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Reaction of Sugar Esters with Hydrogen Fluoride

XII. Derivatives of D-Galactofuranose and D-Talofuranose

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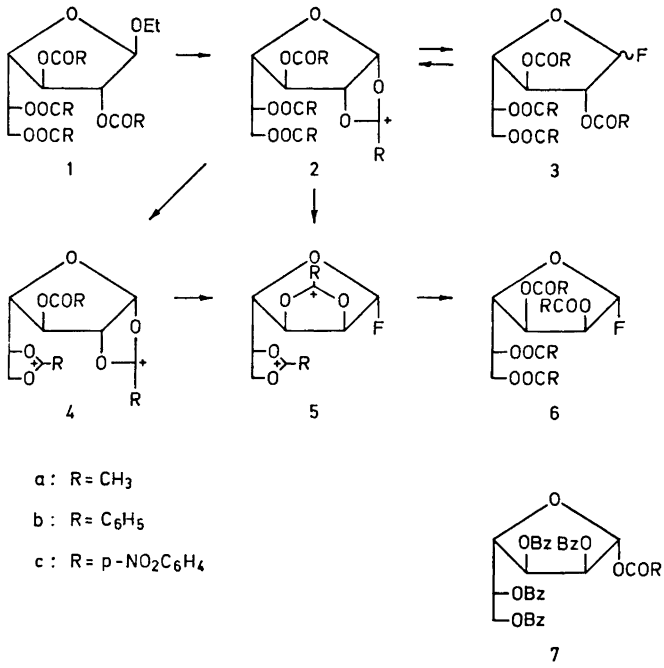
Tetra-*O*-acetyl- and tetra-*O*-benzoyl-β-D-galactofuranosyl fluoride were prepared by brief treatment of the corresponding ethyl glycosides with anhydrous hydrogen fluoride. Prolonged treatment of tetra-*O*-benzoyl-β-D-galactofuranosyl fluoride with hydrogen fluoride led to rearrangement and tetra-*O*-benzoyl-α-D-talofuranosyl fluoride could be isolated in good yield.

In a previous paper it was shown that acetylated or benzoylated glucofuranose derivatives could be rearranged to mannofuranose derivatives by treatment with anhydrous hydrogen fluoride.[1] In the present paper a corresponding rearrangement of D-galactofuranoses to derivatives of D-talofuranose is described.

Brief treatment of ethyl tetra-*O*-benzoyl-β-D-galactofuranoside (*1b*) with anhydrous hydrogen fluoride gave a good yield of tetra-*O*-benzoyl-β-D-galactofuranosyl fluoride (*β-3b*) as the only detectable product. A similar treatment of the tetraacetate (*1a*) gave the β-fluoride (*β-3a*) together with small amounts of tetra-*O*-acetyl-α-D-galactofuranosyl fluoride and 2,3,5,6-tetra-*O*-acetyl-α-D-galactofuranose, the latter isolated as the pentaacetate after acetylation.

The further reaction of the fluorides (*3a* and *b*) and of the glycosides (*1a* and *b*) with hydrogen fluoride was first studied by NMR spectroscopy. The acetylated fluoride (*β-3a*) was dissolved in anhydrous hydrogen fluoride at 0°C and an NMR spectrum was obtained after *ca.* 5 min. This spectrum showed that the 1,2-acetoxonium ion (*2a*) was present as the main product, as seen from an acetoxonium ion signal at 2.98 ppm; H-1 gave a doublet at 7.36 ppm, $J_{12}=5.3$ Hz. Thus the fluoride (*β-3a*) is immediately converted into the acetoxonium ion (*2a*) in hydrogen fluoride, in agreement with previous results.[1,2] When the solution was kept at room temperature further reaction took place and after 24 h spectra showed that (*2a*) was no longer present. After 12 days the diacetoxium ion (*5a*) was the only product as seen from NMR spectra



which gave acetoxonium ion signals at 2.86 and 2.97 ppm; a signal integrating to 6 H corresponding to 2 equivalents of acetic acid was found at 2.52 ppm. The anomeric proton was a doublet centered at 6.51 ppm with a spacing of 61.5 Hz (J_{1F}). Since J_{12} was less than 0.5 Hz the product must be the α-fluoride (*5a*).[3] In analogy with the corresponding reaction in the glucofuranose series [1] the diacetoxonium ion (*4a*) might be expected to be an intermediate in the conversion of (*2a*) into (*5a*), this ion could, however, not be detected with certainty in the NMR spectra. Reaction of the ethyl furanoside (*1a*) with hydrogen fluoride gave the same result. The 1,2-acetoxonium ion was formed at once, and hydrolysis of the solution which contained this ion gave the β-fluoride (*β-3a*) as described above. On further reaction the diacetoxonium ion (*5a*) was formed. The ethanol which was cleaved off from (*1a*) in hydrogen fluoride was quantitatively converted into ethyl acetate by reaction with acetic acid. This is analogous to the reaction of methanol with acetic acid in hydrogen fluoride solution.[2,4]

Work up of the hydrogen fluoride solution which contained the diacetoxonium ion (*5a*) gave only small amounts of products, probably because the diacetates formed by hydrolysis of (*5a*) are water soluble and therefore are lost.

Reaction of the benzoates (*1b*) or (*β-3b*) with hydrogen fluoride proceeded analogously to the reaction of the acetates. Both (*1b*) and (*β-3b*) gave the 1,2-benzoxonium ion (*2b*) at once when dissolved in hydrogen fluoride. The

signal of the anomeric proton was hidden by the aromatic protons; H2 was found at 6.66 ppm, H3 at 6.27, H4 at 5.57, H5 at 6.45, and H6 and H6′ at 5.0 – 5.2 ppm; $J_{12} = 5.3$ Hz; $J_{23} = 0.5$; $J_{34} = 2.5$; $J_{45} = 2.5$. The ion (*2b*) had disappeared completely after 24 h at room temperature. The further reaction was rather slow, but after *ca.* 25 days at room temperature the dibenzoxonium ion (*5b*) was formed as the only detectable product. Its spectrum was quite similar to that of (*5a*); H1 gave a doublet centered at 6.70 ppm, $J_{12} = 0$, $J_{1F} = 60.0$ Hz.

When the hydrogen fluoride solution, which contained (*5b*), was hydrolyzed a mixture of partially benzoylated products was obtained. After benzoylation tetra-*O*-benzoyl-α-D-talofuranosyl fluoride (*6b*) could be isolated in *ca.* 60 % yield. Besides, a smaller amount of penta-*O*-benzoyl-α-D-talofuranose (*7b*) was obtained. The latter product must arise *via* a partial hydrolysis of the fluoride during the work up of the hydrogen fluoride solution. In order to increase the yield of the fluoride (*6b*) the benzoylated product was treated briefly with hydrogen fluoride to convert the pentabenzoate to the fluoride. After this treatment 76 % of (*6b*) was obtained from the galactose derivative (*3b*).

Treatment of (*6b*) with hydrogen bromide in acetic acid gave crude tetra-*O*-benzoyl-D-talofuranosyl bromide. Hydrolysis and *p*-nitrobenzoylation of this gave the known [5] 2,3,5,6-tetra-*O*-benzoyl-1-*O*-*p*-nitrobenzoyl-α-D-talofuranose (*7c*).

EXPERIMENTAL

NMR spectra were obtained on Varian A-60 and HA-100 instruments. Spectra in anhydrous hydrogen fluoride were measured in Teflon sample tubes. Positions of signals in hydrogen fluoride are given in ppm relative to $(CH_3)_3SiCH_2CH_2CH_2SO_3Na$. ^{19}F spectra were measured at 94.1 MHz. Positions of signals (ϕF) are given in ppm relative to internal methyl trifluoroacetate. Thin layer chromatography (TLC) was performed on silica gel PF_{254} (Merck); for preparative work 1 mm layers were used on 20 × 40 cm plates.

Ethyl tetra-O-benzoyl-β-D-galactofuranoside (1b). Ethyl β-D-galactofuranoside [6] (1.51 g) was benzoylated in the usual manner with benzoyl chloride in pyridine. The product crystallized from ether – pentane to give 4.30 g (94 %) of (*1b*) with m.p. 100 – 101°C. An additional recrystallization did not change the melting point, $[\alpha]_D^{24} = -7.1°$ (*c* 1.4, $CHCl_3$). (Found: C 69.44; H 5.11. Calc. for $C_{36}H_{32}O_{10}$: C 69.23; H 5.16).

Tetra-O-acetyl-β-D-galactofuranosyl fluoride (β-3a). Ethyl tetra-*O*-acetyl-β-D-galactofuranoside [7] (2.86 g) was dissolved in anhydrous hydrogen fluoride (8 ml) and the solution was kept at 0°C for 15 min. It was then diluted with dichloromethane and poured on ice. The organic phase was washed with aqueous sodium hydrogen carbonate, dried and evaporated. The residue (2.17 g) was crystallized from ether-pentane (seed crystals were obtained in a separate experiment in which the product was purified by preparative. TLC using ether – benzene (1:1) as eluent) to give 1.01 g (36 %) of (*β-3a*), m.p. 71 – 73°C Recrystallization from ether – pentane gave the pure product, m.p. 76 – 77°C, $[\alpha]_D^{24} = -15.2°$ (*c* 1.5, $CHCl_3$). (Found: C 48.20; H 5.53. Calc. for $C_{14}H_{19}FO_9$: C 48.02; H 5.47.)

The material in the mother liquors was separated into 2 fractions by preparative TLC (benzene – ether 1:1). The fast moving fraction (500 mg, 17 %) consisted of the β-fluoride (*β-3a*) mixed with a small amount of tetra-*O*-acetyl-α-D-galactofuranosyl fluoride (*α-3a*) as seen from an NMR spectrum (Table 1).

The slow moving fraction was acetylated to give 200 mg (7 %) of penta-*O*-acetyl-β-D-galactofuranose, which crystallized from ethanol, m.p. 91 – 95°C, $[\alpha]_D^{24} = -33.3°$ (*c* 1.2, $CHCl_3$) (recorded [8] m.p. 96 – 97°C, $[\alpha]_D = -41.5°$). An NMR spectrum confirmed

Table 1. NMR spectra of D-galactofuranose and D-talofuranose derivatives in deuteriochloroform.

Compound	Chemical shifts (δ-values)								Observed 1st. order coupling constants (Hz)										
	H 1	H 2	H 3	H 4	H 5	H 6	H 6′	ϕ_F	J_{1F}	J_{12}	J_{2F}	J_{23}	J_{34}	J_{4F}	J_{45}	J_{56}	$J_{56'}$	$J_{66'}$
β-3a	5.74	5.23	5.08	4.49	5.42	4.35	4.20	−52.2	58.0	~0	7.3	1.4	4.5	1.9	4.5	4.6	6.8	12.0
α-3a	5.6							−48.4	65.0	3.3	19.0			6.5				
β-3b	6.04	5.67	5.75	4.96	6.14	4.70−	4.85	−49.3	59.0		6.5		≃4	1.5	≃5	4.5	7.0	
6b	6.00	5.70		4.99	6.00	4.83	4.73	−40.5	61.0	~0	2.3		3.6	7.5	6.0	4.0	6.0	12.0 $J_{3F}=4.5$
7b	6.69	5.8−	6.1	5.02	5.87	4.7	4.8			~0								
7c	6.70	5.9	6.0	5.01	5.86	4.6	4.8			~0								

the structure and showed that the product contained small amounts of the corresponding α-anomer.

Tetra-O-benzoyl-β-D-galactofuranosyl fluoride (β-3b). Ethyl tetra-*O*-benzoyl-β-D-galactofuranoside (*1b*) (4.12 g) was dissolved in hydrogen fluoride (12 ml) and the solution was kept at 0°C for 45 min. Work up as described above gave a crystalline product (3.76 g) which was recrystallized from ether−pentane to give 2.84 g (72 %) of (*β-3b*), m.p. 110−111°C, $[\alpha]_D^{24}=+14.9°$ (*c* 1.6, $CHCl_3$). (Found: C 68.07; H 4.69. Calc. for $C_{34}H_{27}FO_9$; C 68.21; H 4.55).

Tetra-O-benzoyl-α-D-talofuranosyl fluoride (6b). A solution of tetra-*O*-benzoyl-β-D-galactofuranosyl fluoride (2.04 g) in anhydrous hydrogen fluoride (8 ml) was kept for 21 d at room temperature. The mixture was then worked up as described above and the crude product was benzoylated with benzoyl chloride (7.0 ml) in pyridine (15 ml). Work up in the usual way gave 2.36 g of product.

A sample of this (800 mg) was separated into two fractions by preparative TLC with ether−pentane (1:1) as eluent. The fast moving fraction gave 400 mg of pure (6b) as seen from NMR spectra. The slower moving fraction gave 135 mg of penta-*O*-benzoyl-α-D-talofuranose (*7b*) as a syrup, $[\alpha]_D^{24}=-30.3°$ (*c* 1.5, $CHCl_3$). (Found: C 70.09; H 4.63. Calc. for $C_{41}H_{32}O_{11}$: C 70.30; H 4.59.).

The remaining product (1.56 g) was treated with anhydrous hydrogen fluoride (6 ml) at 0°C for 5 min. Work up gave a syrup (1.5 g) which was purified by preparative TLC with ether−pentane (1:1) to give 1.22 g of (6b) as seen from an NMR spectrum.

In a separate experiment tetra-*O*-benzoyl-β-D-galactofuranosyl fluoride (1.66 g) was kept in hydrogen fluoride (8 ml) for 29 d at room temp. The product was benzoylated and the benzoylated product was treated with hydrogen fluoride for 5 min at 0°C. Work up and chromatography of the product gave 1.26 g (76 %) of tetra-*O*-benzoyl-α-D-talofuranosyl fluoride. A sample was rechromatographed using ether−pentane (1:1) as eluent, $[\alpha]_D^{24}=-90.3°$ (*c* 3.9, $CHCl_3$). (Found: C 68.06; H 4.73. Calc. for $C_{34}H_{27}FO_9$: C 68.21; H 4.55.).

2,3,5,6-Tetra-O-benzoyl-1-O-p-nitrobenzoyl-α-D-talofuranose (7c). The fluoride (*6b*) (700 mg) was kept in a solution of 30 % HBr in glacial acetic acid (10 ml) over night at +5°C. Dichloromethane was then added and the mixture was washed with water and aqueous sodium hydrogen carbonate, dried and evaporated. The crude tetra-*O*-benzoyl-D-talofuranosyl bromide (740 mg) was dissolved in 10 ml of a mixture of acetone and water (9:1) and stirred with silver carbonate (1.0 g) for 3 h. Filtration and evaporation gave 550 mg of crude 2,3,5,6-tetra-*O*-benzoyl-D-talofuranose. This was nitrobenzoylated in the usual manner with *p*-nitrobenzoyl chloride (190 mg) in pyridine (5 ml). The product was crystallized from ethanol to give 543 mg (62 %) of (*7c*), m.p. 175−185°C. Two additional recrystallizations from dichloromethane-methanol gave 250 mg of pure

product, m.p. 189 – 190°C, $[\alpha]_D^{20} = -27.0°$ (*c* 2.8, $CHCl_3$) (reported [5] m.p. 189 – 189.5°C, $[\alpha]_D = -25.0°$). NMR data are shown in Table 1.

Microanalyses were performed by Dr. A. Bernhardt.

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