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Note

A large-scale synthesis of 2,6-diamino-2,6-dideoxy-D-glucose*

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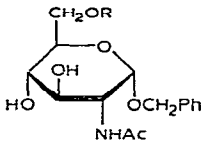
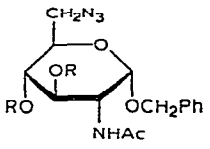
2,6-Diamino-2,6-dideoxy-D-glucose, a constituent of the Neomycin group of antibiotics, is a sugar of considerable interest. Several syntheses have been described[1–3]. The following route has been adapted from a synthesis[4] of 2,3-diamino-2,3-dideoxy-D-glucose and makes the product available on a hundred-gram scale.

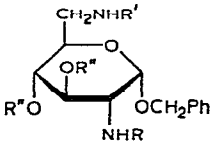
Selective tosylation of benzyl 2-acetamido-2-deoxy-α-D-glucopyranoside[5] (**1**) yielded the 6-toluene-*p*-sulphonate **2** which, with sodium azide in methyl sulphoxide[3], gave the crystalline azide **3** further characterized as its acetate **4**. Hydrogenation of **3** afforded the crystalline amine **5**, from which the *N*-acetyl derivative **6** and the peracetate **7** were obtained. Alkaline hydrolysis of **5** yielded the diamine **8** which was



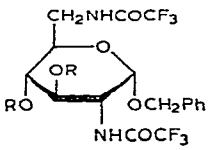
1 R = H
2 R = Ts



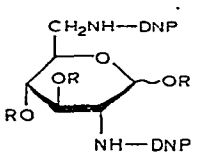
3 R = H
4 R = Ac



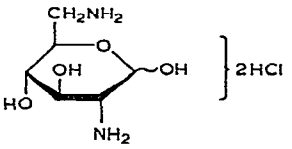
5 R = Ac; R′ = R″ = H
6 R = R′ = Ac; R″ = H
7 R = R′ = R″ = Ac
8 R = R′ = R″ = H
9 R = R′ = R″ = H; · 2HCl



10 R = $COCF_3$
11 R = H
12 R = Ac



13 R = H
14 R = Ac



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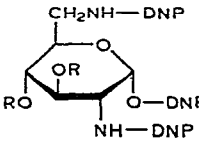

16 R = H
17 R = Ac

*Dedicated to the memory of Dr. Hewitt G. Fletcher, Jr.

isolated as the crystalline hydrochloride **9**. Hydrolysis of **5** with dilute hydrochloric acid readily gave the diamino sugar **15** in crystalline form.

Treatment of the diamine **8** with trifluoroacetic anhydride in chloroform gave the fully esterified product **10**. Hydrolysis of the *O*-trifluoroacetyl groups took place in methanolic solution to give **11**, characterised as the diacetate **12**.

2,4-Dinitrophenylation of the sugar hydrochloride **15** gave a mixture of compounds from which two components were isolated by chromatography in low yield[6]. Both products were acetylated and shown by n.m.r. spectroscopy to be the *N,N*-derivative **13** (acetate **14**, 25%) and the glycoside **16** (acetate **17**, 7%). The formation of the trisubstituted derivative **16** is analogous to the behaviour of 2,3-diamino-2,3-dideoxy-D-glucose[6].

EXPERIMENTAL

Benzyl 2-acetamido-2-deoxy-6-O-toluene-p-sulphonyl-α-D-glucopyranoside (**2**). — To a solution of benzyl 2-acetamido-2-deoxy-α-D-glucopyranoside[5] (**1**, 50 g) in dry pyridine (250 ml) at ~0°, a solution of toluene-*p*-sulphonyl chloride (52 g) in dichloromethane (50 ml) was added with stirring. The mixture was stored overnight at room temperature and the solvents were then evaporated under reduced pressure at 40°. A solution of the residue in chloroform was extracted twice with cold dilute sulphuric acid, aqueous sodium hydrogen carbonate, and water, dried (Na_2SO_4), and concentrated to a glassy mass (~100%), m.p. 63–70°, $[\alpha]_D$ +80° (*c* 1, chloroform).

Anal. Calc. for $C_{22}H_{27}NO_8S$: C, 56.76; H, 5.85; N, 3.01. Found: C, 56.27; H, 5.88; N, 2.94.

Benzyl 2-acetamido-6-azido-2,6-dideoxy-α-D-glucopyranoside (**3**). — The sulphonate **2** (50 g) was treated with sodium azide (25 g) in methyl sulphoxide (250 ml) for 2 h at 90°. The product was precipitated by the addition of water, collected, and recrystallized from ethanol to give **3** (33.5 g, 89%), m.p. 151–153° (after resolidification 164–167°), $[\alpha]_D$ +195° (*c* 1, methanol).

Anal. Calc. for $C_{15}H_{20}N_4O_5$: C, 53.56; H, 5.99; N, 16.66. Found: C, 53.06; H, 6.07; N, 16.24.

Benzyl 2-acetamido-3,4-di-O-acetyl-6-azido-2,6-dideoxy-α-D-glucopyranoside (**4**). — To a solution of **3** (400 mg) in pyridine (4 ml), acetic anhydride (2 ml) was added and the mixture was stored at room temperature overnight. The product was precipitated on addition of ice–water, and recrystallized from water–methanol (3:1) to give **4** (~100%), m.p. 116–117°, $[\alpha]_D$ +147° (*c* 1, methanol).

Anal. Calc. for $C_{19}H_{24}N_4O_7$: C, 54.28; H, 5.75; N, 13.33. Found: C, 53.99; H, 5.82; N, 13.05.

Benzyl 2-acetamido-6-amino-2,6-dideoxy-α-D-glucopyranoside (**5**). — To a solution of **4** (1 g) in methanol (30 ml), palladium-on-charcoal (200 mg, 10%) was added and hydrogenation was effected for 30 min. The mixture was filtered and concentrated, and the residue (0.55 g, 60%) was recrystallized from ethanol to give **5**, m.p. 164–167°, $[\alpha]_D$ +193° (*c* 1, methanol).

Anal. Calc. for $C_{15}H_{22}N_2O_5$: C, 58.00; H, 7.14; N, 9.03. Found: C, 58.26; H, 7.25; N, 8.81.

Benzyl 2,6-diacetamido-2,6-dideoxy-α-D-glucopyranoside (**6**). — The amine **5** (0.46 g) was treated with acetic anhydride (0.3 ml) in methanol (25 ml) for 2 h at room temperature. The residue obtained on concentration of the mixture was recrystallized from chloroform–methanol–ether to give **6** (318 mg, 61%), m.p. 232–235°, $[\alpha]_D$ +150° (*c* 1, chloroform–methanol, 1:1).

Anal. Calc. for $C_{17}H_{24}N_2O_6$: C, 57.94; H, 6.86; N, 7.95. Found: C, 57.73; H, 6.82; N, 7.93.

*Benzyl 2,6-diacetamido-3,4-di-*O*-acetyl-2,6-dideoxy-α-D-glucopyranoside* (**7**). — The diamine **8** (266 mg) was treated with acetic anhydride (0.9 ml) in pyridine (2 ml) for 7 h at room temperature. The syrupy product (416 mg, 97%), isolated in the usual manner, was recrystallized from chloroform–methanol–ether to give **7**, m.p. 95–97° $[\alpha]_D$ +122° (*c* 1, methanol).

Anal. Calc. for $C_{21}H_{28}N_2O_8$: C, 57.78; H, 6.47; N, 6.41. Found: C, 57.26; H, 6.49; N, 6.39.

Benzyl 2,6-diamino-2,6-dideoxy-α-D-glucopyranoside (**8**). — A solution of **5** (0.9 g) in water (30 ml) containing sodium hydroxide (1.2 g) was heated under reflux for 20 h. Continuous extraction with chloroform for 20 h yielded **8** as a thick syrup (0.8 g, ~100%), $[\alpha]_D$ +130° (*c* 1, chloroform).

Anal. Calc. for $C_{13}H_{20}N_2O_4$: C, 58.19; H, 7.51; N, 10.44. Found: C, 57.90; H, 7.68; N, 9.89.

Neutralisation of **8** (266 mg) with 0.2M hydrochloric acid in methanol gave the dihydrochloride **9** (300 mg, 90%). Crystallisation from ethanol–ether gave very hygroscopic crystals, m.p. 223–230° (dec.), $[\alpha]_D$ +117° (*c* 1, methanol).

Anal. Calc. for $C_{13}H_{22}Cl_2N_2O_4.0.5H_2O$: C, 44.58; H, 6.62; N, 7.99. Found: C, 44.58; H, 6.65; N, 7.86.

*Benzyl 2,6-dideoxy-2,6-bis(trifluoroacetamido)-3,4-di-*O*-trifluoroacetyl-α-D-glucopyranoside* (**10**). — To a solution of **8** (750 mg) in chloroform (100 ml), trifluoroacetic anhydride (1 ml) was added at 0°. A portion of the starting material separated as the trifluoroacetic acid salt and was isolated by decantation. The chloroform solution was concentrated and the product (0.95 g, 52%) was recrystallised from chloroform–ether to give **10**, m.p. 194–196°, $[\alpha]_D$ +125° (*c* 1, methanol).

Anal. Calc. for $C_{21}H_{16}F_{12}N_2O_8$: C, 38.66; H, 2.47; N, 4.29. Found: C, 38.93; H, 2.78; N, 4.68.

Benzyl 2,6-dideoxy-2,6-bis(trifluoroacetamido)-α-D-glucopyranoside (**11**). — (*a*) To a solution of the trifluoroacetic acid salt (0.74 g) obtained above in chloroform (50 ml), triethylamine (0.5 ml) and trifluoroacetic anhydride (0.5 ml) were added with cooling. After stirring the mixture for 30 min, water was added, and the precipitate was collected, dried, and recrystallised from ethanol to give **11** (0.33 g, 50%), m.p. 253–254°, $[\alpha]_D$ +166° (*c* 1, methanol).

(*b*) A solution of **10** (0.1 g) in methanol was stored for several hours at room temperature and then concentrated to yield **11**.

Anal. Calc. for $C_{17}H_{18}F_6N_2O_6$: C, 44.35; H, 3.94; N, 6.08. Found: C, 44.21; H, 3.70; N, 6.00.

Benzyl 3,4-di-O-acetyl-2,6-dideoxy-2,6-bis(trifluoroacetamido)-α-D-glucopyranoside (**12**). — Treatment of **11** (0.35 g) with acetic anhydride (0.4 ml) in pyridine (2.5 ml) at room temperature overnight, followed by the usual work-up and recrystallisation of the product from ethanol, gave **12** (0.32 g, 77%), m.p. 224–225°, $[\alpha]_D$ +100° (*c* 1, chloroform).

Anal. Calc. for $C_{21}H_{22}F_6N_2O_8$: C, 46.33; H, 4.07; N, 5.15. Found: C, 46.13; H, 4.20; N, 5.35.

2,6-Diamino-2,6-dideoxy-D-glucose dihydrochloride (**15**). — The amine **5** (50 g) was treated with boiling conc. hydrochloric acid–water (1:1; 1 litre) for 3 h. The brown solution was concentrated, water (3 × 100 ml) was evaporated from the residue, and a solution of the residue in water was then decolorized with charcoal. The clear filtrate was concentrated and the residue was crystallized from ethanol to give **15** as almost colourless crystals (31 g, 74%), m.p. ~150° (dec.), $[\alpha]_D$ +20° (2 min)→+68° (*c* 1, water), which was identical with an authentic sample[3] (i.r., t.l.c., $[\alpha]_D$).

Reaction of 2,6-diamino-2,6-dideoxy-D-glucose dihydrochloride (**15**) *with 1-fluoro-2,4-dinitrobenzene.* — To a solution of **15** (250 mg) in water (4 ml), ethanol (16 ml), sodium hydrogen carbonate (500 mg), and 1-fluoro-2,4-dinitrobenzene (600 mg) were added. After stirring for 48 h at room temperature in the dark, the mixture was concentrated and the residue was extracted with acetone. The extract contained 2 main components (t.l.c.; silica gel, chloroform–methanol, 9:1). Fractionation by p.l.c. (chloroform–methanol, 4:1) yielded, as the faster-moving product, amorphous 2,6-dideoxy-2,6-bis(2,4-dinitroanilino)-D-glucopyranose (**13**; 118 mg, 25%), m.p. softening at 100°, $[\alpha]_D$ +8° (*c* 1, chloroform–methanol, 1:1).

Anal. Calc. for $C_{18}H_{18}N_6O_{12}$: C, 42.36; H, 3.55; N, 16.47. Found: C, 41.55; H, 4.08; N, 16.02.

The slower-moving product was amorphous 2,4-dinitrophenyl 2,6-dideoxy-2,6-bis(2,4-dinitroanilino)-α-D-glucopyranoside (**16**; 44 mg, 7%), m.p. 140°, $[\alpha]_D$ +106° (*c* 1, chloroform–methanol, 1:1).

Anal. Calc. for $C_{24}H_{20}N_8O_{16}$: C, 42.61; H, 2.98; N, 16.56. Found: C, 42.27; H, 2.74; N, 16.03.

1,3,4-Tri-O-acetyl-2,6-dideoxy-2,6-bis(2,4-dinitroanilino)-α-D-glucopyranose (**14**). — Compound **13** (100 mg) was treated with pyridine (5 ml) and acetic anhydride (2 ml) at room temperature overnight, the solvents were then evaporated, and the residue was purified by t.l.c. (chloroform–methanol, 49:1) to give **14** (75 mg, 60%), m.p. 275–285°, $[\alpha]_D$ +126° (*c* 0.5, acetone). N.m.r. data (methyl sulphoxide): δ 6.10 (d, 1H, $J_{1,2}$ 3Hz, H-1), 2.10, 1.97, 1.78 (3s, 3Ac).

Anal. Calc. for $C_{24}H_{24}N_6O_{15}$: C, 45.28; H, 3.80; N, 13.21. Found: C, 45.10; H, 3.80; N, 13.00.

2,4-Dinitrophenyl 3,4-di-O-acetyl-2,6-dideoxy-2,6-bis(2,4-dinitroanilino)-α-D-glucopyranoside (**17**). — The derivative **16** (100 mg) was acetylated and the product was isolated as described above to give **17** (89 mg, 79%), m.p. 135–145°, $[\alpha]_D$ +108°

(*c* 1, acetone). N.m.r. data (acetone-d_6): δ 6.66 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 2.13, 1.87 (2s, 2Ac).

Anal. Calc. for $C_{28}H_{24}N_8O_{18}$: C, 44.22; H, 3.18; N, 14.73. Found: C, 44.57; H, 3.32; N, 14.74.

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