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Reaction of Sugar Esters with Hydrogen Fluoride. XIII. Preparation of 1,6-Anhydro-β-D-gulopyranose Derivatives

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Reaction of methyl 2,3,6-tri-*O*-benzoyl-4-*O*-*p*-nitrobenzoyl-α-D-galactopyranoside with hydrogen fluoride leads to formation of 2-*O*-benzoyl-4-*O*-*p*-nitrobenzoyl-1,6-anhydro-β-D-gulopyranose, which was converted into tri-*O*-acetyl-1,6-anhydro-β-D-gulopyranose. The reaction in hydrogen fluoride takes place *via* dioxolanylium ions which were observed by ^{13}C NMR spectroscopy.

In view of the results obtained previously from the reaction of glucopyranose or mannopyranose pentabenzoates with anhydrous hydrogen fluoride it might be expected that treatment of galactopyranose pentabenzoate with hydrogen fluoride should lead to formation of talose derivatives.[1,2] Rearrangement of galactopyranose pentaacetate into talopyranose derivatives has been shown to take place with antimony pentachloride.[3] Conversion of galactofuranose derivatives into talofuranose derivatives has been achieved with hydrogen fluoride.[4]

We have found that prolonged treatment of penta-*O*-benzoyl-D-galactopyranose with hydrogen fluoride gives mainly galactose derivatives. It was shown previously that methyl tetra-*O*-benzoyl-α-D-glucopyranoside gave a good yield of 1,6-anhydro-β-D-altropyranose when treated with hydrogen fluoride for a few days. Methyl tetra-*O*-benzoyl-D-galactopyranose was found to give a complex mixture of products by the same treatment and the reaction was therefore not investigated further.

The results obtained previously by treatment of mixed esters of cyclohexanediol [5] and of 1,5-anhydro-arabinitol [6] with hydrogen fluoride indicated that it would be of interest to study the reactions of benzoylated carbohydrates, which had *p*-nitro- or *p*-methoxy-benzoyl groups in selected positions. For this purpose methyl 2,3,6-tri-*O*-benzoyl-4-*O*-*p*-nitrobenzoyl-α-D-galactopyranoside (*1*) was prepared from the readily available methyl 2,3,6-tri-*O*-benzoyl-α-D-galactopyranoside.

When *1* was dissolved in anhydrous hydrogen fluoride at 0 °C it reacted rapidly to give the 1,2-benzoxonium ion (*3*) as seen from a ^{1}H NMR spectrum of the hydrogen fluoride solution. This ion is probably in equilibrium with the fluoride (*2*),[2] but the latter could not be seen in the spectrum. When the hydrogen fluoride solution was kept at room temperature further reactions took place for *ca.* 48 h. A ^{1}H NMR spectrum of the solution at this stage was not well resolved and could not be analyzed. Good ^{13}C NMR spectra could, however, be obtained when the reaction was carried out in deuterium fluoride solution. A spectrum measured within 1 h after *1* had been dissolved in deuterium fluoride gave the ^{13}C chemical shifts of *3*. A ^{13}C spectrum after 48 h (Table 1) showed that the benzoxonium ion (*8*) was almost the only species present since only a few other small signals could be seen. The low field position of C1 and C2 in *3* shows that a 1,2-benzoxonium ion is present. In *8* C2 and C3 are found at relatively low field in agreement with the structure. The chemical shifts of the ionic carbon atoms in the benzoxonium ions (187.17 and 185.35) are in agreement with results found for other dioxolanylium ions.[7] The signal at 60.64 ppm is due to methanol cleaved off from *1* whereas the signal at 64.02 arises from methyl benzoate, formed in a secondary reaction.[2] The absence of $^{13}C—^{19}F$ couplings shows that glycosyl fluorides or ortho-

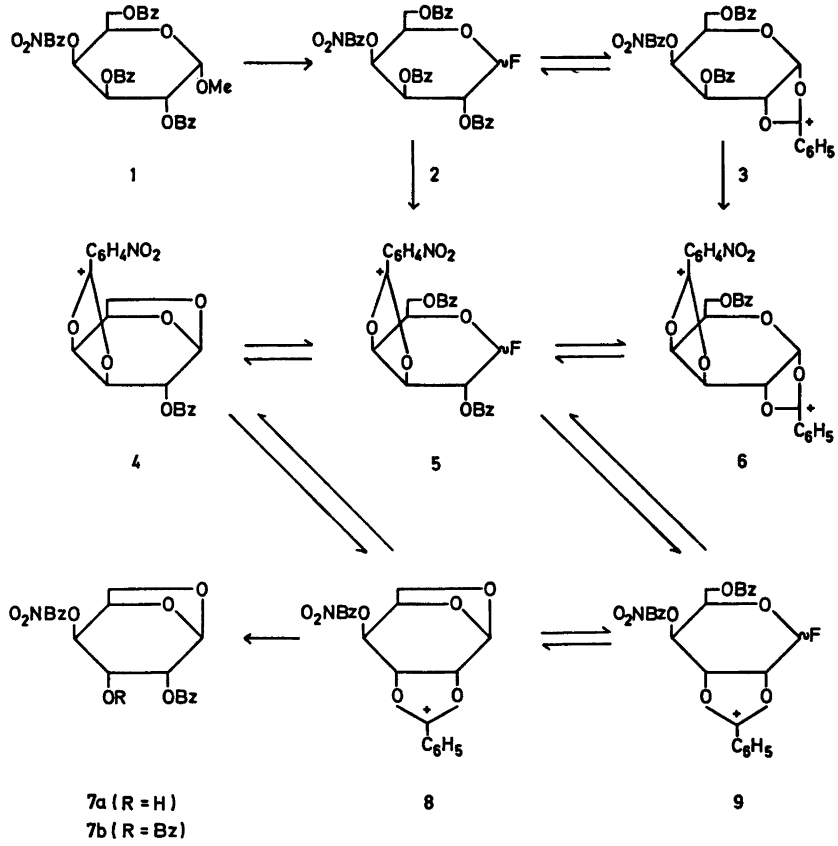

Table 1. Chemical shifts in $CDCl_3$ (ppm) and observed first-order coupling constants (Hz).

Compound	H1	H2	H3	H4	H5	H6	H6′	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$
1	5.30	5.68	5.99	6.06		4.7–4.3		3.5	10.8	3.4				
7a	5.58	5.25	4.30	5.38	4.72	4.10	3.72	2.5	4.5	9.0	5.0	0	5.0	−8.0
7b	5.77	5.72	5.92	5.68	4.93	4.34	3.89	2.2	4.6	9.3	4.0	0	4.8	−8.1
[a]	5.43		5.1–5.3		4.62	4.10	3.72	2.0			2.6	0	4.6	−8.0

^{13}C NMR data in deuterium fluoride (ppm values)

	C1	C2	C3	C4	C5	C6	$-C^{a}-$	OMe
3	117.56	84.81	76.56	72.92	76.43	69.47	187.17	60.64
8	101.06	90.79	88.06	75.58	75.19	69.41	185.35	64.02

[a] Tri-*O*-acetyl-1,6-anhydro-β-D-gulopyranose.

acid fluorides are not present.

The 1,2-benzoxonium ion (*3*), which is the first product formed in hydrogen fluoride, could rearrange to a 2,3-benzoxonium ion with the *talo*-configuration by attack of the benzoyloxy group of C3 upon C2. This would be analogous to the rearrangement of glucopyranose derivatives into mannopyranose derivatives.[2] Such a rearrangement did, however, not take place to any detectable extent. Since *1* has a pair of 3,4-*cis*-oriented acyloxy-group it could, alternatively, give a 3,4-dioxolanylium ion, analogous to the reactions of esters of 1,2-*cis*-cyclohexanediol. According to the results found with mixed esters [5] (*3*) would be expected to give the *p*-nitrobenzoxonium ion (*6*). The latter ion would be in equilibrium with the fluoride (*5*) and probably also with the 1,6-anhydride (*4*).[2] The *p*-nitrobenzoxonium ions (*4* and *5*) would undoubtedly rearrange to the more stable benzoxonium ions (*8* and *9*), in analogy with the results obtained with derivatives of 1,5-anhydro-arabinitol.[6] The equilibrium between *8* and *9* is probably shifted rather strongly towards *8* since a methyl glycoside (*1*) was used.[2]

Hydrolysis of *8* should give *7a*, with an axial *O*-benzoyl group,[8] and this compound was actually obtained in 55 % yield when the hydrogen fluoride solution was hydrolyzed. The structures of *7a* and of the benzoylated product *7b* were evident from the ^{1}H NMR spectra (Table 1). In a separate experiment the crude product, obtained by treating *1* with hydrogen fluoride, was deacylated and then acetylated. In this manner a 40–50 % yield of the known tri-*O*-acetyl-1,6-anhydro-β-D-gulopyranose could be isolated.

EXPERIMENTAL

^{1}H NMR spectra and thin layer chromatography was performed as described previously.[2] ^{13}C NMR spectra were measured at 0 °C with deuterium fluoride as solvent in Teflon sample tubes on a Bruker WH-90 instrument. Positions of signals are given in ppm relative to internal $(CH_3)_3SiCH_2CH_2CH_2SO_3Na$.

*Methyl 2,3,6-tri-*O*-benzoyl-4-*O*-p-nitrobenzoyl-α-D-galactopyranoside (1).* Methyl 2,3,6-tri-*O*-benzoyl-α-D-galactopyranoside [9] (3.52 g) was dissolved in pyridine (15 ml) and cooled in ice while *p*-nitrobenzoyl chloride (1.0 g) was added. The mixture was stirred over night at room temperature and it was then worked up in the usual way to give 3.73 g of product, m.p. 99–102 °C. Recrystallization from ethanol gave *1*, m.p. 128–129 °C, $[\alpha]_D^{25}$ +185.3° (*c* 1.4, $CHCl_3$). (Found: C 64.12; H 4.46; N 2.12. Calc. for $C_{35}H_{25}NO_{12}$: C 64.12; H 4.43; N 2.14).

Reaction of 1 *with hydrogen fluoride. A.* A solution of *1* (600 mg) in anhydrous hydrogen fluoride (2 ml) was kept at room temperature for 48 h in a polyethylene bottle. It was then diluted with dichloromethane and poured on ice. The organic phase was washed with water and with aqueous sodium hydrogencarbonate, dried ($MgSO_4$) and evaporated. The residue (600 mg) was purified by preparative TLC with benzene-ether (1:1) as eluent. The main fraction gave 205 mg (55 %) of 2-*O*-benzoyl-4-*O*-*p*-nitrobenzoyl-1,6-anhydro-β-D-gulopyranose (*7a*) as a syrup, which was characterized through its spectrum only (Table 1). The product was benzoylated with benzoyl chloride in pyridine to give 2,3-di-*O*-benzoyl-4-*O*-*p*-nitrobenzoyl-1,6-anhydro-β-D-gulopyranose (*7b*), which was crystallized from ethanol, yield 233 mg, m.p. 150–151 °C, $[\alpha]_D^{25}$ +225° (*c* 1.0, $CHCl_3$).

B. In a second experiment 2.13 g of *1* was treated with hydrogen fluoride (10 ml) as described above. The crude product (1.97 g) was benzoylated with benzoyl chloride (3 ml) in pyridine (10 ml). This gave 2.13 g of a product which was crystallized from ethanol to give 600 mg (36 %) of *7b*, m.p. 153–153.5 °C, $[\alpha]_D^{25}$ +229.5° (*c* 1.9, $CHCl_3$). (Found: C 62.25; H 4.03; N 2.69. Calc. for $C_{27}H_{21}NO_9$: C 62.42; H 4.05; N 2.70).

C. In a third experiment 9.3 g of *1* was treated with hydrogen fluoride. The crude product was dissolved in methanol (36 ml) containing 0.3 % sodium methoxide and kept over night. The solution was then deionized with Amberlite IR-120, filtered and evaporated. The residue was dissolved in water and extracted twice with ether. The water was evaporated and the residue was acetylated with acetic anhydride in pyridine. Work up in the usual way and crystallization from ether-pentane gave 1.634 g (40 %) of tri-*O*-acetyl-1,6-anhydro-β-D-gulopyranose, m.p. 95–102 °C. Recrystallization gave a product with m.p. 110–111 °C, $[\alpha]_D^{25}$ +22.1° (*c* 2.2, $CHCl_3$) (recorded [10] m.p. 114–115 °C, $[\alpha]_D^{25}$ +22.1°).

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