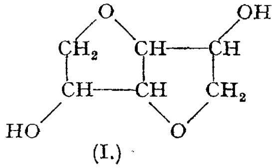
60. *Anhydrides of Polyhydric Alcohols. Part IX. Derivatives of* 1 : 4-*Anhydrosorbitol from* 1 : 4-3 : 6-*Dianhydrosorbitol.*

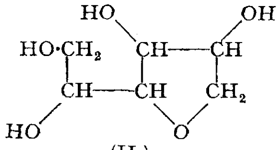
By R. Montgomery and L. F. Wiggins.

Ring scission of 1 : 4-3 : 6-dianhydrosorbitol with hydrochloric acid gives rise to 1 : 6-dichloro sorbitol and 6-chloro 1 : 4-anhydrosorbitol. Exceptional properties of 6-chloro 3 : 5-benzylidene 1 : 4-anhydrosorbitol are described.

When sorbitol is heated with acid catalysts it readily undergoes dehydration to form anhydro-compounds. Thus, Montgomery and Wiggins (this vol., p. **433**) found that high yields of a dianhydrosorbitol were obtained when sorbitol was heated with sulphuric, hydrochloric, or *p*-toluenesulphonic acids until dehydration was complete. Soltzberg, Goepp, and Freudenberg (*J. Amer. Chem. Soc.*, 1946, **68**, 919) found however that, if the reaction was allowed to proceed for only a short time, a monoanhydrosorbitol was formed. The dianhydrosorbitol has been shown to possess the 1 : 4-3 : 6 ring structure by Montgomery and Wiggins (*J.*, 1946, 390) and by Hockett, Fletcher, Sheffield, and Goepp (*J. Amer. Chem. Soc.*, 1946, **68**, 927). The constitution of the monoanhydrosorbitol has been shown [Soltzberg, Goepp, and Freudenberg (*loc. cit.*); Hockett, Conley, Yusem, and Mason, *J. Amer. Chem. Soc.*, 1946, **68**, 922] to be that of 1 : 4-anhydrosorbitol (II). Thus, the dehydration of sorbitol proceeds in such a way that anhydridisation between C_1 and C_4 occurs with greater ease than that between C_3 and C_6.



(I.)

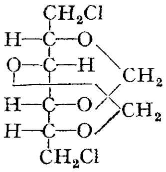


(II.)

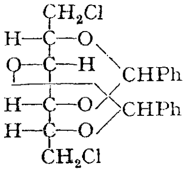
Experiments have now been carried out on the ring scission of 1 : 4-3 : 6-dianhydrosorbitol and evidence obtained that the pentaphane ring in the 3 : 6-position is more easily broken than the 1 : 4-anhydro-ring. When dianhydrosorbitol was heated for a short time under pressure with fuming hydrochloric acid, it was partly converted into a dichloro sorbitol (*a*) [isolated as a dibenzylidene derivative (*A*)] and a monochloro anhydrosorbitol (*b*) [isolated as a monobenzylidene derivative (*B*)].

When (*A*) was treated with paraformaldehyde and sulphuric acid, the benzylidene residues were replaced by methylene groups giving 1 : 6-dichloro 2 : 4-3 : 5-dimethylene sorbitol (III) the constitution of which had already been determined (Haworth and Wiggins, *J.*, 1944, 58). Therefore in (*A*) the chlorine atoms must be attached to C_1 and C_6, and (*A*) must have arisen through scission of both the 1 : 4- and the 3 : 6-ring of dianhydrosorbitol, the chlorine atoms having attached themselves to both primary carbon atoms. The orientation of the benzylidene residues in (*A*) is, however, on this evidence alone not certain. Nevertheless, by analogy with such compounds as 1 : 6-dibenzoyl 2 : 4-3 : 5-dimethylene mannitol, 1 : 6-dibenzoyl 2 : 4-3 : 5-dimethylene sorbitol, and 1 : 3-2 : 4-dibenzylidene, 1 : 3-2 : 4-dimethylene, and 1 : 3-2 : 4-diethylidene sorbitol, in all of which the aldehyde residues are linked in acetal formation to alternate carbon atoms, the most likely allocation of the benzylidene groups in this compound will be to $C_2 : C_4$ and $C_3 : C_5$, and thus (*A*) must be 1 : 6-*dichloro* 2 : 4-3 : 5-*dibenzylidene sorbitol* (IV).

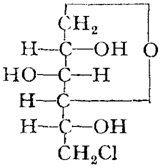
It is reasonable to suppose that substance (*b*) arises through the scission of either the 1 : 4- or the 3 : 6-anhydro-ring of dianhydrosorbitol with the addition of the chloride ion to the primary carbon atom so released. It is certainly well known in the sugar series that when ethylene oxide anhydro-rings involving primary carbon atoms suffer ring scission, the entering anion attaches itself mainly to that atom, in which case there can be no question of Walden inversion occurring. Thus there are two possible structures for (*b*), namely 6-chloro 1 : 4-anhydrosorbitol (V) and 1-chloro 3 : 6-anhydrosorbitol (VI).



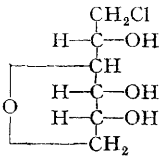
(III.)



(IV.)

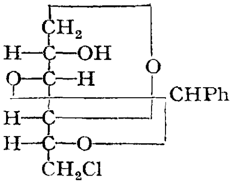


(V.)

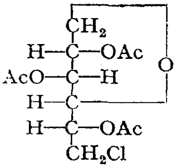


(VI.)

We know, however, that 1 : 4-anhydrosorbitol can be obtained in fair yield from sorbitol (Soltzberg, Goepp, and Freudenberg, *loc. cit.*), and therefore the 1 : 4-ring is probably more stable than the 3 : 6-ring, so that as a working hypothesis the structure (V) is considered most likely for (*b*). The benzylidene derivative (*B*) can then only have the structure (VII), that is, with the benzylidene residue allotted to C_3 and C_5. The other possible allocations of the benzylidene group, *i.e.*, between C_2 and C_3 or between C_2 and C_5, are precluded on stereochemical grounds by a study of the scale-models. The chemical properties of (*B*) prove the correctness of this supposition.



(VII.)



(VIII.)

Treatment of (*B*) with sodium iodide in acetone solution effected the liberation of 80% of the theoretical yield of sodium chloride. This exchange of a chlorine for an iodine atom in (*B*) provides evidence for the supposition that the chlorine atom is attached to a primary carbon atom which, though not quite unequivocal, is very strong, since it is known that the chlorine atoms in 1 : 6-dichloro 2 : 4-3 : 5-dimethylene mannitol can be almost quantitatively exchanged for iodine atoms with the formation of 1 : 6-di-iodo 2 : 4-3 : 5-dimethylene mannitol (Micheel, *Annalen*, 1942, **496**, 77), whereas the chlorine atoms in 2 : 5-dichloro 1 : 4-3 : 6-dianhydromannitol do not react with sodium iodide in acetone (Wiggins, *J.*, 1945, 4).

(*B*) is stable in the cold towards sodium methoxide, a reagent which promotes anhydro-ring formation when this is readily possible, so the free hydroxyl group in (*B*) cannot be in such a position as to engage in ring formation. Structure (VII) agrees with this fact.

On removal of the benzylidene residue from (*B*) by hydrolysis with oxalic acid, there is obtained a crystalline chloro anhydrosorbitol which, if formula (VII) is correct, will be 6-*chloro* 1 : 4-*anhydrosorbitol* (V). This on acetylation yields 6-*chloro* 2 : 3 : 5-*triacetyl* 1 : 4-*anhydrosorbitol* (VIII). Further evidence of the correctness of structure (VII) for (*B*) is adduced from the fact that treatment of (VIII) with sodium methoxide yields 1 : 4-3 : 6-dianhydrosorbitol, isolated as its 2 : 5-bismethanesulphonyl derivative, though this reaction is complicated in as much as another methanesulphonyl derivative of unknown constitution is also formed. That 1 : 4-3 : 6-dianhydrosorbitol is formed, however, proves the presence of one hydrofuranol ring in (*B*); that the ring is in the 1 : 4-position is proved by the fact that treatment of (*B*) with thionyl chloride and pyridine gave the same product as was prepared from 1 : 4-anhydrosorbitol itself, namely, bis-(6-chloro 3 : 5-benzylidene 1 : 4-anhydrosorbitol) 2 : 2′-sulphite (see following paper). Therefore, proof that (*B*) is 6-*chloro* 3 : 5-*benzylidene* 1 : 4-*anhydrosorbitol* is complete.

The benzylidene group in (*B*) has, however, somewhat curious properties which require comment.

It was found that the benzylidene residue was partly removed by boiling the compound with distilled water, and that if steam distillation conditions were employed the hydrolysis, adjudged by the yield of benzaldehyde *p*-nitrophenylhydrazone obtained from the distillate, was complete. The original compound (*B*) could be recovered in fair yield from the non-volatile residues after rebenzylidenation, but the residues on acetylation yielded two products, 6-chloro 2 : 3 : 5-triacetyl 1 : 4-anhydrosorbitol and 2 : 5-*diacetyl* 1 : 4-3 : 6-*dianhydrosorbitol* identical with a specimen prepared from dianhydrosorbitol. Therefore, although the main reaction has been merely the removal of the benzylidene group, some cyclisation between C_6 and C_3 has also occurred.

It might be considered possible that dissolved carbon dioxide was making the distilled water (pH 5·5) sufficiently acid to initiate the hydrolysis of the benzylidene residues. This was, however, not the case, since (*B*) on treatment with potassium hydroxide solution under steam distillation conditions lost benzaldehyde in the same way, although the yield of benzaldehyde isolated as the *p*-nitrophenylhydrazone was only 48% of the theoretical; this was, however, probably due to some of the benzaldehyde undergoing the Cannizzaro reaction.

This then must be a case in which a benzylidene acetal of a polyhydroxy-compound is unstable to alkali, a phenomenon so rare in the sugar or sugar alcohol series that the authors are unaware of another example.

EXPERIMENTAL.

Action of Fuming Hydrochloric Acid on 1 : 4-3 : 6-*Dianhydrosorbitol.*—Dianhydrosorbitol (40 g.) was heated in a sealed tube with fuming hydrochloric acid (200 c.c.) for 1 hour at 110°. The liquid was then evaporated under reduced pressure and the residual hydrochloric acid removed as far as possible by continuous distillation with water. Complete removal of the water gave a syrup which was benzylidenated by shaking with freshly distilled benzaldehyde (200 c.c.) and anhydrous zinc chloride (40 g.) for 24 hours. The product was neutralised by adding sodium carbonate (80 g.) dissolved in water, the excess of benzaldehyde removed by steam distillation under reduced pressure, and the solution evaporated to dryness. The last traces of water were removed by distillation with benzene, and the dry residue extracted 6 times with 100 c.c. portions of chloroform. The combined extracts were dried ($MgSO_4$) and evaporated to dryness. From this residue, by fractional recrystallisation from chloroform–petrol, were isolated 1 : 6-*dichloro dibenzylidene sorbitol* (1 g.), m. p. 223—224°, $[\alpha]_D^{18°}$ − 16·4 (*c*, 0·730 in chloroform) (Found : C, 60·7; H, 5·3; Cl, 18·4. $C_{20}H_{20}O_4Cl_2$ requires C, 60·7; H, 5·1; Cl, 18·0%), 6-*chloro* 3 : 5-*benzylidene* 1 : 4-*anhydrosorbitol* (10·4 g.), m. p. 154—155°, $[\alpha]_D^{19°}$ − 17·4 (*c*, 0·810 in chloroform) (Found : C, 57·6; H, 5·4; Cl, 12·4. $C_{13}H_{15}O_4Cl$ requires C, 57·8; H, 5·5; Cl, 13·1%), and unchanged 1 : 4-3 : 6-dianhydrosorbitol (17 g., m. p. 61—63°).

In an experiment in which the heating at 110° was continued for 2 hours instead of 1 hour, 1 : 6-dichloro dibenzylidene sorbitol (2·6 g.), 6-chloro 3 : 5-benzylidene 1 : 4-anhydrosorbitol (25·5 g.), and 1 : 4-3 : 6-dianhydrosorbitol (4·0 g.) were isolated in the same way as described above. 6-Chloro 3 : 5-benzylidene 1 : 4-anhydrosorbitol, on treatment with sodium iodide in acetone at 100° for 5 hours under anhydrous conditions, gave 80% of the theoretical yield of sodium chloride.

1 : 6-*Dichloro* 2 : 4-3 : 5-*Dimethylene Sorbitol.*—1 : 6-Dichloro dibenzylidene sorbitol (1 g.) was warmed with paraformaldehyde (1 g.) and concentrated sulphuric acid (4 drops) for about 20 minutes. The product was then shaken with chloroform overnight and the extract washed with concentrated ammonia solution and with water, dried, and the solvent evaporated. The syrupy product was dissolved in alcohol from which crystallised 1 : 6-dichloro 2 : 4-3 : 5-dimethylene sorbitol (0·3 g.), m. p. 116—117°, alone or in admixture with an authentic specimen.

Treatment of 6-*Chloro* 3 : 5-*Benzylidene* 1 : 4-*Anhydrosorbitol with Sodium Methoxide.*—To the compound (2·68 g.) dissolved in chloroform and cooled to 0° was added an ice-cold solution of sodium (0·25 g.) in dry methyl alcohol (10 c.c.). The mixture was kept overnight at room temperature and thereafter diluted with chloroform. The chloroform layer was separated, washed with water, and dried ($MgSO_4$). Evaporation of the chloroform solution and recrystallisation of the residue from chloroform–petrol gave the original compound (2·6 g.), m. p. 154—155°.

Hydrolysis of 6-*Chloro* 3 : 5-*Benzylidene* 1 : 4-*Anhydrosorbitol.*—The compound (10 g.) was heated under reflux for 6 hours with oxalic acid (15 g.) dissolved in acetone (400 c.c.) and water (50 c.c.). The solution was then neutralised with barium carbonate, filtered, and the acetone removed from the filtrate under reduced pressure. On cooling the residual solution, some of the original compound (3·6 g.) separated and was filtered off. The filtrate was filtered and evaporated to dryness under reduced pressure, and the residue recrystallised from ethyl acetate. It was 6-*chloro* 1 : 4-*anhydrosorbitol*, m. p. 108—109°, $[\alpha]_{\mathrm{D}}^{14^\circ}$ − 14·0° (*c*, 2·9 in acetone). Yield, 1·9 g. (Found : C, 39·7; H, 6·1; Cl, 20·0. $C_6H_{11}O_4Cl$ requires C, 39·6; H, 6·0; Cl, 19·5%). The residues from the crystallisation were acetylated to give 6-chloro 2 : 3 : 5-triacetyl 1 : 4-anhydrosorbitol (2·2 g.), m. p. 81—82° (see below).

Action of Sodium Methoxide on 6-*Chloro* 1 : 4-*Anhydrosorbitol.*—6-Chloro 1 : 4-anhydrosorbitol (0·85 g.) was dissolved in dry methyl alcohol (5 c.c.) and added to dry methyl alcohol (4 c.c.) containing sodium (0·117 g.). After 24 hours at room temperature the solution was exactly neutralised with dilute sulphuric acid and evaporated to dryness under reduced pressure. The residue was extracted with ethyl acetate, the extract dried ($MgSO_4$) and evaporated. The syrupy product (0·5 g.) was dissolved in dry pyridine (15 c.c.), and methanesulphonyl chloride (1·3 c.c.) carefully added at 0°. The mixture was kept at room temperature for 24 hours and then poured into water. The aqueous solution was extracted several times with chloroform, and the combined extracts were washed successively with 5N-sulphuric acid, sodium hydrogen carbonate solution and water, and dried ($MgSO_4$). The chloroform was then removed, and the residue, which only partly crystallised, was fractionally recrystallised, giving 2 : 5-bismethanesulphonyl 1 : 4-3 : 6-dianhydrosorbitol, m. p. 121—122°, alone or in admixture with an authentic specimen (see following paper), and a substance, m. p. 82—83°, of unknown constitution. A fraction of m. p. 114° was apparently impure 2 : 5-bismethanesulphonyl dianhydrosorbitol.

Action of Water on 6-*Chloro* 3 : 5-*Benzylidene* 1 : 4-*Anhydrosorbitol.*—(*a*) A suspension of the compound (0·558 g.) in distilled water (50 c.c.) was distilled at constant volume until no more benzaldehyde was produced. The benzaldehyde in the distillate, estimated as the *p*-nitrophenylhydrazone, was 0·208 g. (95%).

The residue in the distillation flask was evaporated under reduced pressure, and the syrupy product (0·3 g.) was shaken with benzaldehyde (10 c.c.) and anhydrous zinc chloride for 12 hours. The benzylidene derivative, isolated in the usual way and recrystallised from chloroform–petrol, had m. p. 154—155°, alone or in admixture with the original compound.

(*b*) A suspension of the compound (5 g.) in distilled water (150 c.c.) was distilled at constant volume until no more benzaldehyde was produced. The solution was then evaporated to dryness under reduced pressure, and the syrupy product (2·7 g.) acetylated with acetic anhydride (10 c.c.) and fused sodium acetate (2 g.). The product was a syrup, which distilled b. p. 190—200° (bath temp.)/10 mm. The distillate partly crystallised, and after recrystallisation from alcohol showed m. p. 81—82°, $[\alpha]_{\mathrm{D}}^{18^\circ}$ − 21·9° (*c*, 1·550 in chloroform). It was 6-*chloro* 2 : 3 : 5-*triacetyl* 1 : 4-*anhydrosorbitol*. Yield, 0·9 g. (Found : C, 47·1; H, 5·6. $C_{12}H_{17}O_7Cl$ requires C, 46·8; H, 5·5%). The mother liquor from the recrystallisation was evaporated; the residue crystallised, and after recrystallisation from alcohol had m. p. 60—61° alone or in admixture with authentic 2 : 5-diacetyl 1 : 4-3 : 6-dianhydrosorbitol (see below). Yield, 2·3 g.

2 : 5-*Diacetyl* 1 : 4-3 : 6-*Dianhydrosorbitol.*—1 : 4-3 : 6-Dianhydrosorbitol (10 g.) was mixed with fused sodium acetate (10 g.) and acetic anhydride (30 c.c.) and the mixture heated under reflux for 1½ hours. The solution was cooled and poured on to ice. The precipitated syrup slowly crystallised. The *diacetate* was filtered off, washed with water and recrystallised from alcohol, m. p. 60—61° $[\alpha]_{\mathrm{D}}^{16^\circ}$ − 133·6° (*c*, 2·29 in chloroform) (Found : C, 52·4; H, 5·9. $C_{10}H_{14}O_6$ requires C, 52·2; H, 6·1%).

Action of Aqueous Potassium Hydroxide on 6-*Chloro* 3 : 5-*Benzylidene* 1 : 4-*Anhydrosorbitol.*—(*a*) The compound (4·5 g.) was heated under reflux for 2 hours with potassium hydroxide (2·1 g., 2 mols.) in water (60 c.c.). The compound quickly dissolved, and the solution developed a slight brown colouration with an odour of benzaldehyde which increased as the reaction proceeded. The resulting solution was cooled, and the solid, which crystallised as long needles, m. p. 154—155°, was identified as the original compound. The aqueous mother liquor was exactly neutralised with dilute hydrochloric acid and evaporated to dryness. Recrystallisation of the residue from chloroform–petrol gave the unchanged compound together with an uncrystallisable syrup.

(*b*) A suspension of the compound (1·846 g.) in distilled water was submitted to steam distillation in the presence of potassium hydroxide (0·88 g., 2 mols.) until no more benzaldehyde distilled. The benzaldehyde in the aqueous distillate, estimated as the *p*-nitrophenylhydrazone, was 0·346 g.(48%).

Action of Thionyl Chloride on 6-*Chloro* 3 : 5-*Benzylidene* 1 : 4-*Anhydrosorbitol.*—6-Chloro 3 : 5-benzylidene 1 : 4-anhydrosorbitol (0·5 g.) was dissolved in dry pyridine (0·5 c.c.) and the solution cooled to 0°. After addition of a little anhydrous magnesium sulphate, thionyl chloride (0·2 c.c.) was added and the mixture kept for 2 hours at room temperature, and then 2 hours on a boiling water-bath. The mixture was cooled, poured on ice-water, and the chloro-compound extracted with chloroform. The combined chloroform extracts were washed successively with 5N-sulphuric acid, 10% sodium hydrogen carbonate solution, and water, and dried ($MgSO_4$). The chloroform solution was then evaporated and the residue recrystallised from alcohol. Yield, 0·2 g., $[\alpha]_D$ — 47·0° (*c*, 1·49 in chloroform), m. p. 107°, alone or in admixture with authentic specimen (see following paper) of bis-(6-chloro 3 : 5-benzylidene 1 : 4-anhydrosorbitol) 2 : 2′-sulphite.

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