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Preparation of Some 2-Bromo-2-deoxy-D-hexopyranoses

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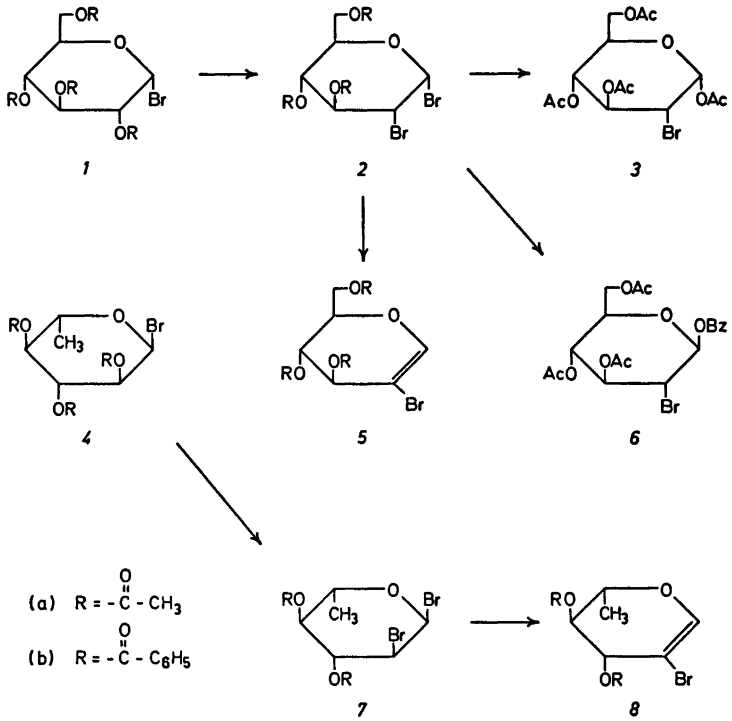
Dedicated to Professor K. A. Jensen on his 70th birthday

The zinc bromide catalyzed reaction of tetra-*O*-acetyl-α-D-glucopyranosyl bromide (*1a*) with acetyl bromide gives tri-*O*-acetyl-2-bromo-2-deoxy-α-D-glucopyranosyl bromide (*2a*). A similar treatment of tri-*O*-acetyl-6-deoxy-α-L-glucopyranosyl bromide (*4a*) yields di-*O*-acetyl-2-bromo-2,6-dideoxy-α-L-glucopyranosyl bromide (*7a*). An analogous reaction takes place with the corresponding benzoylated pyranosyl bromides. The 2-bromo-2-deoxy bromides form 2-bromo-1,2-dideoxy-hex-1-enopyranoses on treatment with triethylamine.

In previous work it was shown that reaction of tri-*O*-acetyl-D-xylopyranosyl bromide with acetyl bromide and zinc bromide led to the formation of di-*O*-acetyl-2-bromo-2-deoxy-D-xylopyranosyl bromide in moderate yield.[1] A better yield was obtained when the corresponding benzoylated bromide was treated with benzoyl bromide. Other acetylated or benzoylated pentopyranosyl bromides did not give bromo-deoxy-pentoses by this treatment.



The reaction of some acetylated and benzoylated hexopyranosyl bromides with acetyl bromide and zinc bromide has now been studied.

When tetra-*O*-acetyl-α-D-glucopyranosyl bromide (*1a*) was treated with anhydrous zinc bromide and acetyl bromide it was converted into tri-*O*-acetyl-2-bromo-2-deoxy-α-D-glucopyranosyl bromide (*2a*). After *ca.* 20 h at room temperature the reaction mixture no longer contained *1a*. When the mixture was worked up *2a* could be crystallized in *ca.* 30 % yield. An NMR spectrum showed that the material in the mother liquor contained rather large amounts of *2a* and the α-1-acetate (*3*);[3] besides, some of the unsaturated compound (*5a*) was present. Treatment with hydrogen bromide converted the 1-acetate (*3*) into the bromide (*2a*) and after this treatment additional amounts of *2a* could be obtained. Treatment of the mother liquor from this product with silver benzoate yielded *ca.* 10 % of the known[3] β-1-benzoate (*6*). The 1-acetate (*3*) is probably formed by zinc bromide catalyzed reaction of *2a* with acetic anhydride;[3] the latter arising from the acetic acid cleaved off from *1a*.

It was found necessary to use a rather large amount of zinc bromide to catalyse the reaction of *1a* with acetyl bromide. With smaller amounts of zinc bromide the reaction was slower and coloured by-products were formed. No reaction took place when *1a* was treated with acetyl bromide in the presence of boron trifluoride or aluminium tribromide.

The dibromo compound (*2a*) has been previously obtained, together with other isomers, by addition of bromine to tri-*O*-acetyl-1,2-dideoxy-D-*arabino*-hex-1-enopyranose.[2,4,5] The reaction described above gave *2a* as the only detectable bromo-deoxy bromide.

A similar treatment of tri-*O*-acetyl-6-deoxy-α-L-glucopyranosyl bromide (*4a*) gave the 2-bromo-2-deoxy bromide (*7a*) in *ca.* 50 % yield. The benzoylated bromides, *1b* and *4b*, also reacted with acetyl bromide and zinc bromide to give the corresponding 2-bromo-compounds *2b* and *8b*, respectively, in yields comparable to those obtained with the acetates.

Attempts to prepare bromo-deoxy compounds from acetylated galacto- or mannopyranosyl bromides were unsuccessful. In the pentose series it was also found that only xylopyranosyl bromide gives a bromo-deoxy bromide.[1] Thus, only pyranosyl bromides with the substituents at C2, C3, and C4 *trans*-oriented react with acetyl bromide and zinc bromide.

The mechanism for the formation of *2* from *1*, or *7* from *4*, is probably the same as that proposed for the reaction of tri-*O*-acetyl-D-xylopyranosyl bromide with acetyl bromide-zinc bromide,[1] and for the reaction of pentosyl bromides with dibromomethyl methyl ether.[6] The latter reagent is not, however, suited for the preparation of bromo-deoxy-hexoses.

The bromides *2a* and *2b*, as well as *7a* and *7b*, eliminated hydrogen bromide readily when treated with triethylamine to give the 1,2-unsaturated products *5a* and *5b* and *8a* and *8b*, respectively. The latter compounds rearrange to 2,3-unsaturated bromides with acetyl bromide. This will be described in a forthcoming paper.

EXPERIMENTAL

Melting points are uncorrected. Preparative TLC was performed on 1 mm layers of silica gel (Merck PF_{254}). ^1H NMR spectra were measured on Varian HA-100 or on Bruker HX-90E instruments in deuteriochloroform solution using tetramethylsilane as internal reference. Optical rotations were measured in chloroform solution on a Perkin Elmer 141 instrument.

Tri-O-acetyl-2-bromo-2-deoxy-α-D-glucopyranosyl bromide (2a). A mixture of tetra-*O*-acetyl-α-D-glucopyranosyl bromide (*1a*) (10.0 g), anhydrous zinc bromide (20 g), and acetyl bromide (25 ml) was stirred at room temperature for 20 h. A ^1H NMR spectrum of a sample then showed that the major component present was *2a*; besides, signals corresponding to smaller amounts of the α-1-acetate (*3*)[3] and of the unsaturated compound (*5a*) were seen. The starting material (*1a*) was no longer present. The mixture was diluted with dichloromethane (100 ml) and poured on ice. The organic phase was washed three times with 4 N hydrochloric acid and once with aqueous $NaHCO_3$, dried, filtered through carbon, and evaporated. The syrupy residue was crystallized from ether-pentane to give 3.0 g (28.5 %) of *2a*, m.p. *ca.* 85 °C.

To the material in the mother liquor was added 15 ml of a 30 % solution of hydrogen bromide in glacial acetic acid and the mixture was kept for 1 h at room temperature. Dichloromethane was then added and the solution was washed with water and aqueous $NaHCO_3$, dried and evaporated. The residue was crystallized from ether-pentane to give an additional 2.8 g of *2a*, bringing the total yield to 55 %. The product was sufficiently pure for most purposes, but could be recrystallized from ether-pentane, or from cyclohexane,

m.p. 92–93 °C, $[\alpha]_D^{20}$ 259° (*c* 5) (reported [4] m.p. 92–93 °C, $[\alpha]_D$ +260 °). A ^{1}H NMR spectrum confirmed the structure.

The material in the mother liquor contained some *2a* as seen from an NMR spectrum. It was dissolved in acetonitrile and stirred with silver benzoate for 3 h. Filtration through carbon and evaporation gave a yellow syrup which was dissolved in dichloromethane and washed with aqueous $NaHCO_3$. The solvent was evaporated and the residue was crystallized from ether-pentane to give 800 mg (12 %) of tri-*O*-acetyl-1-*O*-benzoyl-2-bromo-2-deoxy-β-D-glucopyranose (*6*), m.p. 150–153 °C. Recrystallization from ether-pentane gave the pure product, m.p. 157–158 °C, $[\alpha]_D^{20}$ 10.5° (*c* 2.8) (reported [3] m.p. 161–162 °C, $[\alpha]_D^{28}$ 15.3°). ^{1}H NMR: δ 6.08 (H1), 4.09 (H2), 5.44 (H3), 5.09 (H4), 3.99 (H5), 4.37 (H6), 4.10 (H6′); J_{12} = 9.0 Hz, J_{23} = 10.4, J_{34} = 9.1, J_{45} = 9.8, J_{56} = 4.5 $J_{56'}$ = 2.6, $J_{66'}$ = 12.5.

Di-O-acetyl-2-bromo-2,6-dideoxy-α-L-glucopyranosyl bromide (7a). A mixture of tri-*O*-acetyl-6-deoxy-α-L-glucopyranosyl bromide [7] (2.0 g), acetyl bromide (20 ml) and anhydrous zinc bromide (4 g) was stirred at room temperature for 3 h. Work up as described above gave 1.9 g of a product which was crystallized from ether-pentane to give 1.1 g (51 %) of *7a*, m.p. 126–128 °C. Recrystallization from ether-pentane gave the pure product, m.p. 130–132 °C, $[\alpha]_D^{20}$ −355° (*c* 1.4). Anal. $C_{10}H_{14}Br_2O_5$: C, H, Br. ^{1}H NMR: δ 6.44 (H1), 4.13 (H2), 5.56 (H3), 4.89 (H4), 4.33 (H5), 1.26 (H6). J_{12} = 3.7 Hz, J_{23} = 10.8, J_{34} = 9.2, J_{45} = 9.9, J_{56} = 6.1.

Tri-O-benzoyl-2-bromo-2-deoxy-α-D-glucopyranosyl bromide (2b). A mixture of tetra-*O*-benzoyl-α-D-glucopyranosyl bromide (*1b*) (5.0 g), acetyl bromide (35 ml), and zinc bromide (10 g) was stirred at room temperature for 15–20 h. Work up as described above and crystallization from ether-pentane gave 3.12 g (66 %) of *2b*, m.p. 151–155 °C. Recrystallization from the same solvent gave 2.35 g (50 %) of pure product, m.p. 165–167 °C, $[\alpha]_D^{20}$ 141° (*c* 3.8). Anal. $C_{27}H_{22}Br_2O_7$: C, H. ^{1}H NMR: δ 6.62 (H1), 4.45 (H2), 6.18 (H3), 5.76 (H4), 4.82 (H5), 4.71 (H6), 4.49 (H6′). J_{12} = 3.5 Hz, J_{23} = 10.5, J_{34} = 9.3, J_{45} = 10.0, J_{56} = 2.5, $J_{56'}$ = 5, $J_{66'}$ = 12.5.

Di-O-benzoyl-2-bromo-2,6-dideoxy-α-L-glucopyranosyl bromide (7b). Tri-*O*-benzoyl-6-deoxy-α-L-glucopyranosyl bromide [7] (*4b*) (1.0 g), acetyl bromide (6 ml) and zinc bromide (2 g) were stirred at 5 °C for 18 h. Work up as described above gave 1 g of product which was crystallized from ether-pentane to give 483 mg (52 %) of *7b*, m.p. 90–94 °C. Recrystallization from ether-pentane gave the pure product, m.p. 91–92 °C, $[\alpha]_D^{20}$ −125° (*c* 4.1). Anal. $C_{20}H_{18}Br_2O_5$: C, H. ^{1}H NMR: δ 6.50 (H1), 4.38 (H2), 6.07 (H3), 5.33 (H4), 4.58 (H5), 1.40 (H6); J_{12} = 3.6 Hz, J_{23} = 10.9, J_{34} = 9.5, J_{45} = 9.5, J_{56} = 6.1.

Tri-O-acetyl-2-bromo-1,2-dideoxy-D-arabino-hex-1-enopyranose (5a). A solution of *2a* (1.0 g) and diethylamine (2.0 ml) in dichloromethane (4 ml) was kept at 0 °C for 30 min. It was then diluted with dichloromethane, washed with 4 N hydrochloric acid and with aqueous $NaHCO_3$, dried and evaporated. The residue was a syrup (802 mg, 99 %) which was pure as seen from TLC and ^{1}H NMR. A sample was purified by preparative TLC (ether-pentane (1:1)), $[\alpha]_D^{20}$ 19.1° (*c* 2.2). Anal. $C_{12}H_{15}BrO_7$: C, H. ^{1}H NMR: δ 6.83 (H1), 5.57 (H3), 5.27 (H4), 4.1–4.6 (H5–H6); $J_{13} \simeq 1$ Hz, J_{34} = 4.8, $J_{45} \simeq 4.8$. Crude *5a* has been prepared in the same way by Hurd and Jenkins.[9]

Tri-O-benzoyl-2-bromo-1,2-dideoxy-D-arabino-hex-1-enopyranose (5b) was prepared as described above from 500 mg of *2b*. The crude product (425 mg) was purified by preparative TLC, using 3 elutions with ether-pentane (1:2), to give 376 mg (87 %) of pure *5b* as a syrup, $[\alpha]_D^{20}$ −92.7° (*c* 1.1). Anal. $C_{27}H_{21}BrO_7$: C, H. ^{1}H NMR: δ 6.98 (H1), 6.02 (H3), 5.85 (H4), 5.0–4.5 (H5–H6); J_{34} = 4.0 Hz, J_{45} = 4.0 Hz.

Di-O-acetyl-2-bromo-1,2,6-trideoxy-L-arabino-hex-1-enopyranose (8a) was prepared analogously from 706 mg of *7a*. The crude product (457 mg) was purified by preparative TLC (ether-pentane 1:1) to give 350 mg (63 %) of *8a* as a syrup, $[\alpha]_D^{20}$ 1.8° (*c* 3.8). Anal. $C_{10}H_{13}BrO_5$: C, H. ^{1}H NMR: δ 6.77 (H1), 5.50 (H3), 5.02 (H4), 4.27 (H5), 1.33 (H6); $J_{13} \simeq 0.8$ Hz, J_{34} = 4.8, J_{45} = 6.3, J_{56} = 6.8.

Di-O-benzoyl-2-bromo-1,2,6-trideoxy-L-arabino-hex-1-enopyranose (8b) was also prepared in the same way from 1.0 g of *7b*. The crude product crystallized from ether to give 369 mg (47 %) of *8b*, m.p. 106–108 °C. Recrystallization from ether gave the pure product, m.p. 109–110 °C, $[\alpha]_D^{20}$ 19.9° (*c* 3.4). Anal. $C_{20}H_{17}BrO_5$: C, H. ^{1}H NMR: δ 6.89 (H1), 6.00 (H3), 5.51 (H4), 4.53 (H5), 1.51 (H6); J_{13} = 1 Hz, $J_{15} \simeq 0.8$, J_{35} = 1, J_{45} = 5.4, J_{56} = 6.8.

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