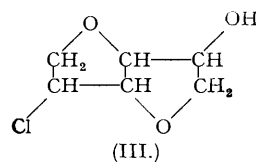
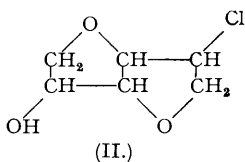
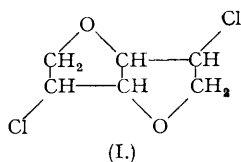


447. *Anhydrides of Polyhydric Alcohols. Part XI. The Action of Phosphorus Tribromide on 1 : 4-3 : 6-Dianhydro-mannitol and -sorbitol. Some New Chloro-derivatives of 1 : 4-3 : 6-Dianhydrosorbitol.*

By W. G. OVEREND, R. MONTGOMERY, and L. F. WIGGINS.

In contrast to the corresponding mannitol derivative, the replacement of the hydroxyl groups in 1 : 4-3 : 6-dianhydrosorbitol by halogens is difficult. 2 : 5-Dichloro 1 : 4-3 : 6-dianhydrosorbitol and a monochloro-derivative, most probably 5-chloro 1 : 4-3 : 6-dianhydrosorbitol, are described. Treatment of dianhydro-mannitol or -sorbitol with phosphorus tribromide under mild conditions leads not to the introduction of bromine atoms at C₂ and C₅ but to ring cleavage, and derivatives of 1 : 6-dibromo-mannitol and -sorbitol are obtained.

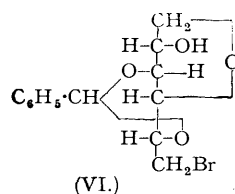
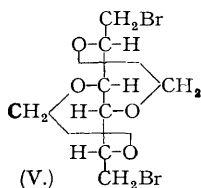
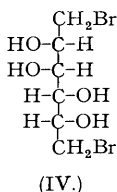
2 : 5-DICHLORO 1 : 4-3 : 6-dianhydromannitol is very readily prepared by treating 1 : 4-3 : 6-dianhydromannitol with thionyl chloride and pyridine (Wiggins, *J.*, 1945, 4). An attempt to prepare 2 : 5-dichloro 1 : 4-3 : 6-dianhydrosorbitol (I), in the same way failed. A sample has, however, been obtained in poor yield by treating 1 : 4-3 : 6-dianhydrosorbitol with thionyl chloride in benzene followed by phosphorus pentachloride. When dianhydrosorbitol was treated with thionyl chloride in xylene followed by thionyl chloride in pyridine, a liquid product was obtained from which there separated a crystalline substance with the composition of a monochloro derivative of dianhydrosorbitol. This must be either 2-chloro 1 : 4-3 : 6-dianhydro-



sorbitol (II) or 5-chloro dianhydrosorbitol (III). Since 1 : 4-3 : 6-dianhydromannitol is however, easily chlorinated in positions 2 and 5, and since the only difference between 1 : 4-3 : 6-dianhydro-mannitol and -sorbitol is in the configuration of C₂, it is reasonable to suppose that it is the hydroxyl at this position which is more difficult to replace by chlorine and so remains unsubstituted in the monochloro-derivative of 1 : 4-3 : 6-dianhydrosorbitol. It is therefore tentatively suggested that this substance is 5-chloro 1 : 4-3 : 6-dianhydrosorbitol. Further work is proceeding in order to prove this.

In view of the stability of 2 : 5-dichloro 1 : 4-3 : 6-dianhydromannitol (see Wiggins, *loc. cit.*) and of the fact that it has been found difficult to make the corresponding sorbitol derivative, an attempt was made to introduce bromine atoms at C₂ and C₅ of both dianhydrides through their interaction with phosphorus tribromide. This also failed, but an interesting and unexpected effect of this reagent on these compounds was observed. When 1 : 4-3 : 6-dianhydromannitol was treated with phosphorus tribromide in carbon tetrachloride first at -10° and then at 50° , no 2 : 5-dibromo-derivative could be isolated; instead, ring scission occurred and the main product was a crystalline dibromo hexitol, which gave rise to a tetra-acetyl derivative. Proof of the structure of this dibromo hexitol was obtained by its conversion into a dimethylene derivative, which on treatment with sodium iodide and acetone readily exchanged its two bromine atoms for iodine, thus giving a compound identical with the 1 : 6-di-iodo 2 : 4-3 : 5-dimethylene mannitol of Micheel (*Annalen*, 1932, 496, 77). Therefore the dibromo dimethylene hexitol from which this was obtained must be 1 : 6-dibromo 2 : 4-3 : 5-dimethylene mannitol (V), and the original dibromo hexitol, 1 : 6-dibromo mannitol (IV), the acetyl derivative of which must be 1 : 6-dibromo 2 : 3 : 4 : 5-tetra-acetyl mannitol.

Ring scission of 1 : 4-3 : 6-dianhydromannitol must have taken place with addition of bromine atoms at C₁ and C₆. Such ring scission, however, did not occur on treatment of the



dianhydride with hydrobromic acid, either at room temperature or at 50°, so that it is probable that the phosphorus tribromide itself, and not the hydrogen bromide formed by its hydrolysis, is responsible for the ring scission.

Similar treatment of 1 : 4-3 : 6-dianhydrosorbitol with phosphorus tribromide gave a dibromo hexitol isolated as its dibenzylidene derivative, which by analogy with the corresponding mannitol derivative must be 1 : 6-dibromo 2 : 4-3 : 5-dibenzylidene sorbitol. This on treatment with sodium iodide in acetone at 100° gave a little over 50% yield of sodium bromide, indicating that both bromine atoms were attached to primary carbon atoms. The product isolated from this reaction, however, was a monobromo moniodo dibenzylidene sorbitol. This preferential reaction at one end of the sorbitol molecule has been observed many times by us, and an account of it has been published by Ness, Hann, and Hudson (*J. Amer. Chem. Soc.*, 1944, **66**, 1901) who found, for example, that treatment of 1 : 6-ditosyl dimethylene sorbitol with sodium iodide gave mainly 6-iodo 1-tosyl dimethylene sorbitol. By analogy, therefore, the product obtained now is probably 1-bromo 6-iodo 2 : 4-3 : 5-dibenzylidene sorbitol (it is practically certain that the benzylidene groups are in this position since in all other similar compounds previously examined this has been found to be so). The same 1 : 6-dibromo dibenzylidene sorbitol was isolated after 1 : 4-3 : 6-dianhydrosorbitol had been treated at 100—110° with 50% hydrobromic acid, though some monobromo monobenzylidene monoanhydrosorbitol (A) was also isolated. It has been shown already that, under similar conditions when hydrochloric acid was the hydrolytic agent, the 3 : 6-anhydro-ring in 1 : 4-3 : 6-dianhydrosorbitol was more easily broken than the 1 : 4 ring. In this way 6-chloro 3 : 5-benzylidene 1 : 4-anhydrosorbitol was obtained and its structure proved by Montgomery and Wiggins in Part IX of this series (this vol., p. 237). Therefore the hydrobromic acid reaction product (A) is most probably 6-bromo 3 : 5-benzylidene 1 : 4-anhydrosorbitol (VI).

EXPERIMENTAL.

2 : 5-Dichloro 1 : 4-3 : 6-Dianhydrosorbitol.—An attempt to prepare this, following precisely the method successful in the case of the mannitol analogue (Wiggins, *loc. cit.*), failed. The following procedure did give a small amount of the compound. 1 : 4-3 : 6-Dianhydrosorbitol (1 g.) was suspended in benzene containing thionyl chloride, and the mixture boiled for 6 hours. Thereafter the solvent was evaporated and the syrupy residue heated with phosphorus pentachloride for 1 hour at 140°. The product was dissolved in chloroform and washed with dilute sodium carbonate solution and then with water, and the chloroform solution dried (MgSO₄) and evaporated to a thin syrup. This was then distilled, but there was extensive decomposition, and only a small amount (0.15 g.) of 2 : 5-dichloro 1 : 4-3 : 6-dianhydrosorbitol, b. p. 105°/15 mm. (74°/0.01 mm.), was obtained; $[\alpha]_D^{19} +55.8^\circ$ in chloroform (*c*, 4.015), $n_D^{20} 1.5269$ (Found: Cl, 38.3. C₆H₈O₃Cl₂ requires Cl, 38.8%).

Monochloro 1 : 4-3 : 6-Dianhydrosorbitol.—Finely powdered 1 : 4-3 : 6-dianhydrosorbitol (5 g.) was heated in dry xylene (50 c.c.) with thionyl chloride (10 c.c.) until solution was complete. The solution was then evaporated to a syrup which was dissolved in dry pyridine (10 c.c.), thionyl chloride (10 c.c.) added, and the mixture heated at 120—140° for 4 hours. The dark liquid was poured into ice-water, and the solution left overnight and then extracted with chloroform. The extract was washed with dilute sulphuric acid, sodium hydrogen carbonate solution, and water, and was then dried (MgSO₄) and evaporated to a syrup which distilled at 200—220° (bath temp.)/12 mm. The distillate (1.7 g.) partly crystallised, and was recrystallised from ether, to form long needles, m. p. 63—64°, $[\alpha]_D^{19} +48.0^\circ$ in chloroform (*c*, 1.625). It is suggested that this compound is 5-chloro 1 : 4-3 : 6-dianhydrosorbitol (Found: C, 43.6; H, 5.5; Cl, 20.0. C₆H₈O₃Cl requires C, 43.8; H, 5.5; Cl, 21.6%).

Action of Phosphorus Tribromide on 1 : 4-3 : 6-Dianhydromannitol.—The dianhydride (14.7 g.) was finely powdered and stirred into carbon tetrachloride (200 c.c.). The suspension was cooled to -10°, and phosphorus tribromide (51.5 g., 2 mols.) added with stirring during 10 hours. The mixture was then heated at 50° for 3 hours. A brown syrup appeared on the surface of the carbon tetrachloride which was removed by distillation. To the residue, ice was added, and after the resulting solution had been kept overnight a solid separated. This was collected and recrystallised from water to form white plates of 1 : 6-dibromo mannitol, m. p. 177—178° (decomp.), $[\alpha]_D^{18} -2.6^\circ$ in water (*c*, 0.765) (Found: C, 22.7; H, 3.8; Br, 51.8. C₆H₁₂O₄Br₂ requires C, 23.3; H, 3.9; Br, 51.9%).

1 : 6-Dibromo 2 : 3 : 4 : 5-Tetra-acetyl Mannitol.—1 : 6-Dibromo mannitol (0.3 g.), fused sodium

acetate (0.2 g.), and acetic anhydride (5 c.c.) were refluxed for 15 minutes. The solution was poured into water, and the solid, which rapidly separated, filtered off. Recrystallised from alcohol-water, the *tetra-acetyl* derivative had m. p. 125—126° (Found: C, 35.0; H, 4.0. $C_{14}H_{20}O_8Br_2$ requires C, 35.3; H, 4.2%).

1 : 6-Dibromo 2 : 4-3 : 5-Dimethylene Mannitol.—The compound (1 g.) was finely powdered and suspended in 40% formaldehyde solution (10 c.c.), and the mixture saturated with hydrogen chloride at 0°. The crystalline material dissolved, and an oily product separated which partly crystallised on long refrigeration. The crystals were separated and freed from occluded syrup by pressing them on a porous tile. After being recrystallised from methyl alcohol-chloroform, these had m. p. 178—179°, $[\alpha]_D^{25} +72.4^\circ$ in chloroform (*c*, 5.52), and were 1 : 6-dibromo 2 : 4-3 : 5-dimethylene mannitol (Found: C, 28.8; H, 3.8. $C_6H_{12}O_4Br_2$ requires C, 28.4; H, 3.9%).

Conversion of 1 : 6-Dibromo 2 : 4-3 : 5-Dimethylene Mannitol into 1 : 6-Di-iodo 2 : 4-3 : 5-Dimethylene Mannitol.—1 : 6-Dibromo dimethylene mannitol (0.24 g.) was heated at 105° for 5 hours in a sealed tube with acetone (10 c.c.) and sodium iodide (0.33 g.; 3 mols.), using anhydrous reagents. Sodium bromide separated. The liquid was then evaporated to dryness and the residue extracted with chloroform-water mixture. The chloroform layer was separated and washed with dilute sodium thiosulphate and with water, and then dried ($MgSO_4$). On evaporation of the solvent a crystalline residue was obtained which, recrystallised from alcohol, had m. p. 195—196° alone or in admixture with authentic 1 : 6-di-iodo 2 : 4-3 : 5-dimethylene mannitol; $[\alpha]_D +50.0^\circ$ in chloroform (*c*, 0.499). Micheel (*loc. cit.*) gives m. p. 195°, $[\alpha]_D +50.2^\circ$.

Action of Hydrobromic Acid on 1 : 4-3 : 6-Dianhydromannitol.—(a) At room temperature. The dianhydride (3.3 g.) was treated with 10% hydrobromic acid (25 c.c.) for 24 hours at room temperature. Thereafter the acid was neutralised with silver carbonate, the solution filtered, and the filtrate evaporated to dryness. The residue was extracted with ethyl acetate and the extract evaporated to a syrup which crystallised on nucleation with 1 : 4-3 : 6-dianhydromannitol. It was recrystallised from ethyl acetate; yield 3.1 g., m. p. 86—87° alone or in admixture with an authentic specimen.

(b) At 50°. From the dianhydride (3.4 g.), treated with 10% hydrobromic acid (25 c.c.) at 50° for 3 hours then overnight at room temperature and worked up as above, 3.0 g. of the dianhydride were recovered unchanged.

Action of Phosphorus Tribromide on 1 : 4-3 : 6-Dianhydrosorbitol.—Finely powdered dianhydrosorbitol (10 g.) was suspended in dry carbon tetrachloride (150 c.c.), and phosphorus tribromide (13 c.c., 2 mols.) added with stirring during $\frac{1}{2}$ hour. The stirring was continued for a further 2 hours at 50—70°. The resulting mixture was cooled, and the carbon tetrachloride decanted from the syrupy product, which was extracted with ethyl acetate. This extract gave a syrup (6 g.) which contained phosphorus tribromide and other products which rapidly decomposed, so that no information could be obtained concerning them. The material insoluble in ethyl acetate (1.8 g.) was shaken with benzaldehyde (10 c.c.) and zinc chloride (2 g.) for 24 hours. The product was evaporated with an aqueous solution of sodium carbonate (2 g.) until all the benzaldehyde had been removed. The solution was then evaporated to dryness, and the residue extracted with chloroform. This gave, on evaporation, a syrup (1.7 g.) which crystallised. Recrystallised from alcohol it gave 1 : 6-dibromo dibenzylidene sorbitol, m. p. 226—227° alone or in admixture with the material obtained below, and showed $[\alpha]_D^{18} +15.1^\circ$ in chloroform (*c*, 1.325).

Action of Hydrobromic Acid on 1 : 4-3 : 6-Dianhydrosorbitol.—The dianhydride (30 g.) was heated in sealed tubes with 50% hydrobromic acid (150 c.c.) for 30 hours at 100—110°. The dark brown liquid was filtered with charcoal and evaporated under reduced pressure until as much as possible of the hydrobromic acid had been removed. The residual syrup was shaken with benzaldehyde (150 c.c.) containing anhydrous zinc chloride (30 g.) for 48 hours. The resulting solution was distilled under reduced pressure with an aqueous solution of sodium carbonate (60 g.) until no more benzaldehyde distilled. Thereafter it was evaporated to a syrup which deposited a few crystals of 1 : 6-dibromo dibenzylidene sorbitol; these, separated and recrystallised from alcohol-water, had m. p. 226—227°, $[\alpha]_D^{18} +15.3^\circ$ in chloroform (*c*, 1.32) (Found: C, 50.2; H, 4.5; Br, 32.1. $C_{20}H_{26}O_4Br_2$ requires C, 50.0; H, 4.2; Br, 33.1%). The alcoholic mother liquors were evaporated to a syrup, which was extracted with water. This extract deposited crystals (0.1 g.) of a monobromo monobenzylidene monoanhydrosorbitol, probably 6-bromo 3 : 5-benzylidene 1 : 4-anhydrosorbitol which, after being recrystallised from alcohol, had m. p. 136—138°, $[\alpha]_D^{24} +16.5^\circ$ in chloroform (*c*, 1.09) (Found: C, 49.5; H, 5.0. $C_{13}H_{15}O_4Br$ requires C, 49.5; H, 4.8%). From the aqueous mother liquors, unchanged dianhydrosorbitol (8.1 g.) was recovered.

1-Bromo 6-Iodo 2 : 4-3 : 5-Dibenzylidene Sorbitol.—1 : 6-Dibromo 2 : 4-3 : 5-dibenzylidene sorbitol (0.09 g.) was dried and heated at 100—110° for 6 hours in a sealed tube with dry sodium iodide (0.1 g.) in dry acetone (10 c.c.). Crystals of sodium bromide separated [0.02 g., 52% (assuming 2 mols.)]. The acetone solution was evaporated to dryness, and the residue extracted with chloroform. The extract was washed with sodium thiosulphate solution and with water, dried ($MgSO_4$), filtered, and evaporated. The residual 1-bromo 6-iodo 2 : 4-3 : 5-dibenzylidene sorbitol, recrystallised from alcohol-acetone, had m. p. 232—233°, $[\alpha]_D^{24} +25.4^\circ$ in chloroform (*c*, 1.71) (Found: C, 44.9; H, 3.9. $C_{20}H_{26}O_4BrI$ requires 45.2; H, 3.8%).

The authors thank Professor Sir Norman Haworth, F.R.S., and Dr. J. L. Simonsen, F.R.S., for their interest, and the Colonial Products Research Council for financial aid.

THE A. E. HILLS LABORATORIES,
THE UNIVERSITY, EDGBASTON, BIRMINGHAM, 15.

[Received, February 16th, 1948.]