dioxy-3,11-dioxopregn-4-en-21-oic acid, 21321-81-3; 20β,21-isopropylidenedioxy-11β,1-dihydroxypregn-4-en-3-one, 18072-49-6.

Acknowledgment.—We wish to thank Dr. John T. Correll and the Upjohn Co. for a generous supply of 21-acetoxy-11β,17,20α-trihydroxypregn-4-en-3-one.

A Synthesis of Methyl 2,3,6-Trideoxy-α-D-*erythro*-hexopyranoside (Methyl α-Amicetoside)[1,2]

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The title glycoside **7**, the parent sugar of which is a constituent of the antibiotic amicetin, was synthesized in a sequence of high-yielding steps from methyl 4,6-*O*-benzylidene-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (**1**), and was characterized as the crystalline 4-(3,5-dinitrobenzoate) (**10**). Hydrogenation of the 2,3 double bond in **1**, followed by treatment of the resultant saturated glycoside (**2**) with *N*-bromosuccinimide, gave methyl 4-*O*-benzoyl-6-bromo-2,3,6-trideoxy-α-D-*erythro*-hexopyranoside (**3**). Treatment of **3** with potassium iodide in *N*,*N*-dimethylformamide gave the crystalline 6-iodo analog **5**, which, after saponification to the 4-hydroxy derivative **6** and subsequent hydrogenation, gave the glycoside **7**. The structures of all products and intermediates were supported by 100-MHz nmr spectral data.

The antibiotic amicetin, isolated from *Streptomyces plicatus* and *Streptomyces vinaceus-drappus*, was shown[5] to contain a 2,3,6-trideoxyhexose component that was named amicetose. In a synthesis[6] that established the stereochemistry of amicetose, ethyl 2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside[7] was reduced to the saturated glycoside, and the latter was converted, by way of the 6-*O*-*p*-tolylsulfonyl and 6-deoxy-6-iodo derivatives, into ethyl 2,3,6-trideoxy-α-D-*erythro*-hexopyranoside, hydrolysis of which gave 2,3,6-trideoxy-α-D-*erythro*-hexose, identical with amicetose. The synthetic sugar and the one isolated from amicetin gave the same 2,4-dinitrophenylhydrazone derivative.

Although the steps in the foregoing sequence of conversions[6] proceed in yields from 47 to 89%, preparation of the starting alkene[7] requires five steps from D-glucose and results in a net yield of only about 10% alkene, corresponding to an over-all yield of about 2% trideoxy sugar. The present communication describes an alternative synthetic route to amicetose by way of methyl 4,6-*O*-benzylidene-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside[8] (**1**), an alkene readily obtained in about 30% yield from the commercially available methyl α-D-glucopyranoside. The synthesis leads from the latter glycoside and proceeds to the methyl α-glycoside (**7**) of amicetose in about 16% over-all yield, with few isolated intermediates. The synthesis makes **7** (methyl 2,3,6-trideoxy-α-D-*erythro*-hexopyranoside) conveniently available for further synthetic transformations into other deoxy sugars,[9] and also amino sugars,[10] that are present in antibiotic substances.

Compound **1**, obtained[8] from methyl α-D-glucopyranoside by the sequence benzylidenation, *p*-toluenesulfonation, and treatment with sodium iodide–zinc dust in *N*,*N*-dimethylformamide (or with potassium ethylxanthate in butyl alcohol), was hydrogenated over palladium on charcoal to give a 95% yield of the saturated glycoside **2**, identical with the crystalline product obtained by Bolliger and Prins,[11] who effected the reduction of **1** to **2** over platinum. Hydrogenation could be terminated readily at the point of saturation of the double bond, with no detectable hydrogenolysis of the *O*-benzylidene group. Treatment of the saturated acetal **2** with *N*-bromosuccinimide in refluxing carbon tetrachloride[12,13] gave methyl 4-*O*-benzoyl-6-bromo-2,3,6-trideoxy-α-D-*erythro*-hexopyranoside (**3**) in 86% yield as an analytically pure syrup. The ir and nmr spectra of **3** confirmed that a benzoate group was present, and the fact that the conversion of **2** into the bromo benzoate had involved a substantial downfield shift of the H-4 signal confirmed that the benzoyloxy group was indeed attached at C-4; the structure **3** was also established independently as the result of further transformations. Full details of all nmr spectra, with assignments that were verified by spin decoupling, are recorded in the Experimental Section.

Attempts to hydrogenate the bromo benzoate **3** in alkaline solution, to remove the *O*-benzoyl group and cleave the bromo substituent to give the 6-deoxy sugar, led mainly to the debenzoylated 6-bromo glycoside **4** and did not appear to provide a convenient route to the desired glycoside (**7**). The syrupy bromo benzoate **3** was converted into the crystalline 6-iodo analog (**5**) in 82% yield by treatment with potassium iodide in *N*,*N*-dimethylformamide at 50°. Conversion of **2** into **5** proceeded in 72–81% yield if careful purification of the intermediate bromide **3** was not performed. The nmr

(1) Presented at the London Meeting of the Carbohydrate Discussion Group of the Chemical Society, Queen Elizabeth College, London, England, Sept 17, 1968.

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(3) Stauffer Chemical Co., Fellow, Oct 1967 through June 1968.

(4) To whom inquiries should be addressed.

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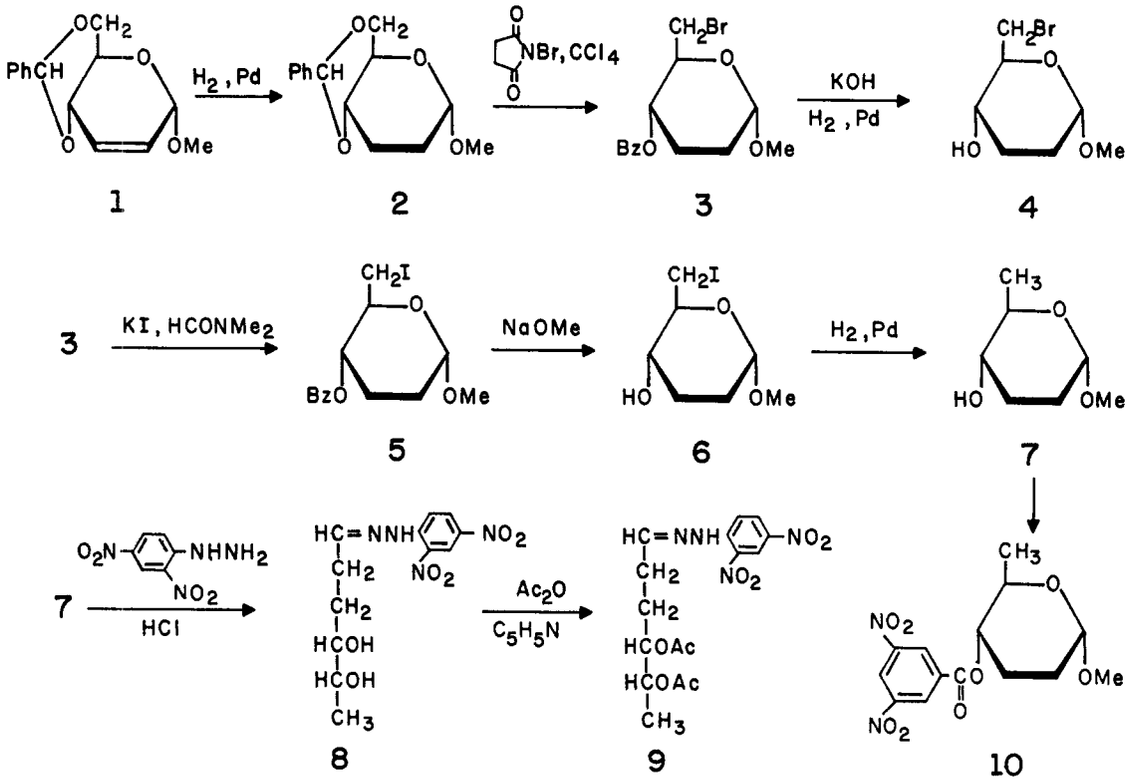
(13) E. L. Albano, D. Horton, and J. H. Lauterbach, *ibid.*, **9**, 149 (1969).



spectrum of the iodide **5** was very similar to that of the bromide **3**, except for very minor differences in chemical shift of the signals.

The iodo benzoate **5** could be saponified to the 4-hydroxy analog **6**, obtained as an analytically pure syrup in near-quantitative yield. The H-4 signal in the nmr spectrum of **6** was observed, as anticipated, at a considerably higher field position than the H-4 signal in the 4-benzoate precursor **5**. Reductive cleavage of the iodo group in **6**, by hydrogenolysis over palladium on charcoal in the presence of triethylamine, gave the desired methyl α-amicetoside, **7**, in 81% yield (based on the iodo benzoate **5**) as a chromatographically homogeneous syrup. The ir and nmr spectra of **7** showed the presence of a hydroxyl group, and the nmr spectrum showed a three-proton doublet at τ 8.26, clearly establishing the presence of the C-methyl group, whose signal is split because of the adjacent H-5 proton ($J_{5,6}$ = 6.0 Hz). The high-resolution mass spectrum of **7** showed a parent, molecular-ion peak at *m/e* 146.093, as calculated for the formula $C_7H_{14}O_3$. The glycoside **7** was converted into a crystalline 3,5-dinitrobenzoate (**10**) that was fully characterized by elemental and spectroscopic analysis (see Experimental Section).

The specific rotation of the glycoside **7** (+142° in water) is close to that recorded[6] for the ethyl analog (+123° in water). The value is higher than the value of +75.1° (in water)[5] for methyl amicetoside obtained by methanolysis of amicetin; this is to be expected since the latter product was an anomeric mixture.

Treatment of the glycoside **7** with 2,4-dinitrophenylhydrazine in 2 *M* hydrochloric acid gave crystalline 2,3,6-trideoxy-D-*erythro*-hexose 2,4-dinitrophenylhydrazone (**8**), further converted into the crystalline 4,5-diacetate (**9**). Both **8** and **9** had melting points in very close agreement with literature values. The nmr spectrum of **8** (see Experimental Section) showed signals for the two hydroxyl groups and the NH proton that disappeared when the sample (in pyridine-d_5) was deuterated. The NH proton in the diacetate **9** gave a signal at τ −1.08 (in chloroform-*d*) that did not disappear on simple deuteration, but addition of a small amount of triethylamine led to rapid exchange of the NH proton. This procedure is the same as that used[14] for effecting exchange of the NH proton in the 2,4-dinitroanilino group. The nmr spectral data for **8** and **9** are fully compatible with the open-chain structures shown, and exclude possible, alternative cyclic formulations.

Experimental Section

General Methods.—Evaporations were performed under diminished pressure below 40°. Nmr spectra were measured at 100 MHz and chemical shifts refer to an internal standard of tetramethylsilane (τ 10.00); the latter also provided a lock signal. Signal assignments were verified by spin decoupling. Deuteration was performed by adding 1 drop of deuterium oxide to the prepared sample. Microanalyses were determined by W. N. Rond. X-Ray powder diffraction data give interplanar spacings, Å, for CuK_α radiation. The camera diameter was 114.59 mm. Relative intensities were estimated visually: m, moderate; s, strong; v, very; w, weak. The strongest lines are numbered (1, strongest); double numbers indicate approximately equal intensities. Thin layer chromatography (tlc) was performed with 0.25-mm layers of silica gel G, activated at 120°, as the adsorbent and sulfuric acid as indicator.

Preparation of Methyl 4,6-*O*-Benzylidene-2,3-dideoxy-α-D-*erythro*-hexopyranoside (2).—Methyl 4,6-*O*-benzylidene-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside[8] (**1**, 4.00 g, 16 mmol) was dissolved in methanol (120 ml) and hydrogenated over 5% palladium on charcoal (Engelhard Industries, Newark, N. J., 400 mg) in a closed system at room temperature at a pressure of *ca.* 1.1 atm. After 1 equiv (*ca.* 390 ml) of hydrogen had been absorbed (*ca.* 1 hr), the catalyst was filtered off, the filtrate was evaporated, and the resulting solid was recrystallized from ether–hexane: yield 3.85 g (95%), mp 82–84°, $[\alpha]^{21}D$ +118 ± 1° (*c* 1, chloroform) [lit.[11] mp 82–83°, $[\alpha]^{15}D$ +120.5 ± 2° (*c* 1, chloroform)]; R_f 0.64 (dichloromethane); λ_{max}^{KBr} 13.3 and 14.3

(14) A. E. El Ashmawy and D. Horton, *Carbohyd. Res.*, **3**, 191 (1966); *cf.* R. H. Bell, D. Horton, and Martha J. Miller, *ibid.*, **9**, 201 (1969).

μm (phenyl); nmr (chloroform-*d*) τ 2.58 (m, 5 H, Ph), 4.46 (s, 1 H, benzylic proton), 5.34 (narrow m, 1 H, H-1), 5.81 (m, 1 H, W = 12 Hz, H-4), 5.95–6.60 (m, 3 H, H-5,6,6′), 6.68 (s, 3 H, OMe), and 8.15 (broad s, 4 H, W = *ca.* 15 Hz, H-2, 2′,-3,3′).

Hydrogenation of **1** with Adams' catalyst (prepared by hydrogenating platinum oxide overnight) according to the procedure of Bolliger and Prins[11] gave essentially the same result, but was more time-consuming because of the necessity of preparing the catalyst.

Methyl 4-*O*-Benzoyl-6-bromo-2,3,6-trideoxy-α-D-*erythro*-hexopyranoside (3).—To a solution of methyl 4,6-*O*-benzylidene-2,3-dideoxy-α-D-*erythro*-hexopyranoside (**2**, 4.00 g, 16 mmol) in dry carbon tetrachloride (100 ml) was added *N*-bromosuccinimide (3.14 g, 17.6 mmol) and barium carbonate (4 g). The mixture was refluxed for 1.5 hr and then cooled to 0°. The mixture was filtered and the filtrate was washed successively with 20-ml portions of 5% aqueous sodium hydrogen sulfite and water. The solution was dried ($MgSO_4$) and evaporated. The resultant syrup was dissolved in the minimum volume of dichloromethane and the solution was loaded onto a column (40 × 2 cm) of Kieselgel (Camag D-O, Muttenz, Switzerland). Elution of the column with dichloromethane gave **3** as a chromatographically homogeneous syrup, yield 4.50 g (86%). Distillation at 150° (bath) and 0.08 Torr gave analytically pure **3**: $[\alpha]^{21}D$ +133 ± 1° (*c* 1.1, chloroform); R_f 0.25 (dichloromethane); λ_{max}^{film} 5.75 (OBz) and 14.0 μm (phenyl); nmr (benzene-d_6) τ 2.04, 2.90 (both m, 5 H, Ph), 5.13 (m, 1 H, W = 25.5 Hz, H-4), 5.64 (q, 1 H, $J_{1,2}$ = 2.5 Hz, $J_{1,2'}$ = 1.5 Hz, H-1), 6.04 (septet, 1 H, $J_{4,5}$ = 9.0 Hz, H-5), 6.69 (q, 1 H, $J_{5,6}$ = 2.5 Hz, $J_{6,6'}$ = 10.5 Hz, H-6), 6.88 (s, 3 H, OMe), 6.90 (q, 1 H, $J_{5,6'}$ = 7.5 Hz, H-6′), 8.04–8.30 (m, 2 H), and 8.42–8.76 (m, 2 H, H-2,2′,3,3′).

Anal. Calcd for $C_{14}H_{17}BrO_4$: C, 51.07; Br, 24.27; H, 5.20. Found: C, 51.14; Br, 24.06; H, 5.31.

Methyl 4-*O*-Benzoyl-2,3,6-trideoxy-6-iodo-α-D-*erythro*-hexopyranoside (5).—A mixture of methyl 4-*O*-benzoyl-6-bromo-2,3,6-trideoxy-α-D-*erythro*-hexopyranoside (**3**, 5.00 g, 15.1 mmol) and potassium iodide (15 g) in *N*,*N*-dimethylformamide (50 ml) was stirred for 15 hr at 50°. The mixture was poured onto ice and the resulting crystalline product was dissolved in dichloromethane (100 ml). The solution was washed successively with 20-ml portions of 5% aqueous sodium hydrogen sulfite and water, and the dried ($MgSO_4$) organic layer was evaporated. The resultant syrup was crystallized from isopropyl alcohol–water to give **5** as white needles: yield 4.65 g (82%), mp 62–63°, $[\alpha]^{22}D$ +121 ± 1° (*c* 1, chloroform); R_f 0.90 (dichloromethane); λ_{max}^{KBr} 5.80 (OBz) and 14.1 μm (phenyl); nmr (benzene-d_6) τ 1.92, 2.86 (both m, 5 H, Ph), 5.14 (m, 1 H, W = 25.5 Hz, H-4), 5.58 (broadened q, 1 H, $J_{1,2}$ = 2.5 Hz, $J_{1,2'}$ = 1.5 Hz, H-1), 6.16 (triplet of doublets, 1 H, $J_{4,5}$ = 9.0 Hz, H-5), 6.72 (s, 3 H, OMe), 6.75 (q, 1 H, $J_{5,6}$ = 2.4 Hz, H-6), 7.03 (q, 1 H, $J_{5,6'}$ = 8.5 Hz, $J_{6,6'}$ = 10.6 Hz, H-6′), 8.00–8.20 (m, 2 H), and 8.42–8.60 (m, 2 H, H-2,2′,3,3′); X-ray powder diffraction data—13.38 (w), 10.75 (s, 2), 5.55 (vw), 5.34 (vw), 4.79 (m), 4.56 (vw), 4.33 (vs, 1), 3.96 (vw), 3.86 (vw), 3.69 (s, 3), 3.25 (m), 2.99 (vw), 2.85 (vw).

Anal. Calcd for $C_{14}H_{17}IO_4$: C, 44.70; H, 4.56; I, 33.73. Found: C, 44.82; H, 4.52; I, 33.40.

In subsequent experiments, the bromide **3** was converted into the iodide **5** without chromatographic purification of **3**; over-all yields from **2** to **5** were 72–81%.

Methyl 2,3,6-Trideoxy-6-iodo-α-D-*erythro*-hexopyranoside (6).—A solution of methyl 4-*O*-benzoyl-2,3,6-trideoxy-6-iodo-α-D-*erythro*-hexopyranoside (**5**, 4.00 g, 10.6 mmol) in dry methanol (100 ml) was treated with sodium (20 mg), and the solution was kept for 14 hr at room temperature. After addition of Dry Ice and evaporation of the solution, the residue was extracted with dichloromethane and the suspension was filtered through a Celite pad. The filtrate was evaporated and the resultant syrup was purified by passing it through a 2 × 30 cm column of Kieselgel (Camag D-O) with dichloromethane–ether (2:1) as eluent. The product **6** was obtained as a chromatographically homogeneous syrup:[15] yield 2.78 g (96%), $[\alpha]^{21}D$ +113 ± 1° (*c* 1.2, chloroform); R_f 0.70 (1:2 dichloromethane–ether), 0.56 (1:1 dichloromethane–ether); λ_{max}^{film} 2.90 μm (OH); nmr (chloroform-*d*) τ 5.27 (broadened narrow t, 1 H, H-1), 6.40 (m, 1 H, H-4), 6.56 (s, 3 H, OMe), 6.55–6.69 (m, 3 H, H-5,6,6′), 7.76 (s, 1 H, disappears on deuteration, OH), and 8.17 (m, 4 H, H-2,2′,3,3′).

Anal. Calcd for $C_7H_{13}IO_3$: C, 30.90; H, 4.81; I, 46.64. Found: C, 31.17; H, 4.97; I, 46.31.

In larger scale preparations, the debenzoylated product was taken to the next step without chromatographic purification. Column chromatography could also be effected on Silica Gel 7734 (E. Merck, Darmstadt, Germany), with 1 g of sample per 20 g of adsorbent and dichloromethane–ether (1:1) as eluent.

Methyl 2,3,6-Trideoxy-α-D-*erythro*-hexopyranoside (Methyl α-Amicetoside) (7).—A mixture of methyl 2,3,6-trideoxy-6-iodo-α-D-*erythro*-hexopyranoside (**6**, 26.5 mmol, prepared from 10.0 g of **5**), methanol (200 ml), triethylamine (7.1 ml, 5.2 g, 53 mmol), and 5% palladium on charcoal (2 g) was shaken under hydrogen at 1 atm pressure and at 25° until absorption of hydrogen ceased (*ca.* 2 hr). The catalyst was filtered off and the filtrate was evaporated to a syrup. A solution of the syrup in the minimum volume of dichloromethane was added to a column containing 300 g of silica gel 7734 (Merck) and the product was eluted off with dichloromethane–ether (1:1) to give **7** as a chromatographically homogeneous[15] syrup: yield 3.17 g (81% from **5**), $[\alpha]^{18}D$ +142 ± 1° (*c* 1.2, water); R_f 0.33 (1:1 dichloromethane–ether); λ_{max}^{film} 2.90 (OH) and 7.30 μm (CMe); nmr (chloroform-*d*) τ 5.38 (broad s, 1 H, H-1), 6.27–6.58 (m, 2 H, H-4,5), 6.65 (s, 3 H, OMe), 7.84 (broad s, 1 H, disappears on deuteration, OH), 8.00–8.35 (m, 4 H, H-2,2′,3,3′), 8.62 (d, 3 H, $J_{5,6}$ = 6.0 Hz, H-6). For analysis the product was distilled at 50° (bath) and 1 Torr.

Anal. Calcd for $C_7H_{14}O_3$: C, 57.50; H, 9.65; mol wt, 146.094. Found: C, 57.65; H, 9.51; mol wt,[16] 146.093.

Methyl 4-*O*-(3,5-Dinitrobenzoyl)-2,3,6-trideoxy-α-D-*erythro*-hexopyranoside (10).—To a solution of methyl 2,3,6-trideoxy-α-D-*erythro*-hexopyranoside (**7**, 156 mg, 1.06 mmol) in pyridine (10 ml) was added 3,5-dinitrobenzoyl chloride (317 mg, 1.38 mmol). The mixture was kept for 8 hr at room temperature and then poured into ice–water (50 ml). The resulting crystalline product was filtered off, washed several times with water and dried; yield 192 mg (55%). Two recrystallizations from methanol gave pure **10** as colorless platelets: mp 100–101°, $[\alpha]^{20}D$ +134 ± 1° (*c* 0.4, chloroform); R_f 0.24 (dichloromethane); λ_{max}^{KBr} 5.80 (C=O), 6.15, 6.50, 6.90, 13.7, 13.9 μm (aryl); nmr (chloroform-*d* at 60 MHz) τ 0.67 (m, 3 H, aryl protons), 5.06 (m, 1 H, H-4), 5.29 (narrow m, 1 H, H-1), 5.95 (octet, 1 H, $J_{4,5}$ = *ca.* 9 Hz, H-5), 6.60 (s, 3 H, OMe), 7.80–8.20 (m, 4 H, H-2,2′,3,3′), and 8.77 (d, 3 H, $J_{5,6}$ = 6 Hz, H-6).

Anal. Calcd for $C_{14}H_{16}N_2O_8$: C, 49.41; H, 4.74; N, 8.23. Found: C, 49.22; H, 4.74; N, 7.89.

2,3,6-Trideoxy-D-*erythro*-hexose (2,4-Dinitrophenyl)hydrazone (8).—To a warm solution of 2,4-dinitrophenylhydrazine (525 mg, 2.65 mmol) in 2 *M* hydrochloric acid (75 ml) was added a solution of methyl 2,3,6-trideoxy-α-D-*erythro*-hexopyranoside (**7**, 329 mg, 2.25 mmol) in 2 *M* hydrochloric acid (25 ml). The mixture was heated for 5 min on a steam bath and then kept for 1 hr at room temperature. The yellow, crystalline product that separated was filtered off, washed with a small amount of water, and dried to give **8**, yield 507 mg (72%). Recrystallization from methanol–benzene gave pure **8**: mp 154–155.5°, $[\alpha]^{19}D$ −9.8 ± 1° (*c* 0.4, pyridine) [lit.[5] mp 152–153°, $[\alpha]^{25}D$ −10° (pyridine)]; λ_{max}^{KBr} 2.95 (OH), 3.05 (NH), and 6.20 μm (C=N); nmr (pyridine-d_5) τ 0.94 (d, 1 H, J_{meta} = 1.0 Hz, aryl H-3), 1.70 (q, 1 H, J_{ortho} = 5 Hz, aryl H-5), 2.06 (t, 1 H, $J_{1,2}$ = 2.5 Hz, H-1), 2.08 (d, 1 H, aryl H-6), 3.30–5.10 (broad hump, 3 H, disappears on deuteration, OH, NH), 5.73–6.20 (broad m, 2 H, H-4,5), 6.92–7.40 7.55–8.20 (both m, 4 H, H-2,2′,3,3′), 8.47 (d, 3H, $J_{5,6}$ = 3 Hz, H-6); X-ray powder diffraction data—14.40 (m), 8.00 (w), 7.40 (w), 5.89 (vw), 5.01 (vs, 1), 4.47 (s, 2), 3.88 (w), 3.69 (vw), 3.57 (vw), 3.43 (m), 3.25 (w), 3.13 (w), 3.00 (w).

4,5-Di-*O*-acetyl-2,3,6-Trideoxy-D-*erythro*-hexose (2,4-Dinitrophenyl)hydrazone (9).—Acetic anhydride (2 ml) was added to a solution of **8** (100 mg, 0.32 mmol) in anhydrous pyridine (2 ml) and the mixture was kept for 24 hr at room temperature. The solution was evaporated at 25° and the residue was treated with cold water, whereupon the product crystallized and was filtered off. Recrystallization from methanol–water gave yellow plate-

(15) Iodine was also used as indicator; it revealed the presence of certain side products in the crude **6** that were not detected by sulfuric acid.

(16) Determined by high-resolution mass spectrometry through courtesy of Dr. R. C. Dougherty and C. R. Weisenberger of this Department.

lets: yield 65 mg (51%), mp 94–95°. A second recrystallization, from ether–petroleum ether (bp 30–60°) gave pure **9**: mp 95.0–95.5°, $[\alpha]^{18}D$ −6.2 ± 1° (*c* 0.2, chloroform) (lit.[5] mp 95–96°); λ_{max}^{KBr} 3.05 (NH), 5.70 (OAc), and 6.15 μm (C=N); nmr (chloroform-*d*) τ −1.08 (s, 1 H, disappears on deuteration in the presence of triethylamine, NH), 0.80 (d, 1 H, J_{meta} = 1 Hz, aryl H-3), 1.66 (q, 1 H, J_{ortho} = 5 Hz, aryl H-5), 2.06 (d, 1 H, aryl H-6), 2.39 (t, 1 H, $J_{1,2}$ = 2.5 Hz, H-1), 4.75–5.09 (m, 2 H, H-4,5), 7.36–7.60, 7.80–8.20 (both m, 4 H, H-2,2′,3,3′), 7.88, 7.93 (both s, 3 H, OAc), 8.73 (d, 3 H, $J_{5,6}$ = 3.5 Hz, H-6).

Registry No.—**2**, 16848-76-3; **3**, 18933-68-1; **5**, 21317-48-6; **6**, 21317-49-7; **7**, 21317-50-0.

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Reduction of 3β-*p*-Toluenesulfonoxycholest-5-en-4β-ol by Lithium Aluminum Hydride. Clarification of an Anomalous Reduction

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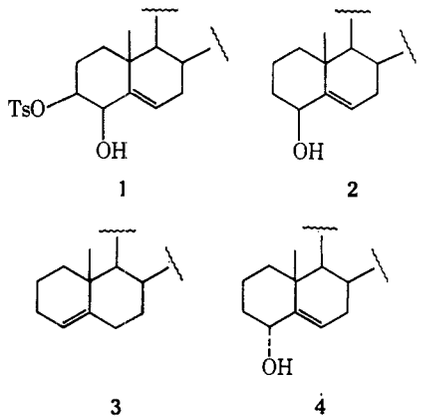
The products of lithium aluminum hydride reduction of 3β-*p*-toluenesulfonoxycholest-5-en-4β-ol (**1**) are shown to be cholest-4-ene (**3**), cholest-5-en-4α-ol (**4**), and 3β-hydroxymethyl-A-norcholest-5-ene (**8**). A mechanism for this unusual reduction is proposed and supported by the deuterium incorporation observed in the reduction of **1** with lithium aluminum deuteride, and the formation of cholest-5-en-4-one on treatment of **1** with sodium hydride.

Reductive cleavage of alkyl tosylates by lithium aluminum hydride has become a useful synthetic operation,[1,2] and it is therefore important to identify and elucidate examples which deviate from expected behavior.

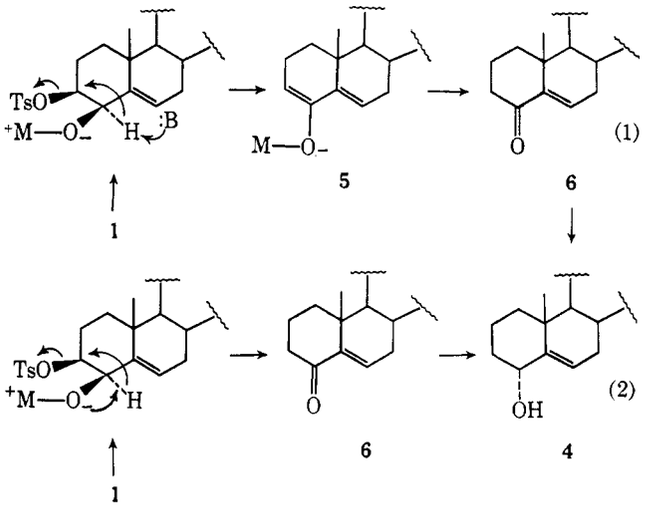
In 1951 Karrer and coworkers[3] reported that lithium aluminum hydride reduction of 3β-*p*-toluenesulfonoxy-4β-hydroxycholest-5-ene (**1**) gave three products, referred to as A, B, and C. Product A (*ca.* 20%) was identified as cholest-5-en-4β-ol (**2**) on the strength of its catalytic reduction to a compound thought to be 5α-cholestan-4β-ol. Product B (*ca.* 4%) was not identified, but C (*ca.* 2%) was shown to be cholest-4-ene (**3**) by a mixture melting point with authentic material. The major product (A) was thus assumed to arise from a simple displacement of the 3β-tosylate group by hydride.



1 2 3 4

That same year, however, Barton and Rosenfelder[4] reported that the physical properties of the compound assumed to be cholestan-4β-ol by Karrer, *et al.*, actually corresponded to the 4α-hydroxy epimer. This fact apparently escaped notice until Jones, *et al.*,[5] demonstrated that compound A was cholest-5-en-4α-ol (**4**) rather than the 4β epimer **2**, an assignment subsequently confirmed by Becker and Wallis.[6] The reduction of **1** thus becomes anomalous, and it is to this subject that we address this paper.

We began by considering two mechanisms (outlined in eq 1 and 2) for the conversion of **1** into **4**. The free hydroxyl group in **1** will be rapidly converted into a



salt (M = Li or Al), which can either suffer E2 elimination of toluenesulfonic acid (mechanism 1) or undergo an intramolecular displacement of arylsulfonate by the 4α-hydride (mechanism 2). Cholest-5-en-4-one (**6**) then becomes a key intermediate in both mechanisms, and it is gratifying to note that Jones, *et al.*,[5] report the reduction of **6** to **4** in excellent yield by the action of lithium aluminum hydride.

A consideration of mechanism 2 led us to propose 3β-hydroxymethyl-A-norcholest-5-ene (**8**) for compound B, since it could be formed by the closely related

(1) L. Fieser and M. Fieser, "Reagents for Organic Synthesis," John Wiley & Sons, New York, N. Y., 1967, p 588.

(2) G. Büchi, W. Hofheinz, and J. Pankstelis, *J. Amer. Chem. Soc.*, **88**, 4113 (1966), describe a particularly high yield example.

(3) P. Karrer, H. Asmis, K. Sareen, and R. Schwyzer, *Helv. Chim. Acta*, **34**, 1022 (1951).

(4) D. H. R. Barton and W. Rosenfelder, *J. Chem. Soc.*, 2875 (1951).

(5) D. N. Jones, J. R. Lewis, C. W. Shoppee, and G. Summers, *ibid.*, 2876 (1955).

(6) E. J. Becker and E. S. Wallis, *J. Org. Chem.*, **20**, 353 (1955).