ACTA CHEMICA SCANDINAVICA 21 (1967) 1239–1243

Rearrangement of Tetra-*O*-benzoyl-2-deoxy-β-D-*arabino*-hexopyranose into 3,6-Di-*O*-benzoyl-2-deoxy-α-D-*ribo*-hexopyranosyl Fluoride with Anhydrous Hydrogen Fluoride

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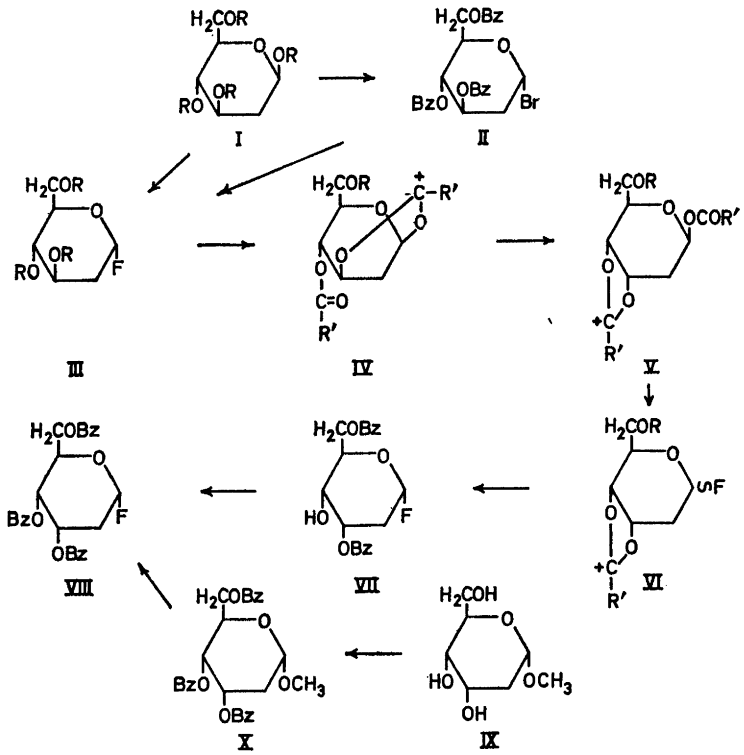
Treatment of tetra-*O*-benzoyl-2-deoxy-β-D-*arabino*-hexopyranose (Ia) with hydrogen fluoride in benzene gave tri-*O*-benzoyl-2-deoxy-α-D-*arabino*-hexopyranosyl fluoride (IIIa). When (Ia) was treated with anhydrous hydrogen fluoride for 1 hour at −17° a Walden inversion took place and 3,6-di-*O*-benzoyl-2-deoxy-α-D-*ribo*-hexopyranosyl fluoride (VII) was obtained in 62 % yield. The reaction was followed by NMR spectroscopy. The mechanism of the reaction is discussed.

As described in a previous article [1] attempts to prepare acylated 2-deoxy-D-glucopyranosyl fluorides by treatment of tri-*O*-acetyl- or tri-*O*-benzoyl-D-glucal with hydrogen fluoride led to the formation of unsaturated fluorides. In the present article the reaction between tetra-*O*-benzoyl-2-deoxy-β-D-*arabino*-hexopyranose (Ia) and hydrogen fluoride is studied.

Treatment of (Ia) [2–4] with an excess of a saturated solution of hydrogen fluoride in benzene for 30 min at 0° gave 77 % of 3,4,6-tri-*O*-benzoyl-2-deoxy-α-D-*arabino*-hexopyranosyl fluoride (IIIa). This compound has recently been prepared by Hall and Manville [4] who proved its structure by NMR spectroscopy. Its infrared spectrum showed the absorption at 762 cm^{-1} which is characteristic of glycopyranosyl fluorides with axially oriented fluorine.[5]

The fluoride (IIIa) was also obtained by treating 3,4,6-tri-*O*-benzoyl-2-deoxy-α-D-*arabino*-hexopyranosyl bromide (II) with silver fluoride in acetonitrile. The bromide (II) was prepared according to Bergmann.[3] An NMR spectrum shows H_1 at 6.68 δ as a broad doublet with a spacing of 3 cps. A small coupling of H_1 with both H_2 protons indicates that H_1 is equatorially oriented and hence that the bromide is the α-anomer.

Prolonged treatment of sugar esters with hydrogen fluoride leads, in many cases, to Walden inversion [6] or to ring contraction.[7] Mechanisms have been proposed which explain the Walden inversion of sugar esters with hydrogen fluoride.[6] The behaviour of acylated 2-deoxy-sugars on prolonged treatment with hydrogen fluoride has not been studied.



Treatment of tetra-*O*-benzoyl-2-deoxy-β-D-*arabino*-hexopyranose (Ia) with anhydrous hydrogen fluoride for 20 h (the conditions used previously [6]) or for 3 h at room temperature resulted in the formation of a black tar. By reaction of (Ia) with hydrogen fluoride for 1 h at −17° a slightly coloured product was obtained. Chromatography of this product gave, as the main component, a 62 % yield of 3,6-di-*O*-benzoyl-2-deoxy-α-D-*ribo*-hexopyranosyl fluoride (VII). Besides, a 12 % yield of the fluoride (IIIa) was isolated. Benzoylation of (VII) gave the corresponding tribenzoate (VIII) which was identified by comparison with an authentic sample prepared by treating methyl 3,4,6-tri-*O*-benzoyl-2-deoxy-α-D-*ribo*-hexoside (X) with anhydrous hydrogen fluoride for 20 min at −70°.

The structure of the dibenzoate (VII) was studied by NMR spectroscopy. This showed the hydroxyl proton as a broad doublet centered at 3.5 δ. By treatment with deuterium oxide this signal disappeared and, at the same time, a complex signal at 3.9 δ changed into a quartet with the coupling constants 3 and 10 cps. On this basis the signal at 3.9 δ is assigned to H_4 since this is the only proton which can give a simple quartet by *cis*-coupling with H_3 and *trans*-coupling with H_5. Thus the hydroxyl group of (VII) must be at C_4.

The tribenzoate (VIII) also showed the signal of H_4 as a quartet shifted to lower field (5.53 δ).

Since studies of NMR spectra of sugar esters dissolved in hydrogen fluoride have given valuable information about the mechanism of this type of reaction in other cases,[8] this technique was also used in the present problem.

Thus (Ia) was dissolved in anhydrous hydrogen fluoride at −70° and an NMR spectrum was taken within a few minutes. This spectrum, although not well resolved, resembled closely the spectrum of the fluoride (IIIa) in deuteriochloroform. The solution was kept at −70° and spectra were taken at intervals. Changes were observed in the spectra in the course of several days; however, the reaction proceeded very slowly at −70° and after 10 days it had not yet reached a final stage. Another experiment was therefore performed at −20°. An NMR spectrum taken 5 min after the tetrabenzoate (Ia) was dissolved in hydrogen fluoride at −20° did not show the presence of the fluoride (IIIa) but was similar to the spectrum obtained from the experiment at −70° after 10 days. Spectra run at intervals at −20° showed that a change took place rapidly within the first hour. After that time no further changes could be seen in the spectrum in the course of several days. However, the solution became dark coloured within a few hours indicating that decomposition took place. As described above, work up of the mixture after one hour at −17° gave a 62 % yield of the rearranged product (VII).

Since the NMR spectra of (Ia) in hydrogen fluoride were not well resolved a study of the spectra of tetra-*O*-acetyl-2-deoxy-D-*arabino*-hexopyranose (Ib) in hydrogen fluoride was also made. The tetraacetate (Ib) [9] was dissolved in anhydrous hydrogen fluoride at −70°. A spectrum taken a few minutes after the solution was made showed that one molar equivalent of acetic acid had been liberated as seen from the sharp signal with intensity 3 at 2.60 δ. Besides, two sharp signals at 2.33 δ and 2.43 δ with intensity 3 and 6 were seen. This indicates that the fluoride (IIIb) was formed. (Hall and Manville [4] isolated this fluoride in high yield by treating (Ib) with hydrogen fluoride at −70°). The solution was kept at −70° and spectra were run at intervals. After 10 days a signal had appeared at 2.82 δ; at the same time the signal of acetic acid had increased and the acetoxy signals had decreased in integral value. In order to get a more rapid reaction, a separate experiment was run at −10°. Spectra showed that a rapid reaction took place for the first 40 min and then no further change took place for several days. The solution turned black. The spectrum taken after 40 min showed a signal corresponding to acetic acid at 2.60 δ with intensity 6. Besides, a sharp signal at 2.38 δ with intensity 3 indicated the presence of one acetoxy group. A third sharp signal with intensity 3 at 2.82 δ indicates that a 2-methyl-1,3-dioxolenium ion is formed.[8] On this basis it is assumed that tetra-*O*-acetyl-2-deoxy-D-*arabino*-hexopyranose (Ib), when dissolved in hydrogen fluoride, initially forms the fluoride (IIIb), and subsequently the ion (VIb) is formed as the final product. The tetrabenzoate (Ia) undoubtly behaves in the same way giving the ion (VIa) since this explains the formation of the fluoride (VII) which is isolated when the mixture is worked up.

The formation of the ions (VIa and b), involving an inversion at C_3, is unlikely to take place directly from the fluorides (IIIa and b) since it has

been found that 1,2-*trans*-diacetoxy-cyclohexane does not react with hydrogen fluoride.[8] It is possible that the first step in the reaction of the fluorides (IIIa and b) with hydrogen fluoride is the formation of a 1,3-cyclic ion (IVa and b), formed by attack of the acyloxy group of C_3 upon C_1 after protonisation of the fluorine atom. The ion (IVa and b) would then be expected to rearrange readily into the ion (VIa and b). The presence of (IVb) could not be seen in the spectra.

Ring contraction to furanose derivatives which takes place when tetra-*O*-benzoyl-2-*O*-methyl-D-glucopyranose is treated with hydrogen fluoride [7] has not been observed in the present case.

EXPERIMENTAL

Melting points are uncorrected. Thin layer chromatography was performed on silica gel HF_{254} (Merck); for preparative work, 1 mm layers of silica gel PF_{254} were used. Spots were visualized under UV light. NMR spectra were obtained with a Varian A-60 instrument using deuteriochloroform as a solvent. Position of signals are given in ppm (δ-values) relative to tetramethyl silane. NMR spectra in anhydrous hydrogen fluoride were obtained by using a Teflon sample tube which was closed with a screw plug. The Teflon tube was fitted inside an ordinary glass sample tube. Position of signals, when hydrogen fluoride was used as solvent, are given in ppm relative to $(CH_3)_3SiCH_2CH_2CH_2SO_3Na$.

Tri-O-*benzoyl-2-deoxy*-α-D-arabino-*hexopyranosyl fluoride (IIIa). (a) From tetra*-O-*benzoyl-2-deoxy*-β-D-arabino-*hexopyranose (Ia).* A solution of (Ia) (3.0 g) in 60 ml of a saturated solution of anhydrous hydrogen fluoride in benzene (the solution was *ca.* 0.5 N with regard to hydrogen fluoride) was kept at 0° for 30 min. The solution was then diluted with methylene chloride, washed with saturated aqueous sodium hydrogen carbonate and water and dried. Evaporation of the solvent left a colourless syrup (2.6 g) which was crystallized from ether-pentane to give 1.9 g (77 %) of fluoride (IIIa), m.p. 110–112°, $[\alpha]_D^{27} = +44.1°$ (*c* 1.5, $CHCl_3$). (Found: C 67.95; H 5.02. Calc. for $C_{27}H_{23}O_7F$: C 67.78; H 4.85). The NMR spectrum was identical with that of the product prepared by Hall and Manville.[4]

(b) From tri-O-*benzoyl-2-deoxy*-α-D-arabino-*hexopyranosyl bromide (II).* The bromide (II) (0.50 g) was dissolved in dry acetonitrile (10 ml) and methylene chloride (1 ml). Silver fluoride (1.0 g) was added and the mixture was stirred for 30 min at room temperature. It was then filtered through activated carbon and concentrated *in vacuo* to a brown syrup (440 mg). The crude product was chromatographed on a column of silica gel (100 g) using ether-pentane (1:1) as eluent. The first fraction to come off the column was the fluoride (IIIa), yield 100 mg (22 %), m.p. 112°. After elution of a small amount of an unidentified compound the slowest moving fraction was collected. It gave 170 mg (38 %) of 3,4,6-tri-*O*-benzoyl-2-deoxy-D-*arabino*-hexopyranose, m.p. 119–120°. The product was identical with the compound described by Bergmann.[3]

Rearrangement of tetra-O-*benzoyl-2-deoxy*-β-D-arabino-*hexopyranose (Ia).* The tetrabenzoate (Ia) (0.50 g) was dissolved in anhydrous hydrogen fluoride (1 ml) at −17° and kept for 1 h after which time the solution had become red. It was then diluted with cold chloroform and washed with ice-water and saturated aqueous sodium hydrogen carbonate, dried and evaporated *in vacuo*. The slightly yellow syrup was separated into two components by preparative thin layer chromatography using ether-pentane (1:1) as eluent. The fast moving fraction gave 50 mg (12 %) of the fluoride (IIIa), identical with the product described above.

The slow moving fraction gave 197 mg (62 %) of 3,6-di-*O*-benzoyl-2-deoxy-α-D-*ribo*-hexopyranosyl fluoride (VIIa) as a colourless syrup which was pure as seen from the NMR spectrum. Since this product was rather unstable it was immediately benzoylated in the usual manner with benzoyl chloride (0.5 ml) in pyridine (2 ml). The crude product was a colourless syrup, obtained in quantitative yield, which gave one spot only on thin layer chromatography in several different solvents. An NMR spectrum showed that the compound was pure; the signal of H_1 showed small coupling constants with both the hydrogen atoms at C_2 indicating that H_1 is equatorial and therefore that it is an α-fluoride (VIII). The infrared spectrum showed a band at 775 cm^{-1} characteristic of compounds

with axial fluorine.[5] $[\alpha]_D^{25} = +166°$ (*c* 1.6, $CHCl_3$). (Found: C 67.93; H 5.03. Calc. for $C_{27}H_{23}O_7F$: C 67.78; H 4.85). After standing for 2 weeks the product crystallized and it was recrystallized from ether-pentane, m.p. 93—95°.

Methyl 3,4,6-tri-O-*benzoyl-2-deoxy*-α-D-ribo-*hexopyranoside (X)*. Methyl 2-deoxy-α-D-*ribo*-hexopyranoside (IX) was prepared according to Jeanloz *et al.*[10] The crude product (420 mg) was benzoylated with benzoyl chloride (2.0 ml) in pyridine (5.0 ml). The crude, syrupy product (1.25 g) was purified by preparative thin layer chromatography using ether-pentane (1:2) as eluent. The purified product crystallized and was recrystallized from methanol, yield 55 %, m.p. 95—96°. $[\alpha]_D^{26} = +204°$ (*c* 1.2, $CHCl_3$). (Found: C 68.80; H 5.28. Calc. for $C_{28}H_{26}O_8$: C 68.57; H 5.34).

3,4,6-Tri-O-*benzoyl-2-deoxy*-α-D-ribo-*hexopyranosyl fluoride (VIII)*. The methyl glycoside (X) (129 mg) was dissolved in anhydrous hydrogen fluoride (0.3 ml) at −70° and the solution was kept at this temperature for 20 min. It was then diluted with chloroform and washed with ice-water, saturated sodium hydrogen carbonate, and water and dried. Evaporation of the solvent left a syrup (110 mg) which was purified by preparative thin layer chromatography using ether-pentane (1:1) as eluent. One recrystallization from ether-pentane gave 66 mg (53 %) of pure fluoride (VIII), m.p. 93—95°, $[\alpha]_D^{26} = +167°$ (*c* 0.9, $CHCl_3$). Infrared and NMR spectra proved its identity with the product described above.

The authors are indebted to civilingeniør S. Refn for the infrared spectra. Microanalyses were performed by Dr. A. Bernhardt.

REFERENCES

1. Lundt, I. and Pedersen, C. *Acta Chem. Scand.* **20** (1966) 1369.
2. Bergmann, M., Schotte, H. and Leschinsky, W. *Ber.* **55** (1922) 158.
3. Bergmann, M., Schotte, H. and Leschinsky, W. *Ber.* **56** (1923) 1052.
4. Hall, L. D. and Manville, J. F. *Private communication.*
5. Lundt, I. and Pedersen, C. *Michrochim. Acta* **1966** 126.
6. Pedersen, C. *Acta Chem. Scand.* **18** (1964) 60.
7. Pedersen, C. *Acta Chem. Scand.* **20** (1966) 963.
8. Pedersen, C. *Tetrahedron Letters* **1967** 511.
9. Bonner, W. A. *J. Org. Chem.* **26** (1961) 908.
10. Jeanloz, R., Prins, D. A. and Reichstein, T. *Helv. Chim. Acta* **29** (1946) 371.

Received January 26, 1967.