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Reaction of Sugar Esters with Hydrogen Fluoride

III. Isomerisation of Tetra-*O*-benzoyl-β-D-xylopyranose

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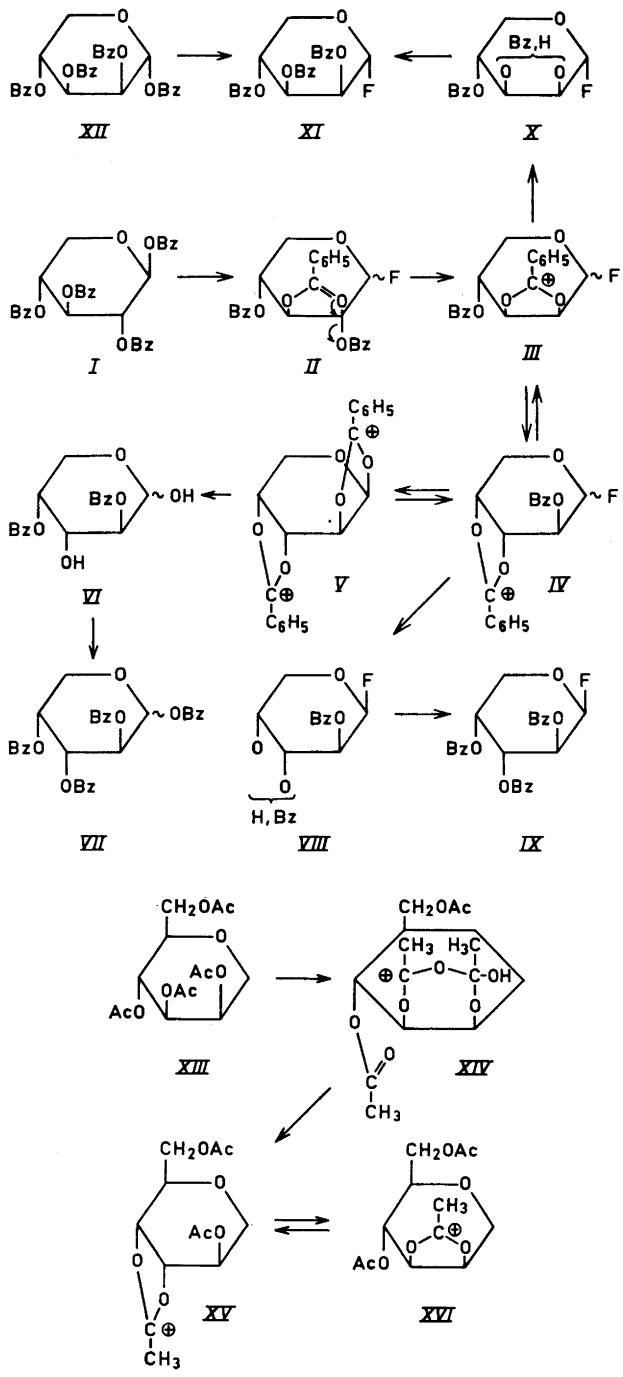
Brief treatment of tetra-*O*-benzoyl-β-D-xylopyranose with anhydrous hydrogen fluoride gives the anomeric tri-*O*-benzoyl-D-xylopyranosyl fluorides. More prolonged reaction leads to the formation of derivatives of D-arabinose and D-lyxose. The manner in which excess hydrogen fluoride is removed has a profound influence on the nature of the products formed. A mechanism which explains the major course of the rearrangement of sugar esters with hydrogen fluoride is proposed.

It has been shown by Pedersen and Fletcher [1] that reaction of β-L-arabinopyranose tetrabenzoate with anhydrous hydrogen fluoride for 6 h gives a 36 % yield of 3,4-di-*O*-benzoyl-β-L-ribopyranosyl fluoride. The same authors found [2] that treatment of β-D-ribopyranose tetrabenzoate with hydrogen fluoride for 24 h gave a syrupy product from which small amounts of ribopyranose and ribofuranose derivatives were isolated. Whether isomerisation to other pentose derivatives had taken place was not certain as no other products were isolated in a pure state.

In view of this it would be of interest to study the behaviour of xylose and lyxose tetrabenzoate towards hydrogen fluoride and in the present paper the reaction of tetra-*O*-benzoyl-β-D-xylopyranose is described.

When β-D-xylopyranose tetrabenzoate (I) was treated with anhydrous hydrogen fluoride at −10° for 20 min a crystalline mixture was obtained which on fractional crystallisation gave levorotatory tri-*O*-benzoyl-β-D-xylopyranosyl fluoride (II) in 32 % yield and the dextrorotatory α-anomer in 15 % yield. Both compounds gave, when treated with sodium methoxide, methyl β-D-xylopyranoside, indicating that they are both xylopyranose derivatives and that they therefore must be a pair of anomers.

Treatment of β-D-xylopyranose tetrabenzoate (I) with hydrogen fluoride for 20 h gave a reaction mixture in which no xylose derivatives could be detected. However, the nature of the product depended on the manner in which the excess hydrogen fluoride was removed.


XII
XI
X
I
II
III
VI
V
IV
VII
VIII
IX
XIII
XIV
XV
XVI

In one series of experiments hydrogen fluoride was removed by pouring the reaction mixture, after dilution with methylene chloride, into aqueous sodium hydrogen carbonate. This gave a reaction product from which was isolated a 47 % yield of a crystalline dibenzoyl pentose. No other crystalline material could be obtained from the mother liquor; but after benzoylation and chromatography on alumina a 4.5 % yield of tri-*O*-benzoyl-β-D-arabinopyranosyl fluoride (IX) was obtained together with 3.4 % of tetra-*O*-benzoyl-β-D-arabinopyranose. The dibenzoyl pentose, on benzoylation, gave a mixture of α- and β-D-arabinopyranose tetrabenzoate (VII). This proves that it is an arabinose derivative and it indicates that it has a free hydroxyl group at C_1 since a mixture of anomeric tetrabenzoates is formed on benzoylation. The dibenzoyl pentose did not consume periodate and it is therefore assumed to be 2,4-di-*O*-benzoyl-D-arabinopyranose (VI). Thus, a total yield of 56 % of D-arabinose derivatives was isolated from the reaction of β-D-xylopyranose tetrabenzoate with hydrogen fluoride when excess hydrogen fluoride was removed by washing with aqueous sodium hydrogen carbonate. In a similar experiment the material remaining after isolation of (VI) was treated with sodium methoxide. The resulting product was paper chromatographed and it was found to consist of methyl α-arabinopyranoside together with some arabinose. No other pentose or methyl glycoside hereof was detected.

In another series of experiments β-D-xylopyranose tetrabenzoate was again kept in anhydrous hydrogen fluoride for 20 h but excess hydrogen fluoride was now removed by evaporation with a stream of dry air. The residue, which contained large amounts of benzoic acid, was dissolved in methylene chloride and washed with aqueous sodium hydrogen carbonate. This procedure gave a product from which no 2,4-di-*O*-benzoyl-D-arabinopyranose (VI) could be crystallised at all. Chromatography on alumina gave a trace of (VI) but no other crystalline compound was obtained. In a similar experiment the crude product was benzoylated. The benzoylated material did not crystallize directly but chromatography on alumina gave a 14.5 % yield of tri-*O*-benzoyl-α-D-lyxopyranosyl fluoride (XI) and a very small amount of tetra-*O*-benzoyl-α-D-arabinopyranose. Since no tri-*O*-benzoyl-α-D-lyxopyranosyl fluoride could be isolated before the reaction mixture was benzoylated it is assumed that the primary product is a partially benzoylated lyxopyranosyl fluoride. (XI) was identified by comparing it with an authentic sample which was obtained by treating α-D-lyxopyranose tetrabenzoate (XII) with hydrogen fluoride for a short time at low temperature. Since (XII) gives the α-bromide when treated with hydrogen bromide [3] the fluoride is probably also the α-anomer. Treatment of (XI) with sodium methoxide gave a 73 % yield of methyl α-D-lyxopyranoside. In another experiment the crude product, obtained after removal of hydrogen fluoride with dry air and subsequent washing with sodium hydrogen carbonate, was treated with sodium methoxide. This gave a mixture which, by paper chromatography, was shown to contain methyl α-lyxopyranoside and methyl α-arabinopyranoside as the major components; a small amount of arabinose was also present.

Mechanism. Hedgley and Fletcher [4,5] * have shown that acylated cyclitols and acylated 1,5-anhydroglycitols are rearranged by the action of anhydrous hydrogen fluoride provided that three acyl-oxygroups in a *cis-cis-trans* configuration are present. Thus, they found that tetra-*O*-acetyl-1,5-anhydro-D-mannitol (XIII), on treatment with hydrogen fluoride, gives a mixture of 1,5-anhydromannitol and 1,5-anhydroaltritol derivatives and they assume that the reaction takes place *via* the intermediates (XIV), (XV), and (XVI). The latter two, on subsequent reaction with aqueous sodium hydrogen carbonate, gives 1,5-anhydroaltritol and 1,5-anhydromannitol, respectively.

In agreement with this mechanism Hedgley and Fletcher found that tetra-*O*-acetyl-1,5-anhydro-D-glucitol did not undergo rearrangement with hydrogen fluoride because this compound, which has an all *trans* configuration, cannot form an intermediate analogous to (XIV). The cyclic carbonium ion in (XIV) withdraws electrons from C_3 and thus makes possible the attack of the acyl-group at C_4 upon C_3 which leads to (XV).

The first step in the reaction of sugar esters with hydrogen fluoride is the formation of glycosyl fluorides, such as the pair of anomeric tri-*O*-benzoyl-D-xylopyranosyl fluoride (II) obtained in the present paper from xylose tetrabenzoate (I), and it might be expected that the acylated glycopyranosyl fluorides would react with hydrogen fluoride in the same way as the acylated 1,5-anhydrides. However, as pointed out by Hedgley and Fletcher,[4] this is not the case since tetra-*O*-acetyl-*α*-D-glucopyranosyl fluoride (part I of this series [6]) and tri-*O*-benzoyl-D-xylopyranosyl fluoride (II) are rearranged although they both have an all *trans* configuration and therefore cannot form an intermediate analogous to (XIV).

The precence of the strongly electronegative fluorine atom at C_1 in the glycosyl fluorides will cause an electron deficiency at C_2 and this could make a direct attack of the acylgroup at C_3 upon C_2 possible when C_2 and C_3 are in a *trans* configuration. In the case of tri-*O*-benzoyl-D-xylopyranosyl fluoride (II) this would lead to the formation of the cyclic carbonium ion (III). In analogy with the equilibrium between (XV) and (XVI) the carbonium ion (III) would be expected to be in equilibrium with (IV) and probably also (V) and when the reaction mixture is washed with aqueous sodium hydrogen carbonate (III) and (IV) or (V) would give derivatives of D-lyxose and D-arabinose, respectively. When the xylose tetrabenzoate — hydrogen fluoride mixture was washed directly with aqueous sodium hydrogen carbonate the products were arabinose derivatives indicating that the equilibrium is shifted towards (IV) and (V) when excess hydrogen fluoride is present. (IV), on hydrolysis, would give a di-*O*-benzoyl-D-arabinopyranosyl fluoride (VIII) isolated as the tribenzoate (IX) after benzoylation. (V) would give a dibenzoyl-D-arabinopyranose. The 2,4-di-*O*-benzoyl-D-arabinopyranose (VI) which was actually isolated is not necessarily the primary product of the reaction since acyl migration could take place when the reaction mixture is worked up. When hydrogen fluoride was removed by evaporation with dry air a considerable amount of lyxose derivatives were formed. This indicates that the equi-

* The author is grateful to Dr. Hedgley and Dr. Fletcher for the permission to study the manuscripts of these papers prior to publication.

librium between (III), (IV), and (V) is shifted towards (III) when hydrogen fluoride is removed. That the equilibrium is reversible was shown in an experiment where hydrogen fluoride was first evaporated with dry air, fresh hydrogen fluoride was then added and the mixture was poured into aqueous sodium hydrogen carbonate. This gave a 20 % yield of 2,4-dibenzoyl-D-arabinopyranose (VI) indicating that (III) is reconverted to (IV) and (V) on addition of hydrogen fluoride.

This mechanism, which explains the rearrangement of xylose tetrabenzoate, also explains the formation of derivatives of mannose and altrose from penta-*O*-acetyl-β-D-glucopyranose [6],* and the conversion of tetra-*O*-benzoyl-β-L-arabinopyranose into 3,4-di-*O*-benzoyl-β-L-ribopyranosyl fluoride [1].

In part II of this series [7] it was shown that penta-*O*-acetyl-α-D-mannopyranose is rearranged with hydrogen fluoride. Since mannose has C_2 and C_3 in a *cis* configuration it should not be able to rearrange by the mechanism just proposed, but it would be expected to rearrange by the mechanism of Hedgley and Fletcher to give a mixture of mannose and altrose derivatives and this was indeed found to be the case. Small amounts of glucose and idose derivatives were also isolated and this cannot be explained by any of the two mechanisms.

EXPERIMENTAL

Melting points are uncorrected.

The anomeric tri-O-benzoyl-D-xylopyranosyl fluorides. Tetra-*O*-benzoyl-β-D-xylopyranose (10.0 g) was dissolved in 15 ml of anhydrous hydrogen fluoride in a polyethylene flask and the solution was kept at *ca.* −10° in an ice-salt mixture for 20 min. Methylene chloride (40 ml) was then added and the mixture was poured into ice-cold saturated sodium hydrogen carbonate (400 ml). The organic layer was separated, washed with sodium hydrogen carbonate and water and dried. Evaporation of the solvent left 8.4 g of a colourless syrup which from ether (50 ml) gave 2.7 g of crystals. Recrystallization from ethanol (50 ml) gave 2.6 g (32 %) of tri-*O*-benzoyl-β-D-xylopyranosyl fluoride as prismatic crystals, m.p. 147−149°, $[\alpha]_D^{20}$ −38.4° (*c*, 1.4, $CHCl_3$). Two additional recrystallizations from ethanol gave the pure compound, m.p. 149−150°, $[\alpha]_D^{20}$ −39.4° (*c*, 1.04, $CHCl_3$). (Found: C 67.10; H 4.78. Calc. for $C_{26}H_{21}O_7F$: C 67.24; H 4.76). The ethereal mother liquor was concentrated to *ca.* 25 ml. Addition of pentane precipitated 2.7 g of a mixture of prisms and needles with m.p. 100−115°. This mixture was recrystallized twice from ether and once from ethanol to give 1.2 g (15 %) of tri-*O*-benzoyl-α-D-xylopyranosyl fluoride as thin needles, m.p. 117−119°. Two additional recrystallizations from ether-pentane gave the pure product, m.p. 119−120°, $[\alpha]_D^{20}$ + 39.2° (*c*, 0.93, $CHCl_3$). (Found: C 67.20; H 4.56).

Methyl β-D-xylopyranoside. Tri-*O*-benzoyl-β-D-xylopyranosyl fluoride (500 mg) was boiled for 2 h in methanol (10 ml) and 1 N sodium methoxide (2 ml). The solution was neutralized with carbon dioxide and evaporated to dryness *in vacuo* and the residue was extracted with hot ethyl acetate. Removal of the ethyl acetate gave a crystalline residue which was recrystallized from ethyl acetate (15 ml) yielding 130 mg (73 %) of colourless crystals, m.p. 153−155°. Mixed melting point and infrared spectrum proved that the product was identical with authentic methyl β-D-xylopyranoside.

* The crude products obtained from the reaction of glucose pentaacetate with hydrogen fluoride were boiled for 3 h with sodium methoxide in order to convert them to methyl glycosides or 1,6-anhydrides [6]. This was done under the assumption that all products were derivatives of glycosyl fluorides. If, however, any compounds analogous to (VI) were present they would probably be destroyed by this procedure and would therefore not be found.

Tri-*O*-benzoyl-α-D-xylopyranosyl fluoride gave a similar yield of methyl β-D-xylopyranoside.

Tri-O-benzoyl-α-D-lyxopyranosyl fluoride. Tetra-*O*-benzoyl-α-D-lyxopyranose (1.0 g) was dissolved in 3 ml of hydrogen fluoride at −10° and kept for 20 min. Methylene chloride was added and the mixture was poured into saturated sodium hydrogen carbonate. The organic layer was washed and dried and the solvent was removed. The residue (900 mg) was crystallized from ether-pentane yielding 590 mg (72 %) of tri-*O*-benzoyl-α-D-lyxopyranosyl fluoride as colourless prisms, m.p. 143−145°. One recrystallization from ether-pentane gave the pure product, m.p. 144−146°, $[\alpha]_D^{20}$ −209° (*c*, 0.60, $CHCl_3$). (Found: C 67.30; H 4.59).

Treatment with sodium methoxide as described above for the corresponding xylose derivatives gave a 73 % yield of methyl α-D-lyxopyranoside, m.p. 105−107°. Mixed melting point and infrared spectrum proved its identity with an authentic sample.

Reaction of tetrabenzoyl xylose with hydrogen fluoride for 20 h. Hydrogen fluoride removed by washing. Tetra-*O*-benzoyl-β-D-xylopyranose (10.0 g) was dissolved in anhydrous hydrogen fluoride (20 ml) and the solution was kept for 20 h at room temperature. Methylene chloride (500 ml) was then added and the mixture was poured into 500 ml of ice-cold saturated sodium hydrogen carbonate. The organic layer was separated and washed with aqueous sodium hydrogen carbonate and water. After drying the solvent was removed *in vacuo* leaving 7.0 g of a brown syrup which from a mixture of ether (50 ml) and pentane (25 ml) deposited 3.0 g (47 %) of 2,4-di-*O*-benzoyl-D-arabinopyranose (VI), m.p. 167−169°, $[\alpha]_D^{20}$ −194° (*c*, 0.5, $CHCl_3$). After several recrystallizations from methylene chloride or ethyl acetate the product melted at 167−171°, $[\alpha]_D^{20}$ −208° (*c*, 0.25, $CHCl_3$). (Found: C 63.40; H 4.97. Calc. for $C_{19}H_{18}O_7$: C 63.68; H 5.06). The product did not consume periodate in the course of 24 h. No mutarotation was observed in chloroform or methanol solution.

The mother liquor from the dibenzoyl-arabinose could not be induced to crystallize. In earlier experiments it was chromatographed on alumina but no crystalline fractions were obtained. It was now benzoylated with benzoyl chloride and pyridine yielding 4.9 g of a syrupy product. This was put on a column of alumina (150 g, "Fluka" grade II, pH 6.5). After elution with hexane the column was eluted with hexane:benzene (1:1, 800 ml) followed by benzene (200 ml). Removal of the solvent from these two fractions gave 1.38 g of syrup which from ether-pentane gave 830 mg of impure crystals. After several recrystallizations from ether-pentane and ethanol 370 mg (4.5 %) of tri-*O*-benzoyl-β-D-arabinopyranosyl fluoride (IX) was obtained, m.p. 159−161°, $[\alpha]_D^{20}$ −105° (*c*, 0.76, $CHCl_3$). The product had infrared spectrum identical with that of tri-*O*-benzoyl-β-L-arabinopyranosyl fluoride [1]. Further elution of the column with benzene (300 ml) gave 450 mg of product which from ether-pentane yielded 340 mg (3.4 %) of tetra-*O*-benzoyl-β-D-arabinopyranose, m.p. 172−174, $[\alpha]_D^{20}$ −322° (*c*, 0.87, $CHCl_3$). Its infrared spectrum was identical with that of an authentic sample of its enantiomorph. Elution of the alumina column with more polar solvents gave syrupy products only.

In a separate experiment xylose tetrabenzoate (1 g) was treated with hydrogen fluoride in the manner described above giving 650 mg of syrup from which 200 mg of dibenzoyl-arabinose (VI) was isolated. The remaining material was dissolved in methanol (10 ml) and 1 N sodium methoxide (2 ml) and kept over night at + 5°. The solution was then deionized by passage through Amberlite IR-400 and IR-50C. Evaporation of the deionized solution gave 80 mg of material which was chromatographed on Whatmann No. 1 paper using ethyl acetate:propanol:water (5:3:2) and butanone, saturated with water. The papers were sprayed with periodate-benzidine. Both solvents gave a strong spot corresponding to methyl α-arabinopyranoside and a weaker spot corresponding to arabinose. Three other very weak spots were present, but none of these corresponded to any of the pentoses or methyl pyranosides hereof.

Hydrogen fluoride removed with dry air. Tetra-*O*-benzoyl-β-D-xylopyranose (10.0 g) was kept in hydrogen fluoride (20 ml) for 20 h at room temperature. Methylene chloride (50 ml) was then added and the mixture was evaporated in a stream of dry air; this was repeated to remove as much hydrogen fluoride as possible. The residue was dissolved in methylene chloride and washed with aqueous sodium hydrogen carbonate and water and the solution was dried (acidification of the sodium hydrogen carbonate solution used for the washing precipitated 4.2 g (1.97 molar equivalents) of benzoic acid). Removal of the solvent gave 6.55 g of syrup which could not be crystallized. In a previous experiment

this product was chromatographed on alumina, but the only crystalline compound obtained was a small amount (40 mg) of dibenzoyl-arabinose (VI). The syrup was now benzoylated with benzoyl chloride and pyridine to give 9.4 g of a product which was put on a column of alumina (150 g, "Fluka" grade II, pH 6.5). Elution with hexane (1000 ml) gave 2.49 g of material which from ether-pentane deposited 1.2 g (14.5 %) of crystals, m.p. 138–142°. Three recrystallizations from ether-pentane gave 800 mg of tri-*O*-benzoyl-α-D-lyxopyranosyl fluoride, m.p. 143–145°, $[\alpha]_D^{20}$ −207° (*c*, 0.45, $CHCl_3$). (Found: C 67.25; H 4.58). The infrared spectrum was identical with that of an authentic sample. Elution of the alumina column with benzene gave a fraction which after recrystallization from ether-pentane yielded 80 mg of tetra-*O*-benzoyl-α-D-arabinopyranose, m.p. 157–159°, $[\alpha]_D^{20}$ −112° (*c*, 0.25, $CHCl_3$).

In a separate experiment 400 mg of crude product obtained as described above was treated with sodium methoxide in methanol (at + 5° over night), deionized and evaporated. Paper chromatography of the product (100 mg) gave strong spots of methyl α-arabinopyranoside and methyl α-lyxopyranoside; besides, a small amount of arabinose was present. No other pentose or methyl pyranoside hereof was detected.

Readdition of hydrogen fluoride after removal with air. β-D-Xylopyranose tetrabenzoate (2.0 g) was kept in 4 ml of hydrogen fluoride for 20 h. Methylene chloride was then added and the mixture was evaporated with dry air, this was repeated once. The residue was again dissolved in hydrogen fluoride (4 ml) and kept at room temperature for 2 h. Methylene chloride was added and the mixture poured into aqueous sodium hydrogen carbonate. The organic layer was separated, washed and dried and the solvent was removed. The residue (1.15 g) gave 250 mg (20 %) of 2,4-di-*O*-benzoyl-D-arabinopyranose (VI), m.p. 167–170°.

Benzoylation of 2,4-di-O-benzoyl-D-arabinopyranose. 2,4-Di-*O*-benzoyl-D-arabinopyranose (1.0 g) was benzoylated with benzoyl chloride (2 ml) in pyridine (4 ml). The crude product (1.9 g) crystallized from ether-pentane and yielded 1.3 g of a mixture of prisms and needles. Recrystallization from ethanol (40 ml) gave mainly prismatic crystals and some needles which were separated by decantation. The prisms were recrystallized from ether-pentane giving 500 mg (32 %) of tetra-*O*-benzoyl-β-D-arabinopyranose, m.p. 173–174°, $[\alpha]_D^{15}$ −325° (*c*, 1.3, $CHCl_3$). The mother liquors were combined and evaporated and the residue was put on a column of alumina (25 g, "Fluka" grade II, pH 6.5). Elution with 50 ml of benzene gave a mixture of prisms and needles (220 mg); further elution with 150 ml of benzene gave 370 mg of material which crystallized as needles only. Recrystallization from ether-pentane gave 250 mg (16 %) of tetra-*O*-benzoyl-α-D-arabinopyranose, m.p. 162–163°, $[\alpha]_D^{21}$ −112° (*c*, 0.55, $CHCl_3$). Both anomers had infrared spectra identical with those of the authentic enantiomorphs.

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