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Reaction of Sugar Esters with Hydrogen Fluoride

VI. Tetra-*O*-benzoyl-2-*O*-methyl-D-glucopyranose

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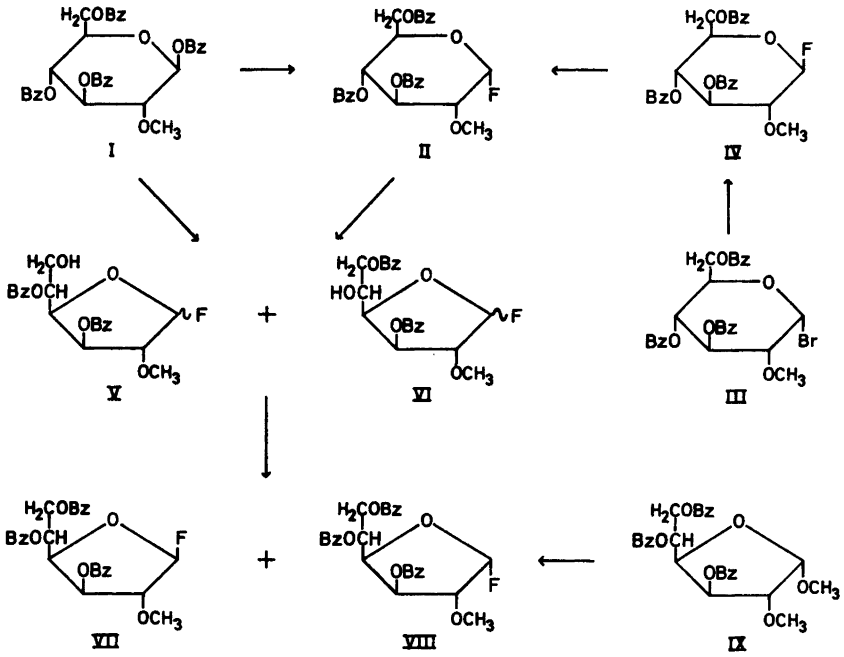
Brief treatment of tetra-*O*-benzoyl-2-*O*-methyl-D-glucopyranose with anhydrous hydrogen fluoride gives tri-*O*-benzoyl-2-*O*-methyl-α-D-glucopyranosyl fluoride. Prolonged treatment with hydrogen fluoride gives a lower yield of the α-pyranosyl fluoride and, in addition, a mixture of the anomeric tri-*O*-benzoyl-2-*O*-methyl-D-glucofuranosyl fluorides is formed. The structures of the latter two compounds were proved by their preparation from the reaction of methyl tri-*O*-benzoyl-2-*O*-methyl-α-D-glucofuranoside with hydrogen fluoride. Thus treatment of tetra-*O*-benzoyl-2-*O*-methyl-D-glucopyranose with hydrogen fluoride causes ring contraction, but no Walden inversion was observed.

In a previous paper of this series [1] it was shown that prolonged treatment of tetra-*O*-benzoyl-3-*O*-methyl-D-glucopyranose with anhydrous hydrogen fluoride did not lead to Walden inversion, presumably because the 3-*O*-methyl group prevents the formation of cyclic carbonium ions which are believed to be intermediates in the rearrangement reactions which a number of sugar esters will undergo when treated with hydrogen fluoride.[2,3]

On basis of the mechanisms which have been proposed for the rearrangement of sugar esters with hydrogen fluoride [2,3] it would also be expected that an acylated 2-*O*-methyl-D-glucopyranose should not undergo Walden inversion by treatment with hydrogen fluoride, provided that the 2-*O*-methyl group is unaffected by hydrogen fluoride. This has been investigated, as described in the present paper, by a study of the reaction of tetra-*O*-benzoyl-2-*O*-methyl-D-glucopyranose with anhydrous hydrogen fluoride.

Brief treatment of tetra-*O*-benzoyl-2-*O*-methyl-β-D-glucopyranose (I) with anhydrous hydrogen fluoride gave tri-*O*-benzoyl-2-*O*-methyl-α-D-glucopyranosyl fluoride (II) in 81 % yield. A similar treatment of tetra-*O*-benzoyl-2-*O*-methyl-α-D-glucopyranose gave the same fluoride in 65 % yield. The anomeric tri-*O*-benzoyl-2-*O*-methyl-β-D-glucopyranosyl fluoride (IV) could not be detected in the reaction mixture; but it was prepared by treatment of the crude bromide [4] (III) with silver fluoride in acetonitrile. When the β-fluoride (IV) was treated with hydrogen fluoride for 10 min it was anomerized to the α-fluoride (II).



The ready conversion of the β-fluoride to the α-fluoride indicates that the latter is the more stable of the two anomers, as generally found for α-D-hexopyranosyl halides,[5] and it explains why the β-fluoride (IV) is not found in the reaction products obtained by treatment of the tetrabenzoates with hydrogen fluoride.

The anomeric structure of the two fluorides was shown through their rotation, the α-fluoride (II) being the more dextrorotatory, and through their NMR spectra. The 60 Mc spectra of both compounds showed the signal for H_1 as two doublets separated by *ca.* 52 cps due to coupling with fluorine.[6] The spacing of these doublets ($J_{H_1H_2}$) was 2.7 cps for the α-fluoride and 5.9 cps for the β-fluoride showing that H_1 and H_2 are *trans*-diaxially arranged in the β-fluoride as would be expected for this compound in the C-1 conformation.

When tetra-*O*-benzoyl-2-*O*-methyl-β-D-glucopyranose (I) was treated with hydrogen fluoride for 24 h a product was obtained from which the α-fluoride (II) could be isolated in 42 % yield only. The material in the mother liquor was separated by column chromatography into three fractions. The fast running fraction gave a small quantity of α-fluoride; besides, it was shown by NMR spectroscopy to contain tri-*O*-benzoyl-2-*O*-methyl-β-D-glucofuranosyl fluoride (VII). NMR spectra of the two slower running fractions showed that they consisted of compounds containing only two benzoyl groups. Although the two fractions were not quite pure their NMR spectra indicated that they were 3,5-di-*O*-benzoyl- (V) and 3,6-di-*O*-benzoyl-2-*O*-methyl-D-glucofuranosyl fluoride (VI) (see experimental section). These two fractions were combined

and benzoylated and the resulting product together with the first fraction was chromatographed to give two pure compounds which were shown to be tri-*O*-benzoyl-2-*O*-methyl-β-D-glucofuranosyl fluoride (VII) and the corresponding α-anomer (VIII). The yield of (VII) was 19 % whereas only 3.8 % of (VIII) was obtained.

The structures of the two furanosyl fluorides (VII) and (VIII) were proved by their preparation from methyl tri-*O*-benzoyl-2-*O*-methyl-α-D-glucofuranoside (IX). Treatment of this compound with anhydrous hydrogen fluoride for 30 min gave a mixture from which was isolated a 33 % yield of (VII) and a 15 % yield of (VIII). Since brief treatment of sugar esters with hydrogen fluoride usually gives the corresponding glycosyl fluorides without rearrangement taking place this method for the preparation of (VII) and (VIII) is considered to be proof of their structures, which were further confirmed by NMR spectroscopy (see experimental section.)

Prolonged reaction of tetra-*O*-benzoyl-2-*O*-methyl-α-D-glucopyranose or the α-pyranosyl fluoride (II) with hydrogen fluoride gave the same products as those obtained from (I).

Thus, as predicted, prolonged treatment of tetra-*O*-benzoyl-2-*O*-methyl-D-glucopyranose with hydrogen fluoride does not lead to Walden inversion, at least not to a detectable extent. However, a transformation from the glucopyranose to the glucofuranose series took place by this reaction as shown by the isolation of the anomeric tri-*O*-benzoyl-2-*O*-methyl-D-glucofuranosyl fluorides.

The transformation of pyranose to furanose derivatives has been observed previously in the reaction of ribopyranose and lyxopyranose tetrabenzoates with hydrogen fluoride.[3,7] The mechanism of this type of ring contraction is as yet unknown. It may be noted that the treatment of penta-*O*-acetyl-D-glucopyranose [8] or tetra-*O*-benzoyl-3-*O*-methyl-D-glucopyranose [1] with hydrogen fluoride did not lead to the formation of detectable amounts of furanose derivatives.

2-*O*-Methyl-D-glucose was prepared by the method of Hodge and Rist [9] from tri-*O*-acetyl-2-*O*-methyl-D-glucopyranosyl piperidine. An improvement was made in this preparation as it was found that the latter compound could be hydrolysed to 2-*O*-methyl-D-glucose with 1 N sulphuric acid in one step giving 77 % yield.

Methyl tri-*O*-benzoyl-2-*O*-methyl-α-D-glucofuranoside (IX) was prepared by methylation of 3,5,6-tri-*O*-benzoyl-D-glucofuranose.[10] Chromatography on a column of silica gel gave a product which was shown by NMR spectroscopy to be pure α-anomer.

EXPERIMENTAL

Melting points are uncorrected. Thin layer chromatography was done on silica gel HF_{254} ("Merck"). Spots were detected under UV light. For column chromatography was used silica gel ("Merck", 0.05—0.2 mm). The NMR spectra were determined with a Varian A60 spectrometer using deuterochloroform as solvent and tetramethylsilane as internal standard. Chemical shifts are reported in δ values.

2-O-Methyl-D-glucose. Tri-*O*-acetyl-2-*O*-methyl-D-glucopyranosyl piperidine [9] was boiled with 250 ml of 1 N sulphuric acid for 3 h. The solution was then neutralized with barium carbonate and the filtrate was deionized by passage through Amberlite IR—120

and IR—4B. The deionized solution was evaporated to dryness and the residue was crystallized from ethanol (50 ml) to give 9.2 g (77 %) of 2-*O*-methyl-D-glucose, m.p. 154—156°. A sample was recrystallized from methanol, m.p. 157—158°, $[\alpha]_D^{22} = +66.5°$ (3^{15} h) (*c* 2.1, H_2O) (reported [9] m.p. 160°, $[\alpha]_D = 66°$ (7 h)).

Benzoylation of 2-O-methyl-D-glucose. A mixture of pyridine (50 ml) and benzoyl chloride (20 ml) was cooled in ice and stirred while 2-*O*-methyl-D-glucose (4.9 g) was added in the course of 1 h. The mixture was then stirred over night at room temperature. Methylene chloride (100 ml) was added and the solution was washed with 3 N sulphuric acid, saturated aqueous sodium hydrogen carbonate and water. The solution was dried and the solvent was evaporated. The residue was crystallized from ethanol (400 ml) to give 8.0 g of a product with m.p. 162—166°. Recrystallization from ethanol gave 7.3 g (47 %) of tetra-*O*-benzoyl-2-*O*-methyl-β-D-glucopyranose as prismatic crystals, m.p. 166—167°, $[\alpha]_D^{26} = -8.3°$ (*c* 2.0, $CHCl_3$) (reported [11] m.p. 176—177°, $[\alpha]_D = -7.0°$).

The mother liquor from the first crystallization was evaporated and the residue was put on a column of alumina (150 g, "Fluka" grade II, pH 6.5). Elution with benzene (300 ml) gave 2.47 g of material which was recrystallized from ethanol to give 2.40 g (15 %) of tetra-*O*-benzoyl-2-*O*-methyl-α-D-glucopyranose as thin needles, m.p. 155—156°, $[\alpha]_D^{26} = +66.3°$ (*c* 1.2, $CHCl_3$) (reported [11] m.p. 157—158°, $[\alpha]_D = +55.9°$).

When 2-*O*-methyl-D-glucose was heated with pyridine prior to benzoylation the same proportion of anomers was obtained.

Methyl tri-O-benzoyl-2-O-methyl-α-D-glucofuranoside. The crystalline carbon tetrachloride addition compound of 3,5,6-tri-*O*-benzoyl-D-glucose [10] (9.1 g) was freed of carbon tetrachloride by several evaporations with benzene. The syrupy residue was dissolved in a mixture of dimethyl formamide (20 ml) and methyl iodide (20 ml) and freshly prepared moist silver oxide (from 35 g of silver nitrate) was added. The mixture was stirred over night at room temperature and then filtered; the solid was washed several times with methylene chloride. The filtrate was washed with water, dried and evaporated leaving 6.3 g of a syrup which on thin layer chromatography gave one large spot and several smaller ones. The syrup was put on a column of silica gel (400 g) and eluted with benzene-ether (8:2). The fraction containing the main component was collected and the solvent was evaporated giving 4.3 g (59 %) of methyl tri-*O*-benzoyl--2-*O*-methyl-α-D-glucofuranoside as a colourless syrup, $[\alpha]_D^{23} = -50.1°$ (*c* 2.6, $CHCl_3$). (Found: C 66.49; H 5.41. Calc. for $C_{29}H_{28}O_9$:C 66.92; H 5.42).

The NMR spectrum showed the methyl groups as two sharp signals at δ 3.50 and 3.53. The signal for H_1 was found as a doublet at δ 5.18 with a spacing of 4.2 cps; a triplet at δ 4.08 was assigned to H_2. A complex signal at δ 5.60—5.95 with intensity 2 was assigned to H_3 and H_5 and another group of signals at 4.5—5.0 with intensity 3 was assigned to H_4 and H_6. A $J_{1,2}$ value of 4.2 cps indicates that H_1 and H_2 are *cis* and thus that the compound is the α-anomer.[12,13] The assignments were verified by spin-decoupling experiments which also gave the following approximate coupling constants: $J_{2,3} = 3.7$ and $J_{3,4} = 5.0$ cps.

Tri-O-benzoyl-2-O-methyl-α-D-glucopyranosyl fluoride. Tetra-*O*-benzoyl-2-*O*-methyl-β-D-glucopyranose (1.0 g) was dissolved in 2 ml of anhydrous hydrogen fluoride and the solution was kept at room temperature for 20 min. Methylene chloride was then added and the mixture was poured into ice-water; the organic layer was washed with aqueous sodium hydrogen carbonate and water and dried. Evaporation of the solvent gave 750 mg of residue which crystallized from ether-pentane, yield 680 mg (81 %), m.p. 150—151°. Recrystallization from ether-pentane gave pure tri-*O*-benzoyl-2-*O*-methyl-α-D-glucopyranosyl fluoride, m.p. 153—154°, $[\alpha]_D^{25} = +39.6°$ (*c* 1.4, $CHCl_3$). (Found: C 66.05; H 4.98. Calc. for $C_{28}H_{25}O_8F$: C 66.13; H 4.96).

When tetra-*O*-benzoyl-2-*O*-methyl-α-D-glucopyranose was treated with hydrogen fluoride in the same manner a 65 % yield of α-fluoride was obtained.

Tri-O-benzoyl-2-O-methyl-β-D-glucopyranosyl fluoride. Tetra-*O*-benzoyl-2-*O*-methyl-β-D-glucopyranose (2.0 g) was dissolved in a mixture of methylene chloride (10 ml) and glacial acetic acid containing 30 % hydrogen bromide (10 ml). The solution was kept at room temperature for 3 h. Methylene chloride (25 ml) was then added and the solution was washed with aqueous sodium hydrogen carbonate and water and dried. Removal of the solvent left a crude, syrupy tri-*O*-benzoyl-2-*O*-methyl-α-D-glucopyranosyl bromide [4] which was dissolved in acetonitrile (15 ml) and stirred with silver fluoride (5.0 g) for 1 h. The silver salts were filtered off and the acetonitrile was evaporated.

The residue was dissolved in methylene chloride and washed with water and the solution was dried and the solvent evaporated. The residue was crystallized from methylene chloride – pentane giving 1.25 g (75 %) of tri-*O*-benzoyl-2-*O*-methyl-β-D-glucopyranosyl fluoride, m.p. 179–181°. Recrystallization from methylene chloride-pentane gave the pure product, m.p. 180–182°, $[\alpha]_D^{20} = -12.8°$ (*c* 2.4, $CHCl_3$). (Found: C 65.90; H 5.20).

The β-fluoride (500 mg) was dissolved in hydrogen fluoride (1 ml) and the solution was kept at room temperature for 10 min. It was then worked up as described above and the product was crystallized from ether-pentane yielding 300 mg (60 %) of tri-*O*-benzoyl-2-*O*-methyl-α-D-glucopyranosyl fluoride, m.p. 148–149°. The NMR spectrum was identical with that of the product described above.

*Tri-*O*-benzoyl-2-*O*-methyl-α-and β-D-glucofuranosyl fluoride.* Methyl tri-*O*-benzoyl-2--*O*-methyl-α-D-glucofuranoside (1.4 g) was dissolved in anhydrous hydrogen fluoride (3 ml) at 0° and the solution was kept for 30 min. It was then worked up as described above yielding 1.0 g of a syrup which on thin layer chromatography gave two spots. The two compounds were separated by chromatography on a column of silica gel (150 g) using ether-pentane (1:1) as eluant.

Removal of the solvent from the fast moving fraction gave 450 mg (33 %) of almost pure tri-*O*-benzoyl-2-*O*-methyl-β-D-glucofuranosyl fluoride. Rechromatography on a column of silica gel with benzene as eluant gave the pure product as a colourless syrup. $[\alpha]_D^{23} = -139°$ (*c* 1.3, $CHCl_3$). (Found: C 65.83; H 5.19. Calc. for $C_{28}H_{25}O_8F$: C 66.13; H 4.96).

The NMR spectrum showed H_1 as a doublet with a spacing of 62.5 cps centered at δ 5.87. Thus J_{F,H_1} is 62.5 cps and J_{H_1,H_2} is $\simeq 0$, the latter indicating that H_1 and H_2 are *trans* and that the compound is the β-anomer.[12,13] A doublet at δ 4.13 is assigned to H_2; the spacing of this doublet is 5.5 cps and it probably represents J_{F,H_2}. H_3 and H_5 gave a complex signal at δ 5.7–6.1 and the signals for H_4 and H_6 were found at 4.6–5.3. The methyl group gave a sharp singlet at 3.62.

Removal of the solvent from the slower moving fraction gave 200 mg (15 %) of tri-*O*-benzoyl-2-*O*-methyl-α-D-glucofuranosyl fluoride. Rechromatography on silica gel using benzene as eluant gave 180 mg of pure product as a colourless syrup, $[\alpha]_D^{23} = 74.2°$ (*c* 0.8, $CHCl_3$). (Found: C 65.54; H 5.03). NMR showed H_1 as two doublets the centers of which were separated by 62.8 cps (J_{F,H_1}); the spacing of each doublet was 3.8 cps representing J_{H_1,H_2}. The chemical shift of H_1 was found to be 5.98. A coupling constant of 3.8 indicates that H_1 and H_2 are *cis* and that the compound is the α-anomer.[12,13] H_2 gave a complex signal centered at δ 4.2 and the methyl group gave a sharp singlet at 3.53.

*Reaction of tetra-*O*-benzoyl-2-*O*-methyl-β-D-glucopyranose with anhydrous hydrogen fluoride for 24 h.* The tetrabenzoate (2.0 g) was dissolved in hydrogen fluoride (4 ml) and the solution was kept at room temperature for 24 h. It was then worked up as described above yielding 1.45 g of a syrup which by crystallization from ether-pentane gave 650 mg of tri-*O*-benzoyl-2-*O*-methyl-α-D-glucopyranosyl fluoride, m.p. 148–150°. The material in the mother liquor gave largely three spots on thin layer chromatography with benzene-ether (8:2) as eluant and by chromatography on a column of silica gel (100 g) it was separated into the corresponding three fractions.

Removal of the solvent from fraction I (with the highest R_F-value) gave 135 mg of syrup which from ether-pentane deposited 50 mg of tri-*O*-benzoyl-2-*O*-methyl-α-D-glucopyranosyl fluoride, m.p. 148–150°, bringing the total yield of this compound to 700 mg (42 %). An NMR spectrum of the remaining material showed that it consisted mainly of tri-*O*-benzoyl-2-*O*-methyl-β-D-glucofuranosyl fluoride (VII).

Fraction II gave 240 mg of a syrup which could not be induced to crystallize. An NMR spectrum of this fraction showed that it contained two benzoyl groups and a hydroxyl group which gave a broad signal at δ 2.95. The spectrum resembled that of (VII) with the difference that the signal for H_5, which in (VII) is found as a complex group of peaks at *ca.* 5.9, is shifted upfield to *ca.* 4.6 where a group of signals with intensity 4 is found (H_4, H_5, and H_6). H_2 gave a doublet at 5.68. On the basis of the NMR spectrum this fraction, although not quite homogeneous, is believed to consist mainly of 3,6-di-*O*-benzoyl-2-*O*-methyl-β-D-glucofuranosyl fluoride (VI).

Fraction III (with the lowest R_F-value) gave 238 mg of syrup. The NMR spectrum of this compound was also similar to that of (VII), but only two benzoyl groups were

present and a broad signal at δ 2.25 was ascribed to a hydroxyl proton. Besides, a group of signals with intensity 2, which are found at 4.8—5.1 in the spectrum of (VII), has moved upfield to *ca.* 4.0. On this basis the main compound in this fraction is believed to be 3,5-di-*O*-benzoyl-2-*O*-methyl-β-D-glucofuranosyl fluoride (V).

Fractions II and III were combined and benzoylated with benzoyl chloride in pyridine and the product (700 mg) was mixed with fraction I and chromatographed on a column of silica gel (100 g) using ether-pentane (1:1) as eluant. The first fraction collected from the column gave 313 mg (19 %) of almost pure tri-*O*-benzoyl-2-*O*-methyl-β-D-glucofuranosyl fluoride (VII). The product was further purified by preparative thin layer chromatography on silica gel PF_{254} (Merck), $[\alpha]_D^{24} = -137°$ (*c* 2.0, $CHCl_3$). Infrared and NMR spectra proved its identity with the product described above.

After an intermediate fraction a third fraction (113 mg) was collected. When dissolved in ether it yielded a small amount of crystalline (II). The non crystalline material was purified by preparative thin layer chromatography on silica gel PF_{254} using ether-pentane (1:1) as eluant. This gave pure tri-*O*-benzoyl-2-*O*-methyl-α-D-glucofuranosyl fluoride (VIII), 63 mg (3.8 %), $[\alpha]_D^{24} = -73.0°$ (*c* 0.5, $CHCl_3$). Infrared and NMR spectra proved its identity with the product described above.

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