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Note

A synthesis of 2-amino-2,6-dideoxy-D-allose and -D-altrose hydrochlorides and their tetraacetyl derivatives*

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This report describes synthesis of the title amino sugars by the Kuhn modification[1] of the cyanohydrin synthesis, in order to obtain n.m.r.-spectral parameters on their tetraacetyl derivatives. An amino sugar obtained[2] by hydrolysis of the antigenic lipopolysaccharide[3] of *Pseudomonas aeruginosa* Strain 2 (classification of Fisher *et al.*[4]) gave a tetraacetyl derivative, the n.m.r. spectrum of which was consistent with its being a 2-acetamido-1,3,4-tri-*O*-acetyl-2,6-dideoxy-α,β-hexopyranose having either the *galacto* or *altro* stereochemistry. Although the paperchromatographic mobility of the amino sugar was in accordance with values recorded[5,6] for the *galacto* isomer, the specific rotation of the *N*-acetyl derivative did not accord with published values[5,6] for either 2-acetamido-2,6-dideoxy-D- or[7] -L-galactose. Accordingly, the present synthesis was undertaken to provide reference data and to permit comparison of the n.m.r. spectra of an acetylated sample of 2-amino-2,6-dideoxy-D-altrose with that of the acetylated derivative of the amino sugar from the *Pseudomonas* antigen.

Methyl 2,3-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-β-D-ribofuranoside[8] (**1**) was converted directly into the 5-deoxy analogue[9] **2** by treatment with lithium aluminum hydride, but the yield (62%) of pure, syrupy **2** was less than that (72%) attainable by an adaptation of the published[9] two-step route through the 5-deoxy-5-iodo derivative[10]. The homogeneity of the product was evident from its n.m.r. spectrum, which was essentially first-order; the fact that the $J_{1,2}$ and $J_{3,4}$ couplings are close to zero leads to a particularly simple spectrum.

The free deoxy sugar **3** obtained[9] by acid hydrolysis of **2** was treated with aniline and hydrogen cyanide, under the conditions used by Kuhn and Fischer[11] with D-ribose. Fractional crystallization of the product gave 11.5% of the pure, strongly dextrorotatory 2-anilino-2,6-dideoxy-D-allononitrile (**5**) and 25% of the pure, strongly levorotatory D-*altro* isomer (**4**). Both products were crystalline and their

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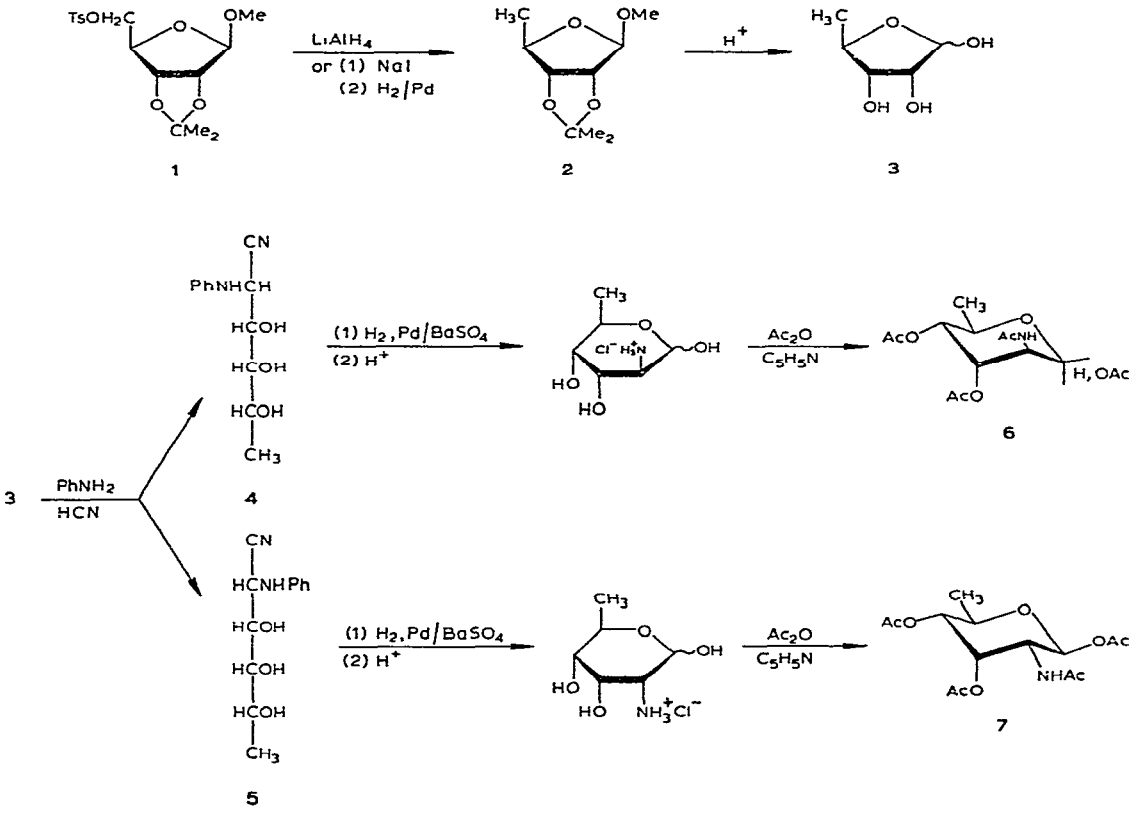

stereochemical attribution was tentatively based on the close similarity of their specific rotations to those[11] of the 6-hydroxy analogues; firm configurational characterization of the two stereoisomers is afforded by data on the derived products.

Reduction of the D-*altro* nitrile **4** with hydrogen in the presence of palladium on barium sulfate[12] led to the uptake of the anticipated three molar equivalents of hydrogen, and 2-amino-2,6-dideoxy-D-altrose was isolated as its amorphous, weakly levorotatory hydrochloride. Acetylation of this chromatographically homogeneous product gave the analytically pure tetraacetyl derivative **6** in 47% net yield from the nitrile **4**.

Similar reduction of the D-*allo* nitrile **5** gave 2-amino-2,6-dideoxy-D-allose hydrochloride, which was acetylated to give 2-acetamido-1,3,4-tri-*O*-acetyl-2,6-dideoxy-β-D-allopyranose (**7**), initially as a syrup that subsequently crystallized. The n.m.r. spectrum of the product indicated that only the β-pyranose form was present, even in the syrup; formation of the α anomer is presumably disfavored because of the 1,3-diaxial interaction of acetoxyl groups that would result.

The 100-MHz n.m.r. spectrum of **7** in chloroform-*d* was completely first-order. At low field, the NH and H-1 signals are observed as wide doublets, and the equatorial

disposition of H-3 brings its signal to low field, immediately upfield of the H-1 resonance, and its appearance as a narrow triplet results from equal, small values of the $J_{2,3}$ and $J_{3,4}$ couplings. At highest field, the C-6 methyl group doublet is readily recognized, as are the four acetyl-group signals, and the doubled quartet for the H-5 signal is immediately evident at δ 4.03. The H-2 signal is observed, as expected[13], at higher field than the signals of H-3 and H-4 because of the acetamido group.

The n.m.r. spectrum of the D-*altro* derivative **6** at 100 MHz in chloroform-*d* was not so readily interpretable as that of **7** because the product was a 1:2 mixture of the α- and β-pyranose anomers. At highest field, the C-6 methyl groups of the two anomers gave rise to two doublets in the approximate ratio of 1:2, and the same ratio was evident in the signals at low field for H-1α and H-1β. The region for acetyl-group signals had the correct integrated intensity but showed multiple peaks as a result of the anomeric mixture. The signals for H-2,3,4, and 5 for the major (β) anomer were clearly evident and well separated in an essentially first-order pattern (see Experimental section). The spin-coupling values observed deviate from those anticipated[14] for the exclusive $^4C_1$(D) conformation (notably the values of $J_{2,3}$ and $J_{4,5}$ for the β anomer and $J_{1,2}$ for the α anomer) and suggest[15] that the $^1C_4$(D) form contributes significantly to the conformational population.

The spectrum of **6** was distinctly different from that of the tetraacetyl derivative of the amino sugar from the *Pseudomonas* antigen, indicating that the natural amino sugar does not have the *altro* stereochemistry. It has since been found[2] that the amino sugar from this antigen and related lipopolysaccharides[16] is a mixture of 2-amino-2,6-dideoxy-D- and L-galactose, which accounts for the discrepancy in the observed specific rotation in comparison with that of the pure enantiomorphs.

The overall yields of the two amino sugars in this synthesis are approximately the same as those reported by Perry and Daoust[17], who used the nitromethane synthesis starting from **3** and isolated the amino sugars as their *N*-acetyl derivatives.

EXPERIMENTAL

General methods. — Solutions were evaporated under diminished pressure. Melting points were recorded with a Thomas–Hoover "Unimelt" apparatus and are uncorrected. Petroleum ether refers to a fraction having b.p. 30–60°. N.m.r. spectra were recorded at 60 or 100 MHz with Varian A-60A or HA-100 spectrometers, with solutions in chloroform-*d* containing tetramethylsilane as the internal standard. Microanalyses were performed by W. N. Rond. X-Ray powder diffraction data give interplanar spacings in Å for CuKα radiation (camera diameter 114.59 mm). Relative intensities were estimated visually: m, moderate; s, strong; v, very; w. weak. The strongest lines are numbered (1, strongest). For column chromatography, an adsorbent to sample ratio of 50–100:1 was used.

Methyl 5-deoxy-2,3-O-isopropylidene-β-D-ribofuranoside (**2**). — *Method A.* To a suspension of lithium aluminum hydride (0.95 g) in tetrahydrofuran (20 ml) was added methyl 2,3-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-β-D-ribofuranoside[9,10] (**1**, 2.9 g, Pfanstiehl Laboratories, Waukegan, Ill. 60085) and the mixture was boiled for

1 h under reflux. Ethyl alcohol was added cautiously to the cooled mixture, the precipitated salts were filtered off, and the filtrate was evaporated. The residue was extracted with chloroform and the extract evaporated, and the product transferred in dichloromethane solution onto a column containing 50 g of silica gel (No. 7734, Merck). Elution with dichloromethane gave the title compound[9] as an oil; yield 0.94 g (62%); n.m.r. (60 MHz, chloroform-*d*): δ 4.97 (1-proton singlet, $J_{1,2}$ ~0 Hz, H-1), 4.69 and 4.52 (two doublets, AB system ,$J_{2,3}$ 6 Hz, H-2 and H-3), 4.39 (1-proton quartet, $J_{3,4}$ ~0, $J_{4,5}$ 7 Hz, H-4), 3.55 (3-proton singlet, OMe), 1.49, 1.36 (3-proton singlets, CMe_2), and 1.30 (3-proton doublet, H-5).

Method B. A solution of **1** (3.33 g) and potassium iodide (6 g) in *N,N*-dimethylformamide (25 ml) was heated for 1 h at 110°. The mixture was cooled, and salts that precipitated were filtered off. The filtrate was evaporated and the residue extracted with dichloromethane. The extract was concentrated to ~5 ml and then passed through a column of silica gel. Elution with dichloromethane gave the 5-iodo derivative[10], which was dissolved in methanol (50 ml) and hydrogenated at 2.1 kg. cm^{-2} for 4 h at ~25° in the presence of triethylamine (4 ml) and 5% palladium-on-charcoal. Removal of the catalyst and evaporation of the solvent gave the 5-deoxy derivative **2**, which was purified by chromatography as described in method *A*; yield 1.26 g (72%, based on the sulfonate **1**).

*5-Deoxy-*D*-ribose*[9] (**3**). — A solution of **2** (2.0 g) in methanol (10 ml) and 0.2M sulfuric acid (4 ml) was boiled for 2 h under reflux, and then concentrated to ~3 ml. Aqueous sulfuric acid (M, 10 ml) was added and the solution was heated for 2 h at 85–90°. The cooled solution was neutralized (barium carbonate) and evaporated to give a syrup that was practically pure **3** by t.l.c.; yield 1.32 g (90%) after drying *in vacuo* over phosphorus pentaoxide.

*2-Anilino-2,6-dideoxy-*D*-allononitrile* (**5**) *and 2-anilino-2,6-dideoxy-*D*-altrononitrile* (**4**). — To a solution of **3** (0.89 g) in abs. ethanol (5 ml) was added aniline (0.6 g) and the mixture was kept for 5 min at 50°. It was then cooled to 3° and a solution of hydrogen cyanide (prepared from 4 g of sodium cyanide and concentrated sulfuric acid) in abs. ethanol (1 ml) was added. The resulting mixture was kept for 16 h at ~25°. Insoluble salts were filtered off and the filtrate was evaporated to give a dark syrup. Upon addition of dichloromethane to the syrup and cooling to 3° the D-*allo* epimer **5** crystallized out. It was recrystallized from chloroform as long needles; yield 180 mg (11.5%), m.p. 143–144°, $[\alpha]_D^{25}$ +153° (*c* 0.9, methanol); X-ray powder diffraction data: 10.04 m, 7.43 w, 5.69 m, 4.69 s (1), 4.37 w, 4.19 vw, 3.90 s (2).

Anal. Calc. for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.82; N, 11.85. Found: C, 61.22; H, 6.66; N, 11.92.

The mother liquors were concentrated to a thick syrup. After addition of dichloromethane and petroleum ether to the syrup, the D-*altro* epimer (**4**) was obtained crystalline; yield 0.4 g (25%), m.p. 104–106°. An analytical sample was obtained by recrystallization from chloroform–petroleum ether; m.p. 106–108°, $[\alpha]_D^{25}$ −184° (*c* 0.8, methanol); X-ray powder diffraction data: 14.97 vw, 9.93 m (3,3), 6.80 m, 5.60 vs (1), 4.95 m (3,3), 4.74 w, 4.31 s (2,2), 3.98 m, 3.78 s (2,2).

Anal. Calc. for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.82; N, 11.85. Found: C, 60.80; H, 6.47; N, 12.01.

*2-Acetamido-1,3,4-tri-*O*-acetyl-2,6-dideoxy-α,β-*D*-altropyranose* (**6**). — The *altro* nitrile (**4**, 100 mg) was dissolved in 0.5M hydrochloric acid (10 ml) and hydrogenated in the presence of palladium oxide-on-barium sulfate catalyst[12] that had previously been suspended in water and reduced. After 5 h, the uptake of hydrogen (27 ml, 3 mol per mol of **4**) ceased. The catalyst was filtered off and the filtrate was evaporated. The residue was dissolved in water (2 ml) and applied to a column (1.5 × 3 cm) of Amberlite IR-120 (H^+) ion-exchange resin. The amino sugar was eluted with 0.5M hydrochloric acid (150 ml). Evaporation of the effluent gave amorphous *2-amino-2,6-dideoxy-*D*-altrose hydrochloride*, $[\alpha]_D^{22}$ −3° (*c* 0.9, methanol, 30 min), which was treated with pyridine (2 ml) and acetic anhydride (0.5 ml) for 30 min at 65°. The mixture was evaporated and the residue dissolved in dichloromethane. The solution was transferred to a column of silica gel, and elution with 1:1 (v/v) dichloromethane–ether followed by ether removed side-products. Elution with 5:1 (v/v) ether–ethyl acetate desorbed the title compound **6**, which was isolated as a colorless, chromatographically homogeneous syrup that did not crystallize; yield 66 mg (47%, based on the nitrile **4**), $[\alpha]_D^{22}$ −13° (*c* 1.3, chloroform); n.m.r. (100 MHz, chloroform-*d*): δ 6.35 (broadened doublet, disappears on deuteration, J 8 Hz, NH), 6.26 (~0.3 proton d, $J_{1,2}$ 4.7 Hz, H-1α), 6.13 (~0.7 proton d, $J_{1,2}$ 2.5 Hz, H-1β), 5.38 (dd, $J_{3,4}$ 3.0 Hz, H-3β), 4.94 (dd, $J_{4,5}$ 7.5 Hz, H-4β), 4.48 (m, collapses to dd on deuteration, $J_{2,3}$ 5.5 Hz, H-2β), 4.12 (5-line m, $J_{5,6}$ 6.5 Hz, H-5β), 2.12, 2.08, 2.02, 1.98, 1.92 (singlets, total 12 protons, Ac), 1.25 (~2-proton d, $J_{5,6}$ 6.5 Hz, H-6β), and 1.22 (~1-proton d, $J_{5,6}$ 6 Hz, H-6α).

Anal. Calc. for $C_{14}H_{21}NO_8$: C, 50.75; H, 6.39; N, 4.23. Found: C, 50.93; H, 6.48; N, 4.50.

*2-Acetamido-1,3,4-tri-*O*-acetyl-2,6-dideoxy-β-*D*-allopyranose* (**7**). — The *D-allo* nitrile **5** (100 mg) in 0.5M hydrochloric acid (10 ml) was hydrogenated as described for the *D-altro* derivative **4**. The reduced compound was applied to a column of Amberlite IR-120 (H^+) resin and eluted with 0.5M hydrochloric acid to give amorphous *2-amino-2,6-dideoxy-*D*-allose hydrochloride*, $[\alpha]_D^{22}$ +7° (*c* 0.8, methanol, 30 min), which was treated with pyridine and acetic anhydride for 30 min at 65°. The product was isolated and purified as for the *altro* derivative **6**, except that impurities were removed from the silica gel column by elution with 5:1 (v/v) ether–ethyl acetate. The pure acetylated amino sugar **7** was eluted by 3:1 (v/v) ether–ethyl acetate and was obtained as a colorless syrup; yield 46 mg (33% based on the nitrile **5**); n.m.r. (100 MHz, chloroform-*d*): δ 6.36 (1-proton doublet, exchanges on addition of D_2O, $J_{2,NH}$ 9 Hz, NH), 5.85 (1-proton doublet, $J_{1,2}$ 8.5 Hz, H-1), 5.51 (1-proton triplet, $J_{2,3}$ and $J_{3,4}$ 2.5 Hz, H-3), 4.67 (1-proton doublet of doublets, $J_{4,5}$ 10 Hz, H-4), 4.40 (1-proton, 6 lines, collapses to 4 lines on deuteration, H-2), 4.03 (1 proton octet, $J_{5,6}$ 6.5 Hz, H-5), 2.17, 2.10, 1.99, 1.94 (3-proton singlets, Ac), and 1.24 (3-proton doublet, H-6).

Addition of ether and petroleum ether gave crystalline **7**, m.p. 165–168°;

X-ray powder diffraction data: 11.51 w, 9.78 m, 8.73 w, 7.91 w, 7.15 vs (2), 6.64 vs (1), 6.01 m, 5.40 s, 4.89 m, 4.58 w, 4.32 w, 3.95 s, 3.70 s (3), 3.58 vw.

Anal. Calc. for $C_{14}H_{21}NO_8$: C, 50.75; H, 6.39; N, 4.23. Found: C, 50.58; H, 6.27; N, 4.47.

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