Carbohydrate Research, 32 (1974) C4–6

Preliminary communication

Selective benzoylation of methyl β-lactoside

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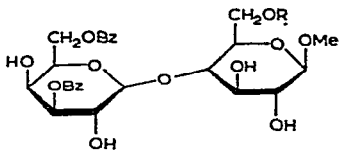
(Received November 23rd, 1973; accepted for publication November 26th, 1973)

Selective acylation of glycosides, particularly benzoylation, has been the subject of several investigations, both by our own group[1] and others[2], and several of the specifically blocked glycosides obtained in this way are useful synthetic intermediates which would otherwise be available only after a long synthetic sequence. We now report on the selective benzoylation of methyl β-lactoside.

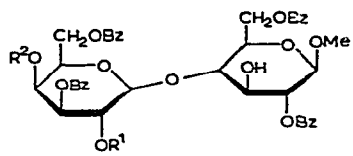
Benzoylation with 2.2 moles of benzoyl chloride in pyridine at between −20 and −40° afforded a complex mixture from which the major component *A* was isolated (31%) by chromatography on silica gel. Benzoylation with 5 moles of the reagent also gave a complex mixture, but this contained four major components (*B*–*E*, in order of decreasing t.l.c. mobility). Chromatography of the mixture afforded pure, crystalline samples of *B*, *D*, and *E* in yields of 9, 22, and 31%, respectively; *C*, contaminated with a little *B*, was obtained in 9% yield. Benzoylation with 6.5 moles of the reagent gave a moderately complex mixture which was composed of a major component *F*, and lesser amounts of *B* and *C*. The component *F* was isolated by chromatography in 33% yield.

The structural analyses of *A*–*F* were based upon (1) silylation followed by mass spectrometry (m.s.), which always showed the oxycarbonium ion resulting from the non-reducing ring as an intense fragment (*e.g.* **11**–**15**) and the C-4 carbonium ion resulting from the reducing ring as a less-intense ion[3]; (2) reaction of each of the benzoates *B*–*F* with sulphuryl chloride which, on the basis of the well-known selectivity of this reagent[4], would replace by chlorine only free hydroxyl groups at C-3, C-4′, C-6, and C-6′, or at C-3′ if preceded by displacement with inversion at C-4, which would remove the impeding 4-axial substituent; (3) the 220-MHz ^{1}H n.m.r. spectra of the six benzoates and the chloro derivatives resulting from the action of sulphuryl chloride.

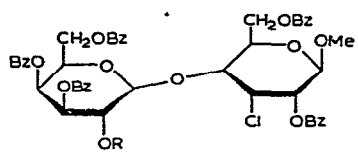
The dibenzoate *A* (m.p. 188–191°, $[\alpha]_D$ +26.8° in methanol) has both benzoate groups attached to the non-reducing ring, since m.s. of the penta-TMS ether showed fragments **11** (*m/e* 515) and **18** (*m/e* 393) emanating from the non-reducing and reducing rings, respectively. The loss of the elements of benzoic acid from *m/e* 515 was indicative of the presence of a 3′-benzoyl group, which was verified from the appearance of the H-3′ resonance as a low-field, double doublet at τ 4.32 (*J* 10 and 3.6 Hz) in the n.m.r. spectrum. Hence *A* is the 3′,6′-dibenzoate **1**.



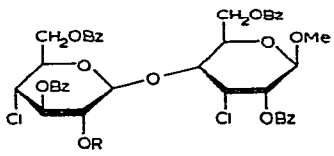
1 R = H
2 R = Bz



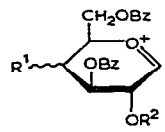
3 $R^1 = R^2 = H$
4 $R^1 = H, R^2 = Bz$
5 $R^1 = Bz, R^2 = H$
6 $R^1 = R^2 = Bz$



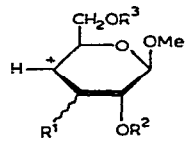
7 R = Bz
8 R = H



9 R = Bz
10 R = H



11 $R^1 = OSiMe_3$, $R^2 = SiMe_3$
12 $R^1 = OSiMe_3$, $R^2 = Bz$
13 $R^1 = OBz$, $R^2 = SiMe_3$
14 $R^1 = Cl$, $R^2 = Bz$
15 $R^1 = Cl$, $R^2 = SiMe$



16 $R^1 = OSiMe_3, R^2 = R^3 = Bz$
17 $R^1 = Cl, R^2 = R^3 = Bz$
18 $R^1 = OSiMe_3, R^2 = R^3 = SiMe_3$
19 $R^1 = OSiMe_3, R^2 = SiMe_3, R^3 = Bz$

Component *B* (m.p. 253–255°, $[\alpha]_D$ +56° in chloroform) is a pentabenzoate, and m.s. of the di-TMS ether showed fragments at *m/e* 547 (**12**) and 457 (**16**) indicating that there was one hydroxyl group in each ring. The compound reacted with sulphuryl chloride to give a dichloro derivative, which must therefore have been the 3,4'-dichloride **9** (m.s. gave ions **14** and **17**). *B* is therefore the 2,2',3',6,6'-pentabenzoate **5**; this was verified by n.m.r. spectroscopy of **5** and the derived dichloride **9**.

Componer.t *C* was contaminated with a little *B*, but afforded a homogeneous monochloro derivative **8** on reaction with sulphuryl chloride. The m.s. of the TMS ether of the chloride contained fragments *m/e* 547 (**13**) and 403 (**17**), showing that the chlorine had been introduced into the reducing ring, and that the hydroxyl group in the non-reducing ring had survived treatment with sulphuryl chloride. The ion *m/e* 547 lost the elements of benzoic acid to give an intense ion at *m/e* 425, indicative of the presence of a 3'-benzoate. Hence *C* is the 2,3',4',6,6'-pentabenzoate **4**, and this was verified by the n.m.r. spectrum.

Component *D* (m.p. 118–120°, $[\alpha]_D$ +31° in chloroform) is a tetrabenzoate, and m.s. of its tri-TMS ether showed fragments **11** (*m/e* 515) and **16** (*m/e* 457) indicating the presence of two hydroxyl groups in the non-reducing ring and one in the other ring. Treatment of the tetrabenzoate with sulphuryl chloride gave a dichloride having a chlorine substituent in each ring (m.s. of the TMS ether showed ions **15** and **17**), which indicated that hydroxyl groups in *D* were located at C-3, C-4', and C-2'. *D* is therefore the 2,3',6,6'-tetrabenzoate **3**, which reacted with sulphuryl chloride to give the 3,4'-dichloride **10**.

Compound *E* (m.p. 238–240°, $[\alpha]_D$ +44° in methanol) is a tribenzoate. M.s. of its tetra-TMS ether showed fragments at *m/e* 515 (**11**) and 424 (**19**) indicative of two benzoate groups in the non-reducing ring and the other in the reducing ring. The loss of the elements of benzoic acid from *m/e* 515 to give an intense ion at *m/e* 393 was indicative of a 3'-benzoate, and the n.m.r. data showed conclusively that only one of the benzoate groups was at a secondary position. Therefore *E* is the 3,6,6'-tribenzoate **2**.

M.s. of the TMS ether of the hexabenzoate (m.p. 119–121°, $[\alpha]_D$ +96° in chloroform) showed fragments at *m/e* 579 and 457 **(16)** which indicated that the lone hydroxyl group was situated in the reducing ring. By analogy with the former products, **6** must therefore be the 2,2',3',4',6,6'-hexabenzoate. This was verified by the fact that **6** reacted with sulphuryl chloride to give the 3-chloro derivative **7**, and by the n.m.r. spectral parameters of both **6** and **7**.

These results indicate that methyl glycosides of disaccharides are capable of considerable selectivity in their reaction towards benzoyl chloride and that the hydroxyl groups which are adjacent to the junction of the two rings (*i.e.*, HO-3, HO-2', and HO-6) react sluggishly. The 3-hydroxyl group of maltose[5] and methyl β-maltoside[6] have been shown to be similarly resistant to acylation, and Vazquez *et al.*[7], concurrent with the early stages of our work, showed that the selective benzoylation of lactose afforded the heptabenzoate having HO-3 free. From these present studies, it appears that the order of reactivity of the hydroxyl groups in methyl β-lactoside is $6' > 3' > 6 > 2 > 2',4' > 3$.

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