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Reaction of Tri-*O*-acetyl- and Tri-*O*-benzoyl-D-glucal with Hydrogen Fluoride

INGE LUNDT and CHRISTIAN PEDERSEN

Organisk-kemisk Laboratorium, Polyteknisk Læreanstalt, Bygning 201, Lyngby, Denmark

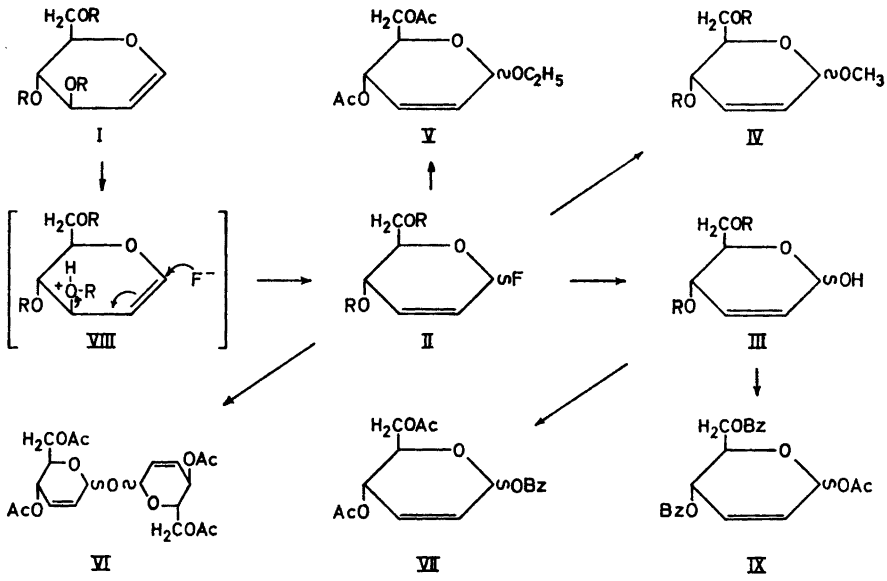
Treatment of tri-*O*-acetyl-D-glucal with hydrogen fluoride in benzene gave a very unstable fluoride which is believed to be 4,6-di-*O*-acetyl-2,3-didehydro-2,3-dideoxy-D-*erythro*hexosyl fluoride. Reaction of this fluoride with water gave, according to the conditions, either an acetylated disaccharide or 4,6-di-*O*-acetyl-D-pseudoglucal. With methanol and ethanol the corresponding unsaturated glycosides were obtained. Tri-*O*-benzoyl-D-glucal reacted in an analogous manner when treated with hydrogen fluoride.

The reaction between tri-*O*-acetyl-D-glucal and hydrogen bromide or hydrogen chloride has been shown to give tri-*O*-acetyl-2-deoxy-D-glucopyranosyl halides.[1,2] The bromide has been used for the preparation of nucleosides.[1,2] Both the bromide and the chloride are unstable syrups neither of which have been obtained in a pure state.

It might be expected that treatment of tri-*O*-acetyl-D-glucal with hydrogen fluoride would proceed in a similar manner to give tri-*O*-acetyl-2-deoxy-D-glucopyranosyl fluoride, and since glycosyl fluorides are usually much more stable than the corresponding chlorides and bromides it was hoped that it should be possible to obtain this fluoride in a pure state. However, as described in the present paper, treatment of tri-*O*-acetyl-D-glucal with hydrogen fluoride did not give a 2-deoxy-D-glucopyranosyl fluoride.

Since the reaction of tri-*O*-acetyl-D-glucal with hydrogen bromide and hydrogen chloride has generally been performed in benzene as solvent this solvent was also used for the reaction with hydrogen fluoride. Treatment of tri-*O*-acetyl-D-glucal with anhydrous hydrogen fluoride without any solvent led to decomposition.

Tri-*O*-acetyl-D-glucal (Ia) was treated with an excess of a saturated solution of hydrogen fluoride in benzene for 30 min at 0° and the excess hydrogen fluoride was then removed by washing with aqueous sodium hydrogen carbonate. Removal of the solvent gave a colourless syrup which, however, rapidly decomposed at room temperature with liberation of hydrogen fluoride and formation of dark coloured products. A NMR spectrum on the crude



a: R=Ac b: R=Bz

product showed that no tri-*O*-acetyl-D-glucal remained and it also showed that none of the expected tri-*O*-acetyl-2-deoxy-D-glucopyranosyl fluoride had been formed. The NMR spectrum indicated that the product was an unsaturated compound with the structure (IIa). A broad singlet at δ 5.9 with intensity 2 was assigned to the vinylic protons at C_2 and C_3 and a broad doublet at δ 5.3 corresponded to H_1 and H_4. The two protons at C_6 gave a signal at 4.15 and H_5 gave a multiplet at 4.1. The acetyl groups gave a sharp signal at δ 2.05 with intensity 6 showing that one of the acetyl groups in tri-*O*-acetyl-D-glucal had been lost.

Attempts to purify the product by column chromatography on silica gel were unsuccessful as the material decomposed on the column. A fluorine determination on the crude product gave values that were too low.

Since it was suspected that the low fluorine value was caused by partial hydrolysis during the washing with aqueous sodium hydrogen carbonate it was tried to remove excess hydrogen fluoride from the reaction mixture by addition of a large excess of dry sodium fluoride. This gave a product which was somewhat more stable and which gave a fluorine analysis that agreed fairly well with that calculated for 4,6-di-*O*-acetyl-2,3-didehydro-2,3-dideoxy-D-erythrosyl fluoride (IIa). A NMR spectrum of this product was similar to the one described above. For all the subsequent experiments the product obtained by removal of hydrogen fluoride with sodium fluoride was used.

A compound with structure (IIa) would be expected to react with water to give 4,6-di-*O*-acetyl-D-pseudoglucal (IIIa) and with alcohols to give the

corresponding glycosides and this was also found to be the case although complications occurred in the reaction with water.

When the crude fluoride (IIa) was kept in aqueous acetone for 24 h a product was obtained which was shown by thin layer chromatography to be a complex mixture; however, infrared and NMR spectra showed that no hydroxy groups were present in this mixture. Column chromatography gave a 30 % yield of a crystalline compound which is believed to be a disaccharide (VI) on the basis of its analysis and molecular weight. The spectrum showed the vinylic protons as a broad singlet at δ 5.97; H_1 and H_4 gave a broad doublet at 5.5; H_6 gave a singlet at 4.2 and H_5 a complex signal at 4.1. The acetyl groups gave a sharp singlet at δ 2.10. The infrared spectrum showed that no hydroxy group was present; besides, it did not show any band at 1650 cm^{-1} indicating that the double bond is not between C_1 and C_2.[3] On hydrogenation a syrupy product was obtained. This was not purified, but its NMR spectrum showed that the vinylic protons had disappeared and a new complex signal at δ *ca.* 1.8 had appeared. (VI) was also obtained in small amounts when it was attempted to purify the fluoride (IIa) by chromatography on a column of silica gel.

In a separate experiment tri-*O*-acetyl-D-glucal was treated with hydrogen fluoride in benzene as described above; but the solution was poured into aqueous acetone without previous removal of excess hydrogen fluoride. This gave a crude product which was shown by NMR to contain a hydroxy group (a broad signal at δ 4.7). This was confirmed by treatment with deuterium oxide which caused this signal to disappear. Benzoylation of the crude product followed by column chromatography gave a 34 % yield of 1-*O*-benzoyl-4,6-di-*O*-acetyl-2,3-didehydro-2,3-dideoxy-D-*erythro*hexose (VII) as a syrup which was identical with an authentic sample prepared by benzoylation of 4,6-di-*O*-acetyl-D-pseudoglucal. The NMR spectrum of (VII) showed 5 aromatic protons; the two acetyl groups gave signals at δ 2.05 and 2.15. The signal of H_1 was a singlet at 6.60 and the vinylic protons gave a singlet at 6.05. H_4 gave a complex signal at 5.3—5.6 and H_5 and H_6 gave a signal at δ 4.25.

Treatment of the crude fluoride (IIa) with methanol gave the corresponding methyl glycoside (IVa). After purification by column chromatography a 54 % yield of this material was obtained as a mixture of the two anomers. The product was identical with the material obtained by Ferrier [3] from the reaction of tri-*O*-acetyl-D-glucal with methanol and the same proportion of anomers was obtained as seen from the NMR spectra.

Analogously reaction of the fluoride (IIa) with ethanol gave a 33 % yield of ethyl 4,6-di-*O*-acetyl-2,3-didehydro-2,3-dideoxy-D-*erythro*hexoside (V) as a crystalline compound identical with the product prepared according to Ferrier.[3] As a byproduct a 20 % yield of the disaccharide (VI) was obtained. This was not isolated from the reaction of (IIa) with methanol.

The formation of the unsaturated fluoride (IIa) probably proceeds *via* a protonated intermediate (VIIIa) which undergoes an allylic displacement of the protonated acetoxy group at C_3 with formation of (IIa) analogous to the reaction of tri-*O*-acetyl-D-glucal with neutral reagents as described by Ferrier.[3] The conversion of (IIa) to (VI) in preference of (III) in the absence of excess hydrogen fluoride cannot be explained at the moment.

The reaction of tri-*O*-benzoyl-D-glucal with hydrogen fluoride was also investigated in the hope that a more stable analogue of (IIa) might be obtained.

Tri-*O*-benzoyl-D-glucal was obtained by benzoylation of D-glucal as a chromatographically pure syrup. Its NMR spectrum was closely similar to that of tri-*O*-acetyl-D-glucal.[4]

Reaction of tri-*O*-benzoyl-D-glucal with hydrogen fluoride in benzene and removal of excess hydrogen fluoride with sodium fluoride gave an unsaturated fluoride (IIb). This fluoride was also too unstable to be purified. The NMR spectrum showed the vinylic protons as a complex signal at δ 6.0—6.1; H_1 and H_4 gave a group of signals at 5.7; H_6 gave a broad singlet at 4.6 and H_5 a multiplet at 4.45. Besides, signals corresponding to the aromatic protons were present.

The hydrolysis of the benzoylated fluoride (IIb) in aqueous acetone proceeded without complications and chromatography of the hydrolysis product gave a 47 % yield of crystalline 4,6-di-*O*-benzoyl-2,3-didehydro-2,3-dideoxy-D-*erythro*hexose (IIIb). The NMR spectrum of this product showed, besides 10 aromatic protons two vinylic protons as a singlet at δ 6.06. H_1 and H_4 gave a complex group of signals at 5.5—5.9 and H_5 and H_6 gave a broad signal at 4.6. A hydroxy group was found as a broad signal at 3.8; this signal disappeared by treatment with deuterium oxide. Acetylation of this compound also caused the NMR signal of the hydroxyl proton to disappear and at the same time a signal for the acetyl group appeared at δ 2.10. In the acetylated compound (IX) the signal for H_1 was shifted downfield to 6.42.

Reaction of the benzoylated fluoride with methanol gave an unsaturated syrupy methyl glycoside (IVb). The NMR spectrum showed the methyl group as a sharp signal at δ 3.48. H_1 gave two signals at 4.98 and 5.13 indicating that the product was a mixture of two anomers. H_2 and H_3 gave a signal at 5.98; H_4 gave a doublet centered at 5.70. H_6 gave a broad singlet at 4.5 and H_5 a multiplet at 4.4.

EXPERIMENTAL

Thin layer chromatography was done on silica gel HF_{254} ("Merck"); for preparative work 1 mm layers of silica gel PF_{254} was used. Spots were visualized by spraying with 10 % sulphuric acid followed by heating to 120° or by viewing under UV light. NMR spectra were taken in deuterochloroform on a Varian A-60 instrument using tetramethyl silane as an internal standard. Position of signals are given in δ-values.

*Reaction of tri-*O*-acetyl-*D*-glucal with hydrogen fluoride.* Tri-*O*-acetyl-D-glucal (1.0 g) was dissolved in 20 ml of a saturated solution of hydrogen fluoride in benzene (the solution was 0.5 N in hydrogen fluoride) at 0° and the solution was kept for 30 min during which time it became slightly red coloured. It was then diluted with methylene chloride and washed with ice-water and saturated aqueous sodium hydrogen carbonate and dried. The solvent was removed *in vacuo* at room temperature leaving a colourless syrup which rapidly became dark and liberated hydrogen fluoride.

The colourless product was found to contain *ca.* 4 % fluorine (calc. for $C_{10}H_{13}FO_5$: 8.2 %); this value is probably too low because it was difficult to remove the solvent completely without decomposing the material. Products which had become dark by standing or by prolonged evaporation were found to contain only 1 % fluorine.*

* For fluorine determination the product was boiled for 3 h with 1 N hydrochloric acid which contained 10 % of hydrogen peroxide. After neutralization with 1 N sodium hydroxide (to pH $\simeq$ 4) the fluorine ions were determined gravimetrically as lead chloride fluoride.[5]

In a separate series of experiments tri-*O*-acetyl-D-glucal was treated with hydrogen fluoride in benzene as described above. The excess hydrogen fluoride was then removed by addition of an excess of dry sodium fluoride which after a few minutes was filtered off. The treatment with sodium fluoride was repeated twice and the solvent was finally removed *in vacuo* at room temperature. This gave a colourless syrup which showed less tendency to become discoloured. Fluorine determinations on this product gave values of 8—10 % (after correction for the acetic acid that remained in the product).

Hydrolysis of the crude fluoride. The fluoride was prepared as described above from 1.0 g of tri-*O*-acetyl-D-glucal; excess hydrogen fluoride was removed with sodium fluoride and the solvent was evaporated. The crude fluoride was dissolved in a mixture of acetone (40 ml) and water (10 ml) and the solution was kept for 24 h at room temperature. The acetone was then removed *in vacuo* and the remaining aqueous phase was extracted three times with methylene chloride. The methylene chloride solution was washed with sodium hydrogen carbonate and dried and the solvent was removed leaving 700 mg of a colourless syrup which gave several spots on thin layer chromatography. The product was chromatographed on a column of silica gel (200 g) using benzene-ether (1:1) as eluant and several fractions were collected. The first fraction to come off the column gave by evaporation of the solvent 240 mg (30 %) of the crystalline disaccharide (VI). Several recrystallizations from ether-pentane gave a pure sample, m.p. 68—72°, $[\alpha]_D^{22} = +78°$ (*c* 1.1; $CHCl_3$). (Found: C 54.27; H 6.02; O 39.18. Calc. for $C_{20}H_{26}O_{11}$: C 54.30; H 5.92; O 39.78). (Molecular weight, found: 408; calc.: 442). The other fractions which were eluted from the column were not homogeneous. NMR and infrared spectra showed that no hydroxy groups were present.

In another experiment tri-*O*-acetyl-D-glucal (1.0 g) was treated with 20 ml of benzene saturated with hydrogen fluoride for 30 min at 0°. The solution was then poured into a mixture of water (25 ml) and acetone (25 ml) and the mixture was stirred for 24 h at room temperature. It was then extracted with methylene chloride and the extract was washed with sodium hydrogen carbonate and dried. Evaporation of the solvent gave 890 mg of a colourless syrup which was benzoylated with pyridine (2 ml) and benzoyl chloride (0.8 ml) in the usual manner. The benzoylated product (1.0 g) was a dark syrup which was chromatographed on a column of silica gel (200 g) using benzene-ether (1:1) as eluant. The largest fraction (which had the highest R_F-value) by evaporation of the solvent gave 400 mg (34 %) of 1-*O*-benzoyl-4,6-di-*O*-acetyl-2,3-didehydro-2,3-dideoxy-D-*erythro*hexose. A sample of the product was further purified by preparative thin layer chromatography using ether-pentane (1:1) as eluant. $[\alpha]_D^{22} = -32.1°$ (*c* 1.4, $CHCl_3$). The NMR spectrum was identical with that of the product described below.

*Methyl 4,6-di-*O*-acetyl-2,3-didehydro-2,3-dideoxy*-D-erythro*hexoside.* Tri-*O*-acetyl-D-glucal (1.0 g) was treated with hydrogen fluoride in benzene as described above; excess hydrogen fluoride was removed with sodium fluoride. The crude fluoride was immediately dissolved in methanol (50 ml). The solution was kept at room temperature for 20 h during which time the pH changed from *ca.* 6 to *ca.* 2; the solution was then neutralized with barium carbonate and filtered. Evaporation of the methanol left 0.61 g of a colourless syrup which was acetylated with acetic anhydride in pyridine. The acetylated product (0.69 g) gave one large spot and three smaller ones on thin layer chromatography. The product was purified by chromatography on a column of silica gel (100 g) using benzene-ether (1:1) as eluant. Removal of the solvent from the fraction which corresponded to the large spot gave 484 mg (54 %) of methyl glycoside, $[\alpha]_D^{25} = +141°$ (*c* 4, $CHCl_3$), (reported [3] $[\alpha]_D = +139°$). The NMR and infrared spectra were identical with those of a product prepared according to Ferrier [3] from tri-*O*-acetyl-D-glucal and methanol.

*Ethyl 4,6-di-*O*-acetyl-2,3-didehydro-2,3-dideoxy*-D-erythro*hexoside.* The crude fluoride obtained from 2.0 g of tri-*O*-acetyl-D-glucal was dissolved in ethanol (50 ml) and the solution was kept over night at room temperature. It was then neutralized with barium carbonate and the ethanol was removed *in vacuo* leaving a colourless syrup (1.7 g) which was acetylated with acetic anhydride in pyridine. The acetylated product (1.5 g) gave 2 spots on thin layer chromatography and it was separated into the corresponding two components by chromatography on a column of silica gel (200 g) using benzene-ether (1:1) as eluant.

The fast moving component was crystallized and recrystallized from ether-pentane yielding 630 mg (33 %) of ethyl glycoside, m.p. 78—79°, $[\alpha]_D^{23} = +118°$ (*c* 1.6, $CHCl_3$).

A sample prepared according to Ferrier [3] had $[\alpha]_D^{23} = +117°$ (*c* 1.4, $CHCl_3$). NMR and infrared spectra proved the identity of the two products.

After elution of a mixed fraction (250 mg) the slower moving fraction was collected. Crystallization from ether-pentane gave 300 mg (18.5 %) of the disaccharide (VI), m.p. 67–70°.

*Tri-*O*-benzoyl-*D*-glucal.* A mixture of pyridine (150 ml) and benzoyl chloride (52 ml) was stirred and cooled in ice while D-glucal [6] (14.5 g) was added in the course of 1 h. The mixture was kept over night at +5°. Water (1 ml) was then added and after 1 h the mixture was diluted with methylene chloride (100 ml) and washed successively with 3 N sulphuric acid, saturated aqueous sodium hydrogen carbonate and water. The solution was dried and the solvent was removed *in vacuo* leaving 41.6 g (91 %) of tri-*O*-benzoyl-D-glucal as a slightly yellow syrup which could not be induced to crystallize. The product gave one spot only on thin layer chromatography in several different solvents. $[\alpha]_D^{26} = -8.1°$ (*c* 5, $CHCl_3$). (Found: C 70.75; H 5.41. Calc. for $C_{27}H_{22}O_7$: C 70.73; H 4.84).

The NMR spectrum showed H_1 as a quartet centered at δ 6.68, $J_{H_1H_2} = 6.0$ cps. H_2 gave a complex signal at δ 5.18. H_3 and H_4 gave a group of signals at *ca.* 5.8, H_5 and H_6 a broad signal at 4.75.

*Reaction of tri-*O*-benzoyl-*D*-glucal with hydrogen fluoride.* Tri-*O*-benzoyl-D-glucal was treated with hydrogen fluoride in benzene as described for the corresponding acetate. Excess hydrogen fluoride was removed with sodium fluoride. Removal of the solvent gave a colourless syrup which on thin layer chromatography with benzene-ether (8:2) gave one large spot and a small spot. Attempts to purify the product by chromatography on a column of silica gel were unsuccessful as the product reacted on the column with the formation of several compounds as seen by thin layer chromatography of the eluate. A small amount of 4,6-di-*O*-benzoyl-D-pseudoglucal was isolated from the column, indicating that some hydrolysis took place.

*Hydrolysis of 4,6-di-*O*-benzoyl-2,3-didehydro-2,3-dideoxy-*D*-erythrohexosyl fluoride.* The crude fluoride obtained from 1.0 g of tri-*O*-benzoyl-D-glucal as described above was dissolved in 50 ml of acetone containing 20 % of water. A few drops of aqueous hydrogen fluoride was added and the solution was kept at room temperature for 24 h. The acetone was then removed *in vacuo* and the aqueous phase was extracted with methylene chloride. The extract was washed with sodium hydrogen carbonate and water and dried. Removal of the solvent left 780 mg of syrup which on thin layer chromatography showed several spots. Crystallization from ether-pentane gave 130 mg of 4,6-di-*O*-benzoyl-2,3-didehydro-2,3-dideoxy-D-*erythro*hexopyranose, m.p. 118–122°. The material in the mother liquor was fractionated by preparative thin layer chromatography using benzene-ether (8:2) as eluant. Thereby an additional amount (210 mg) of the dibenzoate was obtained bringing the total yield of this compound to 340 mg (47 %). The product was recrystallized from ether-pentane, m.p. 124–127°, $[\alpha]_D^{23} = +157°$ (*c* 0.6, $CHCl_3$). (Found: C 67.65; H 5.14; O 27.27. Calc. for $C_{20}H_{18}O_6$: C 67.78; H 5.12; O 27.09. Molecular weight: found 339; calc. 330).

*1-*O*-Acetyl-4,6-di-*O*-benzoyl-2,3-didehydro-2,3-dideoxy-*D*-erythrohexopyranose.* The benzoate (100 mg) was dissolved in a mixture of pyridine (0.5 ml) and acetic anhydride (0.2 ml) and the solution was kept over night at +5°. A few drops of water was then added and 5 min later methylene chloride. The solution was washed with 3 N sulphuric acid, sodium hydrogen carbonate and water. After drying the solvent was removed leaving 100 mg (89 %) of a colourless syrup which gave one spot only on thin layer chromatography in several different solvents. $[\alpha]_D^{25} = +92.4°$ (*c* 1.4, $CHCl_3$). (Found: C 66.68; H 5.12. Calc. for $C_{22}H_{20}O_7$: C 66.66; H 5.09).

*Methyl 4,6-di-*O*-benzoyl-2,3-didehydro-2,3-dideoxy-*D*-erythrohexoside.* The crude fluoride from 1.0 g of tri-*O*-benzoyl-D-glucal was dissolved in methanol (50 ml) and the solution was kept at room temperature for 24 h. It was then neutralized with barium carbonate, filtered and evaporated *in vacuo* leaving 0.80 g of a colourless syrup which on thin layer chromatography gave one large spot and a smaller one. The material corresponding to the large spot was isolated by preparative thin layer chromatography using benzene-ether (1:1) as eluant. Yield 0.72 g (90 %). $[\alpha]_D^{23} = +143°$ (*c* 1.2, $CHCl_3$). (Found: C 68.37; H 5.55. Calc. for $C_{21}H_{20}O_6$: C 68.46; H 5.47).

*Benzoylation of 4,6-di-*O*-acetyl-*D*-pseudoglucal.* Tri-*O*-acetyl-D-glucal (5.0 g) and water (100 ml) was boiled for 15 min and the solution was then extracted 5 times with methylene

chloride. The extract was washed with sodium hydrogen carbonate and water and dried. Removal of the solvent left 3.0 g of crude 4,6-di-*O*-acetyl-2,3-didehydro-2,3-dideoxy-D-*erythro*hexose.[7] This was benzoylated with benzoyl chloride (3.0 ml) in pyridine (6.0 ml). The benzoylated product was a brown syrup which by treatment with ether gave a flocculent precipitate. The ether solution was filtered through activated carbon and the ether was evaporated. The residue (3.0 g) was chromatographed on a column of silica gel (400 g) using benzene-ether (1:1) as eluant. The first fraction to come off the column gave 1.04 g (17 %) of 1-*O*-benzoyl-4,6-di-*O*-acetyl-2,3-didehydro-2,3-dideoxy-D-*erythro*-hexoside, as a colourless syrup, $[\alpha]_D^{22} = -29.2°$ (*c* 2.4, $CHCl_3$). A sample was further purified by preparative thin layer chromatography using ether-pentane (1:1) as eluant. $[\alpha]_D^{22} = -33.7°$ (*c* 2.4, $CHCl_3$). (Found: C 60.71; H 5.35. Calc. for $C_{17}H_{18}O_7$: C 61.08; H 5.43).

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