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Note

Synthesis of 2-amino-2-deoxyarabinose hydrochloride

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In 1959, 2-amino-2-deoxy-D-arabinose hydrochloride (**1**D) was synthesized from 2,4-*O*-ethylidene-D-erythrose via a cyanohydrin reaction, and 2-amino-2-deoxy-L-arabinose hydrochloride (**1**L) was obtained by chain-shortening reactions from ethyl 2-acetamido-2-deoxy-1-thio-α-D-galactofuranoside[2]. Soon thereafter, **1**D was synthesized by periodate oxidation of 3-acetamido-3-deoxy-β-D-mannose or 3-acetamido-3-deoxy-β-D-glucose[3] and by reduction of a nitroso compound prepared by reaction of 3,4-di-*O*-acetyl-D-arabinal with nitrosyl chloride[4]. Recently, starting from 2,3-*O*-isopropylidene-D-glyceraldehyde, **1**D derivatives were synthesized by stereoselective reaction of a chiral imine[5] and ethyl isocyanoacetate[6]. The synthesis in the present paper involves the displacement of a *p*-tolylsulfonyloxy group by nitrogen nucleophiles (sodium azide and hydrazine) and subsequent reduction. Hydrazine was found superior to sodium azide as a nitrogen nucleophile, and the hydrazinolysis route was satisfactory for the synthesis of **1**. By this synthetic route **1**D and **1**L were synthesized starting from D- and L-arabinose, respectively.

Methyl 3,4-*O*-isopropylidene-2-*O*-*p*-tolylsulfonyl-β-D-ribopyranoside (**4**D) was first synthesized from methyl β-D-ribopyranoside by Levene[7]. Methyl 3,4-*O*-isopropylidene-2-*O*-*p*-tolylsulfonyl-β-L-ribopyranoside (**4**L) was obtained by reduction of methyl 3,4-*O*-isopropylidene-β-L-*erythro*-pentopyranosid-2-ulose (**3**L), which was prepared by oxidation of methyl 3,4-*O*-isopropylidene-β-L-arabinoside (**2**L) with chromium trioxide and pyridine[8]. In this work, methyl 3,4-*O*-isopropylidene-β-D-*erythro*-pentopyranosid-2-ulose (**3**D) and **3**L were prepared in better yield by oxidation with ruthenium tetraoxide[9,10]. Compound **3**D and **3**L were reduced with lithium aluminum hydride and subsequently treated with *p*-toluenesulfonyl chloride in pyridine to give **4**D and **4**L in 71% yield.

For displacement of secondary sulfonyloxy groups with inversion of con-

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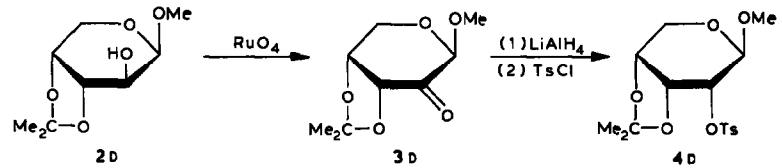
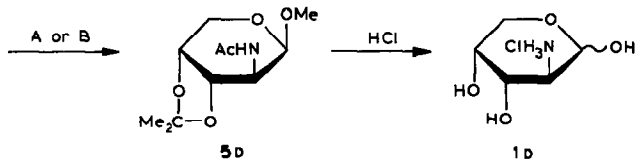
figuration, sodium azide has been used under forcing conditions in *N,N*-dimethylformamide in the synthesis[10] of amino sugars since 1962. When sulfonyloxy groups are adjacent to the anomeric center[11] or are sterically hindered[12], the displacement proceeded with difficulty. Ali *et al.*[13] reported better results using hexamethylphosphoric triamide at a lower temperature. In the present paper, **4**D was converted into the azide by use of an excess of sodium azide in hexamethylphosphoric triamide for 10 h at 120° in a stream of nitrogen. About 68% of the substrate was recovered and could be recycled. The crude azide was reduced with lithium aluminum hydride, and then acetylated to yield crystalline methyl 2-acetamido-2-deoxy-3,4-*O*-isopropylidene-β-D-arabinopyranoside (**5**D), which was hydrolyzed to **1**D in 18% yield (calculated from the **4**D that had reacted).

The hydrazinolysis of *p*-toluenesulfonates with inversion of configuration has been applied[14,15] for amino sugar synthesis since 1922. Hydrazinolysis is generally conducted in anhydrous or highly concentrated hydrazine at temperatures of 120–140°, and the crude, unstable hydrazino compounds are hydrogenated over Raney nickel. Sterically hindered *p*-toluenesulfonates are difficult to convert into hydrazino compounds[16]. In the present paper, **4**L was heated in anhydrous hydrazine for 24 h at 145°. The hydrazino compound was reduced with Raney nickel to the 2-amino derivative without purification of the hydrazino compound, and subsequent acetylation gave the crystalline 2-acetamido derivative **5**L in 44% yield from **4**L. Compound **5**L was hydrolyzed to **1**L.





A: 1. NaN_3, 2. $LiAlH_4$, 3. Ac_2O

B: 1. NH_2NH_2, 2. Raney Ni, 3. Ac_2O

(Formulas are drawn in the D form.)

EXPERIMENTAL

General methods. — Specific rotations were determined in a 2-dm polarimeter tube. Melting points were determined with a Hershberg type of apparatus. I.r. spectra were measured with a Perkin–Elmer Model 137 i.r. spectrometer. Microanalyses were performed by W. N. Rond. X-Ray powder diffraction data give interplanar spacings, in Å, for CuKα radiation. Relative intensities were estimated visually; s, strong; m, moderate; w, weak; v, very. The strongest lines are numbered in order (1, strongest).

*Methyl 3,4-O-isopropylidene-β-*D-erythro-*pentopyranosid-2-ulose* (**3**D). — To methyl 3,4-*O*-isopropylidene-β-D-arabinopyranoside (**2**D, 10 g) in carbon tetrachloride (130 mL) was added ruthenium tetraoxide[9] [prepared from ruthenium dioxide (12.9 g)] in carbon tetrachloride (390 mL) at 0°. After 1 h at room temperature, 2-propanol (50 mL) was added. The mixture was filtered and the ruthenium dioxide was washed with carbon tetrachloride. Evaporation of the combined filtrate and washings gave a slightly brown crystalline solid (7.5 g, 76% yield). The product was recrystallized from diisopropyl ether; m.p. 96–97°, $[\alpha]_D^{22}$ −169° (*c* 1, chloroform); λ_{max}^{Nujol} 5.70 μm (C=O); X-ray powder diffraction data; 8.04 vw, 7.38 s(2), 6.46 s(1), 5.54 vw, 5.22 w, 4.98 w, 4.62 s(3), 4.04 m(1), 3.87 w, 3.39 w, 3.23 w, 3.02 m(2). [Lit.[17] m.p. 97–98°, $[\alpha]_D^{23}$ −161.2° (*c* 1.4, ethanol)].

Anal. Calc. for $C_9H_{14}O_5$: C, 53.46; H, 6.98. Found: C, 53.48; H, 7.05.

*Methyl 3,4-O-isopropylidene-2-*O-p-*tolylsulfonyl-β-*D-*ribopyranoside* (**4**D). — To **3**D (5.05 g) in ether (250 mL) was added lithium aluminum hydride (1.88 g) at 0°. After stirring for 2.5 h at room temperature, ethyl acetate (50 mL) was added. The solution was washed successively with 0.01M hydrochloric acid (100 mL) and 10% aqueous $NaHCO_3$ (500 mL). The aqueous layer was extracted with chloroform (3 × 300 mL). Solvent removal from the dried extract yielded a syrup (5.01 g) that showed no carbonyl band in its i.r. spectrum. To the syrup in pyridine (85 mL) was added *p*-toluenesulfonyl chloride (7.25 g) with cooling and the solution was kept overnight at room temperature. The colorless precipitate (6.37 g, 71% from **3**D) was collected and dried *in vacuo* with phosphorus pentaoxide. Recrystallization from ethanol afforded colorless needles, m.p. 143.5–144.5°, $[\alpha]_D^{22}$ −108° (*c* 1, ethanol), −105° (*c* 2, chloroform); X-ray powder diffraction data: 10.87 s, 7.63 m(1), 7.14 w, 6.76 w, 6.19 m(3), 5.12 m(2), 4.72 s, 4.40 m(4), 4.23 vw, 3.75 s, 3.56 w. [Lit.[18] m.p. 144°, $[\alpha]_D^{20}$ −113° (*c* 1.0, ethanol). For **4**L, lit.[8] m.p. 143–144°, $[\alpha]_D$ +102° (in chloroform), +107° (in ethanol)].

Anal. Calc. for $C_{16}H_{22}O_7S$: C, 53.63; H, 6.20; S, 8.97. Found: C, 53.30; H, 5.99; S, 8.88.

*Methyl 2-acetamido-2-deoxy-3,4-O-isopropylidene-β-*D-*arabinopyranoside* (**5**D). — Compound **4**D (1 g) and sodium azide (1 g) were heated in hexamethylphosphoric triamide (30 mL) for 10 h at 120° in a slow stream of nitrogen. After cooling, the mixture was poured into water (300 mL). The unreacted **4**D (625 mg) was filtered off and the filtrate was extracted with dichloromethane (4 × 150 mL).

The extract was washed with water (5 × 120 mL), dried with magnesium sulfate, and dichloromethane was removed by evaporation. The remaining hexamethylphosphoric triamide was removed by a column (30 × 2.5 cm) of silica gel with ethyl acetate as developer. The syrup obtained by elution showed an absorption band at 2090 cm^{-1} (N_3) in its i.r. spectrum. By adding hexane to the syrup, the unreacted **4D** (56 mg) precipitated. The filtrate was evaporated to a syrup (59 mg). The syrup in ether (5 mL) was boiled for 1 h under reflux with lithium aluminum hydride (50 mg). Ethyl acetate (10 mL) was added and the mixture was boiled under reflux for 10 min. Insoluble material was filtered off and washed with ether. The combined filtrate and washings were dried with magnesium sulfate and concentrated to a syrup (38 mg) which was ninhydrin-positive. To the syrup in methanol (0.8 mL) was added acetic anhydride (0.4 mL). After 1 h of storage at room temperature the solution was evaporated with addition of methanol to give colorless needles; yield 43 mg (20% from the reacted **4D**). The product was recrystallized from acetone–petroleum ether, m.p. 171–172°, $[\alpha]_D^{25}$ −218° (*c* 0.5, chloroform); λ_{max}^{KBr} 3.12 μm (NH), 6.12 and 6.53 μm (NHAc); X-ray powder diffraction data: 13.39 vw, 10.28 s, 7.41 vw, 6.71 vs, 5.46 m(1), 5.10 vw, 4.42 s, 4.20 m(2), 3.66 w, and 3.34 w.

Anal. Calc. for $C_{11}H_{19}NO_5$: C, 53.85; H, 7.83; N, 5.72. Found: C, 53.50; H, 7.58; N, 5.81.

*2-Amino-2-deoxy-*D*-arabinose hydrochloride* (**1D**). — Compound **5D** (100 mg) was hydrolyzed with 4M hydrochloric acid (5 mL) for 1 h at 100°. The hydrolyzate, after removal of hydrochloric acid by repeated evaporation with methanol, was concentrated to a syrup, which crystallized. Recrystallization from methanol and acetone gave **1D**, yield 68 mg (90%); m.p. 154–156° (dec.), $[\alpha]_D^{23}$ −121° (*c* 1, water after 24 h); λ_{max}^{KBr} 3.0–3.5 μm (OH, NH), 6.25 and 6.64 μm (NH_3^+); X-ray powder diffraction data: 7.73 w, 6.31 m(2), 5.25 m(3), 4.74 m(1), 4.15 vs, 3.87 s, 3.37 w, 3.16 w, 2.89 w, and 2.66 w. [Lit.[1] m.p. 154–157° (dec.), $[\alpha]_D$ −124° (water, final)].

Anal. Calc. for $C_5H_{12}ClNO_4$: C, 32.36; H, 6.52; Cl, 19.10; N, 7.53. Found: C, 32.39; H, 6.55; Cl, 19.37; N, 7.44.

*Methyl 2-acetamido-2-deoxy-3,4-*O*-isopropylidene-β-*L*-arabinopyranoside* (**5L**). — Methyl 3,4-*O*-isopropylidene-2-*O*-*p*-tolylsulfonyl-β-L-ribopyranoside (**4L**, 1.4 g), prepared from L-arabinose, was heated in anhydrous hydrazine (15 mL) for 24 h at 145°. After cooling, the solution was extracted with ether (4 × 25 mL). The extract was evaporated to a syrup that was treated with water (10 mL). The resulting precipitate (49 mg) was filtered off. The filtrate was kept with Raney nickel (1 mL) for 2 h at room temperature. The mixture was then hydrogenated with addition of Raney nickel (1 mL) under 3 atm. of hydrogen for 22 h at room temperature. The reduction product was evaporated to a syrup (367 mg) after separation of the catalyst. The syrup was acetylated with acetic anhydride (4.3 mL) and methanol (8.5 mL) for 3 h at room temperature. Evaporation with addition of methanol gave needles, yield 409 mg (44%), which were recrystallized from acetone–petroleum ether; m.p. 169–170°, $[\alpha]_D^{26}$ +196° (*c* 1, chloroform);

λ_{max}^{KBr} 3.08 μm (NH), 6.08 and 6.48 μm (NHAc); X-ray powder diffraction data; 13.39 vw, 10.22 s, 7.38 vw, 6.66 vs, 5.43 m(1), 5.12 vw, 4.41 s, 4.19 m(3), 4.02 m(2), 3.69 w, and 3.34 w.

Anal. Calc. for $C_{11}H_{19}NO_5$: C, 53.85; H, 7.83; N, 5.72. Found: C, 54.02; H, 8.08; N, 5.42.

*2-Amino-2-deoxy-*L*-arabinose hydrochloride* (**1**L). — **5**L (100 mg) was heated in 4M hydrochloric acid (5 mL) for 1 h at 100°. The solution was then evaporated with repeated addition of methanol. The crystalline residue was recrystallized from methanol–acetone; yield 45 mg (59%), m.p. 156–158° (dec.), $[\alpha]_D^{26}$ +120° (*c* 1.05, water, 2 h); X-ray powder diffraction data: 7.66 w, 6.31 m(2), 5.22 m(3), 4.75 m(1), 4.16 vs, 3.84 s, 3.35 w, 3.15 w, 2.89 w, and 2.66 w. [Lit.[2] m.p. 153–155° (dec.), $[\alpha]_D$ +115° (*c* 0.5, water, final)].

Anal. Calc. for $C_5H_{12}ClNO_4$: C, 32.36; H, 6.52; N, 7.53; Cl, 19.10. Found: C, 32.60; H, 6.64; N, 7.46; Cl, 19.14.

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