Synthesis of 3,4-Di-*O*-acetyl-6-azido-2,6-dideoxy-2-(2′,4′-dinitroanilino)-α-D-glucopyranosyl Chloride

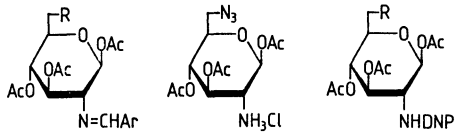
Seiichiro OGAWA, Hitoshi FUJIMORI, and Tetsuo SUAMI

Department of Applied Chemistry, Faculty of Engineering, Keio University, Hiyoshi, Yokohama 223

(Received April 28, 1976)

The title compound has been prepared as an intermediate for the chemical synthesis of glycosides of 2,6-diamino sugar.

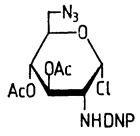
In the present communication, we should like to report a preparation of the title compound which is a useful intermediate for the chemical synthesis of α-glycosides of 2,6-diamino sugar.



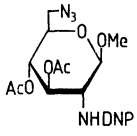
1 R = OTs
2 R = N_3

3

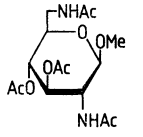
4 R = N_3
5 R = NHDNP



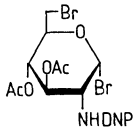
6



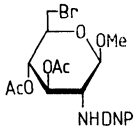
7



8



9



10

Treatment of 1,3,4-tri-*O*-acetyl-2-deoxy-2-(*p*-methoxybenzylideneamino)-6-*O*-tosyl-β-D-glucopyranose (**1**)[1] with sodium azide in *N*,*N*-dimethylformamide at 80—90 °C for 3 h resulted in displacement of the tosyloxy group with an azide ion to give the 6-azido compound (**2**) in 75% yield. Hydrolysis of **2** with hydrochloric acid gave a crystalline 1,3,4-tri-*O*-acetyl-2-amino-6-azido-2,6-dideoxy-β-D-glucopyranose hydrochloride (**3**) in 73% yield. Treatment of **3** with 2,4-dinitrofluorobenzene in an alkaline solution gave 1,3,4-tri-*O*-acetyl-6-azido-2,6-dideoxy-2-(2′,4′-dinitroanilino)-β-D-glucopyranose (**4**) in 74% yield, whose structure was confirmed by converting it into 1,3,4-tri-*O*-acetyl-2,6-dideoxy-bis(2′,4′-dinitroanilino)-β-D-glucopyranose (**5**).[2] Attempt to prepare α-glycosyl bromide of this azido sugar was not successful, because partial replacement of the azido group by a bromine ion was accompanied when **4** was treated with a common brominating reagent. Thus bromination of **4** with hydrobromic acid in acetic acid resulted in the formation of 3,4-di-*O*-acetyl-6-bromo-2,6-dideoxy-2-(2′,4′-dinitroanilino)-α-D-glucopyranosyl bromide (**9**) in 85% yield. Compound **9** reacted with an excess of methanol in the presence of silver carbonate in dioxane to give methyl 3,4-di-*O*-acetyl-6-bromo-2,6-dideoxy-2-(2′,4′-dinitroanilino)-β-D-glucopyranoside (**10**) in 53% yield.

Chlorination of **4** was effected by treatment with hydrogen chloride in ether at 0 °C and gave 3,4-di-*O*-acetyl-6-azido-2,6-dideoxy-2-(2′,4′-dinitroanilino)-α-D-glucopyranosyl chloride (**6**) in 68% yield as a relatively stable crystalline substance. Methanolysis of **6** in the presence of silver carbonate gave methyl β-glucopyranoside (**7**) in 44% yield, which was further converted into methyl 2,6-diacetamido-3,4-di-*O*-acetyl-2,6-dideoxy-β-D-glucopyranoside (**8**) by the usual method.

Experimental[3]

1,3,4-Tri-O-acetyl-2-deoxy-2-(p-methoxybenzylideneamino)-6-O-tosyl-β-D-glucopyranose (1). This compound was prepared from 2-deoxy-2-*p*-methoxybenzylideneamino-D-glucopyranose by the method of Morel.[1] Mp 203—204 °C, $[\alpha]_D^{20}$ +103° (*c* 2, chloroform) [lit,[1] mp 203—204 °C, $[\alpha]_D^{20}$ +99.3° (*c* 2, chloroform)].

1,3,4-Tri-O-acetyl-6-azido-2,6-dideoxy-2-(p-methoxybenzylideneamino)-β-D-glucopyranose (2). A mixture of **1** (12 g), sodium azide (12 g), and *N*,*N*-dimethylformamide (300 ml) was heated at 80—90 °C under stirring for 3 h. The reaction mixture was evaporated and the residue was extracted with chloroform (200 ml). The extract was washed with water, dried over anhydrous sodium sulfate, and evaporated to give a syrup, which was recrystallized from ethanol to give 7.4 g (75%) of **2**, mp 123.5—124 °C, $[\alpha]_D^{25}$ +127° (*c* 2, chloroform). PMR ($CDCl_3$): δ 1.90 (s, 3), 2.03 (s, 3), 2.06 (s, 3) (OAc), 3.33—3.63 (m, 2, $C\underline{H}_2N_3$), 3.87 (s, 3, OMe), 5.15 (t, 1, $J_{3,4}=J_{4,5}=9$ Hz, H-4), 5.50 (t, 1, $J_{2,3}=9$ Hz, H-3), 6.00 (d, 1, $J_{1,2}=9$ Hz, H-1), 6.97 (d, 2), 7.71 (d, 2) (ABq, aromatic ring proton), 8.22 (s, 1, N=C$\underline{H}$Ar).

Found: C, 53.70; H, 5.33; N, 12.21%. Calcd for $C_{20}H_{24}N_4O_8$: C, 53.59; H, 5.40; N, 12.50%.

1,3,4-Tri-O-acetyl-2-amino-6-azido-2,6-dideoxy-β-D-glucopyranose Hydrochloride (3). To a warm solution of **2** (1.33 g) in acetone (5 ml) was added dropwise 5 M aq. hydrochloric acid (2 ml) under vigorous agitation. The white solid precipitated immediately. After the reaction mixture had been set aside at room temperature for several hours, the product was collected by filtration, washed with ether, and recrystallized from methanol to give 0.69 g (73%) of **3**, mp 147—154 °C (dec), $[\alpha]_D^{25}$ +55.8° (*c* 1, H_2O), $[\alpha]_D^{24}$ +43° (*c* 0.5, methanol).

Found: C, 39.46; H, 5.16; N, 15.10; Cl, 9.46%. Calcd for $C_{12}H_{18}N_4O_7\cdot HCl$: C, 39.30; H, 5.22; N, 15.28; Cl, 9.67%.

1,3,4-Tri-O-acetyl-6-azido-2,6-dideoxy-2-(2′,4′-dinitroanilino)-β-D-glucopyranose (4). To a stirred mixture of **3** (1.6 g) and sodium hydrogen carbonate (0.9 g) in 50% aq. acetone (12 ml) was added 2,4-dinitrofluorobenzene (0.9 g), and the mixture was allowed to stand at room temperature overnight. Then the mixture was evaporated to dryness and the residue was extracted with ethyl acetate. The extracts were evaporated to give a syrup, which was recrystallized from ethanol to give 1.6 g (74%) of **4**, mp 115.5—116 °C, $[\alpha]_D^{29}$ +108° (*c* 1, chloroform), $[\alpha]_D^{25}$ +102° (*c* 1, acetone). PMR ($CDCl_3$): δ

1.95 (s, 3), 2.03 (s, 3), 2.11 (s, 3) (OAc), 3.45—3.60 (m, 2, CH_2N_3), 5.29 (t, 1, $J_{3,4}=J_{4,5}=9.5$ Hz, H-4), 5.67 (t, 1, $J_{2,3}=9.5$ Hz, H-3), 6.12 (d, 1, $J_{1,2}=8.5$ Hz, H-1).

Found: C, 44.03; H, 4.17; N, 16.89%. Calcd for $C_{18}H_{20}N_6O_{11}$: C, 43.55; H, 4.06; N, 16.93%.

1,3,4-Tri-O-acetyl-2,6-dideoxy-2,6-bis(2',4'-dinitroanilino)-β-D-glucopyranose (5). A solution of **3** (0.4 g) in methanol containing 6 M hydrochloric acid (0.2 ml) was hydrogenated in the presence of 10% palladium on carbon for 5 h at room temperature (the initial hydrogen pressure of 3.4 kg/cm²). The catalyst was removed by filtration and the filtrate was evaporated to give a crude diamine dihydrochloride. This was directly treated with 2,4-dinitrofluorobenzene (1 g) in ethanol (4 ml) and acetone (16 ml) in the presence of sodium hydrogen carbonate (1 g) for 2 days at room temperature. The reaction mixture was evaporated and the residue was extracted with chloroform. The crude product was chromatographed on silica gel (16 g) with 3: 1 benzene–ethyl acetate as the eluant to give 0.24 g (35%) of **5**, after recrystallization from chloroform–ethanol, mp 280—281 °C, $[\alpha]_D^{15}$ +111° (*c* 1, acetone). PMR (DMSO-d_6): δ 1.87 (s, 3), 1.94 (s, 3), 2.13 (s, 3) (OAc), 4.74 (td, 1, $J_{1,2}=8.5$ Hz, $J_{2,3}=9$ Hz, $J_{2,NH}=3$ Hz, H-2), 5.17 (t, 1, $J_{3,4}=9$ Hz, H-4), 5.90 (t, 1, H-3), 6.30 (d, 1 H-1).

Found: C, 45.53; H, 4.19; N, 13.06%. Calcd for $C_{24}H_{24}N_6O_{15}$: C, 45.28; H, 3.80; N, 13.21%.

3,4-Di-O-acetyl-6-azido-2,6-dideoxy-2-(2',4'-dinitroanilino)-α-D-glucopyranosyl Chloride (6). Dry hydrogen chloride was introduced into a solution of **4** (6 g) in dry ether (100 ml) at 0 °C until saturation was completed. The solution was allowed to stand at room temperature for 20 h. The resulting crystals were collected by filtration to give 4 g (68%) of **6**, mp 164—166 °C (dec). Recrystallization from chloroform–ether gave an analytically pure sample, mp 170 °C (dec), $[\alpha]_D^{25}$ +167° (*c* 1, chloroform). PMR (DMSO-d_6): δ 6.90 (d, 1, $J_{1,2}=3$ Hz, H-1).

Found: C, 40.37; H, 3.62; N, 17.37; Cl, 7.64%. Calcd for $C_{16}H_{17}N_6O_9Cl$: C, 40.63; H, 3.62; N, 17.77; Cl, 7.50%.

Methyl 3,4-Di-O-acetyl-6-azido-2,6-dideoxy-2-(2',4'-dinitroanilino)-β-D-glucopyrauoside (7). A mixture of **6** (1 g), silver carbonate (5 g), and Drierite (14 g) in dioxane (40 ml) and methanol (40 ml) was stirred at room temperature in the dark for a week. An insoluble matter was removed by filtration and the filtrate was evaporated to give a syrup, which was chromatographed on silica gel (40 g) with 40: 3 benzene–ethyl acetate as the eluant. The fractions containing a main component were evaporated and the residue was recrystallized from chloroform–ethanol to give 0.43 g (44%) of **7**, mp 170.5—171 °C, $[\alpha]_D^{25}$ +61.3° (*c* 1, chloroform). PMR (CDCl$_3$): δ 1.96 (s, 3), 2.11 (s, 3) (OAc), 3.58 (s, 3, OMe), 4.71 (d, 1, $J_{1,2}=8$ Hz, H-1), 5.17 (t, 1, $J_{3,4}=J_{4,5}=9$ Hz, H-4), 5.52 (t, 1, $J_{2,3}=9$ Hz, H-3).

Found: C, 43.40; H, 4.30; N, 17.96%. Calcd for $C_{17}H_{20}N_6O_{10}$: C, 43.59; H, 4.30; N, 17.94%.

Methyl 2,6-Diacetamido-3,4-di-O-acetyl-2,6-dideoxy-β-D-glucopyranoside (8). Compound **7** (0.38 g) was treated with methanolic ammonia (16 ml) at room temperature overnight. At this time, the mixture became a clear solution and TLC indicated the formation of a single product. Then Dowex 1×2 (OH^-) was added to the solution and the mixture was stirred until all the product was consumed. The resin was removed by filtration and the filtrate was evaporated to give a syrup, which was hydrogenated in water in the presence of platinum oxide (30 mg) at room temperature overnight. The product was then treated with acetic anhydride (5 ml) in pyridine (5 ml) at room temperature overnight. The crude product was recrystallized from ethyl acetate to give 0.12 g (41%) of **8**, mp 208—210 °C, $[\alpha]_D^{25}$ −39° (*c* 1, acetone). PMR (DMSO-d_6): δ 1.80 (s, 3), 1.85 (s, 3), 1.93 (s, 3), 2.00 (s, 3) (Ac), 4.57 (d, 1, $J_{1,2}=9$ Hz, H-1), 4.80 (t, 1, $J_{3,4}=J_{4,5}=10$ Hz, H-4), 5.17 (t, 1, $J_{2,3}=10$ Hz, H-3).

Found: C, 49.72; H, 6.57; N, 7.76%. Calcd for $C_{15}H_{24}N_8O_{12}$: C, 49.99; H, 6.71; N, 7.77%.

Hydrolysis of **8** with 6 M hydrochloric acid at 100 °C for 2 h gave 2,6-diamino-2,6-dideoxy-D-glucopyranose dihydrochloride, which was identified with an authentic specimen derived by hydrolysis of antibiotic neamine.

Methyl 3,4-Di-O-acetyl-6-bromo-2,6-dideoxy-2-(2',4'-dinitroanilino)-β-D-glucopyranoside (10). To a solution of **4** (2 g) in methylene chloride (10 ml) was added acetic acid (30 ml) ,saturated with hydrobromic acid under stirring at −20—−15 °C, and the reaction mixture was allowed to stand at the same temperature for 2 h. The mixture was poured into ice–water and extracted with chloroform. The extracts were washed with aq. sodium hydrogen carbonate and water, dried over anhydrous sodium sulfate, and evaporated to give a syrup, which was crystallized from chloroform–petroleum ether to give 1.9 g (85%) of 3,4-di-*O*-acetyl-6-bromo-2,6-dideoxy-2-(2',4'-dinitroanilino)-α-D-glucopyranosyl bromide (**9**), mp 146—150 °C (dec). This compound did not give satisfactory analytical data (Found: C, 35.36; H, 3.25; N, 8.12%).

Compound **9** (1 g) was treated in the presence of silver carbonate (9 g) in methanol (25 ml) and dioxane (25 ml) under stirring at room temperature overnight. An insoluble matter was removed by filtration and the filtrate was evaporated to give a syrup, which was chromatographed on silica gel (40 g) with 10: 1 benzene–ethyl acetate as the eluant to give 0.41 g (53%) of **10**, mp 183—186 °C, $[\alpha]_D^{20}$ +46.2° (*c* 0.5, chloroform). PMR (DMSO-d_6): δ 1.77 (s, 3), 2.09 (s, 3) (OAc), 3.57 (s, 3, OMe), 4.17 (broad septet, 1, $J_{1,2}=6.5$ Hz, $J_{2,3}=7.5$ Hz, $J_{2,NH}=3$ Hz, H-2), 5.27 (d, 1, H-1), 9.03 (d, 1, NH).

Found: C, 40.03; H, 3.92; N, 8.18; Br, 15.75%. Calcd for $C_{17}H_{20}N_3O_{10}Br$: C, 40.32; H, 3.98; N, 8.29; Br, 15.79%.

References

1) Ch. J. Morel, *Helv. Chim. Acta*, **61**, 1501 (1958).

2) An α-anomer reported by Meyer zu Reckendorf and his coworkers has physical constants very close to those of **5**, but, in the PMR spectrum, a signal due to the anomeric proton appeared at δ 6.10 as a doublet having 3-Hz spacing, clearly differentiating it from **5**. W. Meyer zu Reckendorf, L. Rolf, and N. Wassiliadou-Micheli, *Carbohydr. Res.*, **45**, 307 (1975).

3) Melting points were determined in capillaries in a liquid bath and are uncorrected. Solutions were evaporated under diminished pressure at 40—50 °C. PMR spectra were measured at 60 MHz on a Varian A-60D spectrometer in chloroform-*d* (CDCl$_3$) or dimethyl-d_6 sulfoxide (DMSO-d_6)with reference to tetramethylsilane as an internal standard and the peak positions are given in δ-values. Values given for coupling constants are of first-order. Elemental analyses were performed by Mr. Saburo Nakada, to whom our thanks are due.