77. *The Anhydrides of Polyhydric Alcohols. Part IV. The Constitution of Dianhydro Sorbitol.*

By R. Montgomery and L. F. Wiggins.

The constitution of dianhydro sorbitol (also known as isosorbide) is shown through its synthesis from 3 : 6-anhydro glucose and the synthesis of its dimethyl derivative from 3 : 6-anhydro 2 : 5-dimethyl glucofuranose to be that of 1 : 4-3 : 6-dianhydro sorbitol.

SORBITOL, on being heated with acidic reagents, readily loses two molecules of water to form a crystalline dianhydro sorbitol. Several references to such an anhydride of sorbitol appear in the literature but it does not seem to have been described very clearly. Müller and Hoffmann (U.S.P., 1,757,468, 1928) describe monoanhydro and dianhydro sorbitol as liquids but do not describe the crystalline dianhydride. Bell, Carr, and Krantz (*J. Phys. Chem.*, 1940, **44**, 862) describe experiments with crystalline dianhydro sorbitol (which they also call isosorbide) but give no preparation. In fact these authors, by the similarity of its behaviour to that of dianhydro mannitol, at that time believed to have the 1 : 4-3 : 6-structure which has since been proved to be so (Wiggins, *J.*, 1945, 4), suggested that it too had the 1 : 4-3 : 6-structure.*

We have prepared the substance in a very similar manner to that used for dianhydro mannitol (Wiggins, *loc. cit.*) but the yield of dianhydride was almost twice as great as that of the mannitol compound. The dianhydrides of mannitol and sorbitol are similar in both chemical and physical properties. They crystallise in the same form, and their m. ps. are of the same order (dianhydro sorbitol, m. p. 61—63°; dianhydro mannitol, m. p. 86—87°). They are both very soluble in water, and crystallise from ethyl acetate. Both are extremely

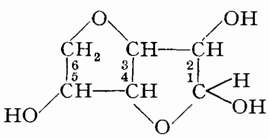
---

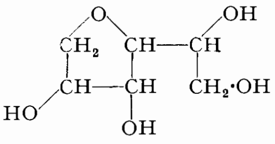
* Since our work was completed it has come to our notice that other workers (Hockett, Fletcher, Soltzberg, and Goepp, paper read at the Detroit meeting of the American Chemical Society, 1943; Fletcher and Goepp, *J. Amer. Chem. Soc.*, 1945, **67**, 1042) have adduced different and additional evidence for the 1 : 4-3 : 6-ring structure of dianhydro sorbitol.

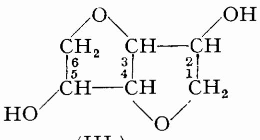
stable to alkaline reagents and can be recovered unchanged after being heated with sodium methoxide or methyl alcoholic ammonia under pressure. Neither reacts with lead tetra-acetate or benzaldehyde, showing that the two hydroxyl groups are relatively far apart. The anhydro rings of both undergo cleavage with acid reagents, hydrochloric acid with dianhydro sorbitol giving 1 : 6-dichloro sorbitol, isolated as its dimethylene derivative, a fact which shows that the primary carbon atoms are involved in the rings. Proof that the constitution of dianhydro sorbitol was indeed precisely analogous to that of dianhydro mannitol was accomplished by the following synthetic methods.

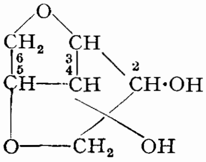
The first step in proving that dianhydro sorbitol had its oxide rings in the 1 : 4 and 3 : 6-positions was to establish the presence of at least one hydrofuranol ring. This was done by a synthesis of dianhydro sorbitol from 3 : 6-anhydro glucose (I) the constitution of which has been already proved. 3 : 6-Anhydro glucose was hydrogenated over Raney nickel to give an excellent yield of crystalline 3 : 6-anhydro sorbitol (II), the catalytic procedure being a distinct improvement on the sodium amalgam reduction originally used by Fischer and Zach (*Ber.*, 1912, **45**, 2068).

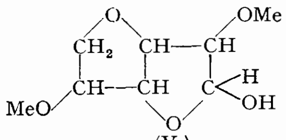
This 3 : 6-anhydro sorbitol was then selectively tosylated at C_1 and, after acetylation, liquid 1-tosyl 2 : 4 : 5-triacetyl 3 : 6-anhydro sorbitol was isolated. That the tosyl group was indeed attached to a primary hydroxyl group was indicated by the fact that the compound on treatment with sodium iodide in acetone solution gave an 80% yield of sodium *p*-toluenesulphonate.

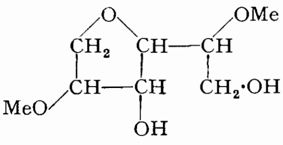

(I.)

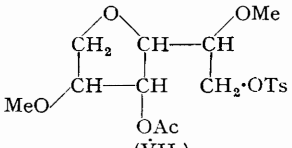

(II.)

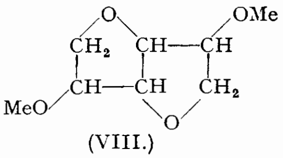

(III.)


(IV.)


(V.)


(VI.)


(VII.)


(VIII.)

The 1-tosyl compound was then treated with sodium methoxide, which detosylates and deacetylates the substance, and dianhydro sorbitol was obtained, thus proving that the 3 : 6-anhydro ring must be present. Moreover, 3 : 6-anhydro sorbitol, by distillation with a trace of concentrated sulphuric acid, could also be transformed into dianhydro sorbitol which was identified as its ditosyl derivative. This second method of conversion of 3 : 6-anhydro sorbitol into dianhydro sorbitol does not, however, constitute a proof of the presence of the 3 : 6-anhydro ring, since it is known that this type of ring (see *J.*, 1945, 4) can be opened by acid reagents and should this happen there is always the possibility that it may close again in a different direction.

Clearly, therefore, the proof that dianhydro sorbitol contains the 3 : 6-anhydro ring limits its structure to two possibilities; 1 : 4-3 : 6- (III) and 1 : 5-3 : 6- (IV) dianhydro sorbitol. (The 1 : 2-3 : 6- structure is eliminated by the fact that the substance is stable to sodium methoxide and to ammonia under quite drastic conditions.) The fact that dianhydro sorbitol does not react with benzaldehyde is evidence against (IV), for in such a molecule the hydroxyls on C_2 and C_4 should approach near enough to permit of such a condensation. To make a final choice between these two structures we synthesised a derivative of one of them, namely (III), by a method ensuring that the two rings were indeed 1 : 4 and 3 : 6. This was done by using a derivative of 3 : 6-anhydro sorbitol in which the hydroxyls at C_2 and C_5 were blocked by methyl groups so that final closure could take place only between C_1 and C_4. A suitable material for this purpose was 3 : 6-anhydro 2 : 5-dimethyl glucofuranose (V) first prepared by Haworth, Owen, and Smith (*J.*, 1941, 88). On catalytic hydrogenation over Raney nickel this substance is quantitatively converted into 2 : 5-*dimethyl* 3 : 6-*anhydro sorbitol* (VI). Selective tosylation followed by acetylation gave liquid 1-*tosyl* 4-*acetyl* 2 : 5-*dimethyl* 3 : 6-*anhydro sorbitol* (VII) which by treatment with sodium methoxide (the usual procedure for anhydro ring formation) gave 1 : 4-3 : 6-*dianhydro* 2 : 5-*dimethyl sorbitol* (VIII). Methylation of dianhydro sorbitol itself gave a dimethyl derivative identical in all respects with this synthetic material.

EXPERIMENTAL.

1 : 4-3 : 6-*Dianhydro Sorbitol.*—Sorbitol (500 g.) was boiled under reflux with concentrated hydrochloric acid for 24 hours. The dark brown liquid was evaporated to a syrup which was dissolved in water and again evaporated to a syrup. This was distilled at 160—165°/10 mm. Yield, 290 g. The light yellow distillate rapidly crystallised and was recrystallised from ethyl acetate–alcohol. Yield, 265 g. (66% of the theoretical). It then had m. p. 61—63°, $[\alpha]_D$ + 43·9° in water (*c*, 0·8) (Found : C, 49·3; H, 6·7. Calc. for $C_6H_{10}O_4$: C, 49·5; H, 6·5%). The anhydride was recovered unchanged after being treated with lead tetra-acetate in acetic acid solution and did not condense with benzaldehyde in the presence of zinc chloride.

2 : 5-*Dimethyl Dianhydro Sorbitol.*—The dianhydride (100 g.) in water (200 c.c.) was stirred at 40°. Methyl sulphate (258 g.) and 30% sodium hydroxide (360 c.c.) were added simultaneously in 10 aliquot portions over 2 hours. The reaction mixture was heated at 100° for 2 hours, cooled, and neutralised with 20% sulphuric acid. The solution was then evaporated to dryness and the residue extracted several times with boiling chloroform. The extract, after being dried ($MgSO_4$), was evaporated and the resulting liquid distilled to yield the *compound* as a colourless oil, b. p. 93—95° (bath temp.)/0·1 mm., showing $n_D^{19°}$ 1·4622, $[\alpha]_D^{21°}$ + 92·9° in chloroform (*c*, 2·20). Yield, 92 g. (Found: C, 55·6; H, 8·0. $C_8H_{14}O_4$ requires C, 55·2; H, 8·0%).

2 : 5-*Dibenzoyl Dianhydro Sorbitol.*—The dianhydride (1 g.) was dissolved in N-sodium hydroxide (25 c.c.), and benzoyl chloride (2 g.) was added and the mixture vigorously shaken for a few hours. The semi-solid material was filtered off and washed with water. The *compound* crystallised from alcohol in short needles, m. p. 102—103°, $[\alpha]_D^{18°}$ + 24·5° in chloroform (*c*, 1·51) (Found : C, 68·0; H, 5·0. $C_{20}H_{18}O_6$ requires C, 67·8; H, 5·0%).

Treatment of Dianhydro Sorbitol with Sodium Methoxide.—The anhydride (1 g.) was heated in a sealed tube for 20 hours with 5% methyl alcoholic sodium methoxide at 120°. The resulting solution was neutralised with N-sulphuric acid and evaporated to dryness, and the residue was extracted with ethyl acetate. The extract, after evaporation, yielded a syrup (0·75 g.) which crystallised rapidly on cooling. It was unchanged 1 : 4-3 : 6-dianhydro sorbitol, m. p. 61—63° after recrystallisation from ethyl acetate.

Treatment of Dianhydro Sorbitol with Ammonia.—The material (1 g.) was heated in a sealed tube at 120° for 30 hours with methyl alcohol, saturated with ammonia at 0°. The resulting solution was evaporated to dryness leaving a crystalline mass (0·87 g.) which, recrystallised from ethyl acetate, had m. p. 61—63° and was unchanged dianhydro sorbitol.

Treatment of 1 : 4-3 : 6-*Dianhydro Sorbitol with Fuming Hydrochloric Acid.*—Dianhydro sorbitol (5 g.) was heated in a sealed tube with fuming hydrochloric acid (50 c.c.) for 24 hours at 100—110°. After evaporation there remained a dark brown syrup (5 g.) which would not crystallise. It was methylenated by warming with paraformaldehyde (5 g.) and concentrated sulphuric acid (2 c.c.) for 15 minutes; after shaking the product with chloroform several times, the combined extracts were washed with sodium bicarbonate solution and with water, dried, and evaporated to dryness. The residue, on recrystallisation from ethyl alcohol, yielded 1 : 6-dichloro 2 : 4-3 : 5-dimethylene sorbitol, m. p. 116° not depressed on admixture with an authentic specimen (Haworth and Wiggins, *J.*, 1944, 58).

Tosylation of 1 : 2-*Monoacetone Glucose.*—Monoacetone glucose (40 g.), prepared by partial hydrolysis of the crude mixture of acetone sugars obtained by the acetonisation of glucose (Freudenberg, Durr and Hochstetter, *Ber.*, 1928, **61**, 1741), was tosylated by the method of Ohle, v. Vargha, and Erlbach (*Ber.*, 1928, **61**, 1211). 5 : 6-Ditosyl 1 : 2-monoacetone glucose (30 g.) was obtained, but in addition another compound was isolated (18·2 g.) having m. p. 129—130°, $[\alpha]_D^{17°}$ − 3·4 in chloroform, (*c*, 4·14) (Found : C, 53·0; H, 5·3; S, 14·7. $C_{30}H_{34}O_{12}S_3$ requires C, 52·8; H, 5·0; S, 14·1%). The same substance was also obtained by the further tosylation of 5 : 6-ditosyl 1 : 2-monoacetone glucose. Therefore, it must be 3 : 5 : 6-*tritosyl* 1 : 2-*monoacetone glucofuranose.* Ohle, Erlbach and Vögl (*Ber.*, 1928, **61**, 1815), however, describe a 3 : 5 : 6-tritosyl 1 : 2-monoacetone glucofuranose as having m. p. 95—96° and $[\alpha]_D$ − 5·2°.

3 : 6-*Anhydro Sorbitol.*—3 : 6-Anhydro glucose (1·0 g.) obtained from the above 5 : 6-ditosyl 1 : 2-monoacetone glucofuranose by the method of Ohle, v. Vargha, and Erlbach (*loc. cit.*) was dissolved in water (250 c.c.) and hydrogenated over Raney nickel at 110—120°/100 atmospheres. The solution was filtered from the catalyst and evaporated to dryness. The residue, recrystallised from methyl alcohol, had m. p. 110—111° and was identical with Fischer's (*Ber.*, 1912, **45**, 450) 3 : 6-anhydro sorbitol.

Distillation of 3 : 6-*Anhydro Sorbitol in the Presence of Concentrated Sulphuric Acid.*—The 3 : 6-anhydro sorbitol (0·2 g.) was melted and a trace of concentrated sulphuric acid added. The mixture was then distilled at 250—280° (bath temp.)/12 mm. Dianhydro sorbitol (25 mg.) distilled and rapidly crystallised. It was identified as its ditosyl derivative obtained as follows. Tosyl chloride (0·1 g.) was added to the material (25 mg.) in dry pyridine (1 c.c.) and the mixture kept for 24 hours. Thereafter it was poured into a little ice-water and the precipitated solid collected, washed with water, and crystallised from alcohol. It then had m. p. 99—100° alone or in admixture with an authentic specimen of 2 : 5-ditosyl 1 : 4-3 : 6-dianhydro sorbitol (see Part V of this series).

Conversion of 3 : 6-*Anhydro Sorbitol into Dianhydro Sorbitol with Alkaline Reagents.*—3 : 6-Anhydro sorbitol (1 g.) was dissolved in dry pyridine (5 c.c.) and a solution of tosyl chloride (1·28 g. in 5 c.c. dry pyridine) carefully added at 0°. The mixture was kept at room temperature for 60 hours, acetic anhydride being added at 0° after the first 16 hours. The solution was poured into water and extracted with chloroform. The extract was washed successively with 5% sulphuric acid, sodium bicarbonate solution, and water, dried ($MgSO_4$), and evaporated. Yield, 1·63 g. of liquid 1-tosyl 2 : 4 : 5-triacetyl 3 : 6-anhydro sorbitol. Of this, 1·2 g. was dissolved in chloroform (10 c.c.), and methyl alcohol (20 c.c.) containing sodium (0·25 g.) added at 0°. The solution was kept overnight, diluted with chloroform, and extracted with water. The aqueous extracts were combined, exactly neutralised with N-sulphuric acid, and evaporated to dryness. The dry residue was extracted with boiling ethyl acetate, the extract evaporated, and the product distilled at 200—210° (bath temp.)/12 mm. The distillate rapidly crystallised; it recrystallised from ethyl acetate in prisms (0·29 g.; 73% of the theoretical), m. p. 60—61°, $[\alpha]_D^{23·2°}$ + 43·9° in water (*c*, 0·86). The m. p. was not depressed when the crystals were mixed with authentic dianhydro sorbitol.

Treatment of the Liquid 1-*Tosyl* 2 : 4 : 5-*Triacetyl* 3 : 6-*Anhydro Sorbitol with Sodium Iodide in Acetone.*—The syrup (0·4 g.) was heated at 110° with sodium iodide (0·29 g.) dissolved in dry acetone (15 c.c.) in a sealed tube. Crystals of sodium *p*-toluenesulphonate were deposited. Yield, 0·14 g. (80% of the theoretical).

2 : 5-*Dimethyl* 3 : 6-*Anhydro Sorbitol.*—2 : 5-Dimethyl 3 : 6-anhydro glucose (1 g.), prepared by the method of Haworth, Owen, and Smith (*loc. cit.*), was subjected to catalytic hydrogenation in water (250 c.c.) at 110—120°/100 atmospheres for 6 hours using Raney nickel catalyst (1 g.). After removing the catalyst the aqueous solution was evaporated to dryness. The crystalline *product* recrystallised from ether in long, extremely hygroscopic needles which did not reduce Fehling's solution. Yield, 1·0 g., m. p. 70—71°, $[\alpha]_D^{22°}$ − 15·6° in chloroform (*c*, 0·173) (Found : OMe, 30·8. $C_8H_{16}O_5$ requires OMe, 30·7%).

2 : 5-*Dimethyl* 1 : 4-3 : 6-*Dianhydro Sorbitol.*—1-*Tosyl* 4-*acetyl* 2 : 5-*dimethyl* 3 : 6-*anhydro sorbitol.* 2 : 5-Dimethyl 3 : 6-anhydro sorbitol (0·30 g.) was dissolved in dry pyridine (5 c.c.), and tosyl chloride (0·32 g.) in dry pyridine (5 c.c.) carefully added at 0°. The mixture was kept at room temperature for 60 hours, acetic anhydride (1·5 c.c.) being added at 0° after the first 45 hours. The solution was poured into water and extracted with chloroform. The extract was

washed successively with 5% sulphuric acid, sodium bicarbonate solution, and water, dried ($MgSO_4$), and evaporated. Yield, 0·23 g.

Detosylation of 1-*tosyl* 4-*acetyl* 2 : 5-*dimethyl* 3 : 6-*anhydro sorbitol.* The material (0·23 g.) was dissolved in chloroform (5 c.c.) and methyl alcohol (10 c.c.) containing sodium (0·027 g.) added at 0°. The solution was kept overnight, diluted with chloroform, and washed with water. The chloroform extract was dried ($MgSO_4$) and evaporated. The residue distilled at 80—90° (bath temp.)/0·02 mm. Yield, 0·07 g., $n_D^{27^\circ}$ 1·4601, $[\alpha]_D^{20 \cdot 3^\circ}$ + 95·3° in chloroform (*c*, 0·125) (Found: OMe, 35·6. $C_8H_{14}O_4$ requires OMe, 35·6%).

The authors wish to express their thanks to Professors W. N. Haworth, F.R.S., and J. L. Simonsen, F.R.S., for their interest in this work and to the Colonial Products Research Council for financial assistance.

THE A. E. HILLS LABORATORIES,
THE UNIVERSITY, EDGBASTON, BIRMINGHAM.

[*Received, November* 16*th*, 1945.]