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Note

Facile syntheses of methyl 2-amino-2-deoxyglucopyranosides

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Methyl 2-amino-2-deoxy-D-glucopyranosides are standard reference substances in sugar chemistry. They are not directly preparable from 2-amino-2-deoxy-D-glucose by the Fischer method but are obtainable via the *N*-acetyl[1] or *N*-benzyloxycarbonyl[2] derivatives. This behavior has been interpreted[1,2] on the basis of repulsion by the charged amino group of the hydronium ion necessary for glycoside formation. Matsushima and Miyazaki[3], however, have successfully prepared, albeit in low yield, these glycosides by the Fischer method, namely, by boiling a methanolic solution of 2-amino-2-deoxy-D-glucose in the presence of a cation-exchange resin. Morgan and Neuberger[4] have also reported the preparation of methyl 2-amino-2-deoxy-D-glucofuranosides by a similar procedure. In this paper, we describe another variant of the Fischer glycosidation. The synthesis involves treatment of 2-amino-2-deoxy-D-glucose with a strong cation-exchange resin (Amberlite IR-120, H^+ form) in methanol at 100° in a sealed tube.

If the reaction is performed in boiling methanol, the products consist mainly of the α- and β-furanosides, as reported by Morgan and Neuberger[4]. However, when the reaction temperature is raised to 80–90°, the furanosides formed initially are gradually converted into α and β pyranosides. This conversion was established by inspection of the products after separation with Dowex-1 resin (see later). When the reaction was effected for 9 h at 100°, the best yields of pyranosides [58 and 22% for α- and β-D-glucopyranosides (**1** and **2**)] were obtained. The α-D-glucoside (**1**) was identical with the compound prepared by the method of Neuberger and Pitt Rivers[2]. When the reaction was performed at 120°, the yields of glucosides decreased and unidentified by-products were formed.

It may be concluded that, for the preparation of methyl 2-amino-2-deoxy-α-D-glucopyranoside (**1**) by the Fischer method in the presence of Amberlite IR-120 (H^+ form), it is only necessary to perform the reaction at 100°.

Separation of the α and β glucosides formed was performed by column chromatography on Dowex-1 (OH form) resin as reported by Matsushima *et al.*[5] and Austin *et al.*[6]. For isolation of the α glucoside (**1**), however, use of a carboxylic-type resin (Amberlite CG-50) was found to be more convenient.

The foregoing procedure was applied for the preparation of methyl 2-deoxy-2-methylamino-α-L-glucopyranoside (**3**). 2-Deoxy-2-methylamino-L-glucose[7], which has been prepared by acidic hydrolysis of dihydrostreptomycin, was similarly treated to give **3** in 51% yield.

EXPERIMENTAL

Preparation of resin. — Commercial Amberlite CG-120 resin (200–400 mesh) was conventionally treated alternately with 2M hydrochloric acid and 2M sodium hydroxide. The H^+ form resin was washed with methanol several times, kept in methanol overnight, filtered, and heated for 3 h at 60° under diminished pressure to constant weight.

Methyl 2-amino-2-deoxy-α- and -β-D-glucopyranoside (**1** *and* **2**). — Amberlite CG-120 (H^+) resin (4.6 g, 200–400 mesh) and dry methanol (~20 mL) were placed in a 50-mL glass pressure-bottle (Taiatsu Glass Industry Co. Ltd., Tokyo) with a stirrer bar. The system was evacuated, and methanol was added to increase the volume to 25 mL. 2-Amino-2-deoxy-D-glucose hydrochloride (500 mg) was added, the bottle was heated to 50°, stoppered well, and the mixture was stirred magnetically in an oil-bath maintained for 9 h at 100°. The mixture was filtered and the resin washed with methanol and methanolic ammonia [1:14 (v/v) commercial 28% ammonia–methanol]. Evaporation of the eluate gave a colorless syrup (syrup A, 475 mg). An aqueous solution (2 mL) of this syrup was charged onto a column of Dowex-1 X2 (OH^-) (100 mL), which was developed with carbon dioxide-free water, and the elution was monitored by t.l.c. on silica gel with 2:3:1.5 chloroform–methanol–17% ammonium hydroxide containing 1% of ammonium chloride. Minor by-products were eluted (70–90 mL fractions, 30 mg, R_F 0.6–0.7), followed by **1** (92–110 mL fractions, 290 mg, R_F 0.49) with slight contamination by a by-product, and then **2** (115–135 mL fractions, 98 mg, 22%, R_F 0.45) was eluted. The α isomer (**1**) was recrystallized from ethanol to give needles; yield 233 mg (52%), m.p. 157–160°, $[\alpha]_D^{25}$ +154° (*c* 1, water); lit.[3] m.p. 155–159°, $[\alpha]_D$ +159.8° (*c* 1, water); ^{1}H-n.m.r. data (D_2O): δ 2.75 (q, 1 H, *J* 3.5 and 10 Hz, H-2), 4.78 (d, 1 H, *J* 3.5 Hz, H-1).

Anal. Calc. for $C_7H_{15}NO_5$: C, 43.51; H, 7.83; N, 7.25. Found: C, 43.76; H, 7.64; N, 7.18.

The β anomer (**2**) was a syrup, $[\alpha]_D^{25}$ −36° (*c* 1.3, water); ^{1}H-n.m.r. data (D_2O): δ 2.60 (unresolved t, 1 H, *J* 9 Hz, H-2; the hydrochloride: δ 3.04, q, *J* 8.5 and 10 Hz), 4.3 (d, 1 H, *J* 8.5 Hz, H-1).

Anal. Calc. for $C_7H_{15}NO_5$: C, 43.51; H, 7.83; N, 7.25. Found: C, 43.41; H, 7.91; N, 6.95.

The hydrochloride of **2** had m.p. 192–194° (dec.), $[\alpha]_D^{25}$ −27° (*c* 1.1, water); lit.[6] m.p. 191–192°, $[\alpha]_D$ −24° (water) (ref. 2).

Separation of **1** *on Amberlite CG-50 resin.* — The syrup A (950 mg) just described was charged onto a column of Amberlite CG-50 resin (220 mL, 100–200 mesh) that was developed with 5mM ammonium hydroxide. The resin used was prepared by

thoroughly washing the resin (NH_4^+ form) with 5mM ammonium hydroxide. The β anomer (**2**) was eluted in the 170–210 mL fractions (260 mg), with contamination by side-products, and then the pure α anomer (**1**) (230–430 mL, 540 mg) was eluted. On seeding, **1** gradually crystallized, and the solid was recrystallized from ethanol; yield 522 mg (58%), $[\alpha]_D^{25}$ +155° (*c* 1, water).

Methyl 2-deoxy-2-methylamino-α-L-glucopyranoside (**3**). — A mixture of 2-deoxy-2-methylamino-L-glucose hydrochloride[7] (100 mg), Amberlite CG-120 (H^+) (0.8 g), and dry methanol (5 mL) in a pressure tube was treated as described for **1**. The syrup (corresponding to syrup A) obtained was chromatographed on a column of Amberlite CG-50 resin (30 mL, equilibrated with 5mM ammonium hydroxide). Elution of products with 0.005→0.1M ammonium hydroxide (linear gradient) gave **3** in the 15–54-mL portion; syrup, 46 mg (51%), $[\alpha]_D^{25}$ −163° (*c* 1, water); ^{1}H-n.m.r. data (D_2O): δ 2.40 (s, 3 H, NCH_3), 2.58 (q, 1 H, *J* 3.5 and 10.5 Hz, H-2), 3.44 (s, 3 H, OCH_3), 4.92 (d, 1 H, *J* 3.5 Hz, H-1).

The hydrochloride of **3** (recrystallized from aqueous acetone) had m.p. 247–249° (dec.), $[\alpha]_D^{25}$ −143° (*c* 1, water). The hydrochloride of the D enantiomer[8] of **3** has m.p. 247° (dec.), $[\alpha]_D$ +128° (*c* 1, water)].

Anal. Calc. for $C_8H_{17}NO_5 \cdot HCl$: C, 39.43; H, 7.03; N, 5.75; Cl, 14.55. Found: C, 39.19; H, 7.15; N, 5.58; Cl, 14.35.

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