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Note

Chemical synthesis of 3-amino-2,3-dideoxy-D-*myo*-inositol (an intermediate in the biosynthesis of 2-deoxystreptamine) and its D-*epi* stereoisomer

HANS H. BAER, LISA SIEMSEN, AND DAVID J. ASTLES
Ottawa–Carleton Institute for Research and Graduate Studies in Chemistry, Department of Chemistry, University of Ottawa, Ottawa K1N 9B4 (Canada)

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The pathway for the biosynthesis of 2-deoxystreptamine, a pivotal component of many important aminoglycoside antibiotics, has been proposed by Rinehart and his coworkers[1] to take its course, from D-glucose, via an aminocyclohexanetetrol, most likely 3-amino-2,3-dideoxy-D-*myo*-inositol (**11**)*. Later biochemical work[2,3] lent support to that assumption, and it was finally proved by the isolation[4,5] of **11** from culture media of certain microorganisms, the definitive structural elucidation[6] of this metabolite by way of comparison with a semisynthetic sample, and by the demonstration[7] that it is indeed biochemically converted into 2-deoxystreptamine. The semisynthetic sample[6] and its enantiomer[8] had been obtained by degradation of chemically modified kanamycin-A derivatives. Convenient preparative access to chiral aminocyclitols of this kind is important for projects of chemical analog synthesis and biochemical mutasynthesis in the field of aminoglycoside antibiotics[1c,9]. We report here the preparation of **11** and its hitherto unknown, D-*epi* stereoisomer **14**; the procedure, starting ultimately from D-glucose, is based on nitroalkane-cyclization methodology[10].

The starting compound required for obtaining the carbocyclic system of **11** and **14** was 5,6-dideoxy-1,2-*O*-isopropylidene-6-nitro-α-D-*xylo*-hexofuranose (**4**). Its most convenient preparative precursor is 6-deoxy-1,2-*O*-isopropylidene-6-nitro-α-D-glucofuranose (**1**), which is readily available from 1,2-*O*-isopropylidene-α-D-glucofuranose and convertible into the nitroalkene **2** by acetylation followed by base-promoted dehydroacetoxylation[10–12]. Compound **2** had previously been transformed[13] into **4** by action of sodium borohydride in ethanol at room temperature, but only on a small scale and with a somewhat unsatisfactory yield (49%). During several trials to improve the procedure for preparations on a larger scale, we experienced complications due to the formation of by-products (as will be disclosed

*Designation in *Chemical Abstracts* (Registry number 75419-36-2), which reflects the numbering system most widely used for derivatives of 2-deoxystreptamine. According to IUPAC terminology, the compound should be (and has been[6,8]) designated as 1L-(1,3,5/2,4)-5-amino-1,2,3,4-cyclohexanetetrol; alternatively, it may be named 5*S*-amino-1*R*,2*S*,3*S*,4*R*-cyclohexanetetrol.

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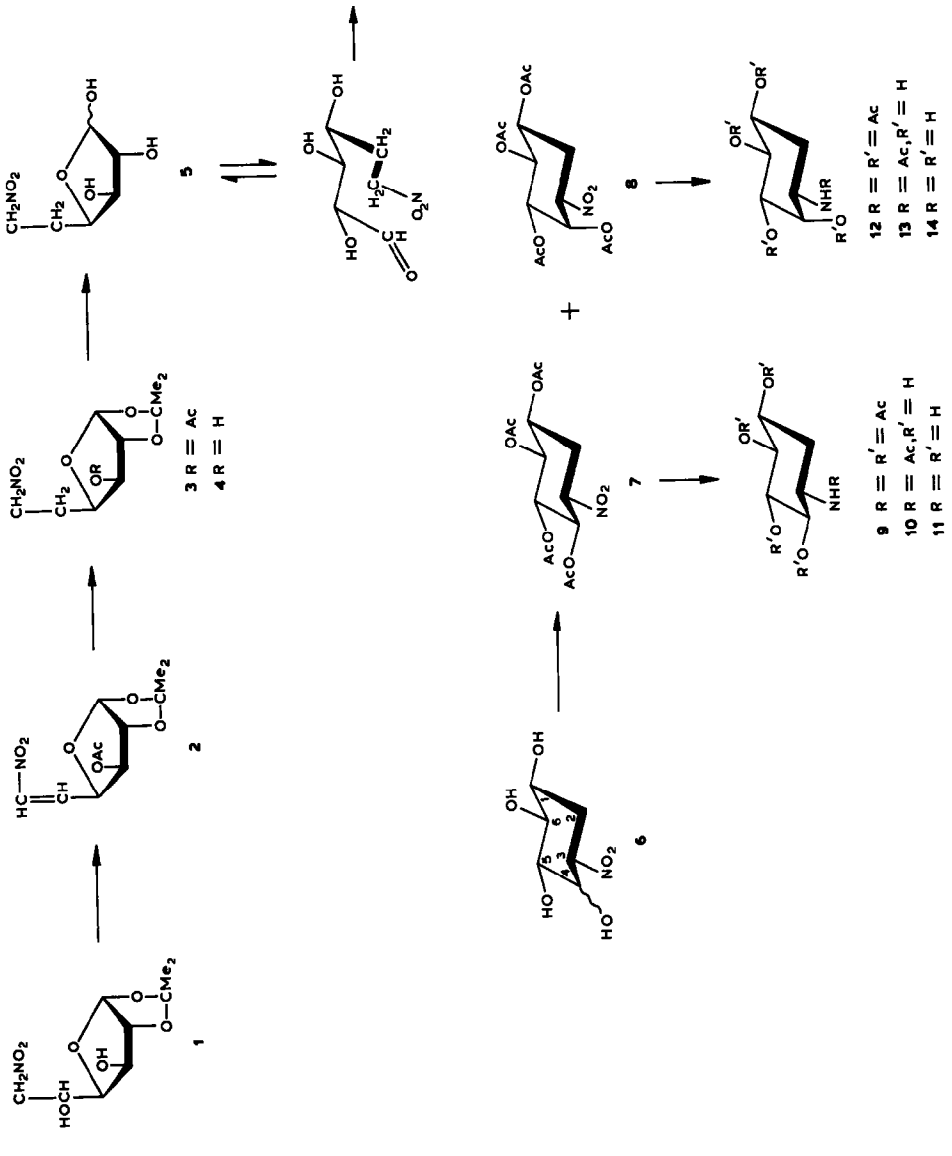
elsewhere), and similar difficulties were encountered when selective, palladium-catalyzed hydrogenation of the alkenic double bond was attempted. However, borohydride reduction of **2** during 20 min at −25°, followed by isolation of the intermediary acetate **3** (a syrup characterized by its ^{1}H-n.m.r. and i.r. spectra), and subsequent saponification with potassium carbonate in methanol did eventually afford crystalline **4** in 92% yield.

Hydrolysis of **4** with dilute sulfuric acid produced the free nitro sugar, presumably as a mixture of furanose anomers (**5**). The sugar was not isolated but, by adjustment of its aqueous solution to pH 8.5–8.8 with barium hydroxide, was caused to cyclize immediately according to well-established precedent[10,14,15], to give a mixture of 4-epimeric, 2,3-dideoxy-3-nitroinositols* (**6**). Attempts to resolve this mixture by column chromatography proved futile, probably because of partial epimerization occurring during the process. However, boron trifluoride-catalyzed acetylation gave two crystalline tetraacetates, **7** (the major product) and **8** (minor product), which were cleanly separated by fractional crystallization. The respective 2,3-dideoxy-3-nitro-D-*myo*- and 2,3-dideoxy-3-nitro-D-*epi*-inositol structures were revealed by well-resolved, high-field ^{1}H-n.m.r. spectra which showed, for the nitromethine proton (H-3), one small and two large vicinal couplings in **7**, and one large and two small vicinal couplings in **8**. All other *J* values were also in harmony with the assigned configurations (see Experimental).

Hydrogenation of **7** over Adams catalyst in acetic acid, followed by acetylation, gave the readily crystallizing and high-melting *N*-acetyltetra-*O*-acetyl derivative **9**, which was sequentially *O*-deacetylated (with sodium methoxide) and *N*-deacetylated (with aqueous barium hydroxide) to give, via the non-crystalline amide **10**, the crystalline target-compound **11**. The epimer **14** was obtained by application of the same operations to **8**. In the latter sequence, the peracetyl derivative (**12**) was difficult to crystallize, but the *O*-deacetylated amide (**13**) was highly crystalline. By virtue of these differential inclinations to crystallize, it was possible and convenient for larger-scale preparations to hydrogenate the nitroinositol *mixture* **6** and perform isomer separation afterwards. Thus, *N*-acetylation of the hydrogenated mixture furnished **13**, isolated in good yield by direct crystallization, and peracetylation of the mother liquor then gave crystalline **9**; the products were converted into **14** and **11**, respectively, as just described.

*According to conformational free-energy calculations, the OH-4*eq* epimer should at thermodynamic equilibrium preponderate ~4:1 over the OH-4*ax* epimer. Judging by the results of subsequent, preparative conversions, the ratio appeared to be smaller; possibly, thermodynamic control was not complete under the conditions used. Two additional isomers, inverted at C-3, are possible products, but their proportions should be insignificant since they would bear either an axial nitro group or, in their alternative chair forms, four and three axial hydroxyl groups, respectively; any of these features would render them highly unstable, and prone to rapid epimerization. For a detailed discussion of this subject. see ref. 16.


1
2
3 R = Ac
4 R = H
5
6
7
8
9 R = R′ = Ac
10 R = Ac, R′ = H
11 R = R′ = H
12 R = R′ = Ac
13 R = Ac, R′ = H
14 R = R′ = H

EXPERIMENTAL

General methods. — The following solvent combinations (v/v) were used for chromatography: (*A*) 1:1 ethyl acetate–hexane, (*B*) the same solvents, but 1:2, (*C*) 1:3 methanol–chloroform, and (*D*) 5:4:1 methanol–chloroform–ammonia (conc., aqueous). Optical rotations were measured at ~25° in a Perkin–Elmer 241 instrument. Unless otherwise indicated, ^{1}H-n.m.r. data refer to 300-MHz spectra for solutions in $CDCl_3$ (chloroform lock signal, δ 7.23).

*5,6-Dideoxy-1,2-*O*-isopropylidene-6-nitro-α-*D*-xylo-hexofuranose* (**4**) *via its acetate* **3**. — The acetylated nitroalkene[11–13] **2** was prepared[12] from the nitrodiol **1**. To a solution of **2** (800 mg) in 99% ethanol (90 mL), magnetically stirred at −25°, was added sodium borohydride (125 mg). The conversion of **2** (R_F 0.53) into **3** (R_F 0.43) was complete after 15 min, with only traces of slower-moving impurities being visible in t.l.c. (solvent *B*). The reaction was quenched after 20 min by addition of Amberlite IR-120 (H^+) cation-exchange resin (6 mL), with which the solution was stirred during 1 h while the temperature was gradually allowed to rise to ~20°; some water (6 mL) was added towards the end. The resin was removed and washed exhaustively with methanol, and the neutral solution was evaporated to give syrupy, faintly yellowish **3** from which several portions of added methanol were evaporated for removal of boric acid. A dried sample showed $[\alpha]_D$ +4.2° (*c* 1, chloroform); ν_{max}^{film} 1735 (ester), and 1547 and 1370 cm^{-1} (nitroalkane); ^{1}H-n.m.r.: δ 5.86 (d, $J_{1,2}$ 4.0 Hz, H-1), 5.15 (d, $J_{2,3}$ 0, $J_{3,4}$ 2.9 Hz, H-3), 4.5 (m, 3 H, H-2,6,6′), 4.31 (septet, *J* 2.9, 5, and 8 Hz, H-4), 2.24 (m, 2 H, H-5,5′), 2.09 (s, 3 H, OAc), 1.47 and 1.28 (s, 3 H each, Me_2C).

Without delay, the syrupy **3** was dissolved in methanol (15 mL) that had been saturated with $K_2CO_3 \cdot 1.5\ H_2O$ by brief boiling with the salt, cooling to room temperature, and filtration. Deacetylation to give **4** (R_F 0.25, solvent *B*) was complete within 1 h. The solution was cooled (+4°), treated with cation-exchange resin until neutral and colorless, and evaporated to give **4** as a syrup that crystallized rapidly and completely on cooling and scratching the inside of the flask. The dried material (630 mg, 92%) had m.p. 106–108°, raised to 110° by recrystallization from ethyl acetate–hexane; $[\alpha]_D$ −13.0° (*c* 2, chloroform); lit.[13] m.p. 103.5–104°, $[\alpha]_D$ −15 ±2° (*c* 0.6); ν_{max}^{Nujol} 3400 (OH) and 1550 cm^{-1} (nitroalkane); ^{1}H-n.m.r.: δ 5.67 (d, $J_{1,2}$ 4 Hz, H-1), 4.55 (dt, 2 H, *J* 1.5 and 6.5 Hz, H-6,6′), 4.48 (d, $J_{1,2}$ 4 Hz, H-2), 4.18 (septet, *J* ~3, 6, and 8 Hz, H-4), 4.10 (dd; d after D_2O exchange, $J_{3,4}$ 3, $J_{3,OH}$ 6 Hz, H-3), 2.35 (m, 2 H, H-5,5′), 1.65 (d, $J_{3,OH}$ 6 Hz, exchangeable, OH-3), 1.45 and 1.28 (s, 3 H each, Me_2C).

Anal. Calc. for $C_9H_{15}NO_6$ (233.2): C, 46.35; H, 6.48; N, 6.01. Found: C, 46.35; H, 6.52; N, 5.99.

Mixture of 2,3-dideoxy-3-nitroinositols (**6**). — A stirred suspension of **4** (3.0 g) in 0.025M H_2SO_4 was boiled under reflux for 40 min. The condenser was removed, a stream of N_2 was passed through the mixture, and boiling was continued for 5 min (with periodic replacement of the evaporated water), in order to expel

the liberated acetone. Completion of the hydrolysis was indicated by t.l.c. (solvent *C*), showing **4** (R_F 0.8) fully replaced by the free sugar **5** (R_F 0.5). A trace spot having R_F 0.2 was probably due to **6** which may have arisen on the t.l.c. plate. (6-Deoxy-6-nitrohexoses have been observed to cyclize slowly in neutral or even slightly acidic media[14].)

The cooled hydrolyzate was placed in a three-necked flask equipped with a glass electrode and nitrogen inlet, magnetically stirred under N_2 at room temperature, and carefully made neutral by dropwise addition of a saturated, aqueous $Ba(OH)_2$ solution. The pH was eventually maintained at 8.5 for 1 h, and at 8.8–8.9 for another 3 h. Progress of the conversion of **5** into **6** (R_F 0.2) was monitored by t.l.c. The mixture was then stirred with some Dry Ice, to adjust the pH value to ~6, and filtered through a layer of Celite. The inorganic residue was washed well with water, and the yellowish filtrate was treated with a cation-exchange resin until it was free from barium ions. The solution was then decolorized with activated carbon, and evaporated, to give **6** as a glassy material. Dried overnight in a desiccator, it weighed 2.69 g and apparently still had retained some water (theoretical yield, 2.48 g).

2,3-Dideoxy-3-nitro-D-myo-*inositol 1,4,5,6-tetraacetate* (**7**) *and 2,3-dideoxy-3-nitro*-D-epi-*inositol 1,4,5,6-tetraacetate* (**8**). — A sample of mixture **6** was evaporated twice with abs. ethanol. The dry foam (1.1 g) was then dissolved in acetic anhydride (7.5 mL), and boron trifluoride etherate (11 drops) was added under ice–water cooling. The acetylation was allowed to proceed at ambient temperature for 2 h, and t.l.c. (solvent *B*) indicated the formation, from practically immobile **6**, of the tetraacetates **7** (R_F 0.2) and **8** (R_F 0.3), with the former appearing to preponderate. The mixture was processed by decomposition of the remaining anhydride with excess methanol, and evaporation of added toluene from the solution to give a colorless, dry, amorphous mixture of **7** and **8** (2.05 g). Trituration of the material with warm, 99% ethanol, followed by refrigeration yielded a first crop (600 mg) of crystals consisting largely of **7**. Recrystallized twice from 95% ethanol, the fine, silky needles were chromatographically homogeneous; m.p. 150°, $[\alpha]_D$ +4.5° (*c* 1.5, chloroform), ν_{max}^{Nujol} 1750 (ester CO) and 1550 cm^{-1} (nitroalkane); ^1H-n.m.r. (500-MHz): δ 5.62 (dd, $J_{3,4}$ 10.5, $J_{4,5}$ 9.9 Hz, H-4), 5.26 (t, $J_{1,6} = J_{5,6} = 9.9$ Hz, H-6), 5.11 (t, $J_{4,5} \approx J_{5,6} \approx 9.9$ Hz, H-5), 4.95 (ddd, $J_{1,6}$ 9.9, $J_{1,2a}$ 11.9, $J_{1,2e}$ 4.7 Hz, H-1), 4.69 (ddd, $J_{2a,3}$ 12.9, $J_{2e,3}$ 4.5, $J_{3,4}$ 10.5 Hz, H-3), 2.71 (dt, $J_{2a,2e}$ 12.7, $J_{1,2e} \approx J_{2e,3} \approx 4.5$ Hz, H-2e), 2.16 (dt, line separations 12–13 Hz, H-2a), 2.04, 2.01, and 2.00 (s, 3, 3, and 6 H, OAc). The assignments were confirmed by a homonuclear shift-correlation experiment.

Anal. Calc. for $C_{14}H_{19}NO_{10}$ (361.3): C, 46.54; H, 5.30; N, 3.87. Found: C, 46.41; H, 5.30; N, 3.94.

The ethanolic mother liquor remaining after the collection of the aforementioned crop of crude **7** was concentrated somewhat by evaporation in the air; upon refrigeration it then deposited slowly the tetraacetate **8** as stout, rectangular prisms (480 mg) which were chromatographically pure after one further recrystallization from 95% ethanol; m.p. 130–131°, $[\alpha]_D$ −21.4° (*c* 1.2, chloroform),

ν_{max}^{Nujol} 1750 (ester CO) and 1550 cm^{-1} (nitroalkane); ^{1}H-n.m.r. (500 MHz): δ 6.10 (narrow m, W_H 6 Hz, H-4), 5.39 (t, $J_{1,6} = J_{5,6} = 10.2$ Hz, H-6), 4.94–4.88 (complex m, 2 H, H-1,5), 4.59 (ddd, $J_{2a,3}$ 13, $J_{2e,3}$ 4.1, $J_{3,4}$ 2.7 Hz, H-3), 2.71 (dtd, $J_{2a,2e}$ 12.6, $J_{1,2e} \approx J_{2e,3} \approx 4.1$, $-J_{2e,4}$ ~0.4 Hz, H-2e), 2.42 (~q, line separations 12.5–13 Hz, H-2a), 2.09, 2.05, 2.01, and 1.98 (s, 3 H each, OAc). The assignments were confirmed by the homonuclear shift-correlation method.

Anal. Calc. for $C_{14}H_{19}NO_{10}$ (361.3): C, 46.54; H, 5.30; N, 3.87. Found: C, 46.79; H, 5.40; N, 3.92.

3-Acetamido-2,3-dideoxy-D-myo-*inositol 1,4,5,6-tetraacetate* (**9**). — Compound **7** (50 mg) and PtO_2 catalyst (50 mg) in acetic acid (2 mL) were vigorously stirred for 18 h, under hydrogen at ordinary temperature and pressure. Freeze-drying of the filtered solution gave a white solid which was treated with a 2:1 mixture of acetic anhydride and pyridine for 4 h at 25°. Processing by evaporation of methanol followed by toluene from the product gave **9** (52 mg, 100%) as a white, crystalline mass, m.p. 191–192°, $[\alpha]_D$ −12° (*c* 1.1, chloroform); lit.[8] m.p. 191.5–192°, $[\alpha]_D$ −11.5°; ν_{max}^{Nujol} 3420–3370 (NH), 1740 (ester CO), 1666 and 1520 (amide); ^{1}H-n.m.r.: δ 5.61 (d, *J* 8.3 Hz, exchangeable, NH), 5.18 (~t, $J_{4,5} \approx J_{5,6} \approx 9.2$ Hz, H-5), 5.10 (~t, $J_{1,6}$ 9.8, $J_{5,6}$ 9.2 Hz, H-6), 4.98 (ddd, $J_{1,2e}$ 4.5, $J_{1,2a}$ 12, $J_{1,6}$ 10 Hz, H-1), 4.90 (dd, $J_{3,4}$ 10.8, $J_{4,5}$ 9.1 Hz, H-4), 4.16 (broad m, ddd after D_2O exchange, $J_{2e,3}$ 4, $J_{3,4}$ 10.8, $J_{2a,3}$ 12.4 Hz, H-3), 2.43 (dt, $J_{2a,2e}$ 12.6, $J_{1,2e} \approx J_{2e,3} \approx 4.3$ Hz, H-2e), 2.02 (s, 3 H), 1.99 (s, 9 H), and 1.89 (s, 3 H) for 5 acetyl groups, and 1.46 (~q, line separations 12–13 Hz, H-2a).

3-Acetamido-2,3-dideoxy-D-epi-*inositol 1,4,5,6-tetraacetate* (**12**). — Compound **8** (50 mg) was catalytically hydrogenated, and the product was acetylated, as just described for **7**. The peracetylated material (**12**), in contrast to **9**, failed to crystallize from toluene, or toluene–ether and various other solvent combinations tried, although prismatic crystals deposited from a chloroform–hexane solution on prolonged refrigeration. However, these were low-melting and tended to liquefy on isolation. The product could only be characterized as a (colorless) glass; $[\alpha]_D$ −13° (*c* 1, chloroform); ν_{max}^{Nujol} 3500–3250 (broad), 1750 (ester CO), 1655 and 1540 cm^{-1} (amide I and II); ^{1}H-n.m.r.: δ 5.39 (m, 2 H; reduced to t, 1 H, after D_2O exchange; $J_{3,4} \approx J_{4,5} \approx 3$ Hz; H-4 and NH), 5.30 (t, $J_{1,6} \approx J_{5,6} \approx 10$ Hz, H-6), 4.92 (dd for H-5, with *J* 3 and 10 Hz, superposed on ddd for H-1, with *J* 5, 10, and 12 Hz), 4.28 (complex m, reduced to ddd on D_2O exchange, $J_{2e,3}$ 2.5, $J_{3,4}$ 4.5, $J_{2a,3}$ 13 Hz, H-3), 2.17 (s, 3 H, for OAc-4, superposed on m, 1 H, for H-2e), 1.99 (s, 6 H), 1.94 (s, 3 H), and 1.92 (s, 3 H) for 4 acetyl groups, and 1.78 (~q, line separations 12–13 Hz, H-2a).

3-Acetamido-2,3-dideoxy-D-epi-*inositol* (**13**). — A sample of syrupy **12** (obtained from 50 mg of **8**) in abs. ethanol (5 mL) was treated with a few drops of methanolic sodium methoxide solution. Crystallization of **13** started within 5 min and was complete after the solution had been kept at 0° overnight. Washed with cold ethanol and air-dried, the fine, colorless needles (25 mg, 88% from **8**) had m.p. 275–276° (dec.), $[\alpha]_D$ −51.8° (*c* 1.8, water), R_F 0.45 (t.l.c., solvent *D*); ν_{max}^{Nujol} 3380, 3300 (OH, NH), 1610 and 1550 (amide) cm^{-1}.

Anal. Calc. for $C_8H_{15}NO_5$ (205.2): C, 46.82; H, 7.34; N, 6.82. Found: C, 46.71; H, 7.34; N, 6.74.

Preparation of **9** *and* **13** *directly from* **6**. — A mixture **6** (2.64 g) in water (25 mL) containing acetic acid (0.85 mL) and Adams catalyst (500 mg of PtO_2, pre-hydrogenated in 12 mL of water) was vigorously agitated under hydrogen at ordinary temperature and pressure. Uptake of H_2 was 885 mL after 26 h. The catalyst was removed, and washed exhaustively with water. The filtrate was concentrated to a colorless syrup to whose solution in a small volume of aqueous methanol was added acetic anhydride (2 mL). After 5 min the mixture was evaporated with several added portions of ethanol followed by toluene, to give an amorphous product-mixture (2.87 g, desiccator-dried over KOH). The material was dissolved in warm, aqueous ethanol, the solution filtered from a small quantity of insoluble matter, and refrigerated, to give crystalline **13** (480 mg, washed with 95% ethanol, and dried), plus additional crops (585 mg) upon concentration of the mother liquor, for a total of 1.065 g (38%), dec. pt. 262–264°, and 275° after recrystallization from aqueous ethanol. The i.r. spectrum was identical with that of **13** prepared from **8**; after *O*-acetylation (acetic anhydride–pyridine), a sample gave an ^{1}H-n.m.r. spectrum identical with that of **12**.

The mother liquor was finally evaporated to a dry, foamy residue (1.5 g) consisting mainly of the isomer **10**. It was treated with acetic anhydride (20 mL) and pyridine (10 mL) at room temperature for 16 h. The mixture was processed by addition of methanol and evaporation of toluene from it. The syrupy, toluene-containing residue gave, upon trituration with ether and seeding with **9**, a first crop (400 mg) of readily-crystallizing **9**, m.p. 184–186° dec. (and 190–191° dec. after recrystallization from ethyl acetate–ether), $[\alpha]_D$ −12.2° (*c* 0.9, chloroform); the i.r. spectrum was identical with that of **9** prepared from **7**.

The toluene–ether mother liquor contained several fast-moving contaminants in addition to **9**, R_F 0.05 (solvent *A*) and 0.5 (ethyl acetate). It is to be noted that **9** is rather difficult to detect on t.l.c. plates as it is reluctant to char on a hot-plate after spraying with 10% sulfuric acid in ethanol. Detection is achieved more readily on aluminum foil plates which are heated over a small flame, without prior spraying. Chromatography of the mother liquor material on silica gel (25 g, 200–400 mesh), starting with solvent *B* and continuing with solvent *A*, produced the contaminants (R_F 0.6–0.2, solvent *A*) totaling 316 mg. Subsequent elution with ethyl acetate furnished crystalline **9** (660 mg), m.p. 179–181°, raised to 191.5–192° by recrystallization from ethyl acetate–ether. Additional **9** (220 mg) emerged on elution with 1:9 methanol–ethyl acetate; total yield, 1.28 g (28%).

3-Amino-2,3-dideoxy-D-myo-*inositol* (**11**). — Crystalline **9** (250 mg) in methanol (3 mL) was *O*-deacetylated by the addition of a few drops of sodium methoxide solution. The reaction was complete after 3 h (t.l.c., solvent *D*). The solution was deionized with a small quantity of Dowex-50 (H^+) resin and concentrated to a colorless syrup which was treated on a steam bath, for 4 h, with aqueous, saturated $Ba(OH)_2$ solution (3 mL), protected from atmospheric CO_2. The cooled

solution was acidified to pH 3 with 0.5M H_2SO_4, freed from the precipitate by filtration through a bed of Celite, stirred with an anion-exchange resin (Dowex-1, OH^- or equivalent) until free from sulfate ions ($BaCl_2$ test), and evaporated. The colorless residue was evaporated twice with added ethanol and then triturated with a small amount of warm 2-propanol, whereby it crystallized. The white powder was dried over KOH in a desiccator; yield, 107 mg (95%), R_F 0.15 (solvent *D*), $[\alpha]_D$ +3.6° (*c* 1.6, water); lit.[8] for **11**-sulfate, $[\alpha]_D$ +3.7 ±0.5°. On heating above 160°, **11** showed gradual browning, turning into a dark solid that melted sharply at 180–182°; ^{13}C-n.m.r. (75.43 MHz) in D_2O (internal 1,4-dioxane standard) for free base: δ 77.4, 75.8, 75.3, 70.0 (C-1,4,5,6), 49.7 (C-3), and 35.4 (C-2); for hydrochloride: δ 77.0, 75.1, 73.7, 69.4 (C-1,4,5,6), 49.9 (C-3), and 35.1 (C-2), in fair agreement with reported[5] data.

3-Amino-2,3-dideoxy-D-epi-*inositol* (**14**). — The *N*-acetyl derivative **13** (200 mg) was heated on a steam bath with aqueous, saturated $Ba(OH)_2$ solution. After 3.5 h, complete replacement of **13** (R_F 0.5) by **14** (R_F 0.1, ninhydrin-positive) was indicated by t.l.c. (solvent *D*). Processing as described for **11** gave **14** as a viscous syrup that solidified on trituration with ethanol; the white solid (150 mg, 94%), $[\alpha]_D$ +5.2° (*c* 1, water), melted sharply at 177–178°, with prior darkening (170–175°), unchanged on recrystallization from 2-propanol–water. Slow evaporation of an acidified (HCl), aqueous solution in the air gave the *hydrochloride* as long needles; ^{13}C-n.m.r. (75.43 MHz) in D_2O (internal 1,4-dioxane standard) for free base: δ 75.1, 73.9, 73.6, 70.9, (C-1,4,5,6), 48.3 (C-2), and 35.3 (C-2); for hydrochloride: δ 74.5, 72.8, 70.0, 70.0 (C-1,4,5,6), 48.7 (C-3), and 31.1 (C-2).

Anal. Calc. for $C_6H_{13}NO_4$ (163.2): C, 44.17; H, 8.03; N, 8.58. Found: C, 44.07; H, 8.20; N, 8.60.

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