

# Reaction of Some Anhydroalditols with Hydrogen Bromide.

## Preparation of Bromodeoxy Anhydroalditols

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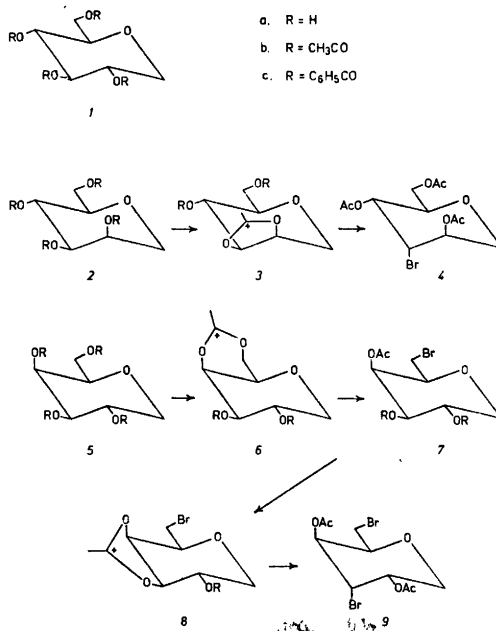
Treatment of anhydroalditols with hydrogen bromide in acetic acid (HBA) has been shown to give bromodeoxy anhydroalditols. Thus 1,5-anhydro-D-mannitol yields a 3-bromo-3-deoxy-D-altro derivative on reaction with HBA whereas 1,5-anhydro-D-galactitol gives a mixture of 3,6-dibromo-3,6-dideoxy-D-gulo- and 6-bromo-6-deoxy-D-galacto derivatives presumably *via* acetoxonium ion intermediates.

Treatment of 1,4-anhydro derivatives of D-glucitol and D-mannitol with HBA leads to more complex reaction mixtures *via* initially formed dianhydro compounds. From 1,4-anhydro-D-mannitol, a 2,6-dibromo-2,6-dideoxy-1,4-anhydro-D-glucitol derivative can be isolated. Racemic 1,4-anhydro-galactitol yields a 6-bromo-6-deoxy-1,4-anhydro-galactitol derivative in high yield on reaction with HBA.

It was previously shown that a concentrated solution of hydrogen bromide in acetic acid (HBA) reacts rapidly with *cis* diols to give *trans* bromoacetoxy compounds, presumably *via* dioxolanylium ions.<sup>1,2</sup> Attempts to extend this reaction to furanoses or pyranoses in which the *cis* diol system was situated inside the five- or six-membered ring were unsuccessful.<sup>2</sup> However, certain galactofuranose or mannofuranose derivatives reacted rapidly with HBA to give the corresponding 6-bromo-6-deoxy compounds,<sup>2,3</sup> indicating that an exocyclic diol system reacts as expected with HBA. In the present paper the behaviour of a number of anhydroalditols towards HBA is described.

The reaction of diols with HBA probably proceeds by partial acetylation followed by formation of an acetoxonium ion which finally, reacts with bromide ion to give a *trans* bromoacetate.<sup>1,2,4</sup> The formation of an acetoxonium ion requires a *cis* diol system and the all *trans*

compound, 1,5-anhydro-D-glucitol (*1a*) would, therefore, not be expected to yield bromodeoxy compounds on treatment with HBA. This was, in fact, found to be the case since reaction of *1a* with HBA gave the tetra-*O*-acetate (*1b*) as the main product; no bromo derivatives could be detected.

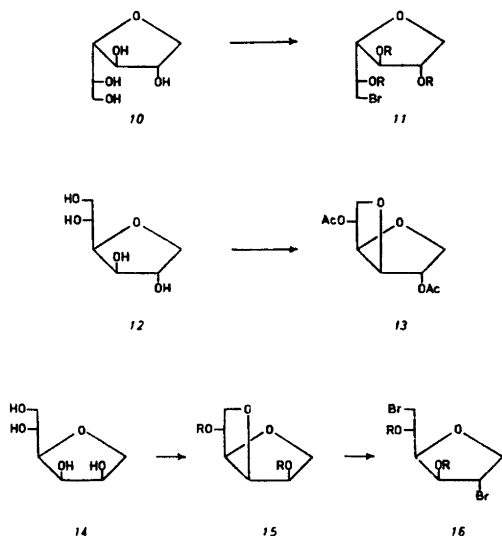


1,5-Anhydro-D-mannitol (*2a*) has a *cis* diol system at C-2 and C-3 and may, therefore, give an acetoxonium ion (*3a* or *b*) after partial acetylation. Treatment of *2a* with HBA for 24 h gave a 56 % yield of 2,4,6-tri-*O*-acetyl-3-bromo-3-deoxy-1,5-anhydro-D-altritol (*4*) to-

gether with 26 % of the tetra-*O*-acetate (2*b*). The bromo-derivative (4) is undoubtedly formed by reaction of the acetoxonium ion 3 with bromide ion and this would be expected to give only the *trans* diaxial product (4).<sup>5</sup>

Treatment of 1,5-anhydro-D-galactitol (5*a*) with HBA gave a 49 % yield of a 3,6-dibromo compound (9), 28 % of the 6-bromo compound (7*b*), and traces of fully acetylated starting material 5*b*. Since both 7*b* and 9 have bromine at C-6 the first step in the reaction of 5*a* with HBA is probably partial acetylation and formation of a 4,6-acetoxonium ion (6). Subsequent reaction of 6 with bromide ion will give 7, either partially or fully acetylated. The fully acetylated product (7*b*) will not react further. In a competitive reaction, however, 7*a* may form the 3,4-acetoxonium ion (8), which will subsequently react with bromide ion to give the *trans* diaxial product 9.

Treatment of 1,4-anhydro-D,L-galactitol (10) with HBA for 4 h gave a 6-bromo derivative (11*b*) as a rather unstable syrup, which could be deacetylated and characterized as its benzoate (11*c*), isolated in a total yield of 60 %. This reaction is analogous to results obtained from mannofuranose derivatives.<sup>3</sup> A similar treatment of 1,4-anhydro-D-glucitol (12) with HBA



might be expected to give a 6-bromo-6-deoxy derivative of 1,4-anhydro-D-glucitol. But work-up after 2 h showed that 2,5-di-*O*-acetyl-1,4-3,6-

dianhydro-D-glucitol (13) was formed as the main product, isolated in 62 % yield. Further treatment with HBA for 24 h led to ring opening of the dianhydro compound and gave a complex mixture of brominated derivatives.

Similarly, reaction of 1,4-anhydro-D-mannitol (14) with HBA for 2 h gave a mixture of 2,5-di-*O*-acetyl-1,4-3,6-dianhydro-D-mannitol (15) and 3,5-di-*O*-acetyl-2,6-dibromo-2,6-dideoxy-1,4-anhydro-D-glucitol (16) in a ratio of 3 to 7. The products were separated by preparative TLC and isolated in 19 and 44 % yield, respectively. Treatment with HBA for 24 h gave, as estimated from a <sup>13</sup>C NMR spectrum of the reaction products, a complex mixture containing no dianhydro compound (15), whereas the dibromo compound (16) was the main product. Several other brominated compounds, resulting from ring opening of the 1,4-anhydro ring were formed. Dianhydro derivatives are also formed when alditols or anhydro-alditols are treated with other acids such as sulfuric acid or ion exchange resin.<sup>6</sup>

Thus we have shown that bromodeoxy derivatives of 1,5- and 1,4-anhydro hexitols can be formed upon reaction of the alditols with hydrogen bromide in acetic acid through acetoxonium ion intermediates, provided the alditol has a *cis* pair of hydroxy groups either exocyclic or in the ring. The hindrance to formation of ring-fused acetoxonium ions observed with reducing sugars<sup>2</sup> has apparently vanished in the anhydro-alditols.

## EXPERIMENTAL

Melting points are uncorrected. Preparative thin-layer chromatography (TLC) was performed on 20 × 40 cm plates using 1 mm layers of Merck silica gel PF<sub>254</sub>. <sup>1</sup>H NMR spectra were obtained at 270 MHz and <sup>13</sup>C NMR spectra at 22.63 MHz on Bruker instruments using deuteriochloroform as solvent and TMS as internal reference unless otherwise stated. The solution of hydrogen bromide in acetic acid (HBA), used throughout this work, was saturated at 0 °C, *i.e.* containing *ca.* 35 % hydrogen bromide.

### Reactions with hydrogen bromide in acetic acid (HBA)

1,5-Anhydro-D-glucitol (1*a*) (745 mg) was treated with HBA (10 ml) at room temperature for 24 h. Acetic anhydride (5 ml) was added and

after 1 h the mixture was poured into ice-water and stirred for 1 h. The products were then extracted with chloroform; the chloroform solution was washed with water and with aqueous  $\text{NaHCO}_3$ , dried ( $\text{MgSO}_4$ ) and evaporated. The crude product (1.68 g) was purified by preparative TLC (ether-pentane 2:1) to give 937 mg (63 %) of tetra-*O*-acetyl-1,5-anhydro-D-glucitol (*1b*), m.p. 70–72 °C,  $[\alpha]_D^{20} = 43.5^\circ$  (c 1.4,  $\text{CHCl}_3$ ), (reported<sup>7</sup> m.p. 73–74 °C,  $[\alpha]_D 47.5^\circ$ ). <sup>1</sup>H NMR data:  $\delta$  4.15 (H1e), 3.30 (H1a), 4.98 (H2), 5.17 (H3), 4.99 (H4), 3.59 (H5), 4.20 (H6), 4.12 (H6');  $J_{1a,1e} - 11.4$  Hz,  $J_{1e,2} 5.7$ ,  $J_{1a,2} 9.8$ ,  $J_{2,3} 9.6$ ,  $J_{3,4} 0.6$ ,  $J_{4,5} 10.0$ ,  $J_{5,6} 4.8$ ,  $J_{5,6'} 2.3$ ,  $J_{6,6'} 12.6$ . <sup>13</sup>C NMR: 66.8 ppm (C1), 69.0 (C2), 73.7 (C3), 68.5 (C4), 76.4 (C5), 62.2 (C6).

1,5-Anhydro-D-mannitol (*2a*) (800 mg) in HBA (15 ml) was kept for 24 h at room temp. Acetic anhydride (5 ml) was then added and after 1 h the mixture was poured into ice-water and stirred for 1 h. The products were then extracted with chloroform; the chloroform solution was washed with water and with aqueous  $\text{NaHCO}_3$ , dried and evaporated. The crude product (1.96 g) crystallized from ether-pentane to give 570 mg (33 %) of tri-*O*-acetyl-3-bromo-3-deoxy-1,5-anhydro-D-altritol (*4*), m.p. 69–72 °C. The material in the mother liquor was separated into two fractions by preparative TLC using ether-pentane (2:1) as eluent. The fast-moving component gave an additional 400 mg (23 %) of (*4*), m.p. 74–76 °C, bringing the total yield to 56 %. Recrystallization from ether-pentane gave pure *4*, m.p. 75–77 °C,  $[\alpha]_D^{20} 12.0^\circ$  (c 1.9,  $\text{CHCl}_3$ ). Anal.  $\text{C}_{12}\text{H}_{17}\text{BrO}_7$ : C, H, Br. <sup>1</sup>H NMR:  $\delta$  4.23 (H1a), 3.94 (H1e), 5.09 (H2), 4.64 (H3), 4.93 (H4), 3.99 (H5), 4.19 (H6), 4.27 (H6');  $J_{1a,1e} - 13.5$  Hz,  $J_{1a,2} \approx 1.2$ ,  $J_{1e,3} 2.0$ ,  $J_{3,4} 3.9$ ,  $J_{4,5} 9.6$ ,  $J_{5,6} 2.4$ ,  $J_{5,6'} 5.1$ ,  $J_{6,6'} - 12.0$ . <sup>13</sup>C NMR: 64.1 ppm (C1), 71.5 (C2), 48.8 (C3), 65.2 (C4), 72.0 (C5), 62.5 (C6).

The slow-moving fraction gave 420 mg (26 %) of tetra-*O*-acetyl-1,5-anhydro-D-mannitol (*2b*) as a syrup,  $[\alpha]_D^{20} - 24.2^\circ$  (c 2.4,  $\text{CHCl}_3$ ), (reported<sup>8</sup> m.p. 58 °C,  $[\alpha]_D - 20.2^\circ$ ). <sup>1</sup>H NMR:  $\delta$  4.06 (H1e), 3.68 (H1a), 5.32 (H2), 5.04 (H3), 5.26 (H4), 3.59 (H5), 4.24 (H6), 4.11 (H6');  $J_{1e,1a} - 13.2$  Hz,  $J_{1e,2} 1.6$ ,  $J_{1a,2} 0.5$ ,  $J_{2,3} 3.6$ ,  $J_{3,4} 10.0$ ,  $J_{4,5} 10.0$ ,  $J_{5,6} 5.6$ ,  $J_{5,6'} 2.2$ ,  $J_{6,6'} - 12.0$ . <sup>13</sup>C NMR: 68.1 ppm (C1), 68.8 (C2), 71.8 (C3), 66.4 (C4), 76.8 (C5), 62.8 (C6).

1,5-Anhydro-D-galactitol (*5a*, 722 mg) by the same procedure gave 1.7 g of crude product. Crystallization from ether-pentane yielded 663 mg (40 %) of di-*O*-acetyl-3,6-dibromo-3,6-dideoxy-1,5-anhydro-D-gulitol (*9*), m.p. 96–99 °C. Preparative TLC of the material in the mother liquor using ether-pentane (2:1) as eluent gave three fractions. The fast-moving fraction gave an additional 143 mg (9 %) of *9*, m.p. 100–102 °C. Two recrystallizations from ether-pentane gave pure *9*, m.p. 102–103 °C,  $[\alpha]_D^{20} - 16.7^\circ$  (c 0.7,  $\text{CHCl}_3$ ). Anal.  $\text{C}_{10}\text{H}_{14}\text{Br}_2\text{O}_5$ : C, H, Br. <sup>1</sup>H NMR:  $\delta$  3.79 (H1a), 3.85 (H1e),

4.98 (H2), 4.62 (H3), 5.28 (H4), 4.36 (H5), 3.34 (H6), 3.29 (H6');  $J_{1a,1e} - 11.0$  Hz,  $J_{1a,2} 10.3$ ,  $J_{1e,3} 5.6$ ,  $J_{1e,3'} 1.2$ ,  $J_{2,3} 3.8$ ,  $J_{3,4} 3.5$ ,  $J_{4,5} 1.2$ ,  $J_{5,6} 6.8$ ,  $J_{5,6'} 6.8$ ,  $J_{6,6'} - 10.5$ . <sup>13</sup>C NMR: 64.2 ppm (C1), 64.9 (C2), 48.9 (C3), 71.3 (C4), 72.7 (C5), 28.9 (C6).

The next fraction gave 522 mg (28 %) of tri-*O*-acetyl-6-bromo-6-deoxy-1,5-anhydro-D-galactitol (*7b*), m.p. 119–120 °C. Recrystallization from ether-pentane yielded a pure sample, m.p. 121–122 °C,  $[\alpha]_D^{20} 38.6^\circ$  (c 2.1,  $\text{CHCl}_3$ ). Anal.  $\text{C}_{12}\text{H}_{17}\text{BrO}_7$ : C, H, Br. <sup>1</sup>H NMR:  $\delta$  3.30 (H1a), 4.17 (H1e), 5.19 (H2), 5.03 (H3), 5.56 (H4), 3.79 (H5), 3.34 (H6), 3.26 (H6');  $J_{1a,1e} - 11.1$  Hz,  $J_{1a,2} 10.1$ ,  $J_{1e,2} 5.4$ ,  $J_{2,3} 10.1$ ,  $J_{3,4} 3.3$ ,  $J_{4,5} 1.1$ ,  $J_{5,6} 6.8$ ,  $J_{5,6'} 6.8$ ,  $J_{6,6'} - 10.5$ . <sup>13</sup>C NMR: 67.1 ppm (C1), 66.3 (C2), 71.6 (C3), 68.3 (C4), 77.2 (C5), 28.5 (C6).

The slowest-moving fraction consisted of 70 mg (5 %) of syrupy tetra-*O*-acetyl-1,5-anhydro-D-galactitol (*5b*). Its structure was demonstrated by comparing its <sup>1</sup>H and <sup>13</sup>C NMR spectra with those of an authentic sample.<sup>9</sup> <sup>1</sup>H NMR:  $\delta$  3.31 (H1a), 4.16 (H1e), 5.18 (H2), 5.03 (H3), 5.42 (H4), 3.86 (H5), 4.05–4.15 (H6, H6');  $J_{1a,1e} - 11.0$  Hz,  $J_{1a,2} 10.0$ ,  $J_{1e,2} 5.1$ ,  $J_{2,3} 10.0$ ,  $J_{3,4} 3.0$ ,  $J_{4,5} 0$ ,  $J_{5,6} 6.0$ ,  $J_{5,6'} 6.0$ , <sup>13</sup>C NMR: 66.8 ppm (C1), 66.1 (C2), 71.3 (C3), 67.5 (C4), 74.6 (C5), 61.7 (C6).

1,4-Anhydro-D-L-galactitol (*10a*)<sup>6</sup> (1.0 g) was treated with HBA (10 ml) for 4 h followed by addition of methanol (50 ml). The reaction mixture was left overnight at room temperature and then evaporated to dryness. The crude product (1.5 g) (~100 %) was seen from a <sup>13</sup>C NMR spectrum to be almost pure 6-bromo-6-deoxy-1,4-anhydro-D-L-galactitol (*11a*). <sup>13</sup>C NMR data in 50 % MeOH–D<sub>2</sub>O: 71.2 ppm (C1), 78.8 (C2), 77.4 (C3), 86.1 (C4), 73.4 (C5), 34.6 (C6). It was not possible to crystallize the product and it was further characterized as its tribenzoate *11c* which could be isolated in 60 % yield as a syrup after preparative TLC using ether-pentane 1:1 as eluent. Anal.  $\text{C}_{27}\text{H}_{33}\text{BrO}_7$ : C, H, Br. <sup>1</sup>H NMR:  $\delta$  4.19 (H1), 4.39 (H1'), 5.50–5.65 (H2, H3) 4.48 (H4), 5.82 (H5), 3.72 (H6), 3.79 (H6');  $J_{1,1'} - 12.0$  Hz,  $J_{1,2} 2.2$ ,  $J_{1,2'} 5$ ,  $J_{3,4} 4.0$ ,  $J_{4,5} 4.0$ ,  $J_{5,6} 6.5$ ,  $J_{5,6'} 6.5$ ,  $J_{6,6'} - 10.6$ . <sup>13</sup>C NMR: 72.2 ppm (C1), 72.2, 78.7, 79.0 (C2, C3, C5), 82.9 (C4), 29.4 (C6).

<sup>1</sup>H NMR data for the corresponding acetate *11b*, which could be isolated in 43 % yield as a rather unstable syrup after treatment with HBA for 4 h and work-up in the usual way: <sup>1</sup>H NMR:  $\delta$  3.91 (H1), 4.08 (H1'), 5.18 (H2), 5.06 (H3), 4.12 (H4), 5.32 (H5), 3.60 (H6), 3.51 (H6');  $J_{1,1'} - 10.8$  Hz,  $J_{1,2} 1.4$ ,  $J_{1,2'} 4.6$ ,  $J_{2,3} 1.4$ ,  $J_{3,4} 3.9$ ,  $J_{4,5} 4.2$ ,  $J_{5,6} 6.4$ ,  $J_{5,6'} 6.6$ ,  $J_{6,6'} - 10.8$ . <sup>13</sup>C NMR: 72.0 ppm (C1), 71.5 (C2), 78.0 (C3), 82.5 (C4), 78.2 (C5), 29.5 (C6).

1,4-Anhydro-D-glucitol (*12*)<sup>6</sup> (685 mg) was treated with HBA and worked up after 2 h in the usual way. The crude product (1.0 g) (~100 %) was mainly 1,4-3,6-dianhydro-2,5-di-*O*-acetyl-D-glucitol (*13*). Preparative TLC

using ether – pentane 2:1 as eluent gave 600 mg (62 %) of (13) as a syrup.  $[\alpha]_D^{20}$  130.1° (c 2.60, CHCl<sub>3</sub>), reported<sup>10</sup> m.p. 60–61 °C,  $[\alpha]_D^{20}$  133.6°. <sup>1</sup>H NMR: δ 3.98 (H1), 3.95 (H1'), 5.16 (H2), 4.47 (H3), 4.85 (H4), 5.13 (H5), 3.93 (H6), 3.79 (H6');  $J_{11'}$  –9.5 Hz,  $J_{12}$  ~0,  $J_{1'2}$  ~0,  $J_{23}$  0,  $J_{34}$  5.0,  $J_{45}$  5.0,  $J_{56}$  5.0,  $J_{56'}$  5.0,  $J_{66'}$  –9.8. <sup>13</sup>C NMR: 73.4 ppm (C1), 74.1 (C2), 85.9 (C3), 80.8 (C4), 78.2 (C5), 70.3 (C6).

Treatment of 12 with HBA for 24 h gave as seen from a <sup>13</sup>C NMR spectrum a complex mixture of brominated alditol, which was not further investigated.

1,4-Anhydro-D-mannitol (14a) (0.45 g) was treated with HBA (10 ml) for 2 h and worked up by dilution with dichloromethane (50 ml) followed by washing twice with water and once with a saturated solution of NaHCO<sub>3</sub>. Drying of the organic phase (MgSO<sub>4</sub>) followed by evaporation of the solvent gave the crude product (0.76 g). Separation by preparative TLC using ether – pentane 2:1 as eluent gave as the fastest-moving fraction syrupy (16a) 480 mg (44 %),  $[\alpha]_D^{20}$  59.5° (c 1.95, CHCl<sub>3</sub>). Anal. C<sub>10</sub>H<sub>14</sub>Br<sub>2</sub>O<sub>5</sub>: C, H, Br. <sup>1</sup>H NMR: δ 4.47 (H1), 4.18 (H1'), 4.20 (H2), 5.47 (H3), 4.56 (H4), 5.13 (H5), 3.75 (H6), 3.62 (H6');  $J_{11'}$  –10.2 Hz,  $J_{12}$  4.3,  $J_{1'2}$  1.5,  $J_{23}$  0,  $J_{34}$  3.5,  $J_{45}$  9.0,  $J_{56}$  2.8,  $J_{56'}$  4.9,  $J_{66'}$  –11.5. <sup>13</sup>C NMR: 75.2 ppm (C1), 48.0 (C2), 77.7 (C3), 78.0 (C4), 68.2 (C5), 33.3 (C6).

The slowest-moving fraction gave (15a) (120 mg, 19 %) as a syrup,  $[\alpha]_D^{20}$  193.0° (c 1.8, CHCl<sub>3</sub>) (reported<sup>6,11</sup>  $[\alpha]_D^{20}$  197.8°). <sup>1</sup>H NMR: δ 4.04 (H1), 3.81 (H1'), 5.09 (H2), 4.69 (H3);  $J_{11'}$  –9.5 Hz,  $J_{12}$  6.3,  $J_{1'2}$  7.0,  $J_{23}$  3.5. <sup>13</sup>C NMR: 70.1 ppm (C1), 73.6 (C2), 80.2 (C3).

*Acknowledgement.* The NMR spectrometers were provided by the Danish Natural Science Research Council.

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Received February 15, 1979.