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Reaction of 1,2-Dideoxy-glyc-1-enopyranoses and 2-Deoxyglycopyranoses with Hydrogen Fluoride. IV*

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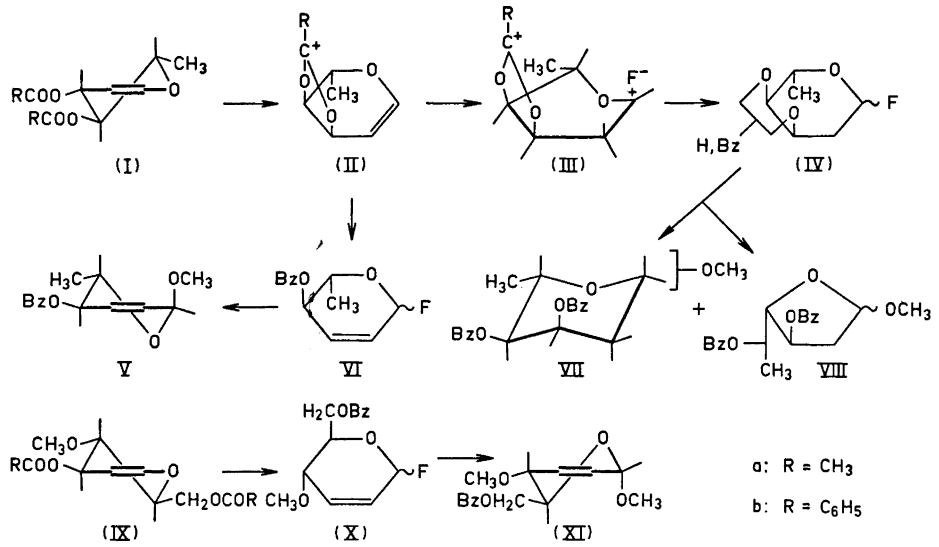
Reaction of 3,4-di-*O*-acyl-1,2,6-trideoxy-L-*arabino*-hex-1-enopyranose (I) with anhydrous hydrogen fluoride yields a 3,4-dioxolanylium ion (III), which by hydrolysis, benzoylation, and treatment with methanol is converted into benzoylated methyl glycosides, derived from 2,6-dideoxy-L-*ribo*-hexose. Treatment of (I) with hydrogen fluoride in benzene gives an unstable 2,3-unsaturated glycosyl fluoride (VI), which was isolated as methyl 2,3,6-trideoxy-α-L-*erythro*-hex-2-enopyranoside (V). 3,6-Di-*O*-benzoyl-4-*O*-methyl-1,2-dideoxy-D-*arabino*-hex-1-enopyranose (IX), when treated with hydrogen fluoride, also gave a 2,3-unsaturated fluoride (X). This was isolated as methyl 4-*O*-methyl-6-*O*-benzoyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (XI).

Treatment of tri-*O*-acyl-1,2-dideoxy-D-*arabino*-hex-1-enopyranose with hydrogen fluoride was previously shown to yield derivatives of 2-deoxy-D-*ribo*-hexopyranose.[3] If the mechanism proposed for this reaction [3] is correct, it would be expected that reaction of di-*O*-acyl-1,2,6-trideoxy-L-*arabino*-hex-1-enopyranose (I) with hydrogen fluoride should lead to derivatives of 2,6-dideoxy-L-*ribo*-hexopyranosyl fluoride (IV), since the acyloxy-groups of (I) have the same relative configuration as those of the corresponding groups in 1,2-dideoxy-D-*arabino*-hex-1-enopyranose derivatives.

The reaction of the acetate (Ia) and of the benzoate (Ib) with anhydrous hydrogen fluoride was first studied by NMR spectroscopy. The spectra showed that (Ia) and (Ib) were rapidly converted into the 3,4-dioxolanylium ions (IIIa) and (IIIb), respectively; even at −70°C, the reaction was complete in less than 2 h. The ion (II), which is probably an intermediate,[3] could not be detected because of the high reaction rate. An NMR spectrum of the diacetate (Ia) in hydrogen fluoride solution, obtained after 1 h at −30°C, showed a 3 proton signal at 2.8 δ, corresponding to the acetoxonium ion of (IIIa), and a

* For previous papers in this series, Refs. 1, 2 and 3.



signal at 2.63 δ, showing that one equivalent of acetic acid was liberated. The signals from the C-2 protons of (IIIa) were partly hidden under the signals of the methyl groups. However, a spectrum of the benzoate (Ib), obtained under the same conditions, showed a complex 2 proton signal at 2.8 – 3.1 δ, arising from H-2 of (IIIb). An analysis of the spectrum of (IIIb) in hydrogen fluoride gave the following δ-values and coupling constants in cps: H-3 (6.3), H-4 (5.9), H-5 (4.9), H-6 (1.7); J_{2e3} (4.5), J_{2a3} (4.5), J_{34} (9.0), J_{45} (4.5), J_{56} (7.0). The assignments were verified by spin decoupling experiments at 100 MHz. The signal of H-1 was obscured by the complex group of signals from H-3 and H-4, and it could not be analysed. As far as it could be seen, the signal was not broad enough to contain an $H_1 - F$ coupling. It is therefore possible that (III) should be formulated as an ion-pair, as shown, and not as a glycosyl fluoride.

When the solution of (IIIb) in hydrogen fluoride was worked up, a mixture of monobenzoylated 2,6-dideoxy-L-*ribo*-hexopyranosyl fluorides (IV) would be the expected product.[3] This was, however, very unstable, and it was partly hydrolysed to the 1-hydroxy-compound. It was therefore immediately benzoylated, and the product thus obtained was treated with methanol and boron trifluoride. This gave a mixture of the anomeric methyl 3,4-di-*O*-benzoyl-2,6-dideoxy-L-*ribo*-hexopyranosides (VII) and the corresponding furanosides (VIII). The anomeric pyranosides (α- and β-VII) were obtained pure, and their structures could be unambiguously established through the spectra (Table 1). Both compounds adopt the $^1C_4$ (L) conformation. The anomeric furanosides (VIII) could not be separated, and a complete analysis of the spectra was therefore not possible. NMR spectra show that only the ion (III) is present in the hydrogen fluoride solution. The furanosides (VIII) must therefore be formed when the hydrogen fluoride solution is worked up and

Table 1. Chemical shifts (δ-values) and coupling constants (cps) in deuteriochloroform of compounds shown in Fig. 1.

Compound	H_1	H_2	H_3	H_4	H_5	H_6	H_6'	$-OCH_3$	Conformation derived from spectrum
Ia	6.44 $J_{12}=6.0$ $J_{13}=1.3$	4.76 $J_{23}=3.0$	5.35 $J_{34}=6.5$	5.01 $J_{45}=8.0$	4.10 $J_{56}=6.5$	1.30			$^5H_4$ (L)
Ib	6.52 $J_{12}=6.0$ $J_{13}=1.3$	5.01 $J_{23}=3.0$	5.74 $J_{34}=6.0$	5.53 $J_{45}=8.0$	4.36 $J_{56}=6.4$	1.46			$^5H_4$ (L)
IXa	6.39 $J_{12}=6.0$ $J_{13}=1.4$	4.78 $J_{23}=3.1$ $J_{25}=0.3$	5.32 $J_{34}=5.6$ $J_{35}=0.6$	3.54 $J_{45}=7.4$	4.11 $J_{56}=4.0$ $J_{56'}=4.5$	4.44 $J_{66'}=11.0$	4.31	3.49	$^4H_5$ (D)
IXb	6.48 $J_{12}=6.0$ $J_{13}=1.2$	4.95 $J_{23}=3.3$ $J_{25}=0.4$	5.64 $J_{34}=5.4$ $J_{35}=0.8$	3.84 $J_{45}=7.4$	4.39 $J_{56}=5.5$ $J_{56'}=3.2$	4.78 $J_{66'}=12.0$	4.64	3.55	$^4H_5$ (D)
XI	4.89 $J_{12}=2.6$ $J_{13}=0.8$ $J_{14}=1.6$	5.80 $J_{23}=10.0$ $J_{24}=1.8$	6.11 $J_{34}=1.5$	3.85 $J_{45}=9.6$	4.09 $J_{56}=2.6$ $J_{56'}=5.2$	4.67 $J_{66'}=11.6$	4.53	3.45; 3.42	$^OH_5$ (D)
VII, α	4.83 $J_{12e}=2.5$ $J_{12a}=3.5$	2.18–2.36 $J_{2e3}=$ $J_{2a3}=3.3$	5.70 $J_{34}=3.3$	5.07 $J_{45}=9.5$	4.53 $J_{56}=6.3$	1.30		3.44	$^1C_4$ (L)
VII, β	4.90 $J_{12e}=2.8$ $J_{12a}=8.8$	He Ha 2.31; 2.01 $J_{2e\,2a}=14.4$ $J_{2e3}=3.8$	5.84 $J_{34}=3.0$ $J_{2a3}=3.0$	5.01 $J_{45}=9.2$	4.27 $J_{56}=6.1$	1.38		3.52	$^1C_4$ (L)

the product converted into the methyl glycosides. Since a mixture of pyranosides and furanosides is obtained, the reaction is not suited for the preparation of 2,6-dideoxy-L-*ribo*-hexose derivatives.

Treatment of (Ib) with a saturated solution of hydrogen fluoride in benzene gave an unstable product, probably the 2,3-unsaturated fluoride (VI), which, by treatment with methanol and boron trifluoride, yielded methyl 4-*O*-benzoyl-2,3,6-trideoxy-α-L-*erythro*-hex-2-enopyranoside (V) in 65 % yield.

The driving force in the reaction of acylated 1,2-dideoxy-D-*arabino*-hex-1-enopyranose [3] or 1,2,3-trideoxy-L-*arabino*-hex-1-enopyranose (I) with hydrogen fluoride is probably the formation of the 3,4-dioxolenium ions, which are stable in hydrogen fluoride solution. In the absence of an acyloxy group at C-4, no dioxolenium ion can be formed, and in order to study the consequences of this, the reaction of 4-*O*-methyl-3,6-di-*O*-acyl-1,2-dideoxy-D-*arabino*-hex-1-enopyranose (IX) with hydrogen fluoride has been investigated.

The NMR spectra of (IXa) or (IXb) in hydrogen fluoride solution could not be analysed in detail. It could be seen, however, that both compounds reacted completely within a couple of minutes at −60°C, and the products decomposed in the course of 1 − 2 days. The spectrum of the acetate (IXa) showed that one equivalent of acetic acid was liberated at once; no signals corresponding to acetoxonium ions were present. The spectrum of the benzoate (IXb) in hydrogen fluoride showed no signals corresponding to deoxy-protons, indicating that addition of hydrogen fluoride to the double bond does not take place.

Treatment of (IXb) with anhydrous hydrogen fluoride for 15 min at −70°C resulted in isolation of a very unstable product, presumably the 2,3-unsaturated fluoride (X). This was immediately treated with methanol, to give methyl 4-*O*-methyl-6-*O*-benzoyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (XI) in 30 % yield. Its NMR spectrum (Table 1) proves the structure and shows that the compound adopts the $^{O}H_{5}$-conformation. Reaction of (IXb) with hydrogen fluoride in benzene at 0°C gave a better yield of the methyl glycoside (XIb). Reaction with anhydrous hydrogen fluoride for 3 h at −25°C resulted in decomposition, as seen from the dark colour of the hydrogen fluoride solution, and no pure products could be isolated.

The hex-1-enopyranose derivatives, so far investigated, loose the substituent at C-3 by treatment with hydrogen fluoride and form an intermediate which yields the 2,3-unsaturated fluoride by work up. This intermediate is unstable and decomposes rather rapidly in the case of the 4-*O*-methyl-compound (IX). When a 4-*O*-acyl-group is present as in (I) or in the 1,2-dideoxy-D-*arabino*-hex-1-enopyranose derivatives previously investigated,[3] the intermediate stabilises by conversion into a dioxolanylium ion.

EXPERIMENTAL

Melting points are uncorrected. For details of thin layer chromatography (TLC) and NMR spectra, see Ref. 3.

*3,4-Di-*O*-benzoyl-1,2,6-trideoxy-*L-arabino-*hex-1-enopyranose (Ib).* A mixture of pyridine (25 ml) and benzoyl chloride (10 ml) was cooled to 0°C, and 1,2,6-trideoxy-L-*arabino*-hex-1-enopyranose [4] (3.0 g) was added with stirring and cooling in the course of 30 min. The mixture was then kept over night at +5°C. Methylene chloride was added,

and the solution was washed with water, 3 N sulfuric acid, and aqueous sodium hydrogencarbonate, dried and evaporated. This gave 6.9 g (91 %) of (Ib) as a colourless syrup which was virtually pure as seen from the NMR spectrum (Table 1). A sample was purified for analysis by preparative TLC, using ether:pentane (1:1) as eluent. (Found: C 71.05; H 5.45. Calc. for $C_{20}H_{18}O_6$: C 70.99; H 5.36.) $[\alpha]_D^{23} = +221°$ (*c* 6.1, $CHCl_3$).

Reaction of 3,4-di-*O*-benzoyl-1,2,6-trideoxy-L-*arabino*-hex-1-enopyranose (Ib) with hydrogen fluoride

With anhydrous hydrogen fluoride at −70°. A solution of (Ib) (220 mg) in anhydrous hydrogen fluoride (1 ml) was kept at −70°C for 30 min. Cold methylene chloride was then added, and the mixture was poured onto ice, and the organic layer was washed with aqueous sodium hydrogencarbonate and dried. Evaporation of the solvent gave an unstable syrup which was immediately dissolved in methanol and kept overnight at room temperature. The solution was then neutralized with solid sodium hydrogencarbonate, filtered and evaporated to give a syrup which was benzoylated with benzoyl chloride and pyridine in the usual manner. The crude product (205 mg) was separated into two fractions by preparative TLC, using ether:pentane (1:2) as eluent. The slow running fraction gave 28 mg (12 %) of (α-VII). The product crystallized and was recrystallized from pentane, m.p. 84–85°C, $[\alpha]_D^{23} = -215°$ (*c* 1.3, $CHCl_3$). (Found: C 68.10; H 5.94. Calc. for $C_{21}H_{22}O_6$: C 68.10; H 5.99.) The fast running fraction was rechromatographed with benzene as eluent. The first fraction thus obtained was a syrup (36 mg, 15 %), which was shown by NMR spectroscopy to be a mixture of the anomeric furanosides (VIII). (Found: C 67.85; H 6.06.) The second fraction gave 38 mg (16 %) of the β-pyranoside (β-VII), $[\alpha]_D^{23} = -103°$ (*c* 2.2, $CHCl_3$). (Found: C 68.10; H 6.05.)

With anhydrous hydrogen fluoride at −27°C. Treatment of (Ib) (258 mg) with hydrogen fluoride at −27°C for 1 h gave an unstable syrup which was immediately benzoylated. The product thus obtained was dissolved in methylene chloride (3 ml), and 0.5 ml of a mixture of methylene chloride, methanol, and boron trifluoride-etherate (17:2:1) was added. The solution was kept for 30 min at room temperature, and was then washed with aqueous sodium hydrogencarbonate, dried and evaporated. The product (300 mg) was chromatographed as described above, giving 73 mg (27 %) of the methyl furanosides (VIII), 56 mg (20 %) of the methyl β-pyranoside (β-VII), and 44 mg (16 %) of (α-VII).

Treatment of (Ib) with hydrogen fluoride for 4 h at −27°C gave the same result. Reaction of the crude product, resulting from treatment of (Ib) with hydrogen fluoride, with methanol and boron trifluoride prior to benzoylation did not change the ratio of furanosides to pyranosides.

With hydrogen fluoride in benzene. A solution of (Ib) (504 mg) in benzene, which was saturated with hydrogen fluoride, was kept at 0°C for 10 min. It was then diluted with methylene chloride, washed with aqueous sodium hydrogencarbonate, dried, and concentrated to a volume of *ca.* 5 ml. To this solution was added 0.7 ml of a mixture of methylene chloride, methanol, and boron trifluoride-etherate (17:2:1), and the solution was kept for 10 min at room temperature. It was then diluted with methylene chloride and washed with aqueous sodium hydrogencarbonate, and dried and evaporated to a syrup (350 mg). Preparative TLC (ether:pentane, 1:3) gave methyl 4-*O*-benzoyl-2,3,6-trideoxy-α-L-*erythro*-hex-2-enopyranoside (V) (230 mg, 65 %), m.p. 43–45°C. The product was identical with that described elsewhere.[5] A minor fraction gave 27 mg (5 %) of methyl 3,4-di-*O*-benzoyl-2,6-dideoxy-α-L-*arabino*-hexopyranoside,[5] resulting from direct addition of hydrogen fluoride to the double bond of (Ib).

3,6-Di-*O*-benzoyl-4-*O*-methyl-1,2-dideoxy-D-*arabino*-hex-1-enopyranose (IXb)

Benzoylation of 4,6-benzylidene-D-glucose (17 g) gave 26 g (71 %) of a mixture of the anomeric 1,2,3-tri-*O*-benzoyl-4,6-benzylidene-D-glucopyranoses after recrystallization from ethanol.[6] Removal of the benzylidene group by hydrolysis yielded 19 g (80 %) of 1,2,3-tri-*O*-benzoyl-α- and β-D-glucopyranose.[6] This product was monobenzoylated with

1.1 equiv. of benzoyl chloride in pyridine.[7] Crystallization of the product from chloroform-pentane gave 10.5 g (45 %) of 1,2,3,6-tetra-*O*-benzoyl-β-D-glucopyranose,[7] m.p. 149–151°C, $[\alpha]_D^{23} = +21.5°$ (*c* 4, $CHCl_3$). NMR data: H_1 (6.42); H_2, H_3 (5.8–6.0); H_4, H_5 (4.0–4.3); H_6 (4.8); –OH (4.1). J_{12} (9 cps). Crystallization of the material in the mother liquor from ether-pentane yielded 10.0 g (43 %) of the corresponding α-anomer, m.p. 119–120°C, $[\alpha]_D^{23} = +138°$ (*c* 5, $CHCl_3$). NMR data: H_1 (7.01); H_2 (5.77); H_3 (6.20); H_4, H_5 (4.0–4.6); H_6 (5.04); H_6' (4.70); –OH (3.7), J_{12} (4.0 cps.); $J_{23} = J_{34}$ (10.5); J_{56} (4); $J_{56'}$ (2); $J_{66'}$ (12.0).

1,2,3,6-Tetra-*O*-benzoyl-α- or β-D-glucopyranose (3.5 g) was dissolved in methylene chloride and methylated with diazomethane in methylene chloride in the presence of boron trifluoride.[8] Crude 1,2,3,6-tetra-*O*-benzoyl-4-*O*-methyl-α- or β-D-glucopyranose were obtained as syrups (3.6 g). The NMR-spectra were in accordance with the structures. The β-anomer gave the following NMR data: H_1 (6.20); H_2,H_3 (5.6–6.0); H_4,H_5 (3.6–4.2); $H_{6,6'}$ (4.6); $-OCH_3$ (3.48). J_{12} (8 cps).

The crude α- or β-compound (3.6 g) was dissolved in methylene chloride (10 ml), and 10 ml of a 30 % solution of hydrogen bromide in acetic acid was added. The solution was kept at room temperature for 20 h. It was then diluted with methylene chloride, washed with water and sodium hydrogen carbonate, dried and evaporated. The syrupy product (3.3 g) consisted of 2,3,6-tri-*O*-benzoyl-4-*O*-methyl-α-D-glucopyranosyl bromide. NMR data: H_1 (6.90); H_2 (5.30); H_3 (6.20); H_4 (3.88); $H_{5,6}$ (4.25–4.8); $-OCH_3$ (3.53). J_{12} (4.0 cps); J_{23} (10.0); J_{34} (9.5); J_{45} (9.5).

The bromide was dissolved in glacial acetic acid (3 ml), and the solution was added, with stirring and ice-cooling, to a mixture of sodium acetate (15 g), water (12 ml), acetic acid (33 ml), acetone (25 ml), and zinc powder (10 g) in the course of *ca.* 10 min. The stirring was continued for 3 h at 0–5°C, and the mixture was then filtered and diluted with water and methylene chloride. The aqueous phase was extracted with methylene chloride, and the combined organic phases were washed with sodium hydrogencarbonate, and dried. Evaporation gave 2.6 g of crude product which was crystallized from a small amount of ether to give 1.02 g (48 %) of 3,6-di-*O*-benzoyl-4-*O*-methyl-1,2,-dideoxy-D-*arabino*-hex-1-enopyranose (IXb), m.p. 86–89°C. Chromatography of the mother liquor on a column of silica gel (100 g), using ether:pentane (1:2) as eluent gave an additional 300 mg of product, m.p. 93–95°C, bringing the total yield to 62 %. Recrystallization from ether-pentane gave pure (IXb), m.p. 95–95.5°C, $[\alpha]_D^{23} = -69.7°$ (*c* 1.5, $CHCl_3$). (Found: C 68.07; H 5.80. Calc. for $C_{21}H_{20}O_6$: C 68.47; H 5.47.) NMR data are presented in Table 1.

Di-O-*acetyl*-4-O-*methyl*-1,2-*dideoxy*-D-arabino-*hex*-1-*enopyranose (IXa).*[9] The dibenzoate (IXb) (511 mg) was debenzoylated by treatment with methanolic barium methoxide for 2 h at room temperature. The solution was evaporated, and the residue was acetylated with acetic anhydride (0.7 ml) in pyridine (2 ml). Work up in the usual way gave a product which was purified by preparative TLC (ether:pentane, 1:1) to give 258 mg (76 %) of pure (IXa) as a syrup, which crystallized on standing at +5°C. The product was characterized through its NMR spectrum (Table 1).

Reaction of (IXb) with hydrogen fluoride in benzene. A solution of (IXb) (100 mg) in benzene (5 ml), saturated with hydrogen fluoride, was kept at 0°C for 5 min. The solution was then diluted with methylene chloride, washed and concentrated to a volume of *ca.* 10 ml. This solution was treated with methanol and boron trifluoride as described above. The product (72 mg) was shown by TLC to contain largely one compound, which was isolated by preparative TLC (ether:pentane, 1:2). This gave 31 mg (41 %) of methyl 4-*O*-methyl-6-*O*-benzoyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (XI) as a syrup, $[\alpha]_D^{23} = +105°$ (*c* 1, $CHCl_3$). (Found: C 64.61; H 6.43. Calc. for $C_{15}H_{18}O_5$: C 64.74; H 6.52.) An NMR spectrum is given in Table 1.

Reaction of (IXb) with anhydrous hydrogen fluoride. A solution of (IXb) (245 mg) in anhydrous hydrogen fluoride (1 ml) was kept for 15 min. at –70°C. It was then worked up as described above, and the very unstable product was immediately treated with methanol and boron trifluoride. This gave 200 mg of product which was separated into several fractions by preparative TLC (ether:pentane, 1:2). The fastest moving fraction gave 55 mg (30 %) of the unsaturated glycoside (XI), identical with the product described above. The other fractions were not pure, as seen from the NMR spectra. None of them showed signals around 2–3 δ, indicating that addition to the double bond of (IX) does not take place.

Microanalyses were performed by Dr. A. Bernhardt.

REFERENCES

1. Lundt, I. and Pedersen, C. *Acta Chem. Scand.* **20** (1966) 1369.
2. Lundt, I. and Pedersen, C. *Acta Chem. Scand.* **21** (1967) 1239.
3. Lundt, I. and Pedersen, C. *Acta Chem. Scand.* **24** (1970) 240.
4. Iselin, B. and Reichstein, T. *Helv. Chim. Acta* **27** (1944) 1146.
5. Bock, K. and Pedersen, C. *To be published.*
6. Brigl, P. and Grüner, H. *Chem. Ber.* **65** (1932) 1428.
7. Wadsworth, W. W., Schroeder, L. R. and Green, J. W. *J. Chem. Soc.* **C 1968** 1008.
8. Gros, E. G. and Mastronardi, I. O. *Carbohyd. Res.* **10** (1969) 318.
9. Wacek, A., Limoutschew, W. and Leitinger, F. *Monatsh.* **88** (1957) 948.

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