Acta Chemica Scandinavica B 28 (1974) 1041—1044

Reaction of Acetylated Methyl Glycosides with Hydrogen Bromide

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Treatment of acetylated methyl glycopyranosides with hydrogen bromide in acetic acid gave, in addition to the expected pyranosyl bromides, large amounts of furanosyl bromides. The reaction was studied with a number of methyl hexopyranosides and pentopyranosides and in almost all cases furanosyl bromides were found to be the major products. Methyl tri-*O*-acetyl-β-D-ribopyranoside was almost completely converted into a mixture of the anomeric tri-*O*-acetyl-D-ribofuranosyl bromides by treatment with hydrogen bromide in acetic acid for 2 h.

It was reported previously that treatment of methyl tri-*O*-acetyl-β-D-arabinopyranoside with hydrogen bromide lead to formation of tri-*O*-acetyl-D-arabinofuranosyl bromide in addition to the expected pyranosyl bromide. A mechanism for the ring-contraction was proposed, and it was shown that the benzoylated arabinoside did not undergo ring-contraction with hydrogen bromide.[1]

In the present paper the behaviour of a number of acetylated glycosides towards hydrogen bromide in acetic acid is described. In most cases the reactions were studied by NMR spectroscopy only. In these experiments the acetylated glycosides were dissolved in a solution of 30 % hydrogen bromide in glacial acetic acid in an NMR sample tube and kept at room temperature. NMR spectra were then run at intervals at 90 MHz until no further changes were observed. In Table 1 are given the results of a number of such experiments.

The products formed were identified from the chemical shifts of the anomeric protons of the glycosyl bromides, which were the final products. The relative amounts of products were calculated from the integrated spectra. Authentic spectra of the products shown in Table 1 were obtained from fully acetylated pyranoses and furanoses under the same conditions. Fully acetylated sugars form glycosyl bromides rapidly and ring-changes do not take place, even on prolonged treatment with hydrogen bromide.

The results obtained from these experiments show that when the reactions of acetylated methyl pyranosides with hydrogen bromide are completed furanosyl bromides are the main product in almost all cases (Table 1). Methyl tri-*O*-acetyl-β-D-arabinopyranoside, which was investigated previously,[1] undergoes ring-contraction to a smaller extent than any of the other methyl glycopyranosides investigated. Methyl tri-*O*-acetyl-β-D-ribopyranoside is almost completely converted into a mixture of the anomeric tri-*O*-acetyl-D-ribofuranosyl bromides.

In some cases signals, which could not be ascribed to pyranosyl or furanosyl bromides, were observed. These are probably due to the formation of open-chain, *aldehydo*-derivatives. Only in the case of methyl tri-*O*-acetyl-α-D-lyxopyranoside was such a compound formed in larger amounts; it probably has the structure (*11*). The formation of open-chain derivatives by acetolysis of acetylated methyl glycosides is well known.[2,3]

Acetylated methyl α-D-mannofuranoside and ethyl β-D-galactofuranoside underwent ring-expansion to some extent to give pyranosyl bromides when treated with hydrogen bromide (Table 1). This was also the case with methyl tri-*O*-acetyl-α-D-arabinofuranoside.[1] According to the proposed mechanism [1] ring-changes take place with the methyl glycosides and not with glycosyl bromides. Since methyl furanosides give glycosyl bromides more rapidly

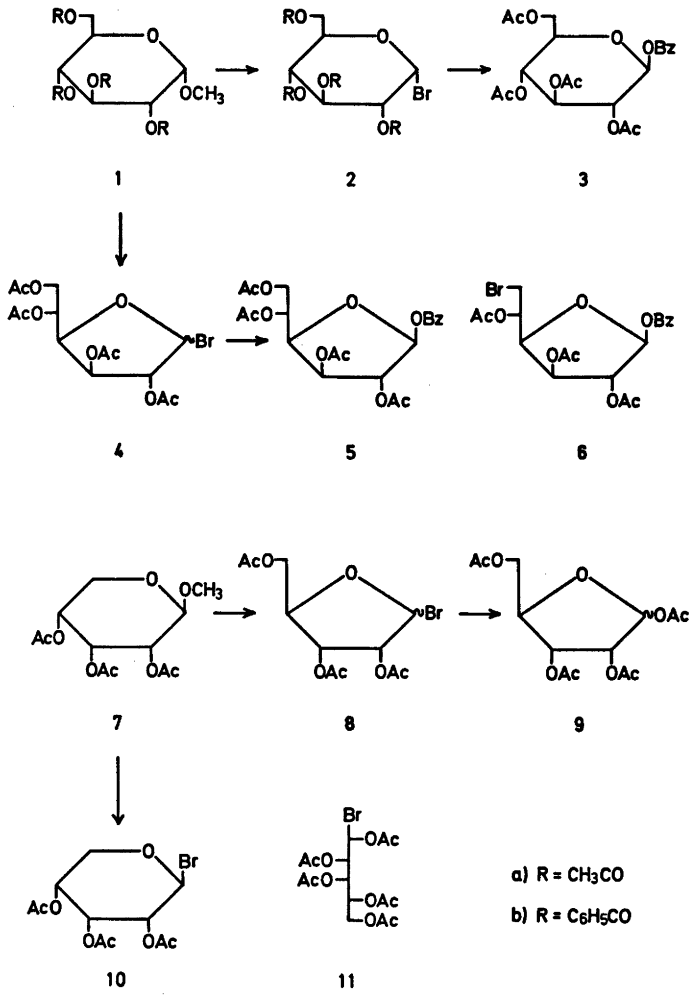
Table 1. Chemical shifts and coupling constants of acetylated glycosyl bromides formed from acetylated glycosides in hydrogen bromide-acetic acid.

Compound, fully acetylated	δ-Value H1, J_{12}(Hz) % Yield				fur./ pyr.	Time for completion of reaction h
	pyranose	α-furanose	β-furanose	*aldehydo*-form		
Methyl α-glucopyranoside	6.79 3.8 41	6.99 4.8 26	6.51 ~0 33	6.82 ~0 trace	1.44	24
Methyl β-glucopyranoside	6.79 3.8 40	6.98 4.8 25	6.51 35		1.50	24
Methyl α-mannopyranoside	6.63 ~0 42	6.58 ~0 46	6.78 3.0 12		1.4	24
Methyl α-mannofuranoside	6.63 ~0 10	6.58 ~0 72	6.78 3.0 18		9	1
Methyl α-galactopyranoside	6.83 3.8 32		6.58 ~0 68		2.1	5
Methyl β-galactopyranoside	6.83 3.8 33		6.58 ~0 67		2.0	5
Ethyl β-galactofuranoside	6.83 3.8 16		6.58 ~0 84		6	2
Phenyl β-galactopyranoside	6.83 3.8 93		6.58 ~0 7		0.08	3
Methyl α-xylopyranoside	6.76 4.0 28	6.97 5.0 41	6.50 ~0 31	6.82 ~0 trace	2.6	2
Methyl β-xylopyranoside	6.76 4.0 45	6.97 5.0 31	6.50 ~0 24	6.82 ~0 trace	1.2	2
Methyl α-lyxopyranoside	6.53 ~0 9	6.62 ~0 50		6.83 ~0 34	5.5	2
Methyl β-arabinopyranoside	6.80 3.5 50	6.57 ~0 50			1	2
Methyl β-ribopyranoside	6.59 ~0 9	6.87 4.0 36	6.54 ~0 55	6.82 ~0 trace	10	2
2,3,4-Tri-*O*-acetyl-xylopyranose	6.76 4.0 65	6.97 17	6.50 18		0.5	0.5

than pyranosides (Table 1) it is understandable that they undergo ring-expansion to a small extent only.

Phenyl tetra-*O*-acetyl-β-D-galactopyranoside gave only a small amount of furanosyl bromide when treated with hydrogen bromide. 2,3,4-Tri-*O*-acetyl-D-xylopyranose gave considerable amounts of furanosyl bromides, but not as much as the corresponding methyl xylopyranosides.

In order to confirm the results shown in Table 1 products were isolated and characterized in two cases. Treatment of methyl tetra-*O*-acetyl-α-D-glucopyranoside (*1a*) with hydrogen bromide in acetic acid for 20 h gave a mixture of glycosyl bromides (*2a*) and (*4*) which were very unstable. They were therefore treated with silver benzoate to give 1-*O*-benzoates. From this product the pyranose (*3*) and the furanose (*5*) were isolated. Besides, 2,3,5,6-tetra-*O*-acetyl-D-glucofuranose was obtained, probably resulting from hydrolysis of the bromide (*4*). A small amount of the 6-bromo-6-deoxy-glucofuranose derivative (*6*) was



also isolated. Thus the reaction of (*1a*) with hydrogen bromide gives a complicated mixture of products, and it is understable that Zemplén [4] could not isolate acetobromoglucose from this reaction.

Treatment of the tetrabenzoate (*1b*) with hydrogen bromide gave a good yield of tetra-*O*-benzoyl-α-D-glucopyranosyl bromide (*2b*).

Methyl tri-*O*-acetyl-β-D-ribopyranoside (*7*) is almost completely converted into a mixture of the anomeric furanosyl bromides (*8*) when treated with hydrogen bromide (Table 1). Since these bromides are unstable the reaction mixture was treated with acetic anhydride and zinc bromide in order to convert them into the tetraacetates (9) which could then be isolated in 58 % yield.

EXPERIMENTAL

Melting points are uncorrected. NMR spectra were recorded on a Bruker HX-90E instrument. The spectra shown in Table 1 were measured on solutions which contained *ca.* 10 % carbohydrate in 30 % HBr/HOAc. The chemical shifts were measured relative to internal chloroform. Thin layer chromatography (TLC) was performed on silica gel PF_{254} (Merck): for preparative work 1 mm layers on 20 × 40 cm plates were used. Spots were visualized with UV light or by charring with a hot wire.

*Methyl tetra-*O*-acetyl-α-*D*-glucopyranoside (1a)* (1.0 g) was dissolved in 4 ml of 30 % HBr/HOAc and the solution was kept at room temp. for 20 h. It was then diluted with dichloromethane, washed with water and aqueous $NaHCO_3$, dried ($MgSO_4$) and evaporated. The crude product (1.15 g) was dissolved in dry acetonitrile (25 ml) and stirred over night with silver benzoate (3.0 g). The mixture was filtered through carbon and the solvent was evaporated. The residue was dissolved in dichloromethane and washed with aqueous $NaHCO_3$, dried and evaporated. The syrupy product was separated into several fractions by preparative TLC using diethyl ether – pentane (2:1) as eluent.

The fastest moving fraction gave 77 mg (6 %) of 2,3,5-tri-*O*-acetyl-1-*O*-benzoyl-6-bromo-6-deoxy-β-D-glucofuranose (*6*) as a syrup, $[\alpha]_D^{20}$ −64.7° (*c* 2.1, $CHCl_3$). (Found: C 48.34; H 4.60; Br 17.12. Calc. for $C_{19}H_{21}BrO_9$: C 48.22; H 4.47; Br 16.89). A 100 MHz NMR spectrum gave the following δ-values and coupling constants (Hz): H1 6.43; H2 5.30; H3 5.55; H4 4.69; H5 5.25; H6 3.67; H6′ 3.76. J_{12} ~0; J_{13} 0.3; J_{23} 0.8; J_{34} 4.7; J_{45} 9.4; J_{56} 3.2; $J_{56'}$ 4.0; $J_{66'}$ −11.8.

The next two fractions could not be identified. The fourth fraction gave 351 mg (28 %) of a mixture of (*3*) and (*5*) in a ratio of 4:1 as seen from an NMR spectrum. Crystallization and recrystallization from ethanol gave tetra-*O*-acetyl-1-*O*-benzoyl-β-D-glucopyranose (*3*), m.p. 140 – 141 °C, $[\alpha]_D^{20}$ −25.5° (*c* 2.9, $CHCl_3$) (reported [5] m.p. 143 – 145°, $[\alpha]_D$ −26.6°). 1-*O*-Benzoyl-tetra-*O*-acetyl-β-D-glucofuranose (*5*) was identified in the mother liquor from (*3*) by comparing its NMR spectrum with that of an authentic sample.[6]

The last fraction gave 140 mg (14.5 %) of a product which consisted mainly of 2,3,5,6-tetra-*O*-acetyl-D-glucofuranose as seen from an NMR spectrum. Acetylation gave a mixture of the anomeric penta-*O*-acetyl-D-glucofuranoses the NMR spectra of which were identical with those previously reported.[7]

*Methyl tetra-*O*-benzoyl-α-*D*-glucopyranoside (1b)* (1.0 g) was dissolved in dichloromethane (1.0 ml) and HBr/HOAc (5.0 ml) was added. The solution was kept for 3 days at room temp. and worked up as described above. The product was crystallized from ether to give 705 mg (65 %) of tetra-*O*-benzoyl-α-D-glucopyranosyl bromide (*2b*), m.p. 122 – 124 °C. One recrystallization gave the pure product, m.p. 125 – 125.5 °C, $[\alpha]_D^{20}$ +123.1° (*c* 1.4, $CHCl_3$) (reported [8] m.p. 129 – 130 °C (corr.), $[\alpha]_D$ +124°). The material in the mother liquor consisted of the same bromide and *ca.* 10 % unreacted (*1b*) as seen from an NMR spectrum. No furanosyl bromide could be detected.

*Methyl tri-*O*-acetyl-β-*D*-ribopyranoside (7)* (2.19 g) was kept in HBr/HOAc (6.0 ml) for 1.5 h at room temp. Acetic anhydride (35 ml) and anhydrous zinc bromide (100 mg) were then added and the mixture was stirred for 15 min. It was then poured on ice and stirred for 3 h. The product was extracted with chloroform; the solution was washed with water and aqueous $NaHCO_3$, dried and evaporated. The product (2.31 g) consisted mainly of a mixture of the anomeric tetra-*O*-acetyl-D-ribofuranoses (9) in an α:β ratio of 1:3 as seen from an NMR spectrum. Crystallization from ethanol gave 510 mg (21 %) of the β-anomer (*β9*), m.p. 55 – 58 °C. Preparative TLC of the material in the mother liquor gave 892 mg (37 %) of α,β-mixture. Crystallization of this from ethanol gave 300 mg of (*β9*), m.p. 56 – 58 °C. Recrystallization from ethanol gave a product with m.p. 57 – 59 °C, $[\alpha]_D^{20}$ −12.7° (*c* 4.5, $CHCl_3$). This is the low melting form of tetra-*O*-acetyl-β-D-ribofuranose;[9] we have not been able to obtain the high melting form.[10] An NMR spectrum was in agreement with the structure and showed no impurities.

Microanalyses were performed by Dr. A. Bernhard Mikroanalytisches Laboratorium.

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Received May 2, 1974.