Studies on Aminosugars. XXXIII. Syntheses of 4-Azido-2,3,6-tri-*O*-benzyl-4-deoxy- and 6-Azido-2,3,4-tri-*O*-benzyl-6-deoxy-α-D-glucopyranosyl Chloride

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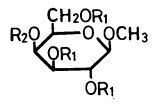
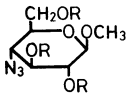
The titled compounds (**8** and **13**) have been prepared as synthetic intermediates.

As key intermediates for the syntheses of aminoglycosides, the titled compounds have been prepared.

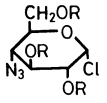
Methyl β-D-galactopyranoside (**1**) was converted into the 2,3,6-tri-*O*-benzoyl derivative (**2**) by means of the procedure of Reist *et al.*[1] utilizing the lower reactivity of C-4 axial hydroxyl group of D-galactose, and after mesylation of the remaining 4-hydroxyl group, the product (**3**) was transformed to methyl 4-azido-2,3,6-tri-*O*-benzoyl-4-deoxy-β-D-glucopyranoside (**4**). After removal of the benzoyl groups, the 4-azido-sugar (**5**) was benzylated to give **6**. Acidic hydrolysis of **6** gave 4-azido-2,3,6-tri-*O*-benzyl-4-deoxy-D-glucose (**7**), unavoidable removal of some of the benzyl groups being accompanied.[2] As for the hydrolysis of methyl glucosides of benzyl sugars, β-anomers generally give higher yields of free sugars than that of α-anomers, as reported by Austin *et al.*[3] The above yield of **7** (48%) was in accord with the above-mentioned view. Treatment of **7** with thionyl chloride gave the desired chloride (**8**). Its NMR spectrum indicated the α-configuration. The chloride was successfully used for the synthesis of 4-amino-4-deoxy-α-D-glucopyranosyl-2-deoxystreptamine.[4]



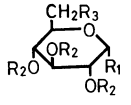
2: R_1=COC_6H_5, R_2=H
3: R_1=COC_6H_5, R_2=SO_2CH_3



4: R=COC_6H_5
5: R=H
6: R=$CH_2C_6H_5$



8: R=$CH_2C_6H_5$



9: R_1=OCH_3, R_2=H, R_3=OTs
10: R_1=OCH_3, R_2=H, R_3=N_3
11: R_1=OCH_3, R_2=$CH_2C_6H_5$, R_3=N_3
13: R_1=Cl, R_2=$CH_2C_6H_5$, R_3=N_3

Methyl 6-azido-6-deoxy-α-D-glucopyranoside (**10**) in a crude state has been prepared by Cramer *et al.*[5] We isolated it in a pure state and converted it into the tri-*O*-benzyl derivative (**11**). Acidic hydrolysis of **11** gave the 6-azido sugar (**12**) in a 37% yield. A similar chlorination as described in the preparation of **8** gave the desired compound (**13**).

The NMR spectrum of **13** indicated the α-configuration. The chloride was useful for the synthesis of 6-amino-6-deoxy-α-D-glucopyranosyl-2-deoxystreptamine.[6]

Experimental

Methyl 2,3,6-Tri-O-benzoyl-β-D-galactopyranoside (2). Mp 146—147 °C, $[\alpha]_D^{21}$ +53.5° (*c* 1, chloroform) (lit,[7] mp 143—144°C, $[\alpha]_D^{18}$ +56.1°).

Methyl 4-Azido-2,3,6-tri-O-benzoyl-β-D-glucopyranoside (4). To a solution of methyl 2,3,6-tri-*O*-benzoyl-4-*O*-mesyl-β-D-galactopyranoside[8] (**3**, 5.05 g) in dry dimethylformamide (DMF) (70 ml), powdered sodium azide (1.75 g) was added and the mixture was stirred at 130—140°C for 4.5 hr. On tlc with benzene–ether (20: 1), the solution showed two spots of R_f 0.6 (**4**, major) and 0.75. Evaporation followed by evaporation with toluene gave a brown residue, which was extracted with chloroform and the extract was washed with water, dried over sodium sulfate and evaporated to give a brown syrup. This was charged on a column of silica gel (150 g) and developed with the solvent system described above. The eluate containing **4** was evaporated to give a pale yellow solid (2.43 g, 53%), which was recrystallized from methanol, mp 124—125°C, $[\alpha]_D^{22}$ +120° (*c* 0.78, chloroform).

Found: C, 63.48; H, 4.78; N, 8.01%. Calcd for $C_{28}H_{25}N_3O_8$: C, 63.27; H, 4.74; N, 7.91%.

Methyl 4-Azido-4-deoxy-β-D-glucopyranoside (5). To a suspension of **4** (1.79 g) in dry methanol (20 ml), 2.4N sodium methylate (0.3 ml) was added and the suspension was stirred at room temperature overnight. The solution, after treatment with Amberlite IR 120 (H form), was evaporated to give a solid, which was washed with ether. Colorless solid obtained (0.70 g, 95%) was recrystallized from ethanol, mp 159.5—161°C, $[\alpha]_D^{22}$ +39° (*c* 0.66, water). NMR (in D_2O): τ 6.44 (3H, s, OCH_3), 5.65 (1H, d, $J_{1,2}$ 7.5 Hz, H-1).

Found: C, 38.63; H, 6.19; N, 19.23%. Calcd for $C_7H_{13}N_3O_5$: C, 38.35; H, 5.98; N, 19.17%.

Methyl 4-Azido-2,3,6-tri-O-benzyl-4-deoxy-β-D-glucopyranoside (6). A solution of **5** (770 mg) in DMF (10 ml) was treated with powdered potassium hydroxide (4.4 g) and benzyl chloride (4.5 g) similarly as described in the preparation of **11**, and chromatographed with benzene–ether (20: 1); colorless solid (1250 mg, 73%) was reprecipitated with benzene–petroleum ether, mp 64—65°C, $[\alpha]_D^{20}$ +80° (*c* 0.82, chloro-

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2) C. M. McCloskey, *Adv. Carbohyd. Chem.*, **12**, 137 (1957).
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5) F. Cramer, H. Otterbach, and H. Springman, *Chem. Ber.*, **92**, 384 (1959).
6) Y. Nishimura, T. Tsuchiya, and S. Umezawa, This Bulletin, **44**, 2521 (1971).
7) J. S. D. Bacon, D. J. Bell, and H. W. Kosterlitz, *J. Chem. Soc.*, **1939**, 1248.
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form). IR (KBr): 2110 cm^{-1} (N_3).

Found: C, 68.93; H, 6.48; N, 8.79%. Calcd for $C_{28}H_{31}N_3O_5$: C, 68.69; H, 6.38; N, 8.58%.

4-Azido-2,3,6-tri-O-*benzyl-4-deoxy*-D-*glucose (7)*. To a solution of **6** (409 mg) in acetic acid (16 ml), 2N hydrochloric acid (5 ml) was added and the solution was heated at 98°C for 4 hr. On tlc with benzene–ethyl acetate (5: 1), the solution showed four spots of R_f 0.80 (**6**, trace), 0.40 (**7**, major), 0.20, and 0.05. After addition of sodium hydrogen carbonate (1 g), the solvent was evaporated to give a residue. The residue was extracted with chloroform and the extrate was washed with sodium hydrogen carbonate solution and water, dried over sodium sulfate and evaporated to give a syrup. The syrup was charged on a column of silica gel (25 g) and developed with benzene–ethyl acetate (3: 1). The eluate containing **7** was evaporated to give a pale yellow solid (190 mg, 48%), which was recrystallized from benzene–petroleum ether, mp 84—85.5°C, $[\alpha]_D^{20}$ +75° (*c* 0.68, chloroform).

Found: C, 68.48; H, 5.84; N, 9.00%. Calcd for $C_{27}H_{29}N_3O_5$: C, 68.19; H, 6.15; N, 8.84%.

4-Azido-2,3,6-tri-O-*benzyl-4-deoxy*-α-D-*glucopyranosyl Chloride (8)*. A solution of **7** (2.9 g) in thionyl chloride (90 ml) was allowed to stand at room temperature overnight. The solution was evaporated with toluene *in vacuo* to give a pale yellow syrup. The product was purified by passing a short column of silica gel (24 g) with dry benzene, and the portion (36—108 ml) containing the main product (tlc with benzene, R_f 0.73) was evaporated to give a syrup, 1.98 g (66%), $[\alpha]_D^{18}$ +200° (*c* 3.0, benzene); IR (KBr): 2100 (N_3), 1460, 1365, 740, 700 cm^{-1}; NMR ($CDCl_3$): τ 5.43 (2H, AB q, *J* 12 Hz, $OC\underline{H}_2C_6H_5$), 5.31 (2H, s, $OC\underline{H}_2C_6H_5$), 5.08 (2H, AB q, *J* 12 Hz, $OC\underline{H}_2C_6H_5$), 3.93 (1H, d, *J* 3 Hz, H-1), 2.68 (15H, s, $OCH_2C_6\underline{H}_5$).

Found: C, 65.75; H, 5.76; N, 8.37; Cl, 7.49%. Calcd for $C_{27}H_{28}N_3O_4Cl$: C, 65.65; H, 5.71; N, 8.51; Cl, 7.18%.

Methyl 6-Azido-6-deoxy-α-D-*glucopyranoside (10)*. To a solution of methyl 6-deoxy-6-*O*-tosyl-α-D-glucopyranoside[5] (**9**) (9.51 g) in dry DMF (130 ml), powdered sodium azide (3.7 g) was added and the mixture was stirred under gentle boiling for 1 hr. Evaporation followed by evaporation with toluene gave a black residue, which was extracted with acetone. The solution, after treatment with charcoal, was evaporated to give a reddish brown syrup. This was charged on a short column of silica gel (40 g) and developed with ethyl acetate. The eluate was evaporated and the residue was dissolved in chloroform. Addition of *n*-hexane gave a thick syrup, 4.41 g (74%), $[\alpha]_D^{22}$ +122° (*c* 1, water); IR: 2100 cm^{-1} (N_3).

Found: C, 38.61; H, 6.03; N, 19.40%. Calcd for $C_7H_{13}N_3O_5$: C, 38.35; H, 5.98; N, 19.17%.

Methyl 6-Azido-2,3,4-tri-O-*benzyl-6-deoxy*-α-D-*glucopyranoside (11)*. To a solution of **10** (7.41 g) in dry DMF (140 ml), powdered potassium hydroxide (44 g) was added and to the mixture, benzyl chloride (~40 ml) was added at intervals under stirring with occasional cooling. After completion of the reaction (*ca.* 2 hr), the organic layer was separated from an insoluble matter and the latter was washed with chloroform. The combined organic solution was evaporated with toluene to give a residue, which was extracted with chloroform and the extract was evaporated. The residual syrup was heated at 100°C *in vacuo* (~0.1 Torr) to remove volatile materials. The syrup was then dissolved in chloroform and the solution was washed with water, dried over sodium sulfate and evaporated to give a syrup, which was chromatographed on a short column of silica gel (50 g) with benzene–chloroform (1: 1). The eluate containing **11** was evaporated to give a pale-yellow syrup, 12.42 g (75%), $[\alpha]_D^{21}$ +48.2° (*c* 1, chloroform) (lit,[9] +53.1°).

Found: C, 68.73; H, 6.65; N, 8.79%. Calcd for $C_{28}H_{31}N_3O_5$: C, 68.69; H, 6.38; N, 8.58%.

6-Azido-2,3,4-tri-O-*benzyl-6-deoxy*-D-*glucose (12)*. To a solution of **11** (9.68 g) in acetic acid (160 ml), 3N hydrochloric acid (40 ml) was added and the solution was heated at 90—95°C for 4 hr. On tlc (silica gel) with benzene–ether (10: 1), the solution showed three spots of R_f 0.80 (**11**), 0.35 (**12**, major) and 0, the last spot being strengthened on prolonged reaction. After addition of sodium hydrogen carbonate (8 g), the brown solution was treated with charcoal, and evaporated. The residue was dissolved in chloroform and the solution was washed with water, dried over sodium sulfate and evaporated. The resulting syrup was chromatographed on a column of silica gel (400 g) with benzene–ether (10: 1). The eluate containing **12** was evaporated to give a syrup, which crystallized on scratching, 3.44 g (37%). From the earlier eluate, **11** was recovered (1.80 g). Recrystallization from benzene–petroleum ether gave crystals, mp 78.5—80.5°C, $[\alpha]_D^{21}$ +65° (*c* 1, chloroform), IR (KBr): 3380, 2110 (N_3), 750, 735, 695 cm^{-1}.

Found: C, 68.06; H, 6.36; N, 8.95%. Calcd for $C_{27}H_{29}N_3O_5$: C, 68.19; H, 6.15; N, 8.84%.

6-Azido-2,3,4-tri-O-*benzyl-6-deoxy*-α-D-*glucopyranosyl Chloride (13)*. A solution of **12** (1.42 g) in thionyl chloride (23 ml) was allowed to stand at 0°C for 2 hr and then at room temperature for 38 hr. On tlc with benzene, the solution gave a single spot at R_f 0.65. The solution was evaporated and then co-evaporated with toluene to give a syrup, which was further purified by column chromatography with silica gel (10 g) and dry benzene to give a pale yellow syrup, 0.95 g (65%), $[\alpha]_D^{24}$ +119° (*c* 0.94, chloroform): IR (liquid film): 2110 (N_3), 730, 695 cm^{-1}: NMR (in $CDCl_3$): τ 3.93 (1H, d, *J* 3.5 Hz, H-1).

Found: C, 65.44; H, 5.60; N, 8.65; Cl, 7.52%. Calcd for $C_{27}H_{28}N_3O_4Cl$: C, 65.65; H, 5.71; N, 8.51; Cl, 7.18%.

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