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Note

The selective acetylation of benzyl β-maltoside

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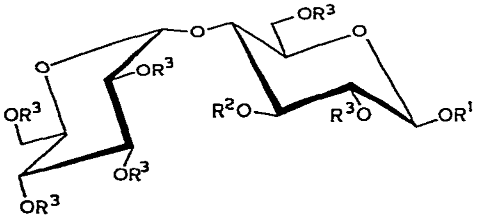
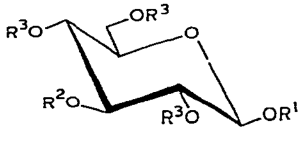
In selective acylations[1–4] of maltose (**1**) and some of its derivatives with acid chlorides, it appears that HO-3 is the least reactive. It has been suggested[2] that the presence of the α-glycosidic link in maltose causes steric hindrance of HO-3 and allows intramolecular hydrogen bonding between HO-3 and HO-2′. Such hydrogen bonding has been observed in X-ray crystallographic studies of maltose[5,6]. However, a similar lack of reactivity of HO-3 has been observed for the β-linked disaccharide lactose[7], and, moreover, intramolecular hydrogen bonding may enhance the rate of substitution by acid chlorides[8]. Hough and co-workers[9] pointed out that, in (1→4)-linked disaccharides, the hydroxyl groups adjacent to the junction of the two glycopyranose rings (*i.e.*, HO-3, HO-2′, and HO-6) are hindered most, and hence are only slowly acylated.

We have reported on selective acylations[10–13] with acetic anhydride–sodium acetate. The known[14] differences in selective acylation mediated by anhydrides and acid chlorides prompted an examination of the selective acetylation of benzyl β-maltoside (**2**) with acetic anhydride–sodium acetate. With 20 equiv. of acetic anhydride at room temperature for 10 days, **2** gave a mixture that contained (t.l.c.) one major component (**4**) together with a small proportion of benzyl 2,3,6,2′,3′,4′,6′-hepta-*O*-acetyl-β-maltoside (**3**). Both **3** (10%) and **4** (71%) were isolated by fractional



1 $R^1 = H{\cdot}H_2O,\ R^2 = R^3 = H$
2 $R^1 = Bzl,\ R^2 = R^3 = H$
3 $R^1 = Bzl,\ R^2 = R^3 = Ac$
4 $R^1 = Bzl,\ R^2 = H, R^3 = Ac$
5 $R^1 = Bzl,\ R^2 = Me,\ R^3 = Ac$
6 $R^1 = Bzl,\ R^2 = Me,\ R^3 = H$
7 $R^1 = Me,\ R^2 = R^3 = H$



8 $R^1 = Bzl,\ R^2 = R^3 = Ac$
9 $R^1 = R^3 = Ac,\ R^2 = Me$
10 $R^1 = R^2 = Me,\ R^3 = Ac$

crystallisation, and the latter was shown to be a hexa-acetate by p.m.r. spectroscopy (see Experimental).

Treatment of **4** with diazomethane–boron trifluoride etherate[15] yielded the crystalline methyl ether **5**, which was deacetylated with sodium methoxide to give syrupy **6**. ^{13}C-N.m.r. data (see below) showed that **6** was benzyl 3-*O*-methyl-β-maltoside, thus **5** was benzyl 2,6,2′,3′,4′,6′-hexa-*O*-acetyl-3-*O*-methyl-β-maltoside, and **4** was benzyl 2,6,2′,3′,4′,6′-hexa-*O*-acetyl-β-maltoside. Hence, in the selective acetylation of benzyl β-maltoside, HO-3 is the least reactive, as in other maltose derivatives, regardless of the acylating agents used. The resulting derivatives having HO-3 unsubstituted are useful for further modifications of maltose[16].

^{13}C-N.m.r. data for some derivatives of β-maltose and β-D-glucopyranose are given in Table I. Comparison of the data for **6** and **2** indicated the structure of **6**, since the signal for the methoxyl-bearing carbon (C-3) had undergone a substantial (10 p.p.m.) downfield-shift (β-shift)[17]. The only other differences were in the signals for C-4 and C-1′, which were shifted upfield by 3.7 and 1.2 p.p.m., respectively, for **6**. The ^{13}C-n.m.r. spectrum of **2** was assigned by analogy with that of **7**[18].

Methylation of equatorial hydroxyl groups causes[19,20] a large downfield-shift in the ^{13}C-signal of the methoxylated carbon and also changes the signals of the adjacent carbons. If both C_a and C_b bear equatorial hydroxyl groups, there are three principal conformations of the methoxyl group (**11**–**13**). The signals of C_a and C_b undergo upfield shifts of 0.7 ±0.2 p.p.m., and these shifts are associated with **12** and **13**, the sterically more favoured and equally populated conformers. It has been inferred[21] that the steric perturbations in **11** can cause larger shielding of C_a and C_b, perhaps by as much as 5 p.p.m. For compound **6**, the pyranoid ring substituted at C-4 would impose a strong, steric restriction on conformer **13**; this interaction would be reinforced by the intramolecular hydrogen bonding[2,5,6] between HO-2′ and O-3. A resulting increase in the population of **11** could cause the upfield shift in the C-4

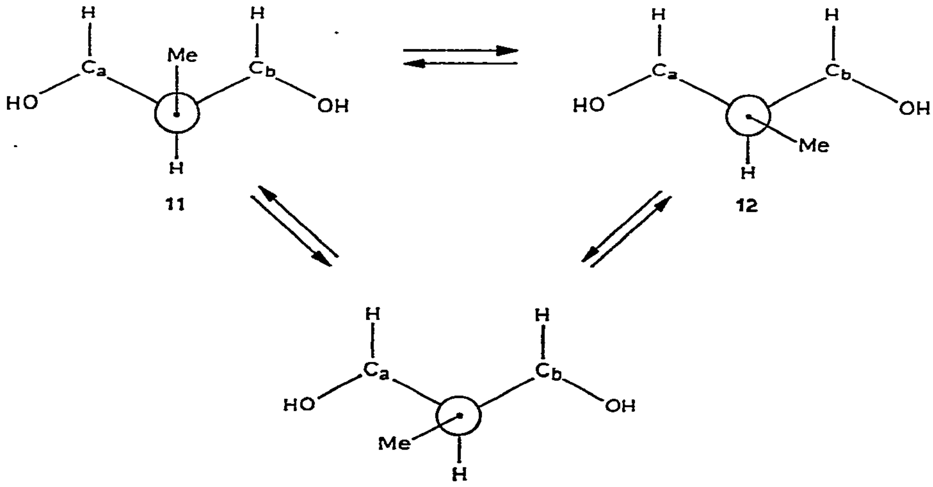


TABLE I

^{13}C-N.M.R. DATA[a]

Compound	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*C-1′*	*C-2′*	*C-3′*	*C-4′*	*C-5′*	*C-6′*	$C_6H_5CH_2$	$C_6H_5CH_2$	CH_3O	CH_3CO	CH_3CO
7[18,b]	104.4	74.6	77.8	78.7	76.1	62.3	101.1	74.3	74.6	70.9	73.4	62.3			58.7		
2[b]	102.2	73.9	77.3	78.2	75.7	61.7	100.8	74.1	74.1	70.5	72.8	61.9	72.6	129.8, 137.6			
6[b]	102.1	73.7	87.3	74.5	75.7	61.7	99.6	73.9	73.9	70.6	72.6	62.1	72.6	129.9, 137.8	60.5		
3[c]	98.8	70.1	72.9	75.6	72.3	61.6	95.6	69.4	72.3	68.6	68.2	62.9	70.8	128.1, 136.7		20.6	169.3–170.4
4[c]	99.1	70.5	80.3	75.2	73.9	61.8	97.9	69.7	72.3	68.3	68.3	63.1	70.5	127.8, 128.4, 136.9		20.6	169.3–170.5
5[c]	99.1	70.4	83.5	74.9	72.5	61.9	96.5	69.7	72.3	68.4	68.4	63.2	70.4	127.7, 128.4, 136.9	57.9	20.6	169.3–170.4
8[c]	99.3	71.4	72.9	68.6	71.9	62.1							70.8	127.7, 128.4, 136.7		20.6	169.1–170.6
9[c]	92.1	73.1	81.4	68.7	71.1	61.9									59.2	20.7	169.2–170.6
10[c]	101.9	71.9	81.4	69.2	72.1	62.4									56.7 58.6	20.8	169.3–170.8

[a] Chemical shifts in p.p.m. downfield from Me_4Si. [b] Measured in D_2O solution relative to external Me_4Si. [c] Measured in $CDCl_3$ solution.

signal. However, since no similar change in the signal of C-2 was observed, and in view of the small shift-increment in the signal of C-1′, the conformation about C-3 is probably intermediate between **11** and **13**; this could be due to steric effects of BzlO-1. Such a conformation would allow strong interaction of the methoxyl group with C-4, and also a smaller interaction with C-1′.

The ^{13}C-spectra of the acetates **3–5** were assigned by reference to the model compounds **8–10** (Table I). There is a general shift to higher field in the spectra of the acetates[21], and it is interesting to note that the C-4 signal for **5** was virtually unshifted relative to that for **4**, whereas that for C-1′ had been shifted upfield by 1.4 p.p.m. Since no hydrogen bonding between O-3 and O-2′ is possible in **5**, the non-reducing end of the molecule would not be held in close proximity to O-3. The removal of steric hindrance allows population of conformer **13**, thereby decreasing the interaction of the methoxyl group with C-4 but preserving a small interaction with C-1′.

EXPERIMENTAL

Melting points were taken on a Kofler hot-stage and are uncorrected. Optical rotations were measured with a Perkin–Elmer Model 241 polarimeter. T.l.c. was performed on silica gel F-254 (Merck) with benzene–methanol (8:2) and detection with methanol–sulphuric acid (25:1). N.m.r. spectra were recorded with Jeol JNM-MH-100 (^{1}H) and Jeol JNM-FX-60 (^{13}C) instruments, operating at 100 and 15 MHz, respectively; chemical shifts are in τ units (^{1}H) and p.p.m. downfield from Me_4Si (^{13}C).

Selective acetylation of benzyl β-maltoside. — Benzyl β-maltoside[22] (**2**) (1.5 g, 3.45 mmol) was pulverised and added to a mixture of acetic anhydride (6.5 ml, 20 mol. equiv.) and anhydrous sodium acetate (1 g). Glacial acetic acid (2–3 ml) was added to ensure mobility of the slurry. The mixture was stirred at room temperature for 10 days, and t.l.c. then showed the presence of one major component (R_F 0.65) together with a small amount of benzyl 2,3,6,2′,3′,4′,6′-hepta-*O*-acetyl-β-maltoside (**3**) (R_F 0.72). Water (20 ml) was added and the mixture was extracted with chloroform (3 × 50 ml). The combined chloroform extracts were washed with saturated, aqueous sodium hydrogen carbonate, dried ($MgSO_4$), and concentrated (with removal of excess acetic anhydride in an azeotrope with methanol), to give a syrup (2.2 g). Crystallisation from ethanol gave hepta-acetate **3** (250 mg, 10%), m.p. 116–118°, $[\alpha]_D$ +28° (*c* 1, chloroform); lit.[22] m.p. 125°, $[\alpha]_D$ +28° (tetrachloroethane). P.m.r. data ($CDCl_3$): τ 2.74 (d, 5 H, *Ph*CH_2), 5.44 (d, 1 H, $J_{1,2}$ 8 Hz, H-1), and 7.84–8.06 (7 s, 21 H, 7 AcO).

The mother liquor yielded benzyl 2,6,2′,3′,4′,6′-hexa-*O*-acetyl-β-maltoside (**4**, 71%), which, on recrystallisation from di-isopropyl ether–ethanol, had m.p. 99–102°, $[\alpha]_D$ +30.4° (*c* 0.5, chloroform). P.m.r. data ($CDCl_3$): τ 2.72 (s, 5 H, *Ph*CH_2), 5.52 (d, 1 H, $J_{1,2}$ 8 Hz, H-1), 6.84 (bs, 1 H, OH), and 7.84–8.04 (6 s, 18 H, 6 AcO).

Anal. Calc. for $C_{31}H_{40}O_{17}$: C, 54.3; H, 5.8. Found: C, 54.6; H, 5.6.

Benzyl 2,6,2',3',4',6'-hexa-O-acetyl-3-O-methyl-β-maltoside (**5**). — A solution of **4** (500 mg) in dichloromethane (10 ml) was methylated with diazomethane–boron trifluoride etherate in the usual manner[15]. Polymethylene was removed, and the filtrate was diluted by a further addition of dichloromethane (50 ml). The solution was washed with saturated, aqueous sodium hydrogen carbonate and water, dried ($MgSO_4$), and concentrated to a syrup (520 mg) that was chromatographically homogeneous. Crystallisation from ethanol afforded **5** (400 mg), m.p. 81–83°, $[\alpha]_D$ $+39°$ (*c* 1.2, chloroform). P.m.r. data ($CDCl_3$): τ 2.7 (m, 5 H, *Ph*CH_2), 5.6 (d, 1 H, $J_{1,2}$ 8 Hz, H-1), 6.7 (s, 3 H, OMe), and 7.9–8.04 (6 s, 18 H, 6 AcO).

Anal. Calc. for $C_{32}H_{42}O_{17}$: C, 55.0; H, 6.0. Found: C, 54.7; H, 6.1.

Benzyl 3-O-methyl-β-maltoside (**6**). — To a solution of the hexa-acetate **5** (150 mg) in dry methanol (10 ml) was added methanolic sodium methoxide (0.1M, 3 ml). The mixture was stirred for 4 h at room temperature, and made neutral with Amberlite IR-120(H^+) resin, the suspension filtered, and the filtrate evaporated. Compound **6** was obtained as a chromatographically homogeneous syrup (85 mg), $[\alpha]_D$ $+36.5°$ (*c* 0.52, water).

Anal. Calc. for $C_{20}H_{30}O_{11}$: C, 53.8; H, 6.7. Found: C, 53.2; H, 6.9.

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