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Note

A modified procedure for the synthesis of 1,6-anhydro disaccharides

ITSUO FUJIMAKI, YOSHITAKA ICHIKAWA, AND HIROYOSHI KUZUHARA*
The Institute of Physical and Chemical Research, Wako-shi, Saitama 351 (Japan)
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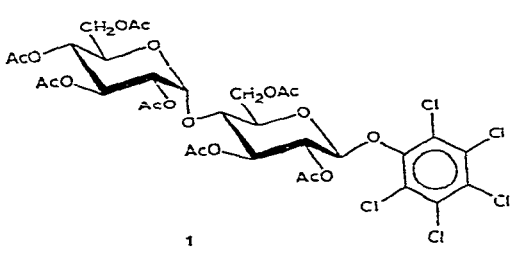
The 1,6-anhydroaldohexopyranoses have found wide application as versatile intermediates in various syntheses[1]. In the case of such reducing disaccharides as maltose or cellobiose, their 1,6-anhydro derivatives have been particularly useful compounds for their chemical transformation and modification[2–6], because one of the two primary hydroxyl groups in the parent disaccharide is masked by formation of the anhydro ring, and their constituent monosaccharide residues have reversed conformations; *i.e.*, one is $^4C_1$(D) and the other $^1C_4$(D). We recently employed 2,3,2′,3′,4′,6′-hexa-*O*-acetyl-1,6-anhydro-β-maltose (3) as an essential starting-material for a study on the chemical conversion of maltose into aminated pseudo-disaccharides[7,8].

The conventional preparation of 1,6-anhydro disaccharides by alkaline degradation of the corresponding phenyl glycosides (or their per-*O*-acetylated derivatives) was recently modified by replacing these starting materials with per-*O*-acetylated *o*- or *p*-chlorophenyl glycosides[2,5]. However, the results of these modifications were still unsatisfactory, because the yield of the per-*O*-acetylated *o*- or *p*-chlorophenyl glycoside from the parent disaccharide was rather low[9]. We now describe a more practical preparation of 1,6-anhydro-maltose and -cellobiose that should have wide applicability to other reducing sugars.

We have found that (commercially available) 95% sodium pentachlorophenoxide readily reacts with per-*O*-acetylated α-maltosyl or α-cellobiosyl bromide in



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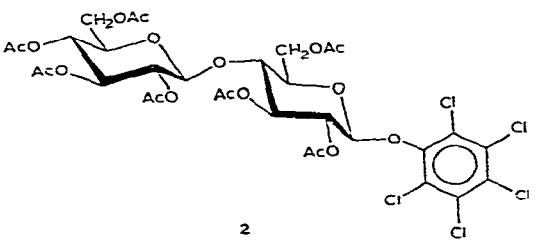

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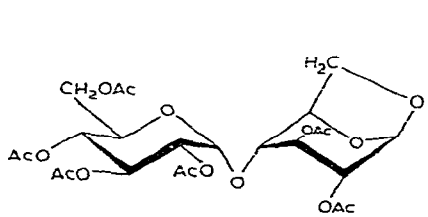
*To whom correspondence should be addressed.

acetone at an elevated temperature, to give pentachlorophenyl 2,3,6,2′,3′,4′,6′-hepta-*O*-acetyl-β-maltoside (**1**) or pentachlorophenyl 2,3,6,2′,3′,4′,6′-hepta-*O*-acetyl-β-cellobioside (**2**) in moderately good yield. The bromides undergoing this glycosidation need not be very pure, but should be used for the reaction soon after having been prepared. These glycosides readily crystallized, and could be purified by recrystallization. The yields of glycosides **1** and **2** were >80 and 60%, respectively, from the crude bromides used, whereas the yields of peracetylated *p*-chlorophenyl β-maltoside and *o*-chlorophenyl β-cellobioside had been reported to be 35 and 40%, respectively[9].

Compounds **1** and **2** were readily converted into the 1,6-anhydro derivatives of the parent disaccharides, with simultaneous loss of all of the acetyl groups, on treatment with aqueous potassium hydroxide solution under reflux. Most of the pentachlorophenol liberated was removable by filtration after neutralization of the base in the reaction mixture. The 1,6-anhydro disaccharides were isolated as the per-*O*-acetylated derivatives, 2,3,2′,3′,4′,6′-hexa-*O*-acetyl-1,6-anhydro-β-maltose (**3**) and 2,3,2′,3′,4′,6′-hexa-*O*-acetyl-1,6-anhydro-β-cellobiose (**4**). The yields of **3** and **4** from **1** and **2** were 78 and 61%, respectively.



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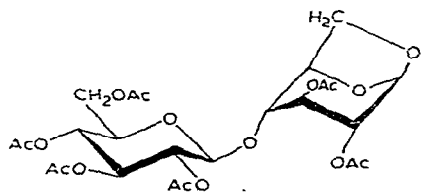

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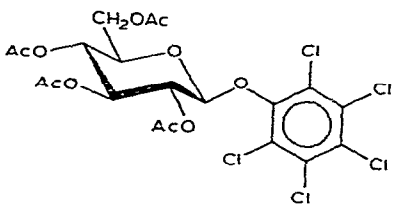
The foregoing procedure should be applicable to the preparation of anhydrides of other reducing sugars. Indeed, crystalline pentachlorophenyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (**5**) was prepared, and it gave 2,3,4-tri-*O*-acetyl-1,6-anhydro-β-D-glucopyranose (**6**) in a similar way.



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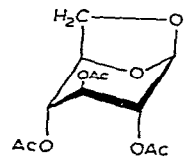

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EXPERIMENTAL

General. — Solutions were evaporated under diminished pressure; solvent extracts were dried with anhydrous sodium sulfate or magnesium sulfate. Melting points are uncorrected. Optical rotations were measured with a Perkin–Elmer Model

241MC polarimeter. I.r. spectra were recorded with a Shimadzu IR-27 instrument. N.m.r. spectra were recorded with a JEOL JNM FX-400 spectrometer, for solutions in deuteriochloroform containing tetramethylsilane as the internal standard.

Pentachlorophenyl 2,3,6,2′,3′,4′,6′-hepta-O-acetyl-β-maltoside (**1**). — To a solution of freshly prepared 2,3,6,2′,3′,4′,6′-hepta-*O*-acetyl-α-maltosyl bromide[10] (230 g, not recrystallized) in acetone (1.0 L) was added commercial, 95% sodium pentachlorophenoxide (157 g). The mixture was boiled for 6 h under reflux, with stirring, cooled, and filtered. The filtrate was evaporated to dryness, and the residue was extracted with dichloromethane. The extract was washed with water, dried, and evaporated, and the resulting residue was dissolved in hot ethanol for crystallization. After the first crystals (200 g) of **1** had been filtered off, the filtrate was concentrated, giving a second crop (23 g) of crystals; total yield 223 g (80%); m.p. 171–172°, $[\alpha]_D^{27}$ +63° (*c* 0.5, chloroform); ν_{max}^{KBr} 1750, 1235, and 1210 cm^{-1}; p.m.r. data (400 MHz): δ 3.63 (m, 1 H, H-5), 3.93 (m, 1 H, H-5′), 4.13 (t, 1 H, *J* 8.8 Hz, H-4), 4.85 (dd, 1 H, *J* 10.2 and 3.9 Hz, H-2′), 5.08 (t, 1 H, *J* 10.0 Hz, H-4′), 5.20–5.27 (m, 2 H, H-1,2), 5.30–5.37 (m, 2 H, H-3,3′), and 5.45 (d, 1 H, *J* 3.9 Hz, H-1′).

Anal. Calc. for $C_{32}H_{35}Cl_5O_{18}$: C, 43.44; H, 3.99; Cl, 20.03. Found: C, 43.43; H, 3.96; Cl, 20.14.

Pentachlorophenyl 2,3,6,2′,3′,4′,6′-hepta-O-acetyl-β-cellobioside (**2**). — Freshly prepared 2,3,6,2′,3′,4′,6′-hepta-*O*-acetyl-α-cellobiosyl bromide[11] (255 g, not recrystallized) was treated with sodium pentachlorophenoxide as described for the preparation of **1**. In this case, the dichloromethane extract of the reaction products was successively washed with ice-cold, M aqueous sodium hydroxide and water, and evaporated, and the crude product was recrystallized from ethyl acetate–hexane*, to give **2** (197 g, 61%); m.p. 212–212.5°, $[\alpha]_D^{28}$ −12° (*c* 1.0, chloroform); ν_{max}^{Nujol} 1746 and 1230 cm^{-1}; p.m.r. data (400 MHz): δ 3.54 (m, 1 H, H-5), 3.68 (m, 1 H, H-5′), 3.89 (t, 1 H, *J* 8.8 Hz, H-4), 4.53 (d, 1 H, *J* 7.8 Hz, H-1′), 4.93 (dd, 1 H, *J* 9.3 and 7.8 Hz, H-2′), 5.08 (t, 1 H, *J* 9.3 Hz, H-4′), 5.15 (t, 1 H, *J* 9.3 Hz, H-3′), 5.20 (d, 1 H, *J* 7.3 Hz, H-1), 5.27 (t, 1 H, *J* 8.8 Hz, H-3), and 5.32 (dd, 1 H, *J* 8.8 and 7.3 Hz, H-2).

Anal. Calc. for $C_{32}H_{35}Cl_5O_{18}$: C, 43.44; H, 3.99; Cl, 20.03. Found: C, 43.43; H, 4.00; Cl, 20.02.

2,3,2′,3′,4′,6′-Hexa-O-acetyl-1,6-anhydro-β-maltose (**3**). — A suspension of **1** (80 g) in 4M aqueous potassium hydroxide (500 mL) was heated for 20 h at 120°, with stirring, cooled, treated with 3M sulfuric acid to pH 3–4, and filtered. The pH of the filtrate was adjusted to 7 by addition of sodium hydrogencarbonate, and the solution was evaporated to dryness. To the residue were added anhydrous sodium acetate (60 g) and acetic anhydride (500 mL). The mixture was boiled for 3 h under reflux, cooled, poured into ice water, stirred at room temperature, kept overnight, and extracted with chloroform. The extract was successively washed with aqueous sodium hydrogencarbonate and water, dried, and evaporated to a syrup; on agitation

*Ethanol, which was used for crystallization of **1**, was unsuitable in this case.

in ethanol, compound **3** crystallized. It was recrystallized from ethanol; yield 42.6 g (78%), m.p. 182–184°, $[\alpha]_D^{27}$ +50° (*c* 0.50, chloroform); lit.[2] m.p. 186–187°, $[\alpha]_D^{14}$ +49° (*c* 0.86, chloroform).

*2,3,2',3',4',6'-Hexa-*O*-acetyl-1,6-anhydro-β-cellobiose* (**4**). — Compound **2** (200 g) was treated as described for the preparation of **3**, giving a brown, solid precipitate which was dissolved in ethanol, decolorized with charcoal, and then recrystallized from the same solvent, to afford **4** (91.5 g, 61%), m.p. 139–140°, $[\alpha]_D^{27}$ −53° (*c* 2.0, chloroform); lit.[5] m.p. 142–143°, $[\alpha]_D^{20}$ −54° (*c* 1.3, chloroform).

*Pentachlorophenyl 2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranoside* (**5**). — Syrupy 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide, prepared directly from D-glucose according to Lemieux[12], was used, without purification, as the starting material. To a solution of the syrupy bromide (153 g) in acetone (1.5 L) was added sodium pentachlorophenoxide (323 g). The mixture was treated as described for the preparation of **1**, giving colored crystals which were washed with a small volume of ethanol, and then recrystallized from 2-propanol, to afford **5** (158 g, 71%); m.p. 160.5–161.5°, $[\alpha]_D^{22}$ −23° (*c* 0.69, chloroform): ν_{max}^{KBr} 1740, 1225, and 1215 cm^{-1}; p.m.r. data (400 MHz): δ 3.65 (m, 1 H, H-5), 4.05 (dd, 1 H, *J* 12.2 and 2.7 Hz, H-6), 4.23 (dd, 1 H, *J* 12.2 and 4.9 Hz, H-6'), 5.20 (t, 1 H, *J* 9.5 Hz, H-4), 5.23 (d, 1 H, *J* 7.8 Hz, H-1), 5.29 (t, 1 H, *J* 9.5 Hz, H-3), and 5.40 (dd, 1 H, *J* 9.5 and 7.8 Hz, H-2).

Anal. Calc. for $C_{20}H_{19}Cl_5O_{10}$: C, 40.26; H, 3.21; Cl, 29.71. Found: C, 40.35; H, 3.23; Cl, 29.85.

*2,3,4-Tri-*O*-acetyl-1,6-anhydro-β-*D*-glucopyranose* (**6**). — Compound **5** (158 g) was treated as described for the preparation of **3**. In this case, acetylation for isolation of the product was performed with acetic anhydride–pyridine. The crude product was recrystallized from ethanol, giving **6** (43 g, 56%): m.p. 107–109°, $[\alpha]_D^{20}$ −63° (*c* 0.46, chloroform); lit.[13] m.p. 108–109°.

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