Base-catalyzed Degradations of Carbohydrates. I. Synthesis and Alkaline Degradation of 2-*O*-β-D-Glucopyranosyl-3-*O*-methyl-D-glucose

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2-*O*-β-D-Glucopyranosyl-3-*O*-methyl-D-glucose has been synthesized by two routes. Alkaline degradation of the disaccharide, followed by reduction, hydrolysis under extremely mild conditions, and further reduction, affords D-glucitol, and 3,4-dideoxy-*trans-erythro*- and -D-*threo*-hex-3-enitol.

Le 2-*O*-β-D-glucopyranosyl-3-*O*-méthyl-D-glucose a été synthétisé de deux façons. La dégradation alcaline du disaccharide suivie d'une réduction et hydrolyse sous des conditions extrêmement douces conduit, après réduction ultérieure, au D-glucitol et 3,4-didéoxy-*trans-erythro*- et -D-*threo*-hex-3-enitol.

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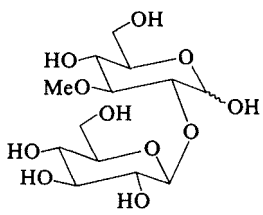
2-*O*-β-D-Glucopyranosyl-3-*O*-methyl-D-glucose (**1**) was required as a model compound in connection with studies on the alkaline degradation of branched oligo- and polysaccharides. Methyl 4,6-*O*-benzylidene-2-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-3-*O*-methyl-α-D-glucopyranoside (**2**) was prepared by two routes: (*i*) by condensation of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide and methyl 4,6-*O*-benzylidene-3-*O*-methyl-α-D-glucopyranoside (1), and (*ii*) by methylation of methyl 4,6-*O*-benzylidene-2-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-α-D-glucopyranoside (2, 3) with (*a*) methyl iodide and silver oxide in *N*,*N*-dimethylformamide or (*b*) diazomethane in the presence of boron trifluoride (4). Acetolysis of the glycoside (**2**) furnished a semi-crystalline disaccharide heptaacetate from which the disaccharide, 2-*O*-β-D-glucopyranosyl-3-*O*-methyl-D-glucose (**1**), was obtained on de-*O*-acetylation. The derived disaccharide alditol was characterized by the formation of a crystalline octaacetate and a crystalline octabenzoate.

Treatment of the disaccharide (**1**) with saturated lime-water gave a syrupy product whose u.v., i.r., and n.m.r. spectra indicated that elimination of methanol had occurred with the formation of 3-deoxy-2-*O*-β-D-glucopyranosyl-D-*erythro*-hex-2-enopyranose (**3**). The unsaturated disaccharide (**3**) was reduced with sodium borohydride, and mild treatment with cation-exchange resin during the work-up to destroy excess of hydride and remove sodium ions gave a syrupy mixture of products whose u.v. (λ_{max} 230 nm) and i.r. (ν_{max} 1690, 1640, and 975 cm^{-1}) spectra were consistent with the presence therein of the unsaturated ketose, 3,4-dideoxy-*trans*-D-*glycero*-hex-3-enos-2-ulose (5). The presence in the mixture of D-glucose and the unsaturated ketose was established by reduction with sodium borohydride to give D-glucitol, 3,4-dideoxy-*trans-erythro*-hex-3-enitol (**4**), and 3,4-dideoxy-*trans*-D-*threo*-hex-3-enitol (**5**), each of which was characterized by the formation of crystalline derivatives.

These results parallel those of Anet (5) on the



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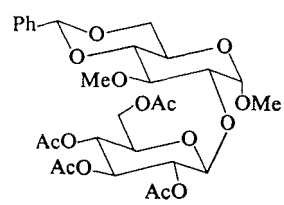

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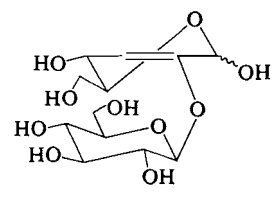

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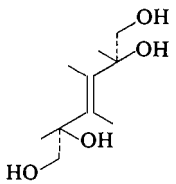

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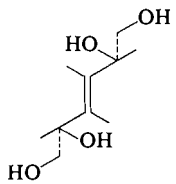

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alkaline degradation of 2,3-di-*O*-methyl-D-glucose. It is noteworthy that the enol glycoside formed on reduction of the unsaturated disaccharide (**3**), like the enol ether, 3-deoxy-2-*O*-methyl-D-*erythro*-hex-2-enitol (5), is extremely labile to acid. The observed sequence of reactions may find application in the determination of the structure of branched oligosaccharides containing a 2,3-di-*O*-substituted reducing group in that (*i*) the 3-*O*-glycosyl substituent would be eliminated on alkaline degradation, (*ii*) the 2-*O*-glycosyl substituent would be subsequently liberated on very mild acid hydrolysis, and (*iii*) the formation of the epimeric hex-3-enitols would indicate the substitution pattern of the reducing sugar residue.

Experimental

Melting points are uncorrected. Optical rotations were measured with a Perkin–Elmer model 141 polarimeter at 20 ± 2°. The i.r. and u.v. spectra were measured on Unicam SP 200 and SP 800A spectrophotometers. The n.m.r. spectra were recorded on a JEOL C-60HL spectrometer with tetramethylsilane or sodium 4,4-dimethyl-4-silapentanesulfonate as internal standards. The t.l.c. was performed with Kieselgel G (Merck) as the adsorbent, and the dried plates were sprayed with ethanolic 5% sulfuric acid and heated at about 150°. Unless otherwise stated, column chromatography was carried out on silica gel (Davison grade 950, 60–200 mesh). Paper ionophoresis was in 0.05 *M* borate buffer at p*H* 10. Unless otherwise stated light petroleum refers to the fraction of b.p. 30–60°. Solutions were concentrated below 50° under reduced pressure.

Methyl 4,6-O-Benzylidene-3-O-methyl-α-D-glucopyranoside

Methyl 4,6-*O*-benzylidene-3-*O*-methyl-2-*O*-tosyl-α-D-glucopyranoside (1) (15 g) in refluxing methanol (400 ml) and benzene (500 ml) was treated with sodium (25 g) (6) for 6 h. The t.l.c. (chloroform–acetone, 4:0.3) showed a single product. Water (200 ml) was added to the cooled reaction mixture, organic solvents were removed, and the suspension was extracted with chloroform. The dried extract was concentrated and crystallization of the residue from methanol containing a little light petroleum gave methyl 4,6-*O*-benzylidene-3-*O*-methyl-α-D-glucopyranoside (9.5 g, 96%), m.p. 137–139° (unchanged on recrystallization), (lit. (1) m.p. 150–151°); n.m.r. data ($CDCl_3$): τ 2.4–2.8 (5-proton multiplet, aromatic H's), 4.40 (1-proton singlet, benzylidene–methine), 5.20 (1-proton doublet, splitting 4 Hz), 6.36, 6.54 (3-proton singlets, C-1 OMe and C-3 OMe), 7.2–7.45 (1-proton, OH).

Methyl 4,6-O-Benzylidene-2-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-O-methyl-α-D-glucopyranoside (2)

(*a*) Methyl 4,6-*O*-benzylidene-3-*O*-methyl-α-D-glucopyranoside (4 g) was dissolved by stirring for 2 h in dichloromethane (38 ml) in the presence of silver carbonate (4 g) and drierite (4 g). Iodine (1 g) and 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (5.5 g) were added and the mixture was stirred for 42 h at room temperature. The mixture was filtered and concentration of the filtrate afforded a crystalline residue which, on trituration with methanol, gave a chromatographically pure product (5 g, 59%), m.p. 245–246°. Recrystallization from methanol gave compound **2**, m.p. 245–246°; $[\alpha]_D$ +33.7° (*c*, 1.15 in dichloromethane); n.m.r. data: τ 2.4–2.8 (5-proton multiplet, aromatic H's), 4.42 (1-proton singlet, benzylidene–methine H), 6.47, 6.57 (3-proton singlets, C-1 OMe and C-3 OMe), 7.9–8.05 (12 protons, OAc's).

Anal. Calcd. for $C_{29}H_{38}O_{15}$: C, 55.59; H, 6.07. Found: C, 55.33; H, 6.14.

(*b*) Methyl 4,6-*O*-benzylidene-2-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-α-D-glucopyranoside (1 g) and methyl iodide (2 ml) were stirred in *N*,*N*-dimethylformamide (15 ml) with silver oxide (1 g) for 30 h. The mixture was filtered, the filtrate was concentrated, and the residue was crystallized from ethoxyethanol to give compound **2**, m.p. 245–246°, $[\alpha]_D$ +33° (*c*, 1.0 in chloroform), whose n.m.r. spectrum was identical to that of the previously prepared sample.

(*c*) Methyl 4,6-*O*-benzylidene-2-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-α-D-glucopyranoside (0.5 g) was dissolved in dichloromethane (15 ml) at 0°, boron trifluoride etherate (0.05 ml) was added, and while the temperature was maintained at 0°, a white solid (polymethylene) was removed by filtration, and the filtrate was concentrated to a syrup which was crystallized from ethoxyethanol to give compound **2**, m.p. 243–245°, $[\alpha]_D$ +31° (*c*, 1.0 in chloroform), whose n.m.r. spectrum was identical with those of previously prepared samples.

2-O-β-D-Glucopyranosyl-3-O-methyl-D-glucose (1)

The foregoing glycoside (**2**) (4 g) in acetic anhydride (10 ml) was stirred with concentrated sulfuric acid 2% in acetic anhydride (20 ml) for 4 h. The mixture was poured into ice-water containing sodium hydrogen carbonate, the product was extracted with chloroform, and the chloroform extract was washed with water, dried, and concentrated to a syrup. The t.l.c. (chloroform–acetone, 4:0.3) showed a major component with fast-moving minor components with the mobilities of the peracetates of glucose and 3-*O*-methylglucose. The mixture was chromatographed on silica gel, elution with ether – light petroleum (3:1) and ether removing benzaldehyde and monosaccharide peracetates, and elution with ether–acetone (7.5:1) giving syrupy 1,4,6-tri-*O*-acetyl-2-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-3-*O*-methyl-

α-D-glucopyranose (2.8 g, 71%), $[\alpha]_D$ +35.3° (*c*, 1.34 in dichloromethane); n.m.r. data ($CDCl_3$): τ 3.77 (1-proton doublet, $J_{1,2}$ = 3 Hz, H-1), 6.57 (3-proton singlet, C-3 OMe), 7.85–8.05 (21 protons, OAc's).

Anal. Calcd. for $C_{27}H_{38}O_{18}$: C, 49.87; H, 5.89. Found: C, 49.91; H, 5.96.

This compound was later obtained in semi-crystalline form from ether–light petroleum.

Anal. Calcd. for $C_{27}H_{38}O_{18}$: C, 49.87; H, 5.89; OMe, 4.76. Found: C, 49.97; H, 5.86; OMe, 4.51.

Methanolic barium methoxide (1.5 *N*, 3 ml) was added to the above heptaacetate (3 g) in methanol (50 ml) and the mixture was kept at room temperature for 4 h. The solution was diluted with methanol and passed through columns of Amberlite resins IR-120(H) and IR-45(OH), the resins were washed with methanol–water (1:1), and the combined eluate and washings were concentrated to a syrup. The syrup was chromatographed on a column (90 × 1.5 cm) of Dowex resin 50 WX2 (Li^+; 200–400 mesh) with water as eluant to give chromatographically and ionophoretically pure syrupy 2-*O*-β-D-glucopyranosyl-3-*O*-methyl-D-glucose (**1**), $[\alpha]_D$ +19° → +13° (*c*, 1.0 in water); n.m.r. data (D_2O): τ 4.63 (1-proton doublet, $J_{1,2}$ = 3 Hz, H-1), 6.57 (3-proton singlet, C-3 OMe).

Anal. Calcd. for $C_{13}H_{24}O_{11}$: C, 43.71; H, 6.74; OMe, 8.70. Found (after drying over P_2O_5 at 60°): C, 43.40; H, 7.02; OMe, 8.41.

In subsequent preparations chromatographically pure disaccharide (**1**) was obtained by chromatography on a cellulose column using acetone–water (7:1) as eluant.

The disaccharide (**1**) (750 mg) was treated with sodium borohydride (125 mg) in water (25 ml) for 24 h. Excess of hydride was destroyed and sodium ions were removed by treatment with cation-exchanger, and the solution was concentrated several times with methanol to remove boric acid as methyl borate to give syrupy disaccharide alditol (500 mg). The syrup (200 mg) was treated with acetic anhydride and pyridine, and the product was recrystallized from ether–light petroleum (b.p. 30–60°) to give 1,4,5,6-tetra-*O*-acetyl-2-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-3-*O*-methyl-D-glucitol (300 mg), m.p. 88–90°, $[\alpha]_D$ −13.6° (*c*, 1.04 in dichloromethane); n.m.r. data ($CDCl_3$): τ 6.46 (3-proton singlet, C-3 OMe), 7.72–7.88 (24 protons, OAc's).

Anal. Calcd. for $C_{29}H_{42}O_{19}$: C, 50.21; H, 6.10. Found: C, 50.33; H, 6.16.

A further portion (100 mg) of the syrupy disaccharide alditol was treated with benzoyl chloride and pyridine, and the product was recrystallized from ethanol to give 1,4,5,6-tetra-*O*-benzoyl-2-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-3-*O*-methyl-D-glucitol (75 mg), m.p. 80–83°, $[\alpha]_D$ +25.5° (*c*, 1.35 in dichloromethane).

Anal. Calcd. for $C_{69}H_{58}O_{19}$: C, 69.58; H, 4.91. Found: C, 69.49; H, 4.67.

Alkaline Degradation of Disaccharide (1)

The disaccharide (**1**) (1 g) was kept in oxygen-free saturated lime-water (100 ml) for 40 h at 50°. The cooled solution was neutralized with carbon dioxide and concentrated, the residue was extracted with acetone, and the extract was concentrated to a syrup, $[\alpha]_D$ +3° → −4° (*c*, 1.0 in water); λ_{max} (H_2O) 198 nm (ε 5500); ν_{max} (film) 1645 cm^{-1} (C=C); n.m.r. data (D_2O): OMe protons absent.

Anal. Calcd. for $C_{12}H_{20}O_{10}\cdot H_2O$: C, 42.10; H, 6.43. Found (after drying for 1 day at 40°): C, 41.99; H, 6.57.

Anal. Calcd. for $C_{12}H_{20}O_{10}$: C, 44.44; H, 6.17. Found (after extended drying at 40°): C, 43.40; H, 7.02.

Sodium borohydride (0.3 g) was added to the syrupy alkaline degradation product (0.2 g) in water (10 ml), and the solution was warmed to 40° and then kept at room temperature overnight. Excess of hydride was destroyed by the addition of acetone, sodium ions were removed by treatment with cation-exchange resin, and the solution was repeatedly concentrated with methanol to remove boric acid as methyl borate to give a syrup (0.2 g); λ_{max} (H_2O) 230 nm; ν_{max} (film) 1690 (C=O), 1640 (C=C), 975 cm^{-1} (*trans* H—C=C—H).

The syrup (0.2 g) containing the unsaturated ketose was treated with sodium borohydride (0.3 g) in water (10 ml) overnight and the reaction product was worked-up as described above. The t.l.c. of the resulting syrup (ethanol–chloroform, 3:1) showed components with the mobilities of glucitol and 3,4-dideoxy-*trans*-D-*threo*-hex-3-enitol. A further quantity (4 g) of syrup, similarly prepared, was separated by chromatography on a column of silica gel to give two fractions. The slower-moving component (1.6 g) was characterized as D-glucitol by conversion into the hexaacetate, m.p. and mixed m.p. 99°, $[\alpha]_D$ +9° (*c*, 1.0 in chloroform).

Anal. Calcd. for $C_{18}H_{26}O_{12}$: C, 49.76; H, 5.99. Found: C, 49.74; H, 5.88.

The faster-moving fraction (2 g) was triturated with warm acetone (4 ml) and separated into acetone-soluble and acetone-insoluble fractions. The acetone-soluble fraction (0.5 g) was stirred for 24 h with anhydrous cupric sulfate (2 g) in acetone (50 ml) containing concentrated sulfuric acid (0.15 ml). The filtered solution was neutralized with sodium carbonate, filtered, and concentrated to a syrup which was extracted with warm pentane. Removal of solvent from the extract and crystallization from methanol furnished 3,4-dideoxy-1,2:5,6-di-*O*-isopropylidene-*trans*-D-*threo*-hex-3-enitol (0.25 g), m.p. and mixed m.p. (with sample prepared by the method of Tipson and Cohen (7)) 80–81°, $[\alpha]_D$ +57.1° (*c*, 1.0 in chloroform).

Anal. Calcd. for $C_{12}H_{20}O_6$: C, 63.15; H, 8.78. Found: C, 62.98; H, 8.81.

The di-*O*-isopropylidene derivative (0.2 g) was heated at 50° for 1 h in 0.05 *N* hydrochloric acid in 50% aqueous methanol (3 ml). The cooled solution was diluted with water, neutralized with anion-exchanger, and concentrated. The residue was crystallized from ethanol to give 3,4-dideoxy-*trans*-D-*threo*-hex-3-enitol (**5**) (70 mg), m.p. and mixed m.p. 63–64°, $[\alpha]_D$ −14° (*c*, 1.0 in chloroform).

Anal. Calcd. for $C_6H_{12}O_4$: C, 48.64; H, 8.10. Found: C, 48.52; H, 8.38.

In a similar manner the acetone-insoluble fraction (0.5 g) was converted into 3,4-dideoxy-1,2:5,6-di-*O*-isopropylidene-*trans-erythro*-hex-3-enitol (0.3 g), m.p. and mixed m.p. (with sample prepared from 1,2:5,6-di-*O*-isopropylidene-D-glucitol 3,4-thionocarbonate (8)) 69–70°, $[\alpha]_D$ +0.5° (*c*, 1.0 in chloroform).

Anal. Calcd. for $C_{12}H_{20}O_4$: C, 63.15; H, 8.78. Found: C, 63.11; H, 9.09.

Hydrolysis of the di-*O*-isopropylidene derivative

furnished 3,4-dideoxy-*trans-erythro*-hex-3-enitol (**4**) (80 mg), m.p. and mixed m.p. 63–64°, $[\alpha]_D$ 0° (*c*, 5.0 in chloroform).

Anal. Calcd. for $C_6H_{12}O_4$: C, 48.64; H, 8.10. Found: C, 48.62; H, 8.40.

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