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Note

Partial benzoylation of methyl β-kojibioside and methyl β-sophoroside

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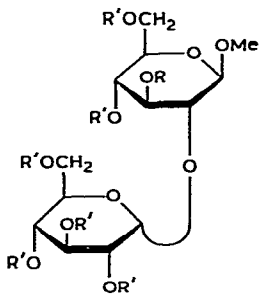
As a further extension of our studies on the regioselective benzoylation of oligosaccharides[1–4], we report herein the results obtained from the partial benzoylation of methyl β-kojibioside[5] (methyl 2-*O*-α-D-glucopyranosyl-β-D-glucopyranoside) (**1**) and methyl β-sophoroside[6] (methyl 2-*O*-β-D-glucopyranosyl-β-D-glucopyranoside) (**5**).

Treatment of **1** with 7 mol. equiv. of benzoyl chloride in pyridine at −40° gave, as the major product, methyl 4,6,2′,3′,4′,6′-hexa-*O*-benzoyl-β-kojibioside (**3**), which was directly crystallized from the reaction mixture in 75% yield. The structure of **3** was assigned on the basis of elementary analysis (a hexabenzoate) and methylation studies. Reaction of **3** with diazomethane–boron trifluoride etherate[7] gave the hexa-*O*-benzoyl-mono-*O*-methyl derivative **4**. *O*-Debenzoylation of **4**, followed by methanolysis, produced methyl 3-*O*-methyl-α,β-D-glucopyranoside and methyl α,β-D-glucopyranoside, identified by g.l.c. as the *O*-trimethylsilyl derivatives. This result indicated that the free hydroxyl group in **3** is located at C-3 or -3′. Compound **4** was successively



1 R = R′ = H
2 R = R′ = Bz
3 R = H, R′ = Bz
4 R = Me, R′ = Bz

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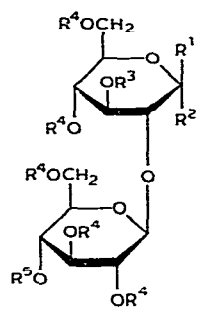
acetolyzed with 2% sulfuric acid in acetic anhydride[4,8], *O*-deacylated, reduced with sodium borohydride, and methanolyzed to give 3-*O*-methyl-D-glucitol and methyl α,β-D-glucopyranoside (g.l.c.), which confirmed the structure of **3**. Fractionation of the mother liquor of **3** on a column of silica gel afforded methyl β-kojibioside heptabenzoate (**2**) in 2% yield, together with another 17% of **3**. The structure of **2** was established by comparison with an authentic specimen synthesized from **1** with an excess of benzoyl chloride.

Benzoylation of **5** with 7 mol. equiv. of benzoyl chloride in pyridine at −40° gave a mixture of three products (t.l.c.), which were isolated by chromatography[9] on a dry-packed column of silica gel. The first component eluted was obtained in 37% yield and identified as methyl β-sophoroside heptabenzoate (**6**) by comparison with an authentic specimen. The second and third components eluted from the column were obtained in 28% and 27% yield, respectively. The structures of methyl 4,6,2′,3′,4′,6′-hexa-*O*-benzoyl- (**7**) and methyl 3,4,6,2′,3′,6′-hexa-*O*-benzoyl-β-sophoroside (**8**) were assigned to the second and third components, respectively, on the basis of the elementary analysis and the following sequence of reactions: Methylation of **7** and **8** gave the hexa-*O*-benzoyl-mono-*O*-methyl derivatives **9** and **10**, respectively, which, on *O*-debenzoylation and methanolysis, afforded methyl 3-*O*-methyl-α,β-D-glucopyranoside and methyl α,β-D-glucopyranoside, and methyl 4-*O*-methyl-α,β-D-glucopyranoside and methyl α,β-D-glucopyranoside, respectively (g.l.c.). Acetolysis of **9** and **10**, followed by *O*-deacylation, reduction, and methanolysis gave 3-*O*-methyl-D-glucitol and methyl α,β-D-glucopyranoside, and methyl 4-*O*-methyl-α,β-D-glucopyranoside and D-glucitol, respectively (g.l.c.), thus proving the structures of **7** and **8**.

The yields of the reaction products suggest that, in **1**, HO-3 is the least reactive, and that, in **5**, HO-3 and -4′ have similarly the lowest reactivities. The resistance of



5 R^1 = OMe, R^2 = R^3 = R^4 = R^5 = H
6 R^1 = OMe, R^2 = H, R^3 = R^4 = R^5 = Bz
7 R^1 = OMe, R^2 = R^3 = H, R^4 = R^5 = Bz
8 R^1 = OMe, R^2 = R^5 = H, R^3 = R^4 = Bz
9 R^1 = OMe, R^2 = H, R^3 = Me, R^4 = R^5 = Bz
10 R^1 = OMe, R^2 = H, R^3 = R^4 = Bz, R^5 = Me
11 R^1 = R^3 = R^4 = R^5 = H, R^2 = OMe

HO-3 in **1** and **5** towards benzoylation with benzoyl chloride in pyridine confirms previous observations[2-4,10-14] that the hydroxyl groups adjacent to the inter-sugar glycosidic linkages in oligosaccharides display low reactivity. Comparison of the products and yields, obtained by the benzoylation of **5**, with those previously obtained for a similar benzoylation of the α-D anomer[4] **11** demonstrates the great influence of the orientation of the aglycon on the reactivity of the hydroxyl groups of the disaccharide glycosides towards benzoylation.

EXPERIMENTAL

General methods. — Unless otherwise stated, the general experimental conditions were the same as those described previously[2]. G.l.c. was performed with a Hitachi gas chromatograph 063 equipped with a column (200 × 0.25 cm) of 5% Silicone SE-30 on 80-100 mesh Chromosorb W (operating temperature 180°), nitrogen being the carrier gas at a flow rate of 70 mL/min; retention times are quoted relative to per-*O*-(trimethylsilyl)-D-glucitol. Dry-packed column chromatography was performed on Silica gel No 7734 (Merck) according to the procedure described by Hough *et al.*[9]; the following solvent systems (v/v) were used: (*A*) 9:1 and (*B*) 4:1 benzene–ethyl acetate.

Methyl 3,4,6-tri-O-benzoyl-2-O-(2,3,4,6-tetra-O-benzoyl-α-D-glucopyranosyl)-β-D-glucopyranoside (**2**). — To a cooled solution of **1** (163 mg) in anhydrous pyridine (3 mL) was added benzoyl chloride (1.1 mL), and the mixture was kept for 2 days at room temperature, and then poured into ice–water. The resulting precipitate was filtered off, washed with water, dried, and purified by elution from a column of silica gel (20 g) with solvent *A* to give **2** as an amorphous powder (450 mg, 91%), $[\alpha]_D^{22}$ +152.1° (*c* 1.7, chloroform).

Anal. Calc. for $C_{62}H_{52}O_{18}$: C, 68.63; H, 4.83. Found: C, 68.71; H, 4.89.

Benzoylation of **1** *with 7 mol. equiv. of benzoyl chloride.* — Benzoyl chloride (7.25 mL, 7 mol. equiv.) was added over a period of 20 min to a stirred solution of **1** (3.17 g) in anhydrous pyridine (120 mL) at −40°. The reaction mixture was stirred for 1 h at −30°, 2 h at −20°, and 1 h at 0°, and then poured into ice–water. The precipitate formed was filtered off, washed extensively with water, and dried. T.l.c. (solvent *A*) showed the presence of a minor and a major component having R_F values of 0.71 (**2**) and 0.55 (**3**), respectively. Crystallization of the mixture from ethanol and recrystallization from ethanol–chloroform gave methyl 4,6-di-*O*-benzoyl-2-*O*-(2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl)-β-D-glucopyranoside (**3**) (6.51 g, 74.6%), m.p. 178–179°, $[\alpha]_D^{22}$ +106.0° (*c* 1.4, chloroform).

Anal. Calc. for $C_{55}H_{48}O_{17}$: C, 67.34; H, 4.93. Found: C, 67.25; H, 4.86.

The mother liquors of **3** were evaporated and the residue was fractionated on a column of silica gel (150 g) with solvent *A*. The initial fraction from the column gave **2** (170 mg, 1.8%), $[\alpha]_D^{24}$ +152.8° (*c* 1.7, chloroform).

The second fraction afforded an additional amount of **3** (1.48 g, 17.0%), m.p. 178–179°, $[\alpha]_D^{24}$ +106.5° (*c* 1.4, chloroform).

Methyl 4,6-di-O-benzoyl-3-O-methyl-2-O-(2,3,4,6-tetra-O-benzoyl-α-D-glucopyranosyl)-β-D-glucopyranoside (**4**). — Diazomethane in dichloromethane was gradually added to a cooled solution of **3** (2 g) in dichloromethane (10 mL) containing boron trifluoride etherate (0.2 mL) until a yellow color persisted, and the mixture was kept for 1 h at room temperature. Polymethylene was filtered off, and the filtrate was washed successively with aqueous sodium hydrogencarbonate and water, dried (Na_2SO_4), and evaporated. The residue was eluted from a column of silica gel (40 g) with solvent *A* to give **4** as an amorphous powder (1.81 g, 89%), $[\alpha]_D^{22}$ +95.5° (*c* 1.8, chloroform); n.m.r. (chloroform-*d*): δ 3.65 (s, 3 H, OMe-3).

Anal. Calc. for $C_{56}H_{50}O_{17}$: C, 67.60; H, 5.07. Found: C, 67.78; H, 4.95.

A solution of **4** (50 mg) in dry methanol (3 mL) and dry chloroform (3 mL) was treated with 0.5M sodium methoxide (1 mL). The solution was kept for 2 h at room temperature, and then neutralized with Amberlite IR-120 (H^+) cation-exchange resin, and evaporated to dryness. Methanolysis of the residue [1% methanolic hydrogen chloride (3 mL) at reflux for 18 h] and g.l.c. of the resulting methyl glycosides as the per(trimethylsilyl) ethers gave peaks corresponding to methyl 3-*O*-methyl-α,β-D-glucopyranoside (*T* 0.37, 0.39) and methyl α,β-D-glucopyranoside (*T* 0.69, 0.77).

Compound **4** (300 mg) was acetolyzed with 2% sulfuric acid in acetic anhydride, *O*-deacylated with sodium methoxide, and reduced with sodium borohydride, as described previously[4], and methanolyzed as just described. G.l.c. of the methanolyzates as the per(trimethylsilyl) ethers gave peaks corresponding to 3-*O*-methyl-D-glucitol (*T* 0.72) and methyl α,β-D-glucopyranoside.

Methyl 3,4,6-tri-O-benzoyl-2-O-(2,3,4,6-tetra-O-benzoyl-β-D-glucopyranosyl)-β-D-glucopyranoside (**6**). — Treatment of **5** (190 mg) with benzoyl chloride (0.9 mL) in pyridine (3 mL), and subsequent purification of the resulting product on a column of silica gel, as described for the preparation of **2**, afforded **6** as an amorphous powder (541 mg, 93%), $[\alpha]_D^{22}$ +15.0° (*c* 1.8, chloroform).

Anal. Calc. for $C_{62}H_{52}O_{18}$: C, 68.63; H, 4.83. Found: C, 68.40; H, 4.95.

Benzoylation of **5** *with 7 mol. equiv. of benzoyl chloride.* — Treatment of **5** (3.15 g) with benzoyl chloride (7.21 mL, 7 mol. equiv.) in pyridine (120 mL), as described for **1**, gave a mixture which was shown by t.l.c. (solvent *B*) to be composed of three benzoylated derivatives having R_F values of 0.72 (**6**), 0.54 (**7**), and 0.42 (**8**), respectively. The mixture was fractionated on a dry-packed column of silica gel (500 g) with solvent *A*. The first fraction from the column gave **6** (3.55 g, 37.0%), $[\alpha]_D^{24}$ +14.9° (*c* 1.3, chloroform).

The second fraction gave methyl 4,6-di-*O*-benzoyl-2-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-β-D-glucopyranoside (**7**) (2.39 g, 27.6%), m.p. 185–186° (methanol–acetone), $[\alpha]_D^{22}$ +21.8° (*c* 2.8, chloroform).

Anal. Calc. for $C_{55}H_{48}O_{17}$: C, 67.34; H, 4.93. Found: C, 67.45; H, 5.06.

The third fraction afforded methyl 3,4,6-tri-*O*-benzoyl-2-*O*-(2,3,6-tri-*O*-benzoyl-β-D-glucopyranosyl)-β-D-glucopyranoside (**8**) as an amorphous solid (2.35 g, 27.1%), $[\alpha]_D^{22}$ +35.2° (*c* 1.1, chloroform).

Anal. Calc. for $C_{55}H_{48}O_{17}$: C, 67.34; H, 4.93. Found: C, 67.53; H, 4.84.

Methyl 4,6-di-O-benzoyl-3-O-methyl-2-O-(2,3,4,6-tetra-O-benzoyl-β-D-glucopyranosyl)-β-D-glucopyranoside (**9**). — Treatment of **7** (1 g) with diazomethane–boron trifluoride etherate in dichloromethane, as described for the preparation of **4**, gave **9** (856 mg, 85%), m.p. 200–201° (ethanol), $[\alpha]_D^{22}$ +12.7° (*c* 1.4, chloroform); n.m.r. (chloroform-*d*): δ 3.19 (s, 3 H, OMe-3).

Anal. Calc. for $C_{56}H_{50}O_{17}$: C, 67.60; H, 5.07. Found: C, 67.75; H, 5.15.

O-Debenzoylation of **9** (30 mg), followed by methanolysis, as described for **4**, and g.l.c. of the methanolyzates as the per(trimethylsilyl) ethers showed the presence of methyl 3-*O*-methyl-α,β-D-glucopyranoside and methyl α,β-D-glucopyranoside.

After sequential acetolysis of **9** (300 mg), *O*-deacylation, reduction, methanolysis, and trimethylsilylation, g.l.c. examination showed the presence of 3-*O*-methyl-D-glucitol and methyl α,β-D-glucopyranoside.

Methyl 3,4,6-tri-O-benzoyl-2-O-(2,3,6-tri-O-benzoyl-4-O-methyl-β-D-glucopyranosyl)-β-D-glucopyranoside (**10**). — Compound **8** was methylated and processed as described previously to give **10** (878 mg, 87%) as an amorphous solid, $[\alpha]_D^{22}$ +42.8° (*c* 1.2, chloroform); n.m.r. (chloroform-*d*): δ 3.41 (s, 3 H, OMe-4').

Anal. Calc. for $C_{56}H_{50}O_{17}$: C, 67.60; H, 5.07. Found: C, 67.77; H, 4.93.

After sequential *O*-debenzoylation of **10** (30 mg), followed by methanolysis, and trimethylsilylation, g.l.c. examination showed the presence of methyl 4-*O*-methyl-α,β-D-glucopyranoside (*T* 0.41, 0.46) and methyl α,β-D-glucopyranoside.

Acetolysis of **10** (300 mg), followed by *O*-deacylation, reduction, and methanolysis, and g.l.c. of the methanolyzates as the per(trimethylsilyl) ethers gave peaks corresponding to methyl 4-*O*-methyl-α,β-D-glucopyranoside and D-glucitol (*T* 1.00).

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