Preparation of Tri-*O*-benzoyl-2-deoxy-α-D-*ribo*-hexopyranosyl Fluoride from Derivatives of D-Glucal and Anhydrous Hydrogen Fluoride

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The reaction of acetylated or benzoylated D-glucal, 3-*O*-methyl-D-glucal, and methyl 2,3-dideoxy-D-*erythro*-hex-2-eno-pyranoside with anhydrous hydrogen fluoride at −70° has been studied. The three compounds give identical products. On brief treatment with hydrogen fluoride, 4,6-di-*O*-acyl-2,3-dideoxy-D-*erythro*-hex-2-eno-pyranosyl fluoride is formed. More prolonged reaction gives 3,6-di-*O*-acyl-2-deoxy-D-*ribo*-hexopyranosyl fluoride which on benzoylation yields the tribenzoate. The mechanism of the reaction has been investigated through NMR spectroscopic studies of the hydrogen fluoride solutions.

In a previous paper,[1] the reaction of tri-*O*-acetyl- or tri-*O*-benzoyl-D-glucal with hydrogen fluoride in benzene leading to the formation of 4,6-di-*O*-acyl-2,3-dideoxy-D-*erythro*-hex-2-eno-pyranosyl fluoride (VI) was described. Attempts to carry out the reaction in anhydrous hydrogen fluoride at room temperature resulted in complete decomposition. It has now been found, however, that the reaction with anhydrous hydrogen fluoride, when carried out at low temperature, leads to well defined products.

Treatment of tri-*O*-benzoyl-D-glucal (Ib) with anhydrous hydrogen fluoride at −70° for 30 min gave the 2,3-unsaturated fluoride (VIb). When the reaction was allowed to proceed for 20 h at −70°, (VIb) was no longer present, but 3,6-di-*O*-benzoyl-2-deoxy-α-D-*ribo*-hexopyranosyl fluoride (VIIb), previously obtained by reaction of tetra-*O*-benzoyl-2-deoxy-D-*arabino*-hexopyranose with hydrogen fluoride,[2] could now be isolated. The same two products were obtained when 3-*O*-methyl-4,6-di-*O*-benzoyl-D-glucal (IIb) or methyl 4,6-di-*O*-benzoyl-2,3-dideoxy-D-*erythro*-hex-2-eno-pyranoside (IIIb) were treated with anhydrous hydrogen fluoride under the same conditions. Benzoylation of (VIIb) gave the tribenzoylated fluoride (VIIIb), which could be crystallized directly from the crude mixture in 30—35 % yield. The crude dibenzoate (VIIb) could be converted into the corresponding methyl glycosides (X) by

treatment with methanol in the presence of a small amount of hydrogen chloride. Thus, 2-deoxy-D-*ribo*-hexose derivatives can be conveniently prepared from tri-*O*-benzoyl-D-glucal.
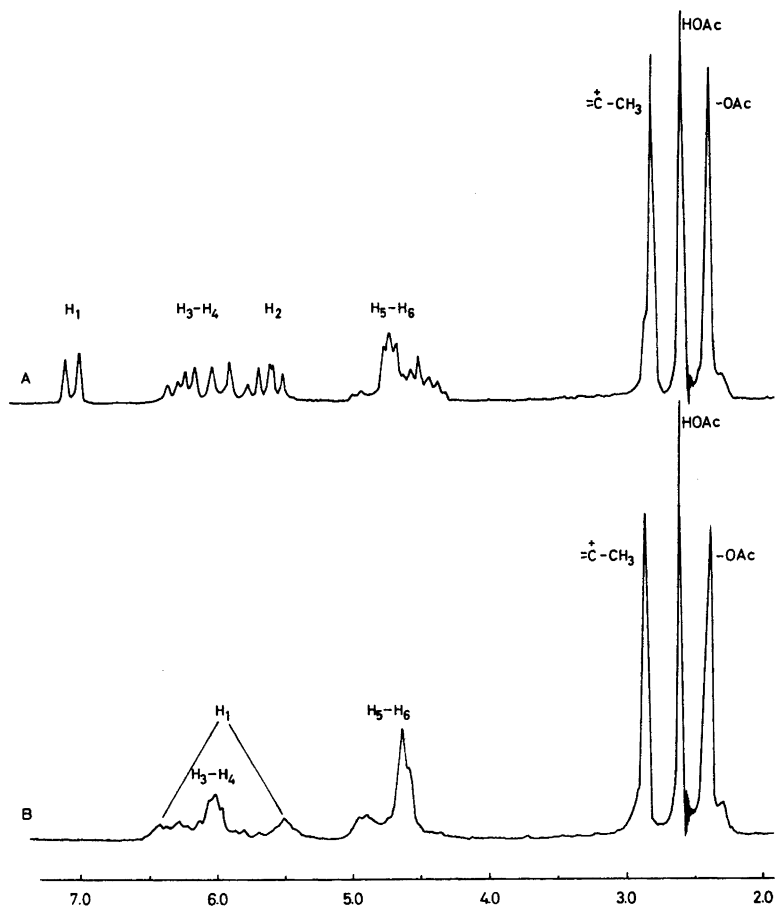

Fig. 1. Ia in HF at −70°. A: after 5 min. B: after 24 h.

In order to gain insight into the mechanism of these reactions compounds (I), (II), and (III) were dissolved in hydrogen fluoride at −70°, and NMR spectra were recorded after a few minutes. Both the acetates and the benzoates were studied, but the products resulting from the acetates were not isolated. It was found that the three compounds gave identical spectra. In Fig. 1 is reproduced the spectrum obtained ·from tri-*O*-acetyl-D-glucal (Ia); (IIa) and (IIIa) exhibited spectra which were identical with that of (Ia) save for the *O*-methyl signal. This indicates that the *O*-acyl group at C-3 is cleaved off from (I) and that the *O*-methyl groups are cleaved off from (II) and (III).

The spectrum of (Ia), (IIa), or (IIIa) in hydrogen fluoride is highly similar to that of (Ia) in chloroform [3] with a doublet at 7.1 δ, characteristic of H-1 in glycal derivatives. However, the spectrum does not represent (Ia) since this compound can impossibly be formed from (IIa) or (IIIa); on the other hand, the spectrum clearly reveals the presence of a glycal in the hydrogen fluoride solution. The three proton signal at 2.40 δ shows that an unchanged acetoxy group is present and the three proton signal at 2.79 δ indicates that an acetoxonium ion [4] has been formed (Fig. 1). Correspondingly, the signal at 2.60 δ in the spectrum of (Ia) reveals that one molar equivalent of acetic acid has been liberated. This signal is, of course, absent from the spectra deriving from (IIa) and (IIIa). The spectra of the benzoates (Ib), (IIb), and (IIIb) were identical with those of the acetates, with the exception that the

a: R=CH$_3$

b: R=C$_6$H$_5$
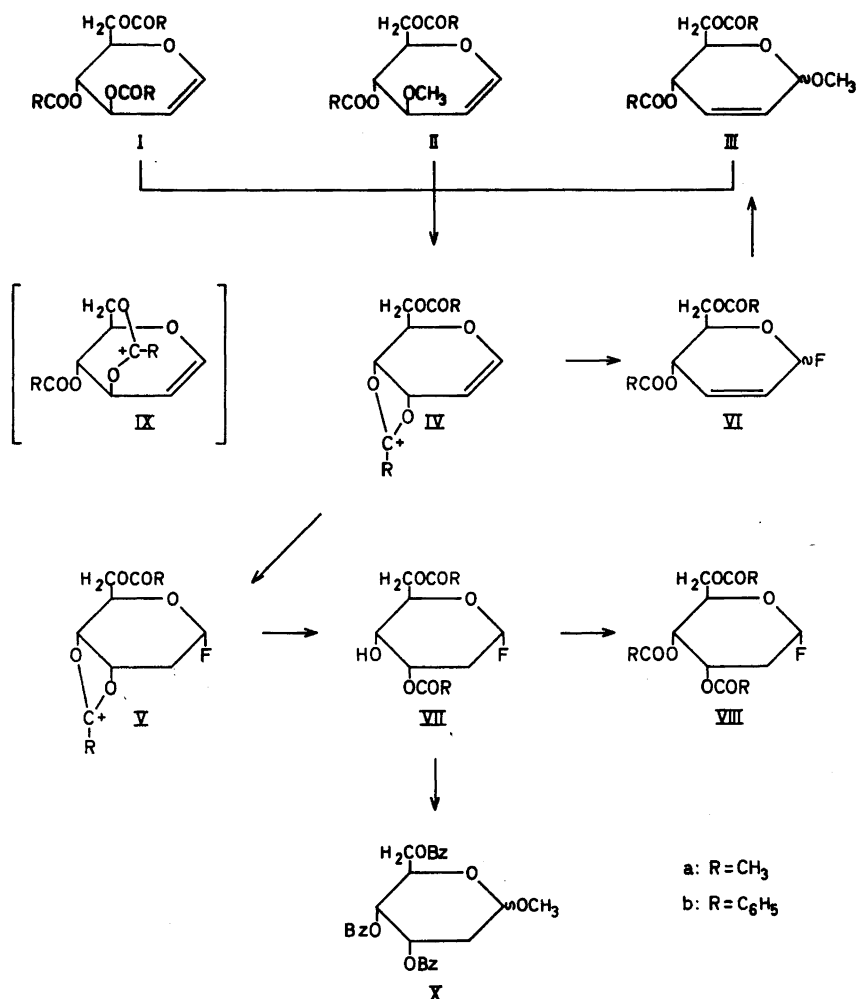
acetate signals were replaced by a complicated group of aromatic signals. No signals attributable to deoxy protons were noted around 3 δ, indicating that no addition to the double bond had taken place.

From these spectra it is concluded that (I), (II), and (III), when dissolved in hydrogen fluoride, yield the unsaturated dioxolenium ion (IV). The formation of (IV) probably takes place by protonation of the oxygen atom at C-3 in (I) and (II), or at C-1 in (III). The protonated groups are subsequently cleaved off, possibly assisted by attack from the acyloxy group at C-4; in the case of (III) an allylic shift of the double bond occurs simultaneously. When the hydrogen fluoride solution is worked up at this stage, the unsaturated fluoride (VI) is obtained. The latter is not present in anhydrous hydrogen fluoride and must therefore be formed when the solution is poured into water during the work up of the mixture. Probably a fluoride ion attacks at C-1 of (IV), accompanied by an allylic shift and opening of the dioxolenium ion.

When the hydrogen fluoride solution containing the ion (IV) was kept at −70° for several hours the signals of (IV) disappeared and a new compound was formed, as seen from the NMR spectra. The spectrum obtained from (Ia) is shown in Fig. 1, and is identical with that obtained from a solution of tetra-O-acetyl-2-deoxy-D-arabino-hexopyranose in hydrogen fluoride after 1 h at −70°.[2] Similarly, the benzoate (Ib), when kept for a few hours in hydrogen fluoride at −70°, gave a spectrum identical with that obtained from tetra-O-benzoyl-2-deoxy-D-arabino-hexopyranose.[2] A complex two proton signal was present at about 3 δ, showing that a deoxy-sugar was formed. This means that, on further reaction, hydrogen fluoride adds to the double bond of (IV) to give (V). When the hydrogen fluoride solution is poured into water, (V) is hydrolyzed to give (VII), as described above. Longer reaction of (V) with hydrogen fluoride leads to decomposition.

The results described above might, of course, equally well be explained by assuming that the ion (IX) is involved rather than (IV). In order to decide which of these two ions were in fact present, 3-O-methyl-4-O-acetyl-6-O-trideuterioacetyl-D-glucal was prepared. An NMR spectrum of this compound in anhydrous hydrogen fluoride at −70° displayed an acetoxonium ion signal at 2.79 δ, but no signal corresponding to an acetoxy group. This proves that (IV), and not (IX), is the ion initially formed in hydrogen fluoride. When the solution was kept at −70°, (IV) was converted into the 6-trideuterioacetyl-analogue of (V) which gave an NMR signal at 2.81 δ, corresponding to an acetoxonium ion, and no signal corresponding to an acetoxy group.

When (Ib), (IIb), or (IIIb) were treated with deuterium fluoride, the reaction was much slower, presumably owing to an isotope effect. The products, (VIIb) or (VIIIb), contained one deuterium atom at C-2, in agreement with the proposed mechanism. The stereochemical course of the addition reaction is at present unknown.

<div align="center">EXPERIMENTAL</div>

Melting points are uncorrected. For details of thin layer chromatography (TLC) and NMR spectra, see Ref. 2. 100 Mc spectra were obtained on a VarianHA-100 instrument.

Preparation of tri-O-benzoyl-D-glucal from tetra-O-benzoyl-α-D-glucopyranosyl bromide.[7] Tri-O-benzoyl-D-glucal may be prepared as described previously [1] or, alternatively, as follows:

Sodium acetate (5 g) was dissolved in a mixture of water (4 ml), acetic acid (11 ml), and acetone (10 ml), and cooled to −10°. Zinc dust (2 g) was then added, and a solution of the glucosyl bromide (0.5 g) in acetic acid (3 ml) was added with stirring in the course of 5−10 min. The stirring was continued at −5 to 0° for 3 h, when the zinc was filtered off and the filtercake was washed with a little acetic acid. The filtrate was diluted with water and extracted three times with methylene chloride. The organic phase was washed with water and aqueous sodium hydrogen carbonate, dried, and then evaporated *in vacuo* to a syrup (360 mg, 100 %). This product gave only one spot on TLC, and an NMR spectrum was identical with that of tri-*O*-benzoyl-D-glucal.[1]

3-O-Methyl-4,6-di-O-benzoyl-D-glucal (IIb) was prepared by benzoylation of 3-*O*-methyl-D-glucal [5] with benzoyl chloride in pyridine. The product was purified by chromatography on a column of silica gel using ether-pentane (1:2) as the eluent. The yield of pure, syrupy, product was 48 %, based on 3-*O*-methyl-D-glucose. $[\alpha]_D^{25} = +84.3$ (c 1.0, CHCl₃). (Found: C 68.41; H 5.68. Calc. for $C_{21}H_{20}O_6$: C 68.47; H 5.47). The NMR spectrum was in agreement with the structure.

3-*O*-Methyl-4-*O*-acetyl-6-*O*-trideuterioacetyl-D-glucal

3-O-Methyl-4-O-acetyl-6-O-trityl-D-glucal. To a solution of 3-*O*-methyl-D-glucal [5] (350 mg) in pyridine (3 ml) was added an equimolar amount of trityl chloride (615 mg), and the mixture was kept at room temperature for 3 days. Acetic anhydride (0.55 ml) was now added and the solution was left for 24 h. After addition of water and methylene chloride the mixture was washed with 3 N sulphuric acid and sodium hydrogen carbonate, dried and evaporated. The syrupy product (1.05 g) was crystallized from ether-pentane to give 525 mg (54 %) of the trityl derivative, m.p. 94−95°. Preparative TLC of the material in the mother liquor using ether-pentane (1:1) as an eluent gave an additional 236 mg of crystalline product, bringing the total yield to 78 %. Recrystallization from ether-pentane gave the pure product, m.p. 97−98°, $[\alpha]_D^{23} = +54.7$ (c 1.0, CHCl₃). (Found: C 75.85; H 6.36. Calc. for $C_{28}H_{28}O_5$: C 75.65; H 6.35). The product gave a well resolved NMR spectrum which confirmed its structure and purity.

3-O-Methyl-4-O-acetyl-D-glucal. A dry column was prepared from 30 g of silica gel (Merck, 0.05−0.2 mm) containing 3 % of 0.5 N sulfuric acid. The trityl compound (219 mg) was dissolved in a small amount of benzene and placed on top of the column. Benzene was then added in an amount sufficient to wet the whole column which subsequently allowed to stand at room temperature for 2 h. Elution with benzene-ether (1:1) now gave 2 fractions. The first (183 mg) consisted of a mixture of triphenyl carbinol and unchanged trityl compound; the second (58 mg, 58 %) was the detritylated compound. The NMR spectrum of the product confirmed its structure. Only one acetoxy signal was present, and the δ-values of the protons at C-4 and C-6 showed that the acetoxy group was at C-4. Thus acyl-migration had not taken place. The product was not purified further.

If the trityl compound was kept for a longer time on the silica gel column acyl-migration took place. Detritylation on silica gel has been described by Lehrfeld.[6]

3-O-Methyl-4-O-acetyl-6-O-trideuterioacetyl-D-glucal. A mixture of pyridine (0.5 ml) and acetic anhydride-d_6 (50 μl) was added with cooling to 3-*O*-methyl-4-*O*-acetyl-D-glucal (58 mg) and the mixture was kept at room temperature for 18 h. Methylene chloride was then added and the solution was washed successively with water, 3 N sulphuric acid, and sodium hydrogen carbonate and dried. Evaporation of the solvent left 57 mg (80 %) of the trideuterioacetyl compound. In a 100 Mc NMR spectrum of the corresponding diacetate (IIa) the signals of the two acetoxy groups are separated. In the deuterioacetyl derivative only one acetoxy signal was present, confirming that acetyl-migration had not taken place.

REACTIONS WITH HYDROGEN FLUORIDE

For 30 min

Tri-O-benzoyl-D-*glucal* (229 mg) was dissolved in anhydrous hydrogen fluoride (1 ml) at −70° and the solution was kept at this temperature for 30 min. Cold chloroform was then added and the organic layer was washed with ice-water and saturated aqueous sodium hydrogen carbonate and dried. The solvent was removed *in vacuo* leaving a syrup (156 mg). An NMR spectrum in carbon tetrachloride indicated that the product was the 2,3-unsaturated fluoride (VIb); it decomposed rapidly at room temperature. The experiment was repeated with 359 mg of tri-*O*-benzoyl-D-glucal, and the product (251 mg) was immediately dissolved in methanol (5 ml) and a drop of aqueous hydrogen fluoride or hydrogen chloride was added. After standing over night at room temperature the solution was neutralized with barium carbonate, filtered, and evaporated to a colourless syrup (251 mg, 82 %). The product was shown by TLC and NMR spectroscopy to be a mixture of the anomeric 2,3-unsaturated methyl glycosides (IIIb).[1]

3-O-Methyl-4,6-di-O-benzoyl-D-*glucal* (IIb) (231 mg) was kept in hydrogen fluoride (1 ml) for 30 min, at −70°. Work up as described above gave 227 mg of the unsaturated fluoride (VIb) which was treated with methanol. After chromatography, 110 mg (48 %) of the methyl glycoside (IIIb) was obtained.

Treatment of the unsaturated methyl glycoside (IIIb) with hydrogen fluoride in the same manner gave the unsaturated fluoride (VIb) which was characterized through its NMR spectrum.

For 20 hours

Tri-O-benzoyl-D-*glucal* (Ib) (470 mg) was dissolved in anhydrous hydrogen fluoride (1.5 ml) at −70° and the solution was kept at this temperature for 20 h. Work up of the reaction mixture as described above gave a syrup (327 mg) which on TLC (ether-pentane 1:1) showed one very major component. An NMR spectrum indicated that the product was almost pure (VIIb).[2] The product was benzoylated in the usual manner with benzoyl chloride (0.3 ml) in pyridine (2 ml). A syrup (347 mg) was isolated which by TLC and NMR spectroscopy was shown to be tri-*O*-benzoyl-2-deoxy-α-D-*ribo*-hexopyranosyl fluoride (VIIIb).[2] Crystallization from ether-pentane gave 170 mg (35 %) of the latter compound, m.p. 89−92°. Recrystallization gave the pure product, m.p. 94−95°. NMR and IR spectra, and the optical rotation established its identity with the product described previously.[2]

3-O-Methyl-4,6-di-O-benzoyl-D-*glucal* (IIb) (240 mg) was treated with hydrogen fluoride for 20 h at −70°. Work up as described above and purification by preparative TLC using ether-pentane (1:1) as an eluent gave 146 mg (60 %) of (VIIb). An NMR spectrum indicated that the product was homogeneous. Benzoylation gave 181 mg of crude tribenzoate which by recrystallization from ether-pentane gave 95 mg (30 %) of (VIIIb), m.p. 90−92°.

Methyl 4,6-di-O-benzoyl-2,3-dideoxy-D-*erythro-hex-2-enopyranoside* (IIIb) (443 mg), when treated with hydrogen fluoride for 20 h as described above, gave (VIIIb) as a syrup (420 mg) which was characterized by TLC and NMR spectroscopy.

The tribenzoylated fluoride (VIIIb) was, in the three experiments described above, obtained as a syrup in *ca.* 60 % yield. The syrup was pure as far as it could be seen from TLC and NMR spectra. However, only about half of it could be crystallized. A complete crystallization is probably inhibited by small amounts of impurities.

Preparation of methyl 3,4,6-tri-O-benzoyl-2-deoxy-α- and-β-D-*ribo-hexopyranosides directly from tri-O-benzoyl*-D-*glucal.* Tri-*O*-benzoyl-D-glucal (803 mg) was dissolved in anhydrous hydrogen fluoride (2 ml) at *ca.* −60° and the solution was kept for 23 h at −70° to −60°. Work up as described above gave 625 mg of crude (VIIb). The product was dissolved in methanol (5 ml) and one drop of conc. hydrochloric acid was added. After standing over night at room temperature the reaction mixture was neutralized with solid sodium hydrogen carbonate, filtered and evaporated *in vacuo*. The syrup obtained was benzoylated in the usual manner in pyridine (3 ml) with benzoyl chloride

(1 ml) giving 823 mg of crude product. Preparative TLC using ether-pentane (1:1) as an eluent gave 432 mg (50 %) of a syrup which could be induced to crystallization. Recrystallization from ether-pentane and from methanol gave the pure β-glycoside (X), m.p. 100—101°. $[\alpha]_D^{22} = +97.0°$ (c 2.1, $CHCl_3$). (Found: C 68.61; H 5.41. Calc. for $C_{28}H_{26}O_8$: C 68.57; H 5.34). In addition the α-anomer (X) was isolated as a syrup (103 mg, 12 %) which could be crystallized from ether-pentane, m.p. 90—95°. The compound was identical with the product previously described.[2]

Microanalyses were performed by Dr. A. Bernhardt.

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