Reaction of Carbohydrates with Hydrogen Bromide. Preparation of Some 6-Deoxy-D-mannofuranoses

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Reaction of 2,3,5,6-di-O-isopropylidene-α-D-mannofuranose (1) with hydrogen bromide in acetic acid gave 5-O-acetyl-6-bromo-6-deoxy-2,3,6-O-isopropylidene-α-D-mannofuranosyl bromide (3). With methanol 3 gave the methyl furanoside (5) which was converted into methyl 5-O-benzoyl-6-deoxy-2,3,6-O-isopropylidene-α-D-mannofuranoside (4a) and into methyl 5,6-dideoxy-2,3-O-isopropylidene-α-D-lyxo-hex-5-enofuranoside (6). Hydrolysis of 4 gave D-rhamnose.

In a previous paper the conversion of methyl 2,3,6-tri-O-benzoyl-α-D-galactopyranoside into tri-O-benzoyl-6-bromo-6-deoxy-α-D-galactofuranosyl bromide by treatment with hydrogen bromide in acetic acid (HBA) was described. The reaction was assumed to proceed via a ring-contraction to a furanose derivative, formation of a 5,6-benzoxonium ion, and subsequent reaction of the latter with bromide ions.

This reaction indicated that hexofuranoses might also yield 6-bromo-6-deoxy-derivatives by treatment with HBA and a number of compounds has now been studied in order to investigate this reaction. In the present paper the reaction of 2,3,5,6-di-O-isopropylidene-α-D-mannofuranose (1) with HBA is described.

When 1 was treated with HBA for 2 h at room temperature it was converted into a syrup which, as seen from NMR spectra, consisted almost exclusively of 5-O-acetyl-6-bromo-6-deoxy-2,3,6-O-isopropylidene-α-D-mannofuranosyl bromide (3). This product was not purified, but was only characterized through its 1H and 13C NMR spectra. Treatment of 3 with methanol in the presence of silver carbonate gave methyl 5-O-acetyl-6-bromo-6-deoxy-2,3,6-O-isopropylidene-β-D-mannofuranoside (β-5b). When 3 was treated with methanol alone the corresponding
α-anomer was formed, presumably via β-5α and subsequent anomerization catalyzed by the liberated hydrogen bromide. The acidic conditions, arising in the latter reaction, also caused deacetylation of α-5β and the crude α-5α thus obtained was benzoylated. This gave crystalline methyl 5-O-benzoyl-6-bromo-6-deoxy-2,3-O-isopropylidene-α-D-mannofuranoside (α-5c). Reduction of α-5α with lithium aluminium hydride yielded the corresponding 6-deoxy-compound (4α), which was converted into the known 5 crystalline 5-O-benzozate (4c).

Hydrolysis of 4α with aqueous acid gave a 65% yield of D-rhamnose, thus confirming its structure. Alternatively, I could be converted into crystalline D-rhamnose in 30% overall yield via 3, 5, and 4 without purification of any of the intermediates.

Treatment of 5c with zinc in boiling acetic acid yielded the previously described 3 methyl 5,6-dideoxy-2,3-O-isopropylidene-α-D-L-lyxo-hex-5-enofuranoside (6).

Thus the simple treatment of the readily available diisopropylidene derivative with hydrogen bromide offers a convenient route to a number of D-rhamnose derivatives and to 5,6-ununsaturated compounds.

The first step in the conversion of I into 3 must be loss of the 5,6-isopropylidene group and formation of 2,3-O-isopropylidene-α-D-mannofuranoside. This was confirmed by the fact that methyl 2,3-O-isopropylidene-α-D-mannofuranoside also gave 3 in high yield when treated with HBA. The next step is probably acetylation at C5 or C6 and subsequent formation of the acetonium ion (2). The latter finally reacts with bromide ions to give 3,1,4

EXPERIMENTAL

Melting points are uncorrected. Preparative thin layer chromatography (TLC) was performed on 20 x 40 cm plates using 1 mm layers of Merck silica gel PF254. 1H NMR spectra were measured at 270 MHz and 13C NMR spectra at 22.63 MHz on Bruker instruments using deuteriochloroform as solvent and TMS as internal reference.

5-O-Acetyl-6-bromo-6-deoxy-2,3-O-isopropylidene-α-D-mannofuranosyl bromide (3). To a 33% solution of hydrogen bromide in acetic acid (25 ml) was added 2,3,5,6-di-O-isopropylidene-α-D-mannofuranose (J) (5.0 g) and the mixture was stirred at room temperature for 2 h. It was then diluted with dichloromethane (100 ml) and washed with water and aqueous NaHCO₃, dried (MgSO₄) and evaporated. The syrup residue (7.5 g), (~100%) consisted of almost pure 3 as seen from 1H and 13C NMR spectra. It was not purified further. 1H NMR: δ 6.39 (H1), 5.15 (H2), 4.85 (H3), 4.49 (H5), 5.27 (H6), 3.88 (H5), 3.59 (H6); J1, 0 Hz, J3, 5.8, J4, 3.8, J4, 9.5, J8, 2.8, Jα, 4.1, Jβ, 11.6. 13C NMR: 91.5 ppm (C1), 89.5 (C2), 81.1 (C3), 77.7 (C4), 67.6 (C5), 32.5 (C6).

Methyl 5-O-acetyl-6-bromo-6-deoxy-2,3,4-O-isopropylidene-β-D-mannofuranoside (β-5b). A solution of crude 3 (1.8 g) in methanol (20 ml) was stirred with silver carbonate (2.5 g) overnight at room temperature. Filtration and evaporation gave 1.45 g of crude product. Purification by TLC using ether-pentane (3:1) as eluent gave 968 mg (62%) of β-5b as a syrup. [α]D⁰ +10.7° (c 0.4, CHCl₃). Anal. C₁₃H₁₂BrO₅: C, H, Br, 1H NMR: δ 4.70 (H1), 4.66 (H2), 4.72 (H3), 3.98 (H4), 5.22 (H5), 3.88 (H6), 3.72 (H6'); J1, 3.6 Hz, J5, 6.3, J4, 4.4, J4, 8.4, J4, 5.0, J6, 3.6, J6', 11.4. 13C NMR: 103.5 ppm (C1), 80.0 (C2), 79.5 (C3), 79.5 (C4), 79.7 (C5), 53.3 (C6).

Methyl 5-O-benzoyl-6-bromo-6-deoxy-2,3-O-isopropylidene-α-D-mannofuranoside (α-5c). A solution of 3 (7.5 g) in methanol (100 ml) was kept at room temperature for 24 h. Pyridine (5 ml) was then added and the solution was evaporated. The residue was dissolved in chloroform and washed with 4 N hydrochloric acid and with aqueous NaHCO₃, dried and evaporated. The residue (5.9 g ≥100%) consisted of methyl 6-bromo-6-deoxy-2,3-0-isopropylidene-α-D-mannofuranoside (α-5a) as seen from 1H and 13C NMR spectra.

Benzoylation with benzoyl chloride in pyridine in the usual manner and crystallization from pentane gave 4.0 g (52%) of α-5c, m.p. 50-55°C. Two recrystallizations from pentane gave the pure product, m.p. 56-57°C, [α]D⁰ +27.3° (c 2.7, CHCl₃). Anal. C₁₃H₁₂BrO₅: C, H, Br, 1H NMR: δ 4.95 (H1), 4.69 (H2), 4.77 (H3), 4.39 (H4), 5.44 (H5), 4.00 (H6), 3.87 (H6'); J1, 0 Hz, J5, 5.9, J3, 3.6, J4, 8.5, J4′, 2.9, J6, 3.3, J6′, 11.3 13C NMR: 106.9 ppm (C1), 84.9 (C2), 79.1 (C3), 78.1 (C4), 69.5 (C5), 33.7 (C6).

Methyl 5-O-benzoyl-6-deoxy-2,3-O-isopropylidene-α-D-mannofuranoside (4c). A solution of α-5c (3 g) in ether (20 ml) was treated with LiAIH₄ (400 mg) in ether (30 ml) for 24 h at room temperature. The mixture was worked up by careful addition of ethyl acetate followed by 1 N sulfuric acid, separation of the ether phase and extraction of the aqueous phase with ether. The combined ether solutions were washed with aqueous NaHCO₃, dried and evaporated to give 2.28 g (82%) of crude methyl 6-deoxy-2,3-O-isopropylidene-α-D-mannofuranoside (4a) as a syrup. Benzoylation with benzoyl chloride in pyridine gave the benzoate which was crystallized from pentane, yield 2.11 g (51%), m.p. 72-74°C, [α]D⁰ -19.7° (c 2.3, CHCl₃) (reported 1 m.p. 75-76°C, [α]D⁰ +19.9°). 13C
NMR: 107.2 ppm (C1), 84.9 (C2), 79.5 (C3), 81.7 (C4), 69.0 (C5), 17.5 (C6).

D-Rhamnose. Crude 4a (1.55 g) was stirred at 100°C for 1 h with 15 ml 0.5 N hydrochloric acid. The solution was then neutralized with "Amberlite" IR-4B and evaporated to dryness. The residue (834 mg, 65 %) was recrystallized from ethanol-ether to give 554 mg (41 %) of D-rhamnose monohydrate, m.p. 87–89°C, undepressed in admixture with an authentic sample.

Alternatively 1 (25 g) was treated with HBA as described above. The crude dibromo-compound (3) was treated with methanol to give a-5a, which was reduced with LiAlH₄ to give crude a-4a. Hydrolysis as described above gave 7 g crude product and crystallization from ethanol-ether gave 5.2 g (28 %) of D-rhamnose, m.p. 87°C.

Methyl 5,6-dideoxy-2,3-0-isopropylidene-a-D-lyxo-hex-5-enofuranoside (6). A solution of 5c (550 mg) in acetic acid (5 ml) was boiled for 1 h with zinc dust (500 mg). The mixture was then filtered and the filtrate was poured into water. The product was extracted with chloroform and the extract was washed with water, aqueous NaHCO₃, dried and evaporated. The residue was purified by TLC (ether-pentane 1:2) to give pure 6 (130 mg, 57 %) as a syrup, [α]D +28.0° (c 0.7, CHCl₃) (reported [α]D +27.8°). Anal. C₁₅H₂₀O₄; C, H. ¹H NMR: δ 4.90 (H1), 4.57 (H2), 4.67 (H3), 4.37 (H4), 6.00 (H5), 5.40 (H6), 5.32 (H6'); J₁₁ 0 Hz, J₁₂ 6.0, J₁₃ 3.8, J₁₄ 7.3, J₁₅ 17.5, J₁₆ 10.5, J₁₇ 1.8, J₁₈ 1.0, J₁₉ 0.9. ¹³C NMR 107.2 ppm (C1), 81.6, 81.2 (C2) (C3), 85.4 (C4), 132.4 (C5), 119.1 (C6).

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REFERENCES


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