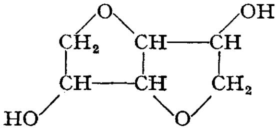
86. *Anhydrides of Polyhydric Alcohols. Part VI.* 1 : 4-3 : 6-*Dianhydro Mannitol and* 1 : 4-3 : 6-*Dianhydro Sorbitol from Sucrose.*

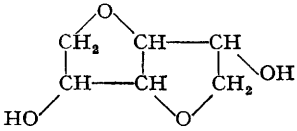
By R. Montgomery and L. F. Wiggins.

Details of methods of production of 1 : 4-3 : 6-dianhydro mannitol and 1 : 4-3 : 6-dianhydro sorbitol in pure crystalline form from sucrose are given.

The dianhydrides of mannitol and sorbitol, known as *iso*mannide and *iso*sorbide respectively, can be prepared from the respective hexahydric alcohols by treatment with acid reagents. Both these compounds have been shown to possess the 1 : 4-3 : 6-ring structure by Wiggins (*J.*, 1945, 4) and Montgomery and Wiggins (*J.*, 1946, 390), so dianhydro sorbitol is represented by (I) and dianhydro mannitol by (II).



(I.)

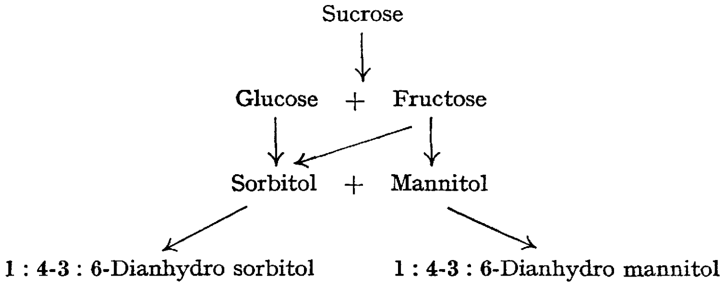


(II.)

These substances are becoming of some interest to chemists, from both the industrial and the academic viewpoint. They have already proved of interest in the former aspect since it has been possible to prepare excellent drying oils from them by condensation with certain unsaturated carboxylic acids, and also wetting agents by condensation with saturated fatty acids. Moreover, recent patents have been granted to the Atlas Powder Company for resinous products derived from these compounds. We have prepared a number of derivatives of these dianhydrides. The 2 : 5-diamino-derivatives give rise to sulphanilamido-derivatives which, however, possess no outstanding chemotherapeutic properties (Montgomery and Wiggins, *J.*, **1946**, 393). Krantz (U.S.P., 2,143,324, 1939) found that dianhydro mannitol was a diuretic agent and that the dinitrates of both dianhydrides are useful in the treatment of angina pectoris and other hypertension conditions (Krantz, Carr, Forman, and Ellis, *J. Pharm.*, 1939, **67**, 191), though we have found that the dinitrate of dianhydro sorbitol possesses twice the activity of the corresponding derivative of dianhydro mannitol. The acrylate and methacrylate of dianhydro mannitol and dianhydro sorbitol (Haworth, Gregory, and Wiggins, *J.*, **1946**, 488) are of interest since they polymerise very easily without catalysts to hard transparent resins and copolymerise homogeneously with methyl methacrylate. Also the 2 : 5-diallyl and 2 : 5-dicrotyl ethers may be valuable as solvents of the plasticizer class (patent applied for).

Since we have been concerned with the development of the chemistry of sucrose to increase its use in industry, it occurred to us that the conversion of sucrose into these dianhydro compounds would help this project.

It is known that sucrose or invert sugar is reduced to a mixture of mannitol and sorbitol by means of catalytic hydrogenation, or, in the case of invert sugar, by electrolytic reduction. We have carried out experiments in order to find the optimum conditions for reducing sucrose and invert sugar under high temperature–high pressure hydrogenating conditions in the presence of Raney nickel catalyst. A theoretical yield of mannitol and sorbitol was obtained by hydrogenating an aqueous solution of sucrose at 160° provided that this working temperature was attained slowly. The necessity for slow heating is due to the fact that the heating of sucrose with water at 135—140° results in the development of acid conditions (pH 3·10), a change which is accompanied by inversion of the sucrose to glucose and fructose (Montgomery and Wiggins, *J. Soc. Chem. Ind.*, 1947, **65**, 31) and a further degradation at slightly higher temperatures (160°) with the formation of 5-hydroxymethyl-2-furfuraldehyde, lævulic acid, formic acid, and humin substances, of which the last tends to deactivate the catalyst. A slow rate of heating in the hydrogenation reaction therefore ensures complete reduction of the glucose and fructose as they are formed and eliminates the degradation reactions. A quantitative yield of the mixture of mannitol and sorbitol from invert sugar was obtained by hydrogenation in the presence of Raney nickel at 120° and 100 atm. pressure in a weakly alkaline buffered solution. It was essential in this case to keep the working temperature below 125°, particularly in the earlier stages of the reduction.



The dianhydrides of mannitol and sorbitol were obtained in the initial experiments by heating the above mixture of mannitol and sorbitol with hydrochloric acid under reflux for 75—95 hours. The syrupy product from this treatment was fractionally distilled; pure dianhydro mannitol distilled first at 136—140°/10 mm. and was obtained crystalline in 30% of the theoretical yield. Dianhydro sorbitol distilled at 160—165°/10 mm. and was obtained crystalline in 59% yield. A slightly better yield of the latter but a poorer yield of the former was obtained when the mixture of hexitols was heated with hydrochloric acid for 12 hours, followed by fractionation of the product, which was mainly dianhydro sorbitol, and re-treatment of the residues with acid for a further 72 hours; there were then obtained further quantities of both dianhydro compounds. In this way crystalline dianhydro sorbitol was obtained in 62% and dianhydro mannitol in 10% of the theoretical yield. The essential scheme for the production of the two dianhydrides from sucrose is shown in the diagram. An investigation has been carried out on the action of acid catalysts other than hydrochloric acid on pure mannitol and sorbitol obtained by fractional recrystallisation of the hexitol mixture from the hydrogenation of sucrose or invert sugar. In general, the experimental procedure consisted of suspending the hexitol in an inert solvent and heating the mixture in the presence of an acid catalyst. The experiments were first carried out so that the water produced in the reaction was azeotropically removed by slow distillation with an entraining liquid (usually xylene) in a vigorous stream of nitrogen. A second experimental procedure involved heating the mixture under reflux with xylene accompanied by vigorous mechanical stirring.

The acids chosen to act as catalysts were *p*-toluenesulphonic, concentrated sulphuric, and phosphoric. The proportion of acid to hexitol was varied, as was the time of the reaction, in order to determine the conditions for each acid at which the maximum yield of dianhydro mannitol and dianhydro sorbitol was obtainable. The results are summarised in the table for *p*-toluenesulphonic and sulphuric acid, but the use of phosphoric acid as a catalyst did not seem to be satisfactory owing to the formation of phosphoric esters, a phenomenon which had been observed by Carre (*Ann. Chim. Phys.*, 1905, **5**, 429), and the recovery of much unchanged hexitol.

It is noteworthy that dianhydro mannitol was never isolated in more than about 30% yield, and this has been found to be due to the additional formation of different anhydro compounds (Montgomery and Wiggins, unpublished work).

Hexitol, and wt. (g.).		Acid catalyst, and wt. (g.).		Reaction temp.	Time (hrs.).	Procedure.	Yield of dianhydride (%).
Mannitol	30	Conc. H_2SO_4	2·0	130—140°	1¼	1	16·0
,,	50	,,	4·0	,,	,,	,,	26·6
,,	30	,,	4·0	,,	2½	,,	29·6
,,	30	,,	2·0	,,	,,	,,	31·2
Sorbitol	30	,,	2·0	,,	1¼	,,	67·0
,,	30	,,	2·8	,,	,,	,,	64·5
,,	30	,,	4·0	130—160	2½	,,	61·0
Mannitol	30	*p*-$C_7H_7{\cdot}SO_3H$	2·0	130—135	2¼	,,	8·3
,,	30	,,	2·0	150—155	1¼	,,	25·4
,,	30	,,	10·5	140—144	4	2	24·2
,,	30	,,	10·5	,,	1	,,	26·2
Sorbitol	20	,,	1·2	,,	1¾	,,	28·1
,,	20	,,	1·2	,,	4	,,	29·4
,,	20	,,	3·7	,,	,,	,,	48·0
,,	20	,,	7·0	,,	,,	,,	61·0

EXPERIMENTAL.

Hydrogenation of Sucrose.—Sucrose (100 g.), dissolved in water (500 c.c.), was hydrogenated at 160° under 100 atm. for 6 hours with Raney nickel catalyst. The reaction mixture was initially heated as rapidly as possible until the temperature was 100°, and the rate of heating was then reduced so that the working temperature was not reached until 2 hours from the commencement of the heating. The resulting mixture was filtered and evaporated to dryness. A theoretical yield of crystalline mannitol and sorbitol was obtained.

Preparation of Invert Sugar Solution.—Sucrose (500 g.) was slowly added to continuously stirred, boiling 0·1N-sulphuric acid (1900 c.c.), and the solution kept boiling for one minute after the sucrose had been added; it was then allowed to cool for one hour, after which it was neutralised with a hot aqueous solution of barium hydroxide octahydrate (32 g.), and the precipitated barium sulphate removed by centrifuging.

Hydrogenation of Invert Sugar Solution.—To the above solution of invert sugar were added anhydrous sodium carbonate (2·0 g.), calcium carbonate (80 g.), and Raney nickel catalyst (8—9 g.), and the mixture was hydrogenated at 110—120° under 75—100 atm. for 6½—7 hours. After cooling, the resulting mixture was filtered, and the filtrate evaporated to dryness. A theoretical yield of hexitols was obtained.

Preparation of Dianhydro Mannitol and Dianhydro Sorbitol from a Mixture of Mannitol and Sorbitol.—(1) A mixture of mannitol and sorbitol (500 g.) obtained from either of the above hydrogenation reactions was heated under reflux with concentrated hydrochloric acid (2 l.) for 12 hours. The resulting solution was concentrated under reduced pressure, and the residue distilled under 12 mm. pressure, the distillate (142 g.) being collected between 125° and 225° (bath temp.). The distillate was fractionally distilled, yielding dianhydro mannitol (3·0 g.) and dianhydro sorbitol (106·1 g.). The residues from these distillations were re-treated for 3 days with boiling concentrated hydrochloric acid (2 l.), and the dianhydro mannitol (12·1 g.) and dianhydro sorbitol (80·4 g.) separated as above. Again all the residues were retreated for 3 days with concentrated hydrochloric acid (1 l.) and yielded dianhydro sorbitol (11·0 g.) and an unidentified high-boiling liquid (48·7 g.), b. p. 145°/0·01 mm. The final yields, after recrystallisation of both compounds from ethyl acetate, were: dianhydro mannitol, 15·1 g. (9·5%), m. p. 85—87°, b. p. 136—140°/10 mm.; dianhydro sorbitol, 143·0 g. (62·0%), m. p. 57—61°, b. p. 160—165°/10 mm.

(2) A mixture of mannitol and sorbitol (500 g.), obtained from the hydrogenation of invert sugar (500 g.), was heated under reflux with concentrated hydrochloric acid (2 l.) for 4 days. The resulting solution was evaporated, and the residue fractionally distilled to yield dianhydro mannitol and dianhydro

sorbitol. Both compounds were recrystallised from ethyl acetate, the final yields being 40 g. (30%) and 162 g. (59%), respectively.

Action of Concentrated Hydrochloric Acid on Mannitol.—Mannitol (30 g.) was refluxed for one hour with concentrated hydrochloric acid (120 c.c.), and the resulting solution evaporated to dryness under reduced pressure. The crystalline residue was treated with boiling ethyl alcohol (30 c.c.), cooled, and filtered, the unchanged mannitol (29 g.) being recovered in this way. The ethyl-alcoholic solution was evaporated, and the residue heated at 200° (bath temp.) under reduced pressure for 2 hours, during which no material distilled.

The above experiment was repeated with the exception that the heating was continued for 3½ days. The products from 1000 g. of mannitol were dianhydro mannitol (193 g.) and a mixture of other anhydro derivatives (144·3 g.).

Action of Concentrated Hydrochloric Acid on Sorbitol.—Sorbitol (30 g.) was refluxed with concentrated hydrochloric acid (120 c.c.) for one hour, and the resulting solution evaporated to dryness under reduced pressure. The syrupy residue was heated at 200—230° (bath temp.)/12 mm. until no more material distilled. The distillate (9·2 g.) rapidly crystallised, and recrystallised to give dianhydro sorbitol, m. p. 60—61° (8·4 g., 35%).

Repetition of the above experiment with 500 g. of sorbitol, with the exception that the heating was continued for 24 hours, yielded dianhydro sorbitol (265 g., 66%).

Dehydration of Mannitol or Sorbitol with Acid Catalysts.—The hexitol, suspended in dry xylene, was heated in the presence of sulphuric, *p*-toluenesulphonic, or phosphoric acid according to one of the procedures given below.

Procedure 1. The reaction mixture was heated at the required temperature in a vigorous stream of nitrogen. At the end of the heating, the mixture was cooled, the xylene decanted off, and the syrupy residue dissolved in aqueous alcohol, neutralised with sodium carbonate, and filtered. The filtrate was evaporated to dryness, and the residue distilled under reduced pressure. Recrystallisation of the distillate from ethyl acetate yielded the pure dianhydro compound.

Procedure 2. The reaction mixture, suspended in xylene, was heated under reflux with vigorous mechanical stirring and the product was then treated exactly as described in Procedure 1.

The results are seen in the table.

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