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Reaction of Sugar Esters with Hydrogen Fluoride

V. Tetra-*O*-benzoyl-3-*O*-methyl-D-glucopyranose

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Brief treatment of tetra-*O*-benzoyl-3-*O*-methyl-α- or β-D-glucopyranose with anhydrous hydrogen fluoride gives a mixture of the anomeric tri-*O*-benzoyl-3-*O*-methyl-D-glucopyranosyl fluorides together with a small amount of 2,4,6-tri-*O*-benzoyl-3-*O*-methyl-D-glucopyranose. Prolonged treatment with hydrogen fluoride gives the same products, and it thus appears that the 3-*O*-methyl group prevents rearrangement at the 2-position.

A number of sugar esters have been shown to undergo Walden inversion when treated with anhydrous hydrogen fluoride. The mechanisms which have been proposed to explain this rearrangement require either that the acyloxygroups at C_2 and C_3 have a *trans* configuration [1] or that three acyloxygroups in a contiguous *cis-trans* sequence are present.[2,3] In both cases it is assumed that cyclic carbonium ions are intermediates in the reaction.

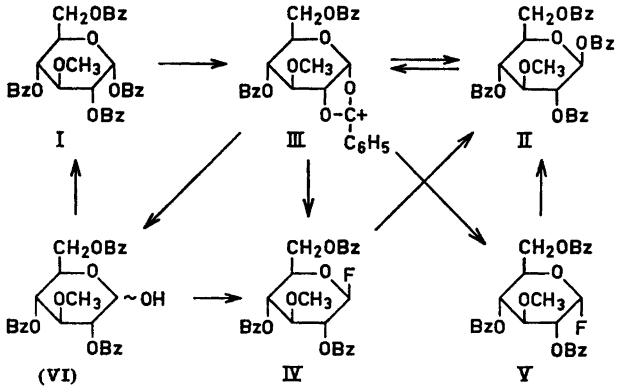
In order to check the validity of the mechanisms proposed it would be of interest to study the behaviour of various *O*-methylated sugar esters towards hydrogen fluoride. Hedgley and Fletcher [4] have shown that the pentaacetate of 5-*O*-methyl-D-inositol undergoes Walden inversion and deacetylation by treatment with hydrogen fluoride without any effect on the *O*-methyl group. Klemer and Ridder [6] prepared a number of *O*-methylated glucopyranosyl fluorides by treatment of the corresponding acetates with hydrogen fluoride. It may therefore be safe to assume that *O*-methyl groups are unaffected by hydrogen fluoride.

In the present paper the reaction of tetra-*O*-benzoyl-3-*O*-methyl-D-glucopyranose with anhydrous hydrogen fluoride has been studied. Since the 3-*O*-methyl group should prevent formation of a cyclic carbonium ion between C_2 and C_3 no Walden inversion is expected to take place on prolonged treatment with hydrogen fluoride.

The anomeric tetra-*O*-benzoyl-3-*O*-methyl-D-glucopyranoses were prepared by benzoylation of 3-*O*-methyl-α-D-glucopyranose in pyridine. Benzoylation at low temperature gave a mixture in which the α-anomer predominated.

When 3-*O*-methyl-α-D-glucopyranose was heated in pyridine prior to benzoylation a mixture was obtained which contained equal amounts of the two anomers.

Treatment of tetra-*O*-benzoyl-3-*O*-methyl-α-D-glucopyranose (I) with hydrogen fluoride for 15 min at −10° followed by removal of excess hydrogen



fluoride by washing with aqueous sodium hydrogen carbonate gave a product from which was crystallised tri-*O*-benzoyl-3-*O*-methyl-β-D-glucopyranosyl fluoride (IV) in *ca.* 40 % yield. Chromatography of the crude product on a column of silica gel gave the β-fluoride in 33 % yield and, besides, 4.8 % of 2,4,6-tri-*O*-benzoyl-3-*O*-methyl-D-glucopyranose (VI) was isolated. In a separate experiment the β-fluoride was isolated by crystallisation and the mother liquor was chromatographed on a column of alumina. This gave 9 % of the tribenzoate (VI) and, besides, a 6.7 % yield of tri-*O*-benzoyl-3-*O*-methyl-α-D-glucopyranosyl fluoride (V) was obtained.

It was found that when the β-fluoride (IV) was chromatographed on alumina it was more or less completely hydrolysed to 2,4,6-tri-*O*-benzoyl-3-*O*-methyl-D-glucopyranose (VI). In one experiment a sample of pure β-fluoride was put on a column of alumina and left for 24 h. When the column was eluted a 57 % yield of the tribenzoate (VI) was obtained, no fluoride was found. The α-fluoride (V) was hydrolysed to a smaller exent by alumina. Chromatography on silica gel did not cause hydrolysis of the β-fluoride. The two anomeric fluorides have very similar solubilities and the α-fluoride could not be isolated from the reaction product by crystallisation or by chromatography on silica gel; but the fact that the β-fluoride is hydrolysed by chromatography on alumina made it possible to obtain the α-fluoride in a pure state.

The anomeric structure of the two fluorides is postulated on the basis of their rotation. The easy hydrolysis of the β-fluoride is in agreement with the behaviour of β-glucosyl halides.[6] Reaction of the β-fluoride (IV) with calcium benzoate in melted benzoic acid gave a 58 % yield of tetra-*O*-benzoyl-3-*O*-methyl-β-D-glucopyranose (II). By the same procedure the less reactive α-fluoride (V) gave a 25 % yield of (II).

The structure of 2,4,6-tri-*O*-benzoyl-3-*O*-methyl-D-glucopyranose (VI) was established by benzoylation in pyridine at low temperature. This gave 75 % of tetra-*O*-benzoyl-3-*O*-methyl-α-D-glucopyranose (I), indicating that (VI) is the α-anomer. Furthermore, treatment of (VI) with hydrogen fluoride gave a 50 % yield of tri-*O*-benzoyl-3-*O*-methyl-β-D-glucopyranosyl fluoride (IV). The latter experiment shows that (VI) has a free hydroxygroup at C_1.

Treatment of tetra-*O*-benzoyl-3-*O*-methyl-β-D-glucopyranose (II) with hydrogen fluoride as described above gave 60 % of the β-fluoride (IV). Thin layer chromatography of the material in the mother liquor indicated that the same compounds were present as those obtained from the α-tetrabenzoate (I).

When tetra-*O*-benzoyl-3-*O*-methyl-α-D-glucopyranose (I) was treated with hydrogen fluoride for 20 h followed by removal of excess hydrogen fluoride by washing with sodium hydrogen carbonate a product was obtained which had almost the same composition as the mixture resulting from brief treatment with hydrogen fluoride.

In previous papers it was shown that removal of hydrogen fluoride by evaporation with dry air could lead to products different from those obtained when hydrogen fluoride was removed by direct washing.[1,3] When tetra-*O*-benzoyl-3-*O*-methyl-α-D-glucopyranose (I) was treated briefly with hydrogen fluoride followed by evaporation with air a mixture was obtained from which a small amount (5 %) of tetra-*O*-benzoyl-3-*O*-methyl-β-D-glucopyranose (II) was isolated. Chromatography on silica gel gave a 6 % yield of tri-*O*-benzoyl-3-*O*-methyl-D-glucopyranose (VI) and a large fraction from which no pure product could be obtained. This fraction was chromatographed on alumina giving a 19 % yield of α-fluoride (V) and 17 % of the tribenzoate (VI). The latter compound is assumed to arise from hydrolysis of the β-fluoride (IV) which has not been isolated in a pure state from this product.

Prolonged treatment of the α-tetrabenzoate (I) with hydrogen fluoride followed by evaporation with dry air gave the same products as those obtained after brief treatment with hydrogen fluoride.

Thus, as expected, prolonged treatment of tetra-*O*-benzoyl-3-*O*-methyl-D-glucopyranose with hydrogen fluoride does not lead to Walden inversion.

The first step in the reaction of the tetrabenzoates (I and II) with hydrogen fluoride is probably the formation of a cyclic carbonium ion (III) and it seems likely that (III) is stable in the presence of excess hydrogen fluoride in which it will be highly solvated. When the reaction mixture is washed, (III) may react with fluoride ions to give the anomeric fluorides (IV) and (V). The fact that prolonged treatment with hydrogen fluoride gives the same ratio of α- to β-fluorides as brief treatment indicates that the two fluorides are not formed until the reaction mixture is worked up since the β-fluoride would be expected to rearrange to the more stable α-fluoride by prolonged exposure to hydrogen fluoride.

The tribenzoate (VI) may be formed by reaction of (III) with water or by hydrolysis of the β-fluoride. Small amounts of water in the hydrogen fluoride could also account for the formation of (VI). However, an experiment in which the α-tetrabenzoate (I) was treated with hydrogen fluoride containing 10 % water did not give an increased amount of (VI) which therefore must be formed when the reaction mixture is worked up.

The β-tetrabenzoate (II) which is formed in small amounts when hydrogen fluoride is removed with dry air can arise from the reaction of (III) with benzoic acid.

EXPERIMENTAL

Melting points are uncorrected. The purity of all products was checked by thin layer chromatography on silica gel H using benzene – 10 % acetone as solvent. Spots were detected with iodine vapor. The identity of all products was established by infrared spectra and mixed melting points.

Benzoylation of 3-O-methyl-α-D-glucopyranose. 3-*O*-Methyl-α-D-glucopyranose (20.0 g) was added in portions to a cooled and stirred mixture of pyridine (250 ml) and benzoyl chloride (72 ml), the temperature being kept between + 5 and + 10°. The mixture was stirred for an additional 2 h and kept at + 5° over night. Water was then added and the syrupy precipitate was extracted with chloroform. The chloroform solution was washed successively with 3 N sulphuric acid, saturated sodium hydrogen carbonate and water. Evaporation of the chloroform left a syrup which from ethanol (1 l) deposited 56.5 g of crystals. The product was extracted several times with boiling ether leaving an insoluble material. The ether was evaporated and the residue was recrystallised twice from ethanol yielding 34.0 g (54 %) of tetra-*O*-benzoyl-3-*O*-methyl-α-D-glucopyranose, m.p. 136 – 137°. $[\alpha]_D^{23} = + 113°$ (*c* 1.0, $CHCl_3$). (Found: C 68.65; H 4.88. Calc. for $C_{35}H_{30}O_{10}$: C 68.87; H 4.95).

The ether insoluble material by recrystallisation from methylene chloride-pentane gave 15.5 g (24 %) of tetra-*O*-benzoyl-3-*O*-methyl-β-D-glucopyranose, m.p. 197 – 198°. One additional recrystallisation from ethyl acetate gave the pure product, m.p. 198 – 199°, $[\alpha]_D^{20} = + 3.4°$ (*c* 3.2, $CHCl_3$), in accord with the values recorded by Oldham.[7] (Found: C 68.55; H 4.93).

In another experiment 3-*O*-methyl-α-D-glucopyranose was dissolved in boiling pyridine and the solution was heated for 30 min. Benzoylation as described above gave 37 % of the α-anomer and 34 % of the β-anomer.

Reaction of α-tetrabenzoate with hydrogen fluoride for 15 min. HF removed by washing. Tetra-*O*-benzoyl-3-*O*-methyl-α-D-glucopyranose (2.0 g) was dissolved in anhydrous hydrogen fluoride (4 ml) and the solution was kept at – 10° for 15 min. Methylene chloride was then added and the mixture was poured into saturated sodium hydrogen carbonate; the organic phase was washed with sodium hydrogen carbonate and water and dried. Evaporation of the solvent left 1.6 g of crude product. Crystallisation from ether followed by two recrystallisations from ethanol gave 700 mg (42 %) of tri-*O*-benzoyl-3-*O*-methyl-β-D-glucopyranosyl fluoride, m.p. 118 – 120°, $[\alpha]_D^{22} = + 51.8°$ (*c* 0.81, $CHCl_3$). After two additional recrystallisations from ether the product had m.p. 121 – 123°, $[\alpha]_D^{25} = + 51.9°$ (*c* 0.82, $CHCl_3$). (Found: C 66.22; H 5.23. Calc. for $C_{28}H_{25}O_8F$: C 66.13; H 4.96).

The combined mother liquors were evaporated and the residue was put on a column of alumina (100 g, "Fluka" grade II, pH 6.5). Elution with benzene gave 283 mg of a mixture from which no pure compound could be isolated. Elution with benzene-ether (1:1) gave 156 mg of material which by crystallisation from ethanol gave 110 mg (6.7 %) of tri-*O*-benzoyl-3-*O*-methyl-α-D-glucopyranosyl fluoride, m.p. 120 – 121°. An additional recrystallisation from ether-pentane did not change the melting point, $[\alpha]_D^{25} = + 104°$ (*c* 0.34, $CHCl_3$). (Found: 66.25; H 4.98). Elution of the column with ether-methanol (19:1) gave 190 mg of product which by crystallisation from methylene chloride-pentane gave 150 mg (9 %) of 2,4,6-tri-*O*-benzoyl-3-*O*-methyl-D-glucopyranose, m.p. 180 – 182°. Recrystallisation from ethanol did not change the melting point, $[\alpha]_D^{20} = + 93.6°$ (*c* 0.55, $CHCl_3$). (Found: C 66.45; H 5.44. Calc. for $C_{28}H_{26}O_9$: C 66.39; H 5.17).

In another experiment the crude product obtained from 2.0 g of tetrabenzoate was put on a column of silica gel (200 g, "Merck"). Elution of the column with benzene-ether (19:1) gave 1.37 g of material which after several recrystallisations from ether and ethanol yielded 550 mg (33 %) of β-fluoride, m.p. 117 – 119°. Elution with benzene-ether (1:1) gave 200 mg of product which by recrystallisation from methylene chloride-pentane gave 80 mg (4.8 %) of 2,4,6-tri-*O*-benzoyl-3-*O*-methyl-D-glucopyranose, m.p. 180 – 182°.

Reaction of β-tetrabenzoate with HF for 15 min. The β-tetrabenzoate (2.0 g) was treated with hydrogen fluoride as described above. Crystallisation from ether gave 950 mg

(57 %) of the β-fluoride, m.p. 120—122°, $[\alpha]_D^{25} = 54.5°$ (*c* 1.0, $CHCl_3$). Thin layer chromatography of the mother liquor gave spots corresponding to α- and β-fluorides and the tribenzoate.

Reaction of α-tetrabenzoate with HF containing 10 % water. The α-tetrabenzoate (1.0 g) was dissolved in 4 ml of hydrogen fluoride which contained *ca.* 10 % water. The solution was kept for 20 min at room temperature and was then worked up as described above. Thin layer chromatography of the product showed a large spot corresponding to a mixture of α- and β-fluoride. Only traces of the tribenzoate were present. Crystallisation from ether-pentane gave 350 mg (42 %) of β-fluoride, m.p. 117—119°.

Reaction of α-tetrabenzoate with HF for 20 h. HF removed by washing. Tetra-*O*-benzoyl-3-*O*-methyl-α-D-glucopyranose (5.0 g) was dissolved in hydrogen fluoride (10 ml) and the solution was kept at room temperature for 20 h. The mixture was worked up as described above. Crystallisation from ether and ethanol gave 1.50 g (36 %) β-fluoride, m.p. 117—119°, $[\alpha]_D^{25} = +51.5°$ (*c* 1.09, $CHCl_3$). The mother liquor was chromatographed on alumina as described above and gave 160 mg (3.8 %) α-fluoride, m.p. 116—118°, $[\alpha]_D^{22} = +101°$ (*c* 0.53, $CHCl_3$) and 170 mg (4 %) 2,4,6-tri-*O*-benzoyl-3-*O*-methyl-D-glucopyranose, m.p. 180—182°.

In a separate experiment the crude product from 1.0 g of α-tetrabenzoate was chromatographed on a column of silica gel giving 350 mg (42 %) β-fluoride, m.p. 117—119° and 23 mg (2.8 %) of the tribenzoate, m.p. 180—182°.

Brief treatment of α-tetrabenzoate with HF. HF evaporated with air. The α-tetrabenzoate (2.0 g) was dissolved in hydrogen fluoride (4.0 ml) at room temperature and evaporation with a stream of dry air was started at once. After *ca.* 10 min when most of the hydrogen fluoride was evaporated methylene chloride (10 ml) was added and again evaporated with air. The residue was dissolved in methylene chloride and the solution was washed with sodium hydrogen carbonate and water and dried. Evaporation of the solvent gave 1.7 g of material which from ether (20 ml) gave 100 mg (5 %) of tetra-*O*-benzoyl-3-*O*-methyl-β-D-glucopyranose, m.p. 195—197°. The mother liquor was put on a column of silica gel (200 g). Elution with benzene-ether (19:1) gave 1.33 g of a mixture of α- and β-fluorides; none of the two compounds could be obtained in a pure state. Elution with benzene-ether (1:1) gave 130 mg which by crystallisation from methylene chloride-pentane yielded 100 mg (6 %) of tribenzoate, m.p. 180—182°.

The mixture of α- and β-fluoride (1.33 g) was put on a column of alumina (100 g) and left over night. The column was eluted with benzene-ether (1:1) and the material, thus obtained was crystallised from ether-pentane yielding 320 mg (19 %) of α-fluoride, m.p. 117—118°, $[\alpha]_D^{22} = +100°$ (*c* 0.45, $CHCl_3$). Further elution of the column with ether-methanol (9:1) gave 280 mg (17 %) of the tribenzoate, m.p. 179—181°.

Reaction of α-tetrabenzoate with HF for 20 h. HF removed with air. When the α-tetrabenzoate was kept in hydrogen fluoride for 20 h at room temperature and then worked up by evaporation of the hydrogen fluoride with dry air as described above, a mixture was obtained which gave the same products in very nearly the same yield as those obtained after brief treatment with hydrogen fluoride.

Chromatography of pure fluorides. Tri-*O*-benzoyl-3-*O*-methyl-β-D-glucopyranosyl, fluoride (700 mg) was dissolved in benzene and put on a column of alumina (45 g, "Fluka" grade II, pH 6.5) and left for 24 h. Elution with benzene-ether (1:1) gave only traces of material. Elution with ether-5 % methanol gave 522 mg which on recrystallisation from methylene chloride-pentane yielded 400 mg (57 %) of 2,4,6-tri-*O*-benzoyl-3-*O*-methyl-D-glucopyranose, m.p. 179—181°.

When the α-fluoride was treated in the same way 50 % of unchanged fluoride was recovered by elution of the column with benzene-ether.

The β-fluoride (200 mg) was put on a column of silica gel (100 g, "Merck") in benzene-10% acetone and left for 24 h. Elution with the same solvent and recrystallisation from ether-pentane gave 170 mg (85 %) of β-fluoride, m.p. 120—121°.

Reaction of α- and β-fluorides with calcium benzoate. A mixture of β-fluoride (500 mg), anhydrous calcium benzoate (1.0 g) and benzoic acid (5.0 g) was heated with stirring to 135—140° for 3 h. The mixture was then extracted with methylene chloride and the solution was washed with dilute hydrochloric acid, saturated sodium hydrogen carbonate and water. The solvent was removed and the residue was recrystallised from methylene chloride-pentane giving 350 mg (58 %) of tetra-*O*-benzoyl-3-*O*-methyl-β-D-glucopyranose, m.p. 195—197°.

The β-fluoride did not react with calcium benzoate in boiling acetonitrile.

By the same procedure the α-fluoride gave a 26 % yield of β-tetrabenzoate together with some unreacted α-fluoride.

Benzoylation of tribenzoate. 2,4,6-Tri-*O*-benzoyl-3-*O*-methyl-D-glucopyranose (100 mg) was dissolved in an ice-cold mixture of pyridine (1 ml) and benzoyl chloride (0.5 ml) and the solution was kept over night. Methylene chloride was then added and the solution was washed with 3 N sulphuric acid, sodium hydrogen carbonate and water. The solvent was removed and the residue was crystallised from ether-pentane giving 90 mg (75 %) of tetra-*O*-benzoyl-3-*O*-methyl-α-D-glucopyranose, m.p. 133—135°. One recrystallisation from ethanol gave the pure product, m.p. 136—137°, $[\alpha]_D^{22} = +116°$ (*c* 0.73, $CHCl_3$).

Reaction of tribenzoate with HF. 2,4,6-Tri-*O*-benzoyl-3-*O*-methyl-D-glucopyranose (500 mg) was dissolved in 1 ml of hydrogen fluoride and kept at room temperature for 20 min. Methylene chloride was then added and the solution was washed with sodium hydrogen carbonate and water and the solvent was removed. The residue was crystallised from ether-pentane giving 250 mg (50 %) of β-fluoride, m.p. 116—118°. One recrystallisation gave the pure product, m.p. 121—123°, $[\alpha]_D^{23} = +51.9°$ (*c* 1,3 $CHCl_3$).

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