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Note

A re-investigation of the reaction of β-cellobiose octaacetate with phosphorus pentachloride

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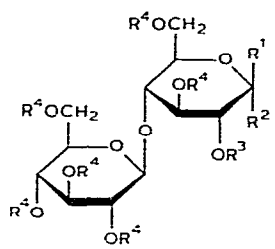
Russian workers reported[1] that the reaction of β-cellobiose octaacetate (**1**) with phosphorus pentachloride in the presence of 1,1,2,2-tetrachloroethane at 100–105° gave 3,6,2′,3′,4′,6′-hexa-*O*-acetyl-2-*O*-(trichloroacetyl)-β-cellobiosyl chloride (**2**). In our hands, however, the reaction of **1** with phosphorus pentachloride under the conditions described[1] gave a very complex mixture from which a compound having physical constants identical with those (m.p. 80°, $[\alpha]_D$ +28.2°) reported[1] for **2** could not be obtained. We report here a re-investigation of the reaction of **1** with phosphorus pentachloride.

Treatment of **1** with 7 mol. equiv. of phosphorus pentachloride, in the presence of acetyl chloride[2], for 6 h at 110° gave a mixture that was fractionated by column chromatography on silica gel to afford, in 41% yield, a crystalline compound having



1 R^1 = OAc, R^2 = H, R^3 = R^4 = Ac
2 R^1 = Cl, R^2 = H, R^3 = $COCCl_3$, R^4 = Ac
3 R^1 = H, R^2 = Cl, R^3 = $COCCl_3$, R^4 = Ac
4 R^1 = Cl, R^2 = R^3 = H, R^4 = Ac
5 R^1 = R^3 = H, R^2 = Cl, R^4 = Ac
6 R^1 = H, R^2 = Cl, R^3 = R^4 = Ac
7 R^1 = H, R^2 = OAc, R^3 = R^4 = Ac
8 R^1 = OAc, R^2 = R^3 = H, R^4 = Ac
9 R^1 = OAc, R^2 = H, R^3 = Ms, R^4 = Ac
10 R^1 = R^3 = H, R^2 = OMe, R^4 = Ac
11 R^1 = R^3 = R^4 = H, R^2 = OMe
12 R^1 = H, R^2 = OMe, R^3 = Ms, R^4 = Ac
13 R^1 = OMe, R^2 = R^3 = H, R^4 = Ac

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m.p. 166–167° and $[\alpha]_D$ −30.1°; and structure **2** was assigned to this compound by reason of its anomerization, and conversion into the known[3] 2,3,6,2′,3′,4′,6′-hepta-*O*-acetyl-α-cellobiosyl chloride (**6**). Compound **2** could be anomerized with titanium tetrachloride[4] in chloroform, or with tetramethylammonium chloride[5,6] in acetonitrile, to give the corresponding α-chloride **3** in crystalline form. Selective removal[7] of the trichloroacetyl group of **2** gave the crystalline β-chloride **4** having a free hydroxyl group at C-2, which was anomerized with titanium tetrachloride or tetramethylammonium chloride to afford the crystalline α anomer **5**. Compound **5** was also obtained by the ammonolysis of **3**. Acetylation of **5** with acetic anhydride–pyridine at 0° furnished the known[3] **6**, thus confirming the structure of **2**. Attempted reaction of α-cellobiose octaacetate (**7**) with phosphorus pentachloride under the same conditions as for **1** resulted in recovery of **7**.

Treatment of **5** with mercuric acetate in acetic acid gave crystalline 1,3,6,-2′,3′,4′,6′-hepta-*O*-acetyl-β-cellobiose (**8**) which, on methanesulfonylation and acetylation, afforded crystalline 1,3,6,2′,3′,4′,6′-hepta-*O*-acetyl-2-*O*-(methylsulfonyl)-β-cellobiose (**9**) and **1**, respectively. Methanolysis of **4** in the presence of pyridine and silver nitrate[6,8–10] gave, in 73% yield, crystalline methyl 3,6,2′,3′,4′,6′-hexa-*O*-acetyl-α-cellobioside (**10**), which was *O*-deacetylated to provide crystalline methyl α-cellobioside (**11**) having physical constants in good agreement with those given in the literature[11,12]. Methanesulfonylation of **10** afforded methyl 3,6,2′,3′,4′,6′-hexa-*O*-acetyl-2-*O*-(methylsulfonyl)-α-cellobioside (**12**) in crystalline form. Methanolysis of **5** under the same conditions as for **4** gave a crystalline product that was homogeneous in t.l.c. in various solvent systems. However, the n.m.r. spectrum of the product in dimethyl sulfoxide-d_6 showed that it was a mixture of methyl 3,6,2′,3′,4′,6′-hexa-*O*-acetyl-β-cellobioside (**13**) and **10** in the ratio of 3.6:1, as deduced from the ratio of the intensity of the methoxyl-proton signals at δ 3.40 (β) and 3.33 (α). Compound **13** could not be obtained pure by repeated fractional recrystallization of the product, because **10** and **13** have a strong tendency to co-crystallize.

EXPERIMENTAL

General, experimental specifications were the same as those described previously[9].

3,6-Di-O-*acetyl-4*-O-(*2,3,4,6-tetra*-O-*acetyl-β*-D-*glucopyranosyl*)-*2*-O-(*trichloroacetyl*)-*β*-D-*glucopyranosyl chloride* (**2**). — Compound **1** (15 g, 22.1 mmol) was thoroughly mixed with phosphorus pentachloride (32.2 g, 155 mmol), and anhydrous acetyl chloride (7 mL) was added. The mixture was stirred at 110°, with exclusion of moisture, and became homogeneous within 2 h. Heating was continued for a further 4 h, when t.l.c. (1:1, v/v, benzene–ethyl acetate) showed the presence of one major (**2**, R_F 0.63) and several minor products, in addition to a small amount of unreacted **1**. The volatile by-products were evaporated under diminished pressure until the bath temperature had risen to ~70°. The residue was extracted with ether (3 × 200 mL), and the extracts were combined, and successively washed with ice–

water, aqueous sodium hydrogencarbonate, and water, dried (Na_2SO_4), and evaporated. The resulting syrup was fractionated on a column of silica gel (300 g) with 1:1 (v/v) benzene–ethyl acetate. The first fraction crystallized from ether, to give **2** (6.87 g, 41%), m.p. 166–167°, $[\alpha]_D^{16}$ −30.1° (*c* 1.8, benzene); lit.[1] m.p. 80°, $[\alpha]_D^{20}$ +28.2°.

Anal. Calc. for $C_{26}H_{32}Cl_4O_{17}$: C, 41.18; H, 4.25; Cl, 18.70. Found: C, 41.27; H, 4.20; Cl, 18.83.

*3,6-Di-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl)-2-*O*-(trichloroacetyl)-α-*D*-glucopyranosyl chloride* (**3**). — (*a*). Compound **2** (1 g) was isomerized with titanium tetrachloride (6 mL) in chloroform (40 mL), according to the procedure of Wolfrom *et al.*[4], to give **3** (0.82 g, 82%), m.p. 172–173° (ether), $[\alpha]_D^{16}$ +64.7° (*c* 1.9, chloroform); n.m.r. data (chloroform-*d*): δ 6.28 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-1).

Anal. Calc. for $C_{26}H_{32}Cl_4O_{17}$: C, 41.18; H, 4.25; Cl, 18.70. Found: C, 41.07; H, 4.31; Cl, 18.57.

(*b*). A solution of **2** (420 mg) in anhydrous acetonitrile (9 mL) was stirred with tetramethylammonium chloride (130 mg) for 4 h at 80°. Evaporation of the solvent left a syrup which was dissolved in chloroform. The solution was washed with water, dried (Na_2SO_4), and evaporated, to give a solid which, on recrystallization from ether, afforded **3** (353 mg, 84%), m.p. 172–173°, $[\alpha]_D^{18}$ +64.9° (*c* 2.0, chloroform); the n.m.r. spectrum was identical with that of the compound obtained by method *a*.

*3,6-Di-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl)-β-*D*-glucopyranosyl chloride* (**4**). — Compound **2** (6 g) was finely powdered, and rapidly dissolved at 0° in ether (180 mL) that had been saturated with ammonia. The mixture was stirred for 30 min, and the crystals formed were filtered off, and recrystallized from ethyl acetate–ether, to give **4** (431 mg, 89%), m.p. 173–174° (dec.), $[\alpha]_D^{16}$ −4.7° (*c* 1.3, ethyl acetate).

Anal. Calc. for $C_{24}H_{33}ClO_{16}$: C, 47.03; H, 5.43; Cl, 5.78. Found: C, 47.18; H, 5.51; Cl, 5.65.

*3,6-Di-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl)-α-*D*-glucopyranosyl chloride* (**5**). — (*a*). Compound **4** (615 mg) was isomerized[4] with titanium tetrachloride (3.6 mL) in chloroform (25 mL), and crystallization of the resulting product from ethyl acetate–ether gave **5** (509 mg, 83%), m.p. 187–188° (dec.), $[\alpha]_D^{16}$ +84.2° (*c* 1.8, chloroform); n.m.r. data (chloroform-*d*): δ 6.12 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1) and 2.47 (broad s, 1 H, exchangeable with D_2O, OH-2).

Anal. Calc. for $C_{24}H_{33}ClO_{16}$: C, 47.03; H, 5.43; Cl, 5.78. Found: C, 47.19; H, 5.33; Cl, 5.66.

(*b*). Treatment of **4** (446 mg) with tetramethylammonium chloride (150 mg) in acetonitrile (10 mL), as described for **2**, afforded **5** (365 mg, 82%), m.p. 187–188° (dec.), $[\alpha]_D^{16}$ +84.1° (*c* 1.0, chloroform).

(*c*). Compound **3** (1 g) was treated at 0°, as described for the preparation of **4**, in ether (30 mL) presaturated with ammonia, to give **5** (687 mg, 85%), m.p. 187–188°, $[\alpha]_D^{15}$ +84.2° (*c* 1.5, chloroform).

*2,3,6-Tri-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl)-α-*D*-gluco-*

pyranosyl chloride (**6**). — A solution of **5** (263 mg) in pyridine (3 mL) was cooled to 0°, treated with acetic anhydride (2 mL), and kept overnight at 0°. The solution was poured into ice–water, and the precipitate formed was filtered off, washed with water, and dried. Crystallization from ethyl acetate–ether gave **6** (236 mg, 84%), m.p. 200–202°, $[\alpha]_D^{16}$ +70.9° (*c* 1.1, chloroform); n.m.r. data (chloroform-*d*): δ 6.21 (s, 1 H, $J_{1,2}$ 4.0 Hz, H-1); lit.[11] m.p. 200–201°, $[\alpha]_D^{15}$ +71.7° (chloroform).

1,3,6-Tri-O-*acetyl-4*-O-(*2,3,4,6-tetra*-O-*acetyl-β*-D-*glucopyranosyl*)-*β*-D-*glucopyranose* (**8**). — Compound **5** (319 mg) was dissolved in acetic acid (4 mL) containing mercuric acetate (320 mg), and the mixture was kept for 4 h at room temperature. The solution was diluted with chloroform, washed with water, dried (Na_2SO_4), and evaporated to a crystalline solid which was recrystallized from ethanol to give **8** (291 mg, 88%), m.p. 186–187°, $[\alpha]_D^{15}$ −2.0° (*c* 1.1, chloroform); n.m.r. data (dimethyl sulfoxide-d_6): δ 5.64 (d, 1 H, $J_{2,2\text{-OH}}$ 6.0 Hz, exchangeable with D_2O, OH-2) and 5.53 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1).

Anal. Calc. for $C_{26}H_{36}O_{18}$: C, 49.06; H, 5.70. Found: C, 48.88; H, 5.78.

Conventional acetylation of **8** (85 mg) with 1 : 1 (v/v) acetic anhydride–pyridine (1 mL) overnight at room temperature gave **1** (74 mg, 82%), m.p. and mixed m.p. 201–202° (ethanol), $[\alpha]_D^{16}$ −14.7° (*c* 0.6, chloroform): lit.[13] m.p. 202–202.5°, $[\alpha]_D$ −15° (chloroform).

1,3,6-Tri-O-*acetyl-2*-O-(*methylsulfonyl*)-*4*-O-(*2,3,4,6-tetra*-O-*acetyl-β*-D-*glucopyranosyl*)-*β*-D-*glucopyranose* (**9**). — Conventional methanesulfonylation of **8** (266 mg) with methanesulfonyl chloride (0.16 mL) in pyridine (3 mL) gave **9** (271 mg, 91%), m.p. 170–171° (ethanol), $[\alpha]_D^{16}$ −5.5° (*c* 1.1, chloroform): n.m.r. data (chloroform-*d*): δ 3.03 (s, 3 H, OMs).

Anal. Calc. for $C_{27}H_{38}O_{20}S$: C, 45.38; H, 5.36; S, 4.49. Found: C, 45.51; H, 5.42; S, 4.40.

Methyl 3,6-di-O-*acetyl-4*-O-(*2,3,4,6-tetra*-O-*acetyl-β*-D-*glucopyranosyl*)-*α*-D-*glucopyranoside* (**10**). — A solution of **4** (2 g) in anhydrous methanol (70 mL) containing pyridine (0.3 mL) and silver nitrate (610 mg) was boiled for 2 h under reflux. The solid was filtered off, and the filtrate was evaporated to dryness. The residue was dissolved in chloroform, and the solution was washed with water, dried (Na_2SO_4), and evaporated to a crystalline mass which was recrystallized from ethanol to afford **10** (1.45 g, 73%), m.p. 186–187°, $[\alpha]_D^{16}$ +73.2° (*c* 1.5, chloroform); n.m.r. data (dimethyl sulfoxide-d_6): δ 5.14 (d, 1 H, $J_{2,2\text{-OH}}$ 6.5 Hz, exchangeable with D_2O, OH-2), 3.32 (s, 3 H, OMe), and 1.92–2.08 (overlapping singlets, 18 H, 6 OAc).

Anal. Calc. for $C_{25}H_{36}O_{17}$: C, 49.34; H, 5.96. Found: C, 49.44; H, 5.92.

Methyl 4-O-*β*-D-*glucopyranosyl*-*α*-D-*glucopyranoside* (**11**). — Compound **10** (915 mg) was deacetylated with 0.1M sodium methoxide (1 mL) in dry methanol (10 mL) for 2 h at room temperature. Neutralization with Amberlite IR-120 (H^+) ion-exchange resin, and crystallization from ethanol, gave **10** (498 mg, 93%), m.p. 144–145°, $[\alpha]_D^{16}$ +97.4° (*c* 1.4, water); n.m.r. data (dimethyl sulfoxide-d_6): δ 4.58 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 4.27 (d, 1 H, $J_{1',2'}$ 7.5 Hz, H-1'), and 3.28 (s, 3 H, OMe);

lit. m.p. 144–145°, $[\alpha]_D^{20}$ +96.8° (*c* 1.0, water)[11]; m.p. 144–145°, $[\alpha]_D^{25}$ +97.3° (*c* 2.0, water)[12].

Methyl 3,6-di-O-acetyl-2-O-(methylsulfonyl)-4-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-α-D-glucopyranoside (**12**). — Conventional methanesulfonylation of **10** (230 mg) with methanesulfonyl chloride (0.15 mL) in pyridine (3 mL) gave **12** (234 mg, 89%), m.p. 197–198° (ethanol), $[\alpha]_D^{16}$ +50.6° (*c* 1.6, chloroform); n.m.r. data (chloroform-*d*): δ 3.05 (s, 3 H, OMs).

Anal. Calc. for $C_{26}H_{38}O_{19}S$: C, 45.48; H, 5.58; S, 4.67. Found: C, 45.32; H, 5.69; S, 4.79.

Attempted methanolysis of **5**. — A solution of **5** (961 mg) in anhydrous methanol (30 mL) containing pyridine (0.14 mL) and silver nitrate (293 mg) was heated for 2 h under reflux. Isolation, as described for the preparation of **10**, and crystallization of the resulting product from ethanol gave a mixture of methyl 3,6-di-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-β-D-glucopyranoside (**13**) and **10** (795 mg, 84%); t.l.c. (3:2, v/v, ethyl acetate–benzene): R_F 0.30; n.m.r. data (dimethyl sulfoxide-d_6): δ 3.40 (s, OMe of **13**) and 3.33 (s, OMe of **10**) (ratio of peaks at δ 3.40 and δ 3.33, 3.6:1). Attempts to isolate **13** by fractional recrystallization failed.

Anal. Calc. for $C_{25}H_{36}O_{17}$: C, 49.34; H, 5.96. Found: C, 49.20; H, 5.96.

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