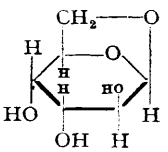
351. *The* iso*Propylidene Derivatives of* D-*Altrose and* 1 : 6-*Anhydro*-β-D-*altrose.*

By F. H. Newth and L. F. Wiggins.

When the equilibrium mixture of D-altrose and 1 : 6-anhydro-β-D-altrose is treated with acetone in the presence of sulphuric acid, three *iso*propylidene derivatives are obtained: 3 : 4-*iso*propylidene 1 : 6-anhydro-β-D-altrose, 1 : 2-3 : 4- and 1 : 2-5 : 6-di*iso*propylidene D-altrose. Evidence is presented which demonstrates the constitution of the first two of these compounds. The third is identical with the compound which Steiger and Reichstein (*Helv. Chim. Acta*, 1936, **19**, 1011) obtained by the treatment of D-altrose itself with acetone.

It was shown by Hudson and Richtmyer (*J. Amer. Chem. Soc.*, 1935, **57**, 1716) that, in acid solution, altrose gives rise to an equilibrium mixture of the sugar itself and 1 : 6-anhydro-β-D-altropyranose (I), the latter compound being later (*idem, ibid.*, 1940, **62**, 961) isolated in crystalline form. A study has now been made of the products which are obtained when this mixture of D-altrose and 1 : 6-anhydro-β-D-altrose is condensed with acetone.

The starting material (*A*) was obtained by the acid hydrolysis of 4 : 6-benzylidene α-methyl-D-altroside (II), prepared from 4 : 6-benzylidene 2 : 3-anhydro-α-methyl-D-alloside. It was a syrup which showed a specific rotation practically identical with that recorded by Hudson and Richtmyer for the product obtained by the treatment of D-altrose with hydrochloric acid. That 1 : 6-anhydro-β-D-altrose was indeed present was shown by acetylation of the mixture and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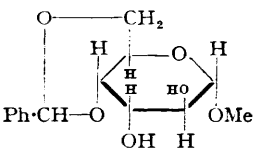
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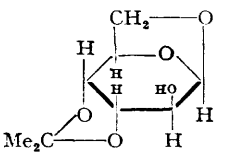
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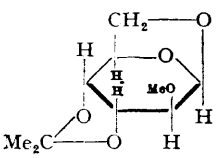
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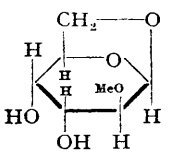
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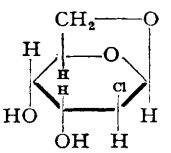
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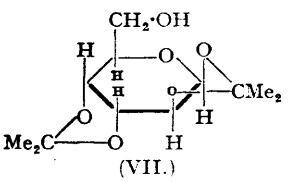
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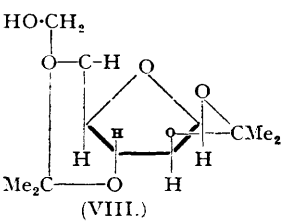
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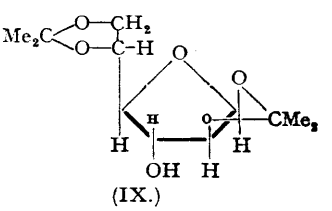

(IX.)

crystallisation, from the product, of 2 : 3 : 4-triacetyl 1 : 6-anhydro-β-D-altrose. Deacetylation of this gave a syrup from which crystalline 1 : 6-anhydro-β-D-altrose separated after seeding with an authentic specimen kindly provided by Dr. N. K. Richtmyer. 1 : 6-Anhydro-β-D-altrose and acetone containing a small amount of sulphuric acid gave 3 : 4-iso*propylidene* 1 : 6-*anhydro*-β-D-*altrose* (III), the structure of which was established by the following observations. With silver oxide and methyl iodide it gave a monomethyl derivative, 2-*methyl* 3 : 4-iso*propylidene* 1 : 6-*anhydro*-β-D-*altrose* (IV), which was hydrolysed by acetic acid to 2-*methyl* 1 : 6-*anhydro*-β-D-*altrose* (V). When this substance was oxidised with lead tetra-acetate (Hockett and McClenahan, *J. Amer. Chem. Soc.*, 1939, **61**, 1667), the reaction followed the normal course for a compound containing one *cis*-glycol group, one atomic proportion of oxygen being rapidly consumed (see figure). Hence, in (III), the *iso*propylidene residue must be allocated to $C_{(3)}$ and $C_{(4)}$. Moreover, the 2-chloro 3 : 4-diacetyl 1 : 6-anhydro-2-deoxy-β-D-altrose of known structure described by Newth, Overend, and Wiggins (*J.*, 1947, 10), on deacetylation, gave crystalline 2-*chloro*-1 : 6-*anhydro*-2-*deoxy*-β-D-*altrose* (VI), which behaved in the same way with lead tetra-acetate

(see figure). Treatment of (III) with toluene-*p*-sulphonyl chloride led to the isolation of 2-*toluene*-p-*sulphonyl* 3 : 4-iso*propylidene* 1 : 6-*anhydro*-β-D-*altrose*.

The reaction of the equilibrium mixture (*A*) with acetone in the presence of sulphuric acid produced a mixture of liquid *iso*propylidene derivatives. With toluene-*p*-sulphonyl chloride in pyridine this gave crystalline 2-toluene-*p*-sulphonyl 3 : 4-*iso*propylidene 1 : 6-anhydro-β-D-altrose, identical with the compound described above, in yield corresponding very closely with that expected from the work of Hudson and Richtmyer on the equilibrium mixture of D-altrose and 1 : 6-anhydro-β-D-altrose; reductive removal of the toluene-*p*-sulphonyl group with sodium amalgam in alcohol afforded smoothly 3 : 4-*iso*propylidene 1 : 6-anhydro-β-D-altrose (III). After separation of the crystalline toluene-*p*-sulphonyl derivative, the residual syrup (*B*) was treated with sodium iodide in acetone at 110°. Sodium toluene-*p*-sulphonate was precipitated, which indicated the detachment of a toluene-*p*-sulphonyl residue from a primary alcohol group. Sodium amalgam in alcohol removed the toluene-*p*-sulphonyl groups and the product was found to contain two di*iso*propylidene derivatives of D-altrose. The first was a liquid, non-reducing *di*iso*propylidene* D-*altrose* which gave a carboxylic acid on oxidation with alkaline permanganate. This acid still contained two *iso*propylidene residues and gave a positive naphtharesorcinol test for uronic acids, a liquid *methyl* ester, and a crystalline *amide*. The di*iso*propylidene altrose must therefore possess a free hydroxyl group at $C_{(6)}$. Depending on whether altrose in this compound has the pyranose or furanose structure, the di*iso*propylidene residues must involve $C_{(1)}$, $C_{(2)}$, $C_{(3)}$, and (*a*) $C_{(4)}$ or (*b*) $C_{(5)}$. On the assumption that altrose here exists in the pyranose modification there are three possible allocations of the *iso*propylidene residues, namely to positions 1 : 3-2 : 4, 1 : 2-3 : 4 (VII), or 1 : 4-2 : 3. Scale models show that of these only (VII) is sterically possible. If, however, D-altrose assumed the furanose modification, then 1 : 2-3 : 5 (VIII), 1 : 5-2 : 3, or 1 : 3-2 : 5 would be theoretically possible positions for the attachment of the *iso*propylidene residues, but of these only (VIII) is at all probable on steric grounds. Although there is a precedent for the 3 : 5-allocation of an *iso*propylidene group as in (VIII) because Ohle and Vargha (*Ber.*, 1928, **61**, 1203) prepared 6-toluene-*p*-sulphonyl 1 : 2-3 : 5-di*iso*propylidene D-glucofuranose from 6-toluene-*p*-sulphonyl 1 : 2-*iso*propylidene D-glucofuranose, it was only possible to prepare such a compound when ketal formation on adjacent carbon atoms was prohibited. Therefore, although the liquid compound, on the evidence at present available, may be either 1 : 2-3 : 4-di*iso*propylidene D-altropyranose (VII) or 1 : 2-3 : 5-di*iso*propylidene D-altrofuranose (VIII), we favour the former, but further work is required to prove this contention definitely.

The crystalline component of the syrup (*B*) was the 1 : 2-5 : 6-di*iso*propylidene D-altrofuranose (IX) obtained from D-altrose itself by Steiger and Reichstein (*Helv. Chim. Acta*, 1936, **19**, 1011) who indicated its structure.

Experimental.

Hydrolysis of 4 : 6-*Benzylidene* α-*Methyl*-D-*altroside*.—This substance (40 g.; Hudson and Richtmyer, *J. Amer. Chem. Soc.*, 1941, **63**, 1716) was dissolved in 5% sulphuric acid (400 c.c.), and the solution boiled under reflux for 17 hours and, when cool, extracted with ether to remove benzaldehyde. It was then made slightly alkaline with barium hydroxide and immediately neutralised with carbon dioxide. The solution was filtered, the residue was washed with water, and the filtrate and washings were evaporated under diminished pressure to a syrup (24·0 g.) containing a mixture of D-altrose and 1 : 6-anhydro-β-D-altrose and showing $[\alpha]_D^{20}$ −94·6° in water (*c*, 2·98). Hudson and Richtmyer (*J. Amer. Chem. Soc.*, 1935, **57**, 1721) give $[\alpha]_D$ −98·2° for this mixture. A portion (6 g.) of the syrup, acetylated in the manner described by the above authors, gave 2 : 3 : 4-triacetyl 1 : 6-anhydro-β-D-altrose (5·5 g.), m. p. 99—100° after recrystallisation from alcohol.

Deacetylation of 2 : 3 : 4-*Triacetyl* 1 : 6-*Anhydro*-β-D-*altrose*.—The above triacetyl derivative (2 g.) was dissolved in dry methyl alcohol (10 c.c.) and a trace of sodium added. After being kept overnight, the solution was evaporated to give 1 : 6-anhydro-β-D-altrose as a clear syrup (1·2 g.). A small portion crystallised completely when seeded with an authentic specimen kindly provided by Dr. N. K. Richtmyer. When recrystallised from ethyl acetate, prisms were obtained which had m. p. 58—59° and $[\alpha]_D^{19}$ −195° in water (*c*, 0·49). The m. p. in admixture with the authentic specimen showed no depression. The sample provided by Dr. Richtmyer had m. p. 58—61° and $[\alpha]_D^{20}$ −185° in water (*c*, 1·16). Hudson and Richtmyer (*J. Amer. Chem. Soc.*, 1939, **61**, 214) described 1 : 6-anhydro-β-D-altrose as having m. p. 135°, but with signs of melting at 80—90°, and $[\alpha]_D$ −215° in water.

3 : 4-iso*Propylidene* 1 : 6-*Anhydro*-β-D-*altrose*.—The 1 : 6-anhydro-β-D-altrose syrup (1·0 g.) obtained on deacetylation of the crystalline triacetate was shaken overnight with acetone (20 c.c.) containing concentrated sulphuric acid (0·1 c.c.). After neutralisation of the acid with anhydrous sodium carbonate, the inorganic residue was removed by filtration and washed with acetone. The combined filtrate and washings were evaporated and a syrup (1·1 g.) was obtained, having b. p. 158° (bath temp.)/0·05 mm. The colourless distillate (0·7 g.) showed $[\alpha]_D^{20}$ −160° in chloroform (*c*, 7·56) and n_D^{20} 1·4879 and subsequently crystallised. The 3 : 4-iso*propylidene* 1 : 6-*anhydro*-β-D-*altrose* recrystallised from ether–light petroleum in prisms, m. p. 84—85°, $[\alpha]_D^{23}$ −171° in chloroform (*c*, 1·0) (Found: C, 53·2; H, 6·7. $C_9H_{14}O_5$ requires C, 52·9; H, 6·8%).

2-*Toluene*-p-*sulphonyl* 3 : 4-iso*Propylidene* 1 : 6-*Anhydro*-β-D-*altrose*.—3 : 4-*iso*Propylidene 1 : 6-

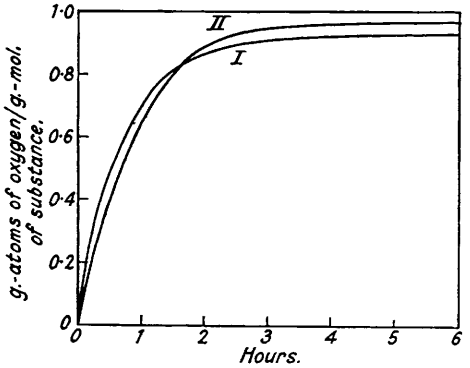
anhydro-β-D-altrose (1·3 g.) was dissolved in dry pyridine (10 c.c.), and toluene-*p*-sulphonyl chloride (1·7 g.) added. After being kept overnight, the mixture was poured into water, whereupon a crystalline product separated. This, recrystallised from alcohol, formed plates, m. p. 176—177°, $[\alpha]_D^{20}$ −150·8° in chloroform (*c*, 2·24) (Found: C, 53·7; H, 5·7. $C_{16}H_{20}O_7S$ requires C, 53·9; H, 5·6%).

Reduction of 2-*Toluene*-p-*sulphonyl* 3 : 4-iso*Propylidene* 1 : 6-*Anhydro*-β-D-*altrose with Sodium Amalgam.*—The substance (10 g.) was suspended in 90% methyl alcohol (200 c.c.) containing 3% sodium amalgam (200 g.). The mixture was stirred at 45° for 4 hours and then kept overnight. The solution was decanted from the mercury which was washed with methyl alcohol. The combined solution and washings were neutralised with carbon dioxide, and the inorganic precipitate was filtered off and washed. The dry residue which was obtained when the combined filtrate and washings were evaporated was extracted with chloroform. Removal of the solvent left a syrup which crystallised spontaneously. Recrystallisation from ether–light petroleum gave 3 : 4-*iso*propylidene 1 : 6-anhydro-β-D-altrose (4·9 g.), m. p. 83—85°.

2-*Methyl* 3 : 4-iso*Propylidene* 1 : 6-*Anhydro*-β-D-*altrose.*—3 : 4-*iso*Propylidene 1 : 6-anhydro-β-D-altrose (0·30 g.) was treated with dry silver oxide and methyl iodide at 45° for 12 hours. The methyl iodide was removed by evaporation and the dry residue extracted with boiling chloroform six times. The solvent was evaporated and the residue treated twice more with the methylating reagents. Final evaporation of the solvent gave a syrup which distilled at 110° (bath temp.)/0·01 mm. as a colourless liquid (0·29 g.). It was 2-*methyl* 3 : 4-iso*propylidene* 1 : 6-*anhydro*-β-D-*altrose* which showed n_D^{20} 1·4689 and $[\alpha]_D^{18}$ −140° in chloroform (*c*, 0·85) (Found: C, 55·5; H, 7·3. $C_{10}H_{16}O_5$ requires C, 55·5; H, 7·4%).

2-*Methyl* 1 : 6-*Anhydro*-β-D-*altrose.*—2-Methyl 3 : 4-*iso*propylidene 1 : 6-anhydro-β-D-altrose (0·25 g.) was boiled under reflux with 20% acetic acid (5·0 c.c.) for 3 hours. Dissolution was then complete. Evaporation under diminished pressure afforded a syrup which distilled as a colourless liquid (0·08 g.) at 165° (bath temperature)/0·04 mm. The 2-*methyl* 1 : 6-*anhydro*-β-D-*altrose* showed n_D^{21} 1·4692 and $[\alpha]_D^{20}$ −198° in alcohol (*c*, 1·03) (Found: C, 47·2; H, 6·6. $C_7H_{12}O_5$ requires C, 47·7; H, 6·8%).

Rates of oxidation of derivatives of 1 : 6-*anhydro*-β-D-*altrose with lead tetra-acetate.*



I. 2-*Methyl* 1 : 6-*anhydro*-β-D-*altrose.*
II. 2-*Chloro* 1 : 6-*anhydro*-2-*deoxy*-β-D-*altrose.*

Oxidation of 2-*Methyl* 1 : 6-*Anhydro*-β-D-*altrose with Lead Tetra-acetate.*—To the substance (0·0568 g.) dissolved in glacial acetic acid (49 c.c.) was added standard lead tetra-acetate solution (50 c.c.) (prepared according to the method of Hockett and McClenahan, *loc. cit.*). Acetic acid was added to make the solution up to 100 c.c. 10-C.c. portions were withdrawn at intervals and run into 20 c.c. of a buffer solution containing sodium acetate (250 g./l.) and potassium iodide (20 g./l.). The iodide liberated was titrated with 0·02N-sodium thiosulphate solution. See figure.

2-*Chloro*-1 : 6-*anhydro*-2-*deoxy*-β-D-*altrose.* — 2-Chloro-3 : 4-diacetyl 1 : 6-anhydro-2-deoxy-β-D-altrose (0·71 g.), prepared according to Newth, Overend, and Wiggins (*loc. cit.*), was dissolved in dry methyl alcohol (10 c.c.), and a trace of sodium added. After being kept overnight the solution was evaporated to give a crystalline residue. 2-*Chloro*-1 : 6-*anhydro*-2-*deoxy*-β-D-*altrose*, recrystallised from ethyl acetate, formed clusters of plates (0·40 g.), m. p. 122—123°, $[\alpha]_D^{28}$ −224° in alcohol (*c*, 1·045) (Found: C, 40·1; H, 5·0. $C_6H_9O_4Cl$ requires C, 40·0; H, 5·0%).

Oxidation of 2-*Chloro*-1 : 6-*anhydro*-2-*deoxy*-β-D-*altrose with Lead Tetra-acetate.*—The substance (0·0756 g.) was oxidised with lead tetra-acetate in the manner described above (see also figure).

Treatment of the D-*Altrose*-1 : 6-*Anhydro*-β-D-*altrose Mixture with Acetone.*—The syrupy mixture (25 g.) was shaken with acetone (400 c.c.) containing concentrated sulphuric acid (2·2 c.c.) for 24 hours. The acid was then neutralised with anhydrous sodium carbonate, the solution was filtered, and washed, and the combined filtrate and washings were evaporated. The product (31 g.) was dissolved in pyridine (150 c.c.), and toluene-*p*-sulphonyl chloride (36 g.) added. After being kept for 24 hours, the mixture was poured into water and the crystalline precipitate which separated recrystallised from alcohol, giving 2-toluene-*p*-sulphonyl 3 : 4-*iso*propylidene 1 : 6-anhydro-β-D-altrose (23 g.), m. p. 170—173°, identical with the product obtained as above. Complete evaporation of the mother-liquors gave a syrup (*B*) (18·5 g.) which could not be crystallised.

Treatment of Syrup (B) *with Sodium Iodide in Acetone.*—The syrup (*B*) (1 g.) was dissolved in dry acetone (200 c.c.) containing dry sodium iodide (1 g.), and the solution heated at 110° for 5 hours; 0·2 g. of sodium toluene-*p*-sulphonate separated, which corresponds with 0·4 primary toluene-*p*-sulphonyl group. The solution was evaporated and the residue extracted with chloroform. The extract was washed with sodium thiosulphate solution, dried ($MgSO_4$), and evaporated. A syrup (0·8 g.) was obtained from which no crystalline product has been separated.

Reduction of Syrup (B) *with Sodium Amalgam.*—The syrup (*B*) (18·5 g.) remaining after the removal of 2-toluene-*p*-sulphonyl 3 : 4-*iso*propylidene 1 : 6-anhydro-β-D-altrose was dissolved in 90% methyl alcohol (300 c.c.), and 3% sodium amalgam (100 g.) added. After being stirred overnight, the solution was decanted from the mercury and neutralised with carbon dioxide. It was then evaporated to dryness and the residue extracted with ether. Evaporation of this extract gave a syrup (6·8 g.) which was fractionally distilled through a Widmer column. Three fractions were collected: (i) B. p. 128—130° (bath temp.)/0·01 mm. (0·65 g.), $[\alpha]_D^{23}$ −13·1° in chloroform (*c*, 1·30), n_D^{27} 1·4570; this was 1 : 2-3 : 4-*di*iso*propylidene* D-*altropyranose* (Found: C, 55·1; H, 7·5. $C_{12}H_{20}O_6$ requires C, 55·4; H, 7·7%); when dissolved in water, it did not reduce Fehling's solution. (ii) B. p. 140—150° (bath temp.)/0·01 mm. (1·34 g.), $[\alpha]_D^{23}$ −1·7° in chloroform (*c*, 1·19), n_D^{27} 1·4615; this partly crystallised when kept and contained

some 1 : 2-5 : 6-di*iso*propylidene D-altrofuranose. (iii) B. p. 152—170° (bath temp.)/0·01 mm. (3·05 g.); this crystallised completely and on recrystallisation from ether–light petroleum 1 : 2-5 : 6-di*iso*propylidene D-altrofuranose was obtained having m. p. 87—88° and $[\alpha]_D^{21}$ +28·7° in acetone (*c*, 1·04) (Found : C, 55·0; H, 7·9. Calc. for $C_{12}H_{20}O_6$: C, 55·4; H, 7·7%); Steiger and Reichstein (*loc. cit.*) give m. p. 89° and $[\alpha]_D$ +28·3° in acetone.

Oxidation of 1 : 2-3 : 4-*Di*iso*propylidene* D-*Altropyranose with Permanganate.*—The substance (1·4 g.) was dissolved in 0·1N-sodium hydroxide (128 c.c.), and potassium permanganate (1·62 g.) added. The solution was set aside overnight, during which time it became colourless and a precipitate of manganese oxide formed. Carbon dioxide was passed into the filtered solution until it was neutral. The solution was then evaporated to dryness under diminished pressure and the residue extracted with cold absolute alcohol. Evaporation of the extract gave a glass (1·15 g.). This was dissolved in 0·1N-sulphuric acid (39 c.c., 1 equiv.), and the solution extracted 6 times with ether. The extract was dried ($MgSO_4$) and evaporated. A syrupy acid (1·05 g.) was obtained which gave a strongly positive naphtharesorcinol test for uronic acids.

The acid (1·05 g.) was dissolved in ether, and ethereal diazomethane added. A vigorous evolution of nitrogen occurred. The solution was set aside overnight in the presence of excess of diazomethane and then evaporated. The syrup obtained distilled at 105° (bath temp.)/0·01 mm. as a clear liquid, showing n_D^{19} 1·4565 and $[\alpha]_D^{17}$ +18·0° in chloroform (*c*, 1·22). It was *methyl* 1 : 2-3 : 4-*di*iso*propylidene* D-*altruronate* (Found : C, 54·4; H, 7·2. $C_{13}H_{20}O_7$ requires C, 54·2; H, 6·9%).

A solution of this ester (0·1 g.) in dry methyl alcohol (5 c.c.) was saturated with ammonia at 0°. After 36 hours, it was evaporated in a desiccator, the residue slowly crystallising. The *amide*, recrystallised from ether–light petroleum, had m. p. 115—116°, $[\alpha]_D^{20}$ −9·4° in acetone (*c*, 0·95) (Found : C, 53·2; H, 7·0. $C_{12}H_{19}O_6N$ requires C, 52·8; H, 7·0%).

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