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Reaction of Sugar Esters with Hydrogen Fluoride. XVI. Rearrangement of Tri-*O*-benzoyl-4, 6-di-*O*-methyl-D-glucopyranose

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Dedicated to Jannik Bjerrum on the occasion of his 70th birthday

Reaction of 1,2,3-tri-*O*-benzoyl-4,6-di-*O*-methyl-α-D-glucopyranose, or -α-D-mannopyranose with anhydrous hydrogen fluoride for 10 – 20 min gave the corresponding pyranosyl fluorides. After 3 days reaction the initially formed anomeric mixture of 2,3-di-*O*-benzoyl-4,6-di-*O*-methyl-D-glucopyranosyl fluoride was rearranged into the corresponding D-mannopyranose derivatives, identified after hydrolysis as the 2-*O*- or 3-*O*-benzoyl-α- and β-D-mannopyranosyl fluorides.

The reaction of acylated D-glucopyranoses and D-mannopyranoses with anhydrous hydrogen fluoride (HF) has been the subject of previous papers in this series.[1,2] Thus, fully acylated D-glucopyranoses have been shown to rearrange into D-mannopyranose derivatives which, in turn, yielded D-altropyranose derivatives. These reactions were complicated, however, by formation of 1,6-anhydrides and by ring contractions to furanose derivatives.[1] Reaction of acylated 2-*O*-methyl and 3-*O*-methyl derivatives of D-glucopyranose and D-mannopyranose with HF did not lead to inversion, but the 2-*O*-methylated compounds were converted into furanose derivatives.[2,3] In order to learn whether treatment of a hexopyranose derivative with HF can lead at all to inversion, fully benzoylated 4,6-di-*O*-methyl-D-glucopyranose and -D-mannopyranose have been studied.

Brief treatment of 1,2,3-tri-*O*-benzoyl-4,6-di-*O*-methyl-α-D-mannopyranose (*1*) with HF gave the corresponding α-fluoride (α-*4*). The HF solution probably contains the benzoxonium ion (*2*) in equilibrium with a small amount of the fluoride (*4*), and on addition of water during work-up *2* reacts with fluoride ion to give α-*4*.[1] Reaction of *1* with HF for 3 days gave only traces of α-*4*, the main products being the monobenzoylated fluorides α-*7a* and β-*7b*, which on benzoylation yielded α-*4* and β-*4*. The fluoride *4* has a pair of *cis* oriented benzoyloxy groups and may therefore form the benzoxonium ions α-*5* or β-*5* on prolonged reaction with HF.[4] Subsequent hydrolysis of *5* yields the monobenzoates α-*7a* and β-*7b*.

When 1,2,3-tri-*O*-benzoyl-4,6-di-*O*-methyl-α-D-glucopyranose (*3*) was treated with HF for 10 min it produced a mixture of the two anomeric fluorides (α- and β-*8*), the β-anomer being the major product. As described above *3* probably forms the benzoxonium ion (*6*) in HF and this on addition of water reacts with fluoride ion to give β-*8*. The small amount of α-*8* which was isolated may arise by subsequent anomerization of β-*8*. Treatment of *3* with HF for 3 days gave a mixture of α-*7a* and β-*7b*, as was obtained from *1*. The conversion of *3* to *7* probably takes place *via* the 1,2-benzoxonium *6*, which rearranges to *5* as previously described.[1]

The structures of the products described above were derived from their NMR spectra. Both the α- and the β-D-mannopyranosyl fluorides have small couplings between H1 and H2. Their $^3J_{H2F}$ values, however, clearly disclose their anomeric structures. The α-D-mannopyranosyl fluorides, (α-*4* and α-*7a*) have small J_{H2F} values (~1 Hz)[5] whereas those of β-*4* and β-*7b* are *ca.* 14 Hz.[6] The structure of the two β-D-glucopyranosyl fluorides (α- and β-*8*)

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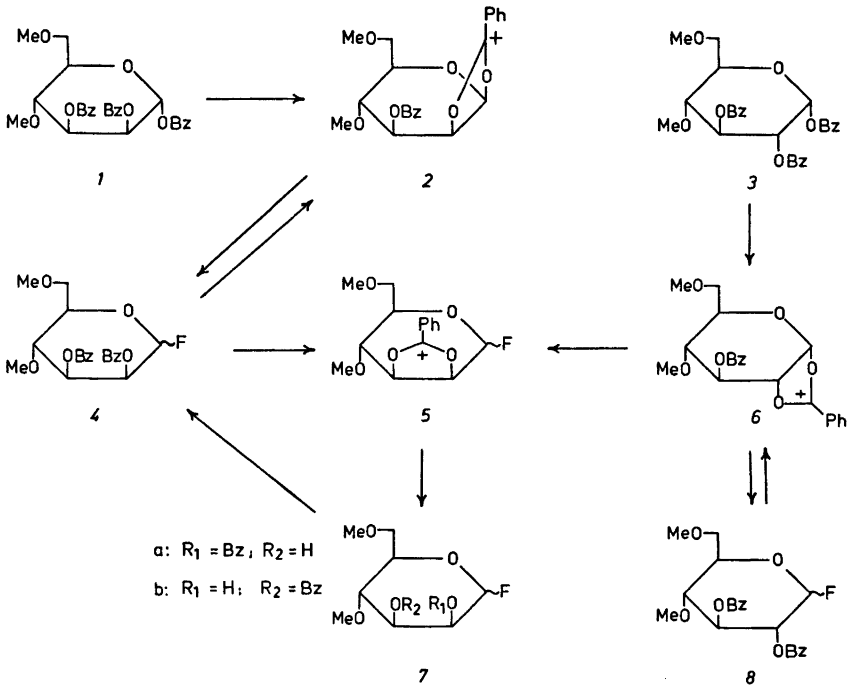

could easily be derived from the proton-proton and proton-fluorine coupling constants.[5] ^{13}C NMR spectra were measured on some of the products. The proton coupled ^{13}C NMR spectra gave $^1J_{C1H1}$ values which confirmed the anomeric structures.[7] From proton decoupled spectra carbon-fluorine coupling constants were obtained. The $^2J_{C2F}$ values of 40 Hz found for α-*4* and α-*7a* clearly show that these are α-D-mannopyranosyl fluorides.[6]

EXPERIMENTAL

Melting points are uncorrected. Preparative TLC was performed on 1 mm layers of silica gel (Merck PF_{256}). ^1H and ^{13}C NMR spectra were measured on Bruker HX-90 E, WH-90, or HX-270 instruments in deuteriochloroform solution. Optical rotations were measured in chloroform solution on a Perkin Elmer 141 instrument.

1,2,3-Tri-O-*benozyl-4,6-di*-O-*methyl*-α-D-*glucopyranose (3)*. A mixture of pyridine (75 ml) and benzoyl chloride (28 ml) was cooled to −10 °C and stirred while 2,6-di-*O*-methyl-α-D-glucopyranose [8] (10.0 g) was added. The mixture was left at room temperature overnight and then treated with water (5 ml). After 0.5 h dichloromethane was added and the solution was washed with 1.5 M sulfuric acid and with aqueous sodium hydrogen carbonate and dried. Evaporation gave a syrup which crystallized from ethanol to give 25.0 g (~100 %) of *3*, m.p. 134–135 °C. Recrystallization from ethanol gave a product with m.p. 134–136 °C, $[\alpha]_D^{20}$ 244° (*c* 0.8). Anal. $C_{28}H_{28}O_9$: C, H. ^1H NMR data: δ 6.72 (H1); 5.47 (H2); 6.07 (H3); 3.5–4.2 (H4, H5, and H6); 3.44 and 3.48 (OMe). J_{12} 3.5 Hz; J_{23} 10.2; J_{34} 8.7.

1,2,3-Tri-O-*benzoyl-4,6-di*-O-*methyl*-α-D-*mannopyranose (1)*. Syrupy 4,6,di-*O*-methyl-D-mannopyranose [9] (20.0 g) was dissolved in pyridine (75 ml) and the solution was left at room temperature for 6 h. It was then cooled to 0 °C and benzoyl chloride (37 ml) was added. After the initial reaction was over the reaction mixture was held at 40 °C for 1 h and then worked up in the usual way to give a syrup which was dissolved in methanol (100 ml) and seeded (seed crystals of *1* were obtained by preparative TLC of a sample of the product). Only a small amount (8.1 g) of *1*, m.p. 71–73 °C, could be crystallized from the product. The mother liquor was evaporated, the residue was dissolved in dichloromethane (100 ml) and a saturated solution of hydrogen bromide in acetic acid (100 ml) was added. After 1 h more dichloromethane was added and the solution was washed with water and aqueous $NaHCO_3$ and dried. The solution of 2,3-di-*O*-benzoyl-4,6-di-*O*-methyl-α-D-mannopyranosyl bromide thus obtained was stirred overnight with silver benzoate (35 g). Filtration and evaporation gave a syrup which crystallized from methanol after seeding to give 27.0 g (total yield 70 %)

of *1*, m.p. 69–72 °C. Two additional recrystallizations from methanol gave a product with m.p. 71–73 °C, $[\alpha]_D^{20}$ 13.0° (*c* 1.2). Anal. $C_{29}H_{28}O_9$: C, H. ^{13}C NMR data: 91.26 ppm (C1); 69.36 (C2); 72.11 (C3); 73.94 (C4); 73.73 (C5); 70.44 (C6); 60.57 and 59.22 (OMe). J_{C1H1} 176.0 Hz.

*Reaction of 1,2,3-tri-*O*-benzoyl-4,6-di-*O*-methyl-α-*D*-mannopyranose* (*1*) *with anhydrous hydrogen fluoride. For 20 min.* A solution of *1* (1.0 g) in HF (4 ml) was kept at 0 °C for 20 min. Dichloromethane was then added and the mixture was poured on ice. The organic phase was washed with aqueous $NaHCO_3$, dried and evaporated leaving 700 mg (87 %) of crystalline 2,3-di-*O*-benzoyl-4,6-di-*O*-methyl-α-D-mannopyranosyl fluoride (α-*4*) which was almost pure as seen from a ^1H NMR spectrum. Preparative TLC using ether-pentane (3:2) as eluent gave a main fraction which was recrystallized from pentane to give α-*4* with m.p. 79–81 °C, $[\alpha]_D^{20}$ −131.1° (*c* 1.8). Anal. $C_{22}H_{23}FO_7$: C, H. ^1H NMR data: δ 5.71 (H1); 5.69 (H2); 5.6 (H3); 3.6–4.15 (H4, H5, and H6); 3.52 (OMe). J_{1F} 49.0 Hz; J_{12} 1.6 ^{13}C NMR data: J_{C1H1} 183.0; J_{C1F} 222.1; J_{C2F} 40.3.

For 3 days. Treatment of *1* (1.0 g) with HF (4 ml) for 3 days at room temperature and work-up as described above gave 580 mg of product. Preparative TLC (ether-pentane, 3:2) separated the product into 3 fractions. The fast-moving fraction gave 33 mg (4 %) of α-*4*, identical with the product described above as seen from a ^1H NMR spectrum.

The next fraction yielded 193 mg (32 %) of 2-*O*-benzoyl-4,6-di-*O*-methyl-α-D-mannopyranosyl fluoride (α-*7*), which was recrystallized from ether–pentane, m.p. 147–148 °C, $[\alpha]_D^{20}$ −36.3° (*c* 1.5). Anal. $C_{15}H_{19}FO_6$: C, H. ^1H NMR data: δ 5.67 (H1); 5.47 (H2); 4.16 (H3); 3.6–3.9 (H4, H5, and H6); 3.44 and 3.56 (OMe). J_{1F} 49.5 Hz; $J_{2F} \simeq 0.5$; J_{12} 2; J_{23} 3.5; J_{34} 8.7. ^{13}C NMR data: J_{C1H1} 182.5; J_{C1F} 221.0; J_{C2F} 40.0.

Benzoylation with benzoyl chloride in pyridine and recrystallization from pentane gave 66 % of α-*4*, m.p. 79–81 °C.

The third fraction gave 111 mg (19 %) of 3-benzoyl-4,6-di-*O*-methyl-β-D-mannopyranosyl fluoride (β-*7b*) as an unstable syrup. ^1H NMR data: δ 5.56 (H1); 4.28 (H2); 5.28 (H3); 3.5–3.9 (H4, H5, and H6); 3.30 and 3.50 (OMe). J_{1F} 52.8 Hz; J_{2F} 14.6; J_{12} 1.8; J_{23} 3.6; J_{34} 6.4. The spectrum showed that the product contained a small amount of the corresponding 2-*O*-benzoate (β-*7a*).

The product was benzoylated with benzoyl chloride in pyridine in the usual way. The product thus obtained was purified by preparative TLC to give syrupy 2,3-di-*O*-benzoyl-4,6-di-*O*-methyl-β-D-mannopyranosyl fluoride (β-*4*), $[\alpha]_D^{20}$ −82.2° (*c* 2.5). Anal. $C_{22}H_{23}FO_7$: C, H. ^1H NMR data: δ 5.75 (H1); 5.8 (H2); 5.6 (H3); 3.7–4.1 (H4, H5, and H6); 3.41 and 3.53 (OMe). J_{1F} 51.6; J_{2F} 12.9; J_{12} 1.5; J_{23} 3.4; J_{34} 6.9.

*Reaction of 1,2,3-tri-*O*-benzoyl-4,6-di-*O*-methyl-α-*D*-glucopyranose* (*3*) *with anhydrous hydrogen fluoride. For 10 min.* Reaction of *3* (1.0 g) with 4 ml of HF for 10 min at 0 °C as described above gave 775 mg of a product which was separated into two fractions by preparative TLC (ether–pentane 3:2). The fast-moving fraction gave 57 mg (7 %) of di-*O*-benzoyl-4,6-di-*O*-methyl-α-D-glucopyranosyl fluoride (α-*8*), crystallized from pentane, m.p. 91–92 °C, $[\alpha]_D^{20}$ 140.4° (*c* 2.1). Anal $C_{22}H_{23}FO_7$: C, H. ^1H NMR data: δ 5.90 (H1); 5.19 (H2); 5.91 (H3); 3.76 (H4); 4.06 (H5); 3.70 (H6); 3.44 (OMe). J_{1F} 53.5 Hz, J_{2F} 23.7; J_{12} 2.8; J_{23} 10.2; J_{34} 9.0; J_{45} 10.0.

The next fraction yielded 336 mg (42 %) of 2,3-di-*O*-benzoyl-4,6-di-*O*-methyl-β-D-glucopyranosyl fluoride (β-*8*), recrystallized from pentane, m.p. 90–91 °C, $[\alpha]_D^{20}$ 100.5° (*c* 1.9). Anal. $C_{22}H_{23}FO_7$: C, H. ^1H NMR data: δ 5.58 (H1); 5.2–5.9 (H2 and H3); 3.6–3.9 (H4, H5, and H6); 3.43 (OMe), J_{H1F} 53.0; J_{12} 6. ^{13}C NMR data: J_{C1F} 215.5; J_{C2F} 22.8.

For 3 days. A solution of *3* (1.0 g) in HF (4 ml) was kept for 3 days at room temperature. It was then worked up as described above to give 560 mg of a product which was separated into two fractions by preparative TLC (ether–pentane 4:2). The fast-moving fraction gave 250 mg (41 %) of α-*7a*, m.p. 145–146 °C. An NMR spectrum was identical with that described above. On benzoylation it yielded α-*4*.

The second fraction gave 160 mg (27 %) of β-*7b*, which on benzoylation yielded β-*4*. Both products were identified through their ^1H NMR spectra, which were identical with those of the products described above.

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