reduction of Dihydroalcohol-Ia to Hexahydronoralcohol-I and Hexahydroalcohol-Iab.—Dihydroalcohol-Ia (6.66 g., $[\alpha]_D$ −50°) was refluxed with 3 g. of lithium aluminum hydride in 30 cc. of tetrahydrofuran for 24 hr. The product was worked up and chromatographed on alumina as usual; elution with petroleum ether–ether (3:1) gave a colorless oil, $[\alpha]_D$ −26 to −33°. Distillation of these fractions in the short path still gave a very viscous oil, $[\alpha]^{26}_D$ −46.5° (3.35). This product had infrared spectrum and elementary and group analyses agreeing with those of the other samples of hexahydronoralcohol-I, $C_{15}H_{30}O_4$, prepared by the two other reduction procedures described above.

Elution of the column with petroleum ether–ether (1:1 and 1:3) gave material of $[\alpha]_D$ 39 to 32°. Short path distillation yielded a viscous oil, $[\alpha]^{26}_D$ 37.6° (4.64), whose infrared spectrum and analysis agreed with that of the sample of hexahydroalcohol-Iab obtained by the other reduction procedures (above and below).

Catalytic Reduction of Tetrahydroalcohol-Ib to Hexahydroalcohol-Iab.—The undistilled alcohol (1.80 g., $[\alpha]_D$ 70°) was hydrogenated in 25 ml. of ethanol at room temperature and pressure with 300 mg. of prereduced platinum. The uptake of hydrogen was virtually complete after 8 hr. (0.93 of 1 mole). Part of the crude product (1.35 g., $[\alpha]_D$ 23°) was chromatographed on 30 g. of alumina, using petroleum ether–ether (4:1). Elution with the same solvents (1:2) and with ether removed 930 mg. of the hexahydroalcohol; this was distilled in the short path still, and the product (790 mg.) was an almost colorless viscous oil, $[\alpha]^{26}_D$ 23.6° (4.18). In spite of its lower rotation, its infrared spectrum and analysis agreed closely with other samples of hexahydroalcohol-Iab.

Tetrahydroketone-I.—This was prepared by oxidation of tetrahydroalcohol-I with chromium trioxide–pyridine[5,22]; it was found advantageous to purify the product by chromatography on alumina (grade II), eluting with 1:3 petroleum ether–ether mixtures. The spectroscopic properties and the rotation agreed with those reported earlier.[5] Two attempts to prepare a semicarbazone from the ketone in an acetate buffer[23] were unsuccessful.

Condensation of Tetrahydroketone-I with Furfural.—Tetrahydroketone-I (1.01 g., $[\alpha]^{28}_D$ −94°) was shaken with 0.72 g. of freshly distilled furfural and 3.5 ml. of 2% aqueous sodium hydroxide. Ethanol (1.5 ml.) was added to give a homogeneous solution. After shaking a few minutes, the solution became slightly warm and cloudy, and an additional ml. of ethanol was added. The flask was flushed with nitrogen and was allowed to stand; after 5 hr., an oil had separated, and after 22 hr., the reaction mixture was diluted with 20 ml. of water and extracted with three 25-ml. portions of ether. The ether solution was washed with water until neutral and with two 25-ml. portions of saturated sodium bisulfite solution. The ether solution was dried, the solvent was removed on the steam-bath, the residue was taken up in 1:1 petroleum ether–ether and was chromatographed on 70 g. of alumina (grade II). Elution with petroleum ether–ether mixtures, and with ether, gave only traces of yellow oil. Elution with ether containing 10% methanol gave 1.1 g. of yellow-orange viscous oil, $[\alpha]^{30}_D$ 158° (0.75). The oil was dissolved in purified benzene, hexane was added to the warm solution and, on scratching, an orange-yellow solid was obtained; it weighed 0.35 g. (27%) and melted at 92.5–96.5°. Several crystallizations from benzene–hexane yielded white crystals, m.p. 96–96.7°; $[\alpha]^{27}_D$ 160°.

Anal. Calcd. for $C_{21}H_{30}O_5$: C, 69.58; H, 8.34; O, 22.07; OCH_3, 8.56. Found: C, 69.76, 69.99; H, 8.52, 8.00; O, 22.13; OCH_3, 8.21. (The oxygen and methoxyl determinations were run on the samples giving the last carbon and hydrogen values.) The spectral properties have been mentioned earlier.

When the tetrahydroketone-I was treated by the above procedure, but in the absence of furfural, the ketone was isomerized slightly, judging by the rotation of the crude product ($[\alpha]^{29}_D$ −41.5°).

In several runs, in which *p*-chlorobenzaldehyde or benzaldehyde were condensed with tetrahydroketone-I under basic conditions for longer periods, fractions were obtained which from their ultraviolet spectra and analyses must have contained some of the benzylidene ketone, but pure crystalline products could not be obtained. The concomitant isomerization of the ketone by the base became important in these runs.

Bromination of Tetrahydroketone-I.—Tetrahydroketone-I (0.299 g., $[\alpha]^{29}_D$ −77.8°) in 30 ml. of glacial acetic acid containing 1.0 g. of bromine was kept in the dark at room temperature for 24 hr. Water was added, and the mixture was extracted twice with ether. The extracts were washed with water, with sodium bicarbonate solution, again with water and the solution was dried and the solvent was removed by an air stream. The residue was dissolved in petroleum ether containing 10% of ether and chromatographed on 30 g. of silica gel. Elution with 1:1 and with 1:4 petroleum ether–ether mixtures gave 0.15 g. of yellow oil, $[\alpha]^{31}_D$ 21.3°. The product appeared to decompose with liberation of hydrogen bromide, after standing some days at room temperature. The ultraviolet spectrum showed stronger absorption than that of tetrahydroketone-I, with a shoulder at 260–270 (3.5, based on mol. wt. of 521).

Anal. Calcd. for $C_{16}H_{25}Br_3O_4$: C, 36.87; H, 4.84; Br, 46.01; O, 12.28. Calcd. for $C_{16}H_{26}Br_2O_4$: C, 43.45; H, 5.93; Br, 36.15; O, 14.47. Found: C, 37.72; H, 4.76; Br, 41.91; O, 15.26.

Tetrahydronorketone-I.—Tetrahydronoralcohol-I (1.0 g., $[\alpha]_D$ −36.6°) in dry pyridine (7 ml.) was added to a slurry of chromic oxide (1.0 g.) in pyridine (10 ml.) at room temperature. After 3 weeks had elapsed the reaction mixture was worked up in the usual manner to afford a pale yellow viscous oil (410 mg.). This was evaporatively distilled, b.p. 133° (3×10^{-4} mm.), $[\alpha]^{26}_D$ −36.2° (1.32).

The ketone showed strong bands at 1724 cm.$^{-1}$ (carbonyl) and 3362 cm.$^{-1}$ (hydroxyl) among others in the infrared spectrum.

Anal. Calcd. for $C_{15}H_{26}O_4$: C, 66.63; H, 9.69; O, 23.67; OCH_3, 11.48; active hydrogen, 2 (1 eq. consumed). Found: C, 66.33; H, 10.26; O, 24.14; OCH_3, 10.10; active hydrogen, 2.09 (0.9 eq. consumed).

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