

## Isomerisation of Penta-*O*-acetyl- $\beta$ -D-glucopyranose with Hydrogen Fluoride

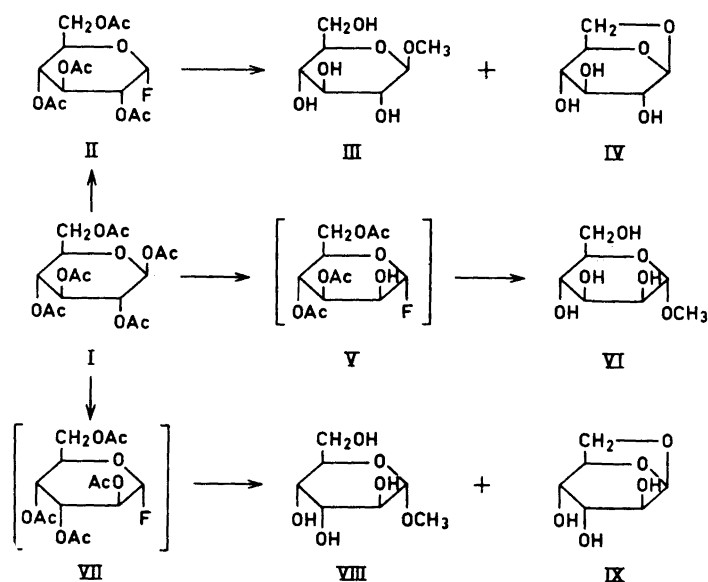
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Prolonged treatment of penta-*O*-acetyl- $\beta$ -D-glucopyranose with anhydrous hydrogen fluoride leads to the formation of derivatives of mannose and altrose identified through their conversion to methyl  $\alpha$ -D-mannopyranoside and 1,6-anhydro- $\beta$ -D-altropyranose, respectively. Addition of small amounts of acetic anhydride causes a higher yield of methyl  $\alpha$ -D-mannopyranoside and a lower yield of 1,6-anhydro- $\beta$ -D-altropyranose. Addition of larger amounts of acetic anhydride prevents rearrangement.

In 1926 Brauns<sup>1</sup> found that prolonged action of anhydrous hydrogen fluoride on cellobiose octaacetate led to the formation of 3,6-di-*O*-acetyl-4-*O*-(tetra-*O*-acetyl- $\beta$ -D-glycopyranosyl)- $\alpha$ -D-mannopyranosyl fluoride in low yield. Recently Pedersen and Fletcher<sup>2</sup> obtained a 36 % yield of 3,4-di-*O*-benzoyl- $\beta$ -L-ribopyranosyl fluoride from the reaction of  $\beta$ -L-arabinopyranose tetrabenzoate with liquid hydrogen fluoride. Thus, in both cases, the configuration at C<sub>2</sub> was inverted with simultaneous loss of an acyl grouping.

The objective of the present study was to reinvestigate the behavior of  $\beta$ -D-glucopyranose pentaacetate (I) towards liquid hydrogen fluoride. This reaction was first studied by Brauns<sup>3</sup> who showed that solution of the ester in hydrogen fluoride for 30 min at low temperature gave tetra-*O*-acetyl- $\alpha$ -D-glucopyranosyl fluoride (II) in *ca.* 40 % yield, similar to that obtained by the present author. Helferich and Böttger<sup>4</sup> found that solutions of  $\beta$ -D-glucopyranose pentaacetate (I) or tetra-*O*-acetyl- $\alpha$ -D-glucopyranosyl fluoride (II) in anhydrous hydrogen fluoride undergo considerable rotational changes during 10–20 h indicating that further reaction of the acetofluoroglucose is taking place. In accord herewith it has now been found that prolonged action of hydrogen fluoride on glucose pentaacetate gives a lower yield of acetofluoroglucose. Thus, after 20 h reaction at room temperature, followed by addition of methylene chloride and washing with water and sodium hydrogencarbonate to remove excess hydrogen fluoride, only traces of acetofluoroglucose was formed and no other crystalline material could be isolated from the syrupy product.



In order to obtain information about the nature of the product it was treated with sodium methoxide in methanol. Provided the product is a mixture of fully or partially acetylated glycosyl fluorides this treatment will, according to Micheel<sup>5,6</sup>, give either 1,2-*trans* methyl glycosides or 1,6-anhydrides. Consequently, acetofluoroglucose (II) would give a mixture of methyl β-D-glucopyranoside (III) and 1,6-anhydro-β-D-glucopyranose (IV), acetofluoromannose methyl α-D-mannopyranoside (VI)<sup>7</sup>, and, in general, a mixture of compounds may be expected which can be separated on paper chromatography.

The sirupy product gave, when treated with methanolic sodium methoxide, a product from which was isolated a 16% yield of methyl α-D-mannopyranoside (VI). Chromatography of the remaining product indicated that it was a mixture of methyl β-D-glucopyranoside (III), 1,6-anhydro-β-D-glucopyranose (IV), methyl α-D-altropyranoside (VIII), and 1,6-anhydro-β-D-altropyranose (IX).

The yield of crude acetofluoro compound was rather low in this experiment and, since it was suspected that losses occurred during washing the product with sodium hydrogen carbonate and water, another experiment was made in which excess hydrogen fluoride was blown off with dry air. This again gave a syrup which was treated with methanolic sodium methoxide. After chromatography on a cellulose column this product afforded a 28% yield of methyl α-D-mannopyranoside (VI) in addition to an 11% yield of 1,6-anhydro-β-D-altropyranose (IX).

Two similar experiments were made in which β-D-glucopyranose pentaacetate was treated with hydrogen fluoride for 3 h only. In the case where the hydrogen fluoride was removed with aqueous sodium hydrogen carbonate a 21% yield of methyl α-D-mannopyranoside (VI) was obtained. Besides, small

amounts of methyl  $\beta$ -D-glucopyranoside (III) and methyl  $\alpha$ -D-altropyranoside (VIII) were isolated. When, however, excess hydrogen fluoride was removed with dry air a 25 % yield of methyl  $\alpha$ -D-mannopyranoside was obtained; 1,6-anhydro- $\beta$ -D-altropyranose (IX) could be detected by paper chromatography but it was not present in sufficient amounts to be isolated. Thus, shortening of the reaction time to 3 h does not have much influence on the amount of mannose derivative formed but it reduces the amount of altrose derivative.

A number of experiments have been made in which varying amounts of acetic anhydride was added to the hydrogen fluoride. It was found that addition of 10 % of acetic anhydride gave a higher yield of methyl  $\alpha$ -D-mannopyranoside (VI), especially in the case where the hydrogen fluoride was removed by washing. The amount of 1,6-anhydro- $\beta$ -D-altropyranose (IX) formed was, on the other hand, lower and in the case where the hydrogen fluoride was removed with dry air only a trace of 1,6-anhydro- $\beta$ -D-altropyranose was isolated whereas an 11 % yield of this compound was obtained when no acetic anhydride was added. Addition of larger amounts of acetic anhydride suppressed the formation of mannose derivatives and when  $\beta$ -D-glucopyranose pentaacetate (I) was treated with a mixture of equal volumes of hydrogen fluoride and acetic anhydride for 20 h a 57 % yield of tetra-*O*-acetyl- $\alpha$ -D-glucopyranosyl fluoride (II) could be isolated together with a small amount of penta-*O*-acetyl- $\alpha$ -D-glucopyranose. Formation of the latter compound is in agreement with Helfferich and Böttger <sup>4</sup> who suggested that this compound might be the first product formed in the reaction between  $\beta$ -D-glucopyranose pentaacetate and hydrogen fluoride.

It would, of course, be of interest to know the structure of the primary products formed in the rearrangement of  $\beta$ -D-glucopyranose pentaacetate and several attempts were made to obtain pure compounds by chromatographing the crude products on alumina. Fractions were obtained which had the composition of tetraacetyl- and triacetyl-glycopyranosyl fluorides indicating that acetyl groups are lost in the reaction with hydrogen fluoride. However, none of these fractions were homogeneous and it is therefore not clear whether loss of acetyl groups is associated with the rearrangement. On the basis of the results of Brauns <sup>1</sup> and Pedersen and Fletcher <sup>2</sup> it may be assumed that the mannose derivative formed is 3,4,6-tri-*O*-acetyl- $\alpha$ -D-mannopyranosyl fluoride (V). The structure of the altrose derivative formed is less certain since rearrangement induced by hydrogen fluoride at both C<sub>2</sub> and C<sub>3</sub> has not been previously observed.

Richtmyer and Hudson <sup>8</sup> found that lactose octaacetate, when treated with a mixture of aluminium chloride and phosphorus pentachloride, yielded 2,3,6-tri-*O*-acetyl-4-*O*-(tetra-*O*-acetyl- $\beta$ -D-galactopyranosyl)- $\alpha$ -D-altropyranosyl chloride and by the same method cellobiose octaacetate was rearranged to 2,3,6-tri-*O*-acetyl-4-*O*-(tetra-*O*-acetyl- $\beta$ -D-glucopyranosyl)- $\alpha$ -D-altropyranosyl chloride <sup>9</sup>. In both cases the configuration at C<sub>2</sub> and C<sub>3</sub> has been inverted without loss of acetyl groups. Similarly, Richtmyer <sup>10</sup> found that  $\beta$ -D-glucopyranose pentaacetate gave derivatives of mannose and altrose when treated with aluminium chloride and phosphorus pentachloride. A mixture of these two reagents thus seems to cause rearrangement similar to those produced by hydrogen fluoride.

## EXPERIMENTAL

Melting points are uncorrected. The followings solvents were used for chromatography on paper (Whatman No. 1) or cellulose: (A) ethyl acetate:1-propanol:water (5:3:2); (B) butanol:pyridine:water (10:3:3); (C) butanone, saturated with water. Papers were sprayed with periodate-benzidine.

## Excess hydrogen fluoride removed by washing

*Reaction time 20 h.* Penta-*O*-acetyl- $\beta$ -D-glucopyranose (I, 5 g) was dissolved in liquid hydrogen fluoride (10 ml) in a polyethylene flask. The solution was kept at room temperature for 20 h. Methylene chloride (25 ml) was then added and the mixture was poured into ice-cold saturated sodium hydrogencarbonate (50 ml); the organic layer was separated and the aqueous phase was extracted with methylene chloride. The combined methylene chloride solutions were washed with saturated sodium hydrogencarbonate and water, and dried. Evaporation of the solvent left 2.1 g of a colourless syrup. The product was dissolved in methanol (50 ml) and 1 N sodium methoxide (20 ml) and boiled under reflux for 3 h. The solvent was removed *in vacuo*, the residue was dissolved in water and deionized by passage through Amberlite IR-400 and IR-50 C. Evaporation of the aqueous solution gave 1.35 g of a colourless syrup, crystallizing from ethanol (10 ml) to give 330 mg (13 %) of methyl  $\alpha$ -D-mannopyranoside (VI), m.p. 188–191°, undepressed in admixture with an authentic sample.

The ethanolic mother liquor was put on a cellulose column (8  $\times$  70 cm) and eluted with solvent A. The eluate was divided into two fractions. Fraction 1, on paper chromatography in solvent A, gave largely one spot corresponding to methyl  $\alpha$ -D-mannopyranoside. On evaporation it gave 520 mg of a syrup from which 70 mg of methyl  $\alpha$ -D-mannopyranoside crystallized, bringing the total yield of this compound to 16 %. Paper chromatography of the mother liquor material in solvent C gave several spots of which the largest two corresponded to methyl  $\alpha$ -D-altropyranoside and 1,6-anhydro- $\beta$ -D-glucopyranose. Fraction 2, on paper chromatography in solvent A, gave one spot with an  $R_F$ -value equal to that of 1,6-anhydro- $\beta$ -D-altropyranose. Evaporation of this fraction gave 230 mg of a syrup from which no crystals could be obtained. Chromatography in solvents B and C gave 3 spots, the largest one corresponding to 1,6-anhydro- $\beta$ -D-altropyranose.

In a similar experiment a 22 % yield of methyl  $\alpha$ -D-mannopyranoside was obtained.

*Reaction time 3 h.* Penta-*O*-acetyl- $\beta$ -D-glucopyranose (5 g) was kept in 10 ml of hydrogen fluoride for 3 h at room temperature. The mixture was then worked up as described above, giving 2.8 g of a colourless syrup. The product was boiled for 3 h with methanol (75 ml) and 1 N sodium methoxide (25 ml). Deionization and evaporation gave 1.75 g of syrup which from ethanol (10 ml) deposited 400 mg of methyl  $\alpha$ -D-mannopyranoside, m.p. 187–190°. The mother liquor was fractionated on a cellulose column using solvent A as eluant. Fraction 1 gave 680 mg of syrupy material which from ethanol gave 120 mg of methyl  $\alpha$ -D-mannopyranoside bringing the total yield of this compound to 21 %. The remaining part of fraction 1 was acetylated and from the product was isolated a small amount (20 mg) of methyl tetra-*O*-acetyl- $\alpha$ -D-altropyranoside, m.p. 87–89° either alone or in admixture with an authentic sample. Its infrared spectrum was identical with that of an authentic sample. Fraction 2 gave 200 mg of syrup from which was isolated 25 mg of impure methyl  $\alpha$ -D-mannopyranoside. Finally, fraction 3 gave 290 mg of syrup which from ethanol deposited 150 mg of methyl  $\beta$ -D-glucopyranoside, m.p. 107–109° either alone or in admixture with an authentic sample.

*Reaction time 20 h – 10 % acetic anhydride.* Penta-*O*-acetyl- $\beta$ -D-glucopyranose (5 g) was added to a mixture of hydrogen fluoride (10 ml) and acetic anhydride (1 ml). The mixture was kept at room temperature for 20 h and then worked up as described above yielding 3.56 g of syrupy product. The product was boiled for 3 h with methanol (75 ml) and 1 N sodium methoxide (20 ml), then deionized and evaporated. Yield 2.1 g of a colourless syrup which from ethanol deposited 930 mg (37 %) of methyl  $\alpha$ -D-mannopyranoside, m.p. 186–189°. The mother liquor, on paper chromatography in solvent C, gave spots corresponding to 1,6-anhydro- $\beta$ -D-glucopyranose, methyl  $\alpha$ -D-mannopyranoside, methyl  $\alpha$ -D-altropyranoside, and 1,6-anhydro- $\beta$ -D-altropyranose.

*Reaction time 20 h — equal volume of acetic anhydride.* Acetic anhydride (5 ml) was slowly added to 5 ml of hydrogen fluoride which was cooled in an ice-salt bath. To this mixture was added 5 g of  $\beta$ -D-glucopyranose pentaacetate and the solution was kept for 20 h at room temperature. Methylene chloride (30 ml) was added and the solution was washed with saturated sodium hydrogencarbonate and water and dried. Evaporation of the solvent left 4.9 g of a colourless syrup which from ether (20 ml) deposited 2.55 g (57 %) of tetra-O-acetyl- $\alpha$ -D-glucopyranosyl fluoride, m.p. 105–107°,  $[\alpha]_D^{20} +91.3^\circ$  (CHCl<sub>3</sub>, c 1.1). Addition of pentane (25 ml) to the mother liquor gave an additional 1.05 g of crystalline material with m.p. 85–90°. This product was put on a column of alumina (35 g "Fluka" grade II, pH 6.0  $\pm$  0.5). Elution with benzene (500 ml) gave 350 mg of tetra-O-acetyl- $\alpha$ -D-glucopyranosyl fluoride. Elution with benzene-ether (1:1, 200 ml) gave 70 mg of crystals which, after two recrystallizations from ether-pentane gave 50 mg of penta-O-acetyl- $\alpha$ -D-glucopyranose with m.p. 110–112°; the product was identified through analysis and mixed melting point with an authentic sample. Further elution of the column with ether gave syrupy products.

### Excess hydrogen fluoride removed with dry air

*Reaction time 20 h.* Penta-O-acetyl- $\beta$ -D-glucopyranose (5 g) was kept in 10 ml of hydrogen fluoride for 20 h at room temperature. Methylene chloride (20 ml) was added and the solution was evaporated in a stream of dry air. The residue was dissolved in methylene chloride and the last trace of hydrogen fluoride was removed by adding calcium carbonate. The mixture was filtered and the solvent was removed *in vacuo* leaving 4.3 g of a brown syrup which was boiled for 3 h with methanol (50 ml) and 1 N sodium methoxide (30 ml). The solution was then deionized and evaporated leaving 2.8 g of a brownish syrup. The product was put on a cellulose column and eluted with solvent A; the eluate was divided into 3 fractions according to paper chromatographic studies. Fraction 1 on evaporation gave 1.7 g of syrup which from ethanol (10 ml) deposited 700 mg (28 %) of methyl  $\alpha$ -D-mannopyranoside, m.p. 188–190°. The mother liquor, when chromatographed in solvent C, gave 5–6 spots and was not studied further. Fraction 2 gave 420 mg of syrup which, from a few ml of ethanol, deposited 230 mg (11 %) of 1,6-anhydro- $\beta$ -D-altropyranose, m.p. 120–130°. After two recrystallizations from ethanol the m.p. was 134–135° either alone or in admixture with an authentic sample,  $[\alpha]_D^{20} -21^\circ$  (methanol, c 0.62). The infrared spectrum was identical with that of an authentic sample. Fraction 3 gave 700 mg of syrup with very low  $R_F$ -value; it was not investigated further.

*Reaction time 3 h.* Penta-O-acetyl- $\beta$ -D-glucopyranose (5 g) was kept for 3 h in 10 ml of hydrogen fluoride, then worked up as described above, yielding 4.5 g of a yellow syrup. Treatment with methanolic sodium methoxide gave 2.55 g of syrup which from ethanol deposited 180 mg of rather impure methyl  $\alpha$ -D-mannopyranoside, m.p. 180–185°. The remaining product was fractionated on a cellulose column using solvent A. The eluate was divided into two fractions. Fraction 1 gave 1.3 g of syrup which from 10 ml of ethanol deposited 450 mg of methyl  $\alpha$ -D-mannopyranoside with m.p. 187–190°, bringing the total yield of this compound to 25 %. The remaining part of fraction 1, on paper chromatography in solvent C, gave spots corresponding to methyl  $\alpha$ -D-mannopyranoside and 1,6-anhydro- $\beta$ -D-glucopyranose. Fraction 2 gave 450 mg of syrup which, on paper chromatography in solvent C, gave spots corresponding to methyl  $\alpha$ -D-mannopyranoside, methyl  $\beta$ -D-glucopyranoside, and 1,6-anhydro- $\beta$ -D-altropyranose. A few milligram of methyl  $\beta$ -D-glucopyranoside was isolated from this fraction.

*Reaction time 20 h — 10 % acetic anhydride.* Penta-O-acetyl- $\beta$ -D-glucopyranose (5 g) was dissolved in a mixture of hydrogen fluoride (10 ml) and acetic anhydride (1 ml). The solution was kept for 20 h and then worked up as described above, yielding 5.0 g of a dark syrup. Treatment with methanolic sodium methoxide gave 2.3 g of a brown syrup which was fractionated on a cellulose column using solvent A as eluant. Fraction 1 (1.40 g) gave, from ethanol, 810 mg (32 %) of methyl  $\alpha$ -D-mannopyranoside with m.p. 187–190°. Paper chromatography of the mother liquor in solvent C showed several components. Fraction 2 (200 mg) gave, from ethanol, 15 mg of impure 1,6-anhydro- $\beta$ -D-altropyranose. Fraction 3 gave 1.6 g of material; it was not investigated further.

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