ACTA CHEMICA SCANDINAVICA 17 (1963) 673–677

Reaction of Sugar Esters with Hydrogen Fluoride

II. Isomerisation of Penta-*O*-acetyl- and Penta-*O*-benzoyl-α-D-mannopyranose

CHRISTIAN PEDERSEN

Department of Organic Chemistry, University of Technology, Copenhagen, Denmark

Brief treatment of penta-*O*-acetyl- and penta-*O*-benzoyl-α-D-mannopyranose with anhydrous hydrogen fluoride gives tetra-*O*-acetyl- and tetra-*O*-benzoyl-α-D-mannopyranosyl fluoride. More prolonged action of hydrogen fluoride leads to the formation of derivatives of mannose and altrose and small amounts of glucose- and idose-derivatives, isolated as methyl glycosides and 1,6-anhydrides.

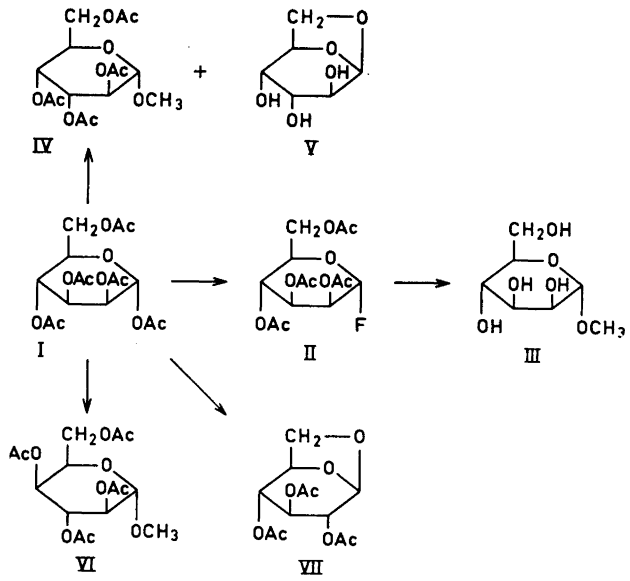
In a previous paper [1] it was shown that prolonged action of anhydrous hydrogen fluoride on penta-*O*-acetyl-β-D-glucopyranose led to the formation of derivatives of mannose and altrose. In the present paper the behaviour of penta-*O*-acetyl- and penta-*O*-benzoyl-α-D-mannopyranose towards hydrogen fluoride is studied.

Brauns [2] found that treatment of penta-*O*-acetyl-α-D-mannopyranose (I) with anhydrous hydrogen fluoride for 40 min at low temperature gave tetra-*O*-acetyl-α-D-mannopyranosyl fluoride (II) in unspecified yield. The present author, using the same conditions, obtained a 49 % yield of II.

Penta-*O*-acetyl-α-D-mannopyranose (I) has now been treated with hydrogen fluoride for 20 h at room temperature and the excess hydrogen fluoride has been removed either by washing with aqueous sodium hydrogen carbonate or by evaporation in dry air as described in part I of this series [1] *. In both cases the product was a syrup from which only traces of acetofluoromannose (II) could be isolated as the sole crystalline compound, even after chromatography on alumina or silica. In order to gain further insight into the reactions the syrupy products were treated with methanolic sodium methoxide to give a mixture of 1,2-*trans* methyl glycosides and 1,6-anhydrides [1] which was chromatographed on a cellulose column.

* In a forthcoming paper it will be shown that the two alternative methods of removing hydrogen fluoride, in the case of xylose tetrabenzoate, lead to entirely different products.

Table 1.



The product which resulted when hydrogen fluoride was removed by washing with sodium hydrogen carbonate gave a 30 % yield of methyl α-D-mannopyranoside (III) and 7 % yield of methyl α-D-altropyranoside, isolated as the tetraacetate (IV). In addition, a small amount of methyl α-D-idopyranoside was isolated as its crystalline tetraacetate (VI) in 1.5 % yield. The structure of (VI) was proved through its identity with an authentic sample, prepared by acetylation of methyl α-D-idopyranoside. A small amount of tri-*O*-acetyl-1,6-anhydro-β-D-glucopyranose (VII) was also isolated.

When hydrogen fluoride was removed with dry air a higher yield of crude product was obtained, indicating that losses occur during the washing procedure. When the product was worked up it gave the same compounds that were obtained when hydrogen fluoride was removed by washing in nearly the same yields. In addition, a 12 % yield of 1,6-anhydro-β-D-altropyranose (V) was isolated.

When penta-*O*-benzoyl-α-D-mannopyranose, or its β-anomer, was reacted with hydrogen fluoride for 30 min at −10°, tetra-*O*-benzoyl-D-mannopyranosyl fluoride was obtained in 85 % yield. Benzoylation of crude α-D-mannopyranosyl fluoride gave the same compound indicating that it is the α-anomer.

Reaction of penta-*O*-benzoyl-α-D-mannopyranose with hydrogen fluoride for 20 h at room temperature and removal of the excess hydrogen fluoride by washing with aqueous sodium hydrogen carbonate gave a syrup from which a 13 % yield of tetra-*O*-benzoyl-α-D-mannopyranosyl fluoride was isolated. No other crystalline compound could be obtained, directly or after chromatography on alumina. The syrupy product gave, after treatment with metha-

nolic sodium methoxide, the same mixture of compounds that were obtained from the acetate with the exception that an 8 % yield of 1,6-anhydro-β-D-altropyranose was isolated. This compound could not be isolated from the mannose pentaacetate-hydrogen fluoride product when hydrogen fluoride had been removed by washing, probably because some of the acetates are lost during the washing whereas the benzoates which are much less water soluble remain in the methylene chloride phase.

Treatment of mannose pentabenzoate with hydrogen fluoride for 20 h and removal of excess hydrogen fluoride with dry air gave a 20 % yield of tetra-*O*-benzoyl-α-D-mannopyranosyl fluoride. When the remaining material was treated with methanolic sodium methoxide a product was obtained which, on paper chromatography, gave a picture very similar to that of the material obtained when hydrogen fluoride was removed by washing.

The reaction of pentaacetyl- and pentabenzoyl-mannopyranose with hydrogen fluoride thus produces as the main products derivatives of mannose and altrose together with very small amounts of glucose and idose derivatives. As described in part I [1], the action of hydrogen fluoride on penta-*O*-acetyl-β-D-glucopyranose leads to the formation of derivatives of mannose, altrose, and glucose in yields that are rather similar to those obtained here. Idose derivatives were not found in the case of glucose pentaacetate but, apart from that, glucose and mannose pentaacetate give nearly the same mixture of products on prolonged treatment with hydrogen fluoride.

The reaction of other carbohydrate esters with hydrogen fluoride is being studied and it is hoped that this work will provide information about the mechanism whereby these rearrangements take place.

EXPERIMENTAL

Melting points are uncorrected. Whatman No. 1 paper and cellulose powder was used for chromatography. Solvents were: (A) butanone, saturated with water; (B) ethyl acetate: propanol: water (5:3:2). Papers were sprayed with periodate-benzidine. All compounds that have been isolated were identified by comparing infrared spectra and mixed melting points with authentic samples.

Reaction of pentaacetyl mannose with hydrogen fluoride

Reaction time 30 min at −15°. Penta-*O*-acetyl-α-D-mannopyranose (5.0 g) was dissolved in 8 ml of anhydrous hydrogen fluoride in a polyethylene flask which was kept at *ca.* −15° in an ice-salt mixture. After 30 min methylene chloride (25 ml) was added and the solution was poured into an excess of ice-cold saturated sodium hydrogen carbonate solution. The organic layer was separated and washed with aqueous sodium hydrogen carbonate and water and dried. Evaporation of the solvent left 4.2 g of a colourless syrup which, from ether-pentane, gave 2.2 g (49 %) of tetra-*O*-acetyl-α-D-mannopyranosyl fluoride with m.p. 65−67° (seed crystals were obtained in a previous experiment in which the product was chromatographed on alumina). After two recrystallizations the product melted at 68−69° and had $[\alpha]_D^{20} = +21.8°$ (*c* 0.87, $CHCl_3$) in agreement with Brauns [2]. (Found: C 48.00; H 5.63. Calc. for $C_{14}H_{19}O_9F$: C 48.00; H 5.47).

Reaction time 20 h; HF removed by washing. Penta-*O*-acetyl-α-D-mannopyranose (5.0 g) was dissolved in anhydrous hydrogen fluoride (10 ml) and the solution was kept

at room temperature for 20 h. The mixture was then worked up as described above giving 2.8 g of a colourless syrup. The product was boiled under reflux for 3 h with methanol (50 ml) and 1 N sodium methoxide (25 ml). The methanol was removed *in vacuo* and the residue was dissolved in water and deionized by passage through Amberlite IR-400 and IR-50c. Evaporation of the aqueous solution gave 1.82 g of a colourless syrup which from ethanol (10 ml) yielded 570 mg of methyl α-D-mannopyranoside (III), m.p. 187–190°.

The ethanolic mother liquor was put on a cellulose column (8 × 70 cm) and eluted with solvent (A). The eluate was divided into 5 fractions. Fraction 1 (80 mg), on paper chromatography in solvents (A) and (B), gave one spot with an R_F-value equal to that of 1,6-anhydro-β-D-glucopyranose and after acetylation *ca.* 10 mg of tri-*O*-acetyl-1,6-anhydro-β-D-glucopyranose (VII) was isolated; no other crystalline material could be obtained. Fraction 2 (70 mg) was acetylated with acetic anhydride in pyridine to give 150 mg of a syrup which from ether-pentane deposited 70 mg (1.5 %) of methyl tetra-*O*-acetyl-α-D-idopyranoside (VI) as colourless needles, m.p. 106–108°. After two recrystallizations from ether-pentane the product melted at 107–108° $[\alpha]_D^{20} = +55.2°$ (*c* 0.50, $CHCl_3$). (Found: C 49.50; H 6.15. Calc. for $C_{15}H_{22}O_{10}$: C 49.72; H 6.12). Fraction 3 (40 mg) contained fluorine and gave an R_F-value equal to that of α-D-glucopyranosyl fluoride. No crystalline product could be isolated from this fraction, before or after acetylation. Fraction 4 (530 mg), on chromatography in solvents (A) and (B), gave two spots with R_F-values equal to those of methyl α-D-mannopyranoside and methyl α-D-altropyranoside. Crystallization from ethanol gave 180 mg of methyl α-D-mannopyranoside (III) with m.p. 185–188°, bringing the total yield of this compound to 30 %. The ethanolic mother liquor was evaporated and the residue was acetylated with acetic anhydride-pyridine to give 530 mg of a syrup which from ether-pentane afforded 320 mg (7 %) of methyl tetra-*O*-acetyl-α-D-altropyranoside (IV), m.p. 87–89°. Fraction 5 (150 mg) gave one spot corresponding to 1,6-anhydro-β-D-altropyranose (V) but no crystalline material was isolated from this fraction.

Reaction time 20 h; HF removed with dry air. 5.0 g of penta-*O*-acetyl-α-D-mannopyranose was kept in 10 ml of hydrogen fluoride for 20 h. Methylene chloride (25 ml) was then added and the solution was evaporated in a stream of dry air. The residue was dissolved in methylene chloride and the last traces of hydrogen fluoride were removed with calcium carbonate. The solution was filtered through carbon and evaporated leaving 4.5 g of a dark syrup. The product was boiled with methanol (75 ml) and 1 N sodium methoxide (30 ml) for 3 h, then deionized and evaporated. 2.4 g of a brown syrup remained which from ethanol (15 ml) gave 510 mg of methyl α-D-mannopyranoside with m.p. 185–188°.

The mother liquor was chromatographed on cellulose and by the procedure described above the following compounds were isolated: tri-*O*-acetyl-1,6-anhydro-β-D-glucopyranose (VII) (10 mg), m.p. 104–106°; methyl tetra-*O*-acetyl-α-D-idopyranoside (VI) (60 mg, 1,3 %), m.p. 107–108; tetra-*O*-acetyl-α-D-glucopyranosyl fluoride (40 mg), m.p. 104–105°; methyl α-D-mannopyranoside (290 mg), m.p. 187–189°, bringing the total yield of this compound to 32 %; methyl tetra-*O*-acetyl-α-D-altropyranoside (IV) (130 mg, 2.8 %), m.p. 88–90°. Fraction 5 (580 mg) was crystallized from ethanol (5 ml) and gave 260 mg (12 %) of 1,6-anhydro-β-D-altropyranose (V), m.p. 120–125°.

Methyl tetra-O-acetyl-α-D-idopyranoside. Methyl 4,6-benzylidene-α-D-idopyranoside [3] (400 mg) was suspended in water (16 ml) containing 0.1 N hydrochloric acid (0.8 ml). The mixture was kept at 60° for 1 h during which time the compound dissolved. The solution was neutralized with Amberlite IR-4B and evaporated *in vacuo*. The residue was acetylated with acetic anhydride-pyridine and the product was crystallized from ether-pentane to give 300 mg (58 % of colourless needles, m.p. 106–108°. Two recrystallizations gave pure methyl tetra-*O*-acetyl-α-D-idopyranoside, m.p. 107–108°, $[\alpha]_D^{20} = +55.8°$ (*c* 0.51, $CHCl_3$). (Found: C 49.94; H 6.12. Calc. for $C_{15}H_{22}O_{10}$: C 49.72; H 6.12)*.

* *Note added in proof.* This compound has recently been prepared by Buchanan and Schwarz (*J. Chem. Soc.* **1962** 4770) by the same method.

Tetra-*O*-benzoyl-*α*-D-mannopyranosyl fluoride

From pentabenzoyl mannose. Penta-*O*-benzoyl-*α*-D-mannopyranose (2.0 g) was dissolved in 4 ml of hydrogen fluoride at −10° and kept for 30 min. Methylene chloride (20 ml) was added and the solution was washed with aqueous sodium hydrogen carbonate and water and dried. Evaporation of the solvent left 1.70 g of a colourless syrup which from ether-pentane deposited 1.45 g (85 %) of tetra-*O*-benzoyl-*α*-D-mannopyranosyl fluoride with m.p. 127−129°. After two recrystallizations from ether-pentane the product was pure. M.p. 129−131°, $[\alpha]_D^{20} = -86.2°$ (*c* 1.47, $CHCl_3$) (Found: C 68.08; H 4.55. Calc. for $C_{34}H_{27}O_9F$: C 68.22; H 4.55). Penta-*O*-benzoyl-*β*-D-mannopyranose gave the same yield of fluoro compound.

From acetofluoro mannose. Tetra-*O*-acetyl-*α*-D-mannopyranosyl fluoride (1.0 g) was dissolved in methanol (5 ml) and 5 drops of 1 N sodium methoxide was added. The solution was kept at room temperature for 10 min and the solvent was then removed *in vacuo*. A mixture of pyridine (10 ml) and benzoyl chloride (4 ml) was added to the residue and the mixture was kept over night at room temperature. Water and methylene chloride was then added, the organic layer was separated and washed with dilute sulphuric acid and sodium hydrogen carbonate. The methylene chloride was removed *in vacuo* leaving 2.2 g of a syrup which from ether-pentane gave 1.2 g of crude product, m.p. 118−123°. One recrystallization gave 1.05 g (61 %) of tetra-*O*-benzoyl-*α*-D-mannopyranosyl fluoride with m.p. 127−128°, idential with the product prepared from pentabenzoyl mannose.

Pentabenzoyl mannose + HF for 20 h. Penta-*O*-benzoyl-*α*-D-mannopyranose (10 g) was dissolved in hydrogen fluoride (20 ml) and the solution was kept at room temperature for 20 h. Methylene chloride was added and the mixture washed with sodium hydrogen carbonate and water and dried. Removal of the solvent left 7.6 g of syrup which from ether-pentane gave 1.1 g (13 %) of tetra-*O*-benzoyl-*α*-D-mannopyranosyl fluoride, m.p. 126−128°. The mother liquor material was treated with methanolic sodium methoxide and deionized and evaporated to give 2.3 g of a syrup. This product was fractionated on cellulose as described above and gave the following compounds: methyl *α*-D-mannopyranoside (III) (27 %), 1,6-anhydro-*β*-D-altropyranose (V) (8 %), methyl tetra-*O*-acetyl-*α*-D-altropyranoside (IV) (3.3 %), and methyl tetra-*O*-acetyl-*α*-D-idopyranoside (VI) (1 %). 1,6-anhydro-*β*-D-glucopyranose could not be isolated in a pure state but paper chromatography indicated its presence.

When hydrogen fluoride was removed with dry air 7.8 g of crude material was obtained and a 20 % yield of tetra-*O*-benzoyl-*α*-D-mannopyranosyl fluoride was isolated. Treatment with sodium methoxide gave a product which on paper chromatography gave the same picture as above and it was not investigated further.

Acknowledgements. The author is indebted to cand.pharm. I. Krogh Andersen for the infrared spectra. Microanalyses were made by Mr. Preben Hansen.

This work is part of an investigation supported by *Kai Hansen's Fond.*

REFERENCES

1. Pedersen, C. *Acta Chem. Scand.* **16** (1962) 1831.
2. Brauns, D. H. *J. Res. Natl. Bur. Std.* **7** (1931) 581.
3. Sorkin, F. and Reichstein, T. *Helv. Chim. Acta* **28** (1945) 1.

Received October 28, 1962.