75. *Anhydrides of Polyhydric Alcohols. Part X. The Conversion of Glucamine into* 1 : 4-*Anhydrosorbitol. The Constitution of Benzylidene* 1 : 4-*Anhydrosorbitol.*

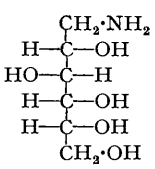
By V. G. BASHFORD and L. F. WIGGINS.

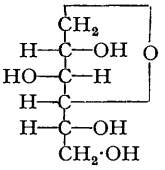
1 : 4-Anhydrosorbitol has been obtained by the deamination of glucamine. Its structure is discussed, and a benzylidene derivative is proved to be 3 : 5-benzylidene 1 : 4-anhydrosorbitol.

THE deamination of glucosamine leads to the formation of the anhydro-sugar, chitose, which almost certainly has a hydroxylated tetrahydrofuran structure. The deamination is accompanied by Walden inversion, since the 2 : 5-anhydro-compound has been shown by Levene (*J. Biol. Chem.*, 1924, **59**, 135) to possess the mannose configuration. More recently it has been shown that 2-amino 4 : 6-benzylidene α-methylaltroside undergoes Walden inversion and concomitant anhydro-ring formation on deamination to yield 4 : 6-benzylidene 2 : 3-anhydro-α-methylalloside (Wiggins, *Nature*, 1944, **157**, 300). As a result of this observation it was anticipated that the deamination of glucamine (1-amino sorbitol), produced by the catalytic hydrogenation of glucose in the presence of ammonia (Adkins and Wayne, *J. Amer. Chem. Soc.*, 1940, **62**, 3314), would also result in the formation of an anhydro-ring. Since the amino-group is attached to C_1, and is therefore free to rotate, it was also expected that this anhydro-ring formation would take place without Walden inversion.

This prediction has now been verified, since treatment of glucamine (I) with nitrous acid has been shown to give a crystalline compound identical with that obtained by the restricted anhydridisation of sorbitol in the presence of sulphuric acid (Soltzberg, Goepp, and Freudenberg, *J. Amer. Chem. Soc.*, 1946, **68**, 919) which Hockett, Conley, Yusem, and Mason (*ibid.*, p. 922) have shown, by a study of its behaviour towards lead tetra-acetate, to be 1 : 4-anhydrosorbitol (II).

It is apparent therefore that there is now available a new method for the introduction of anhydro-rings into the polyhydric alcohols derived from sugars.


(I.)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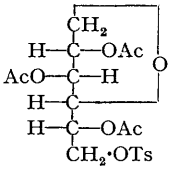
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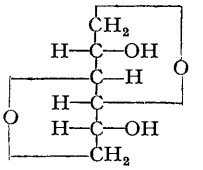
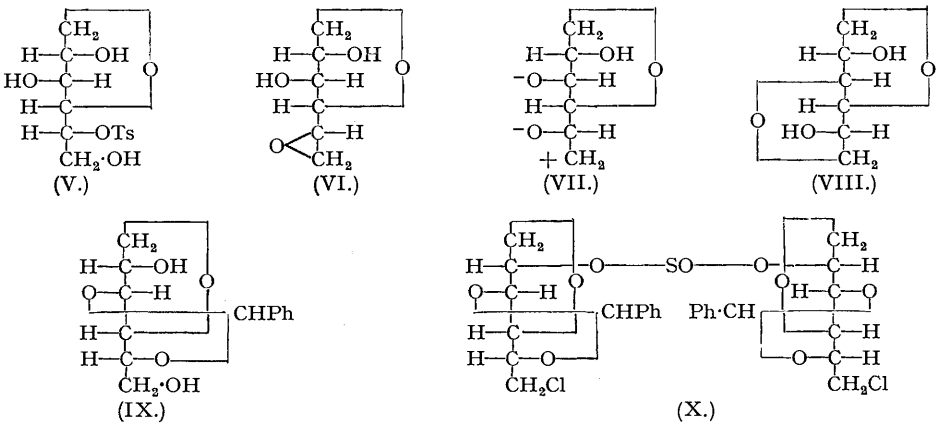

(IV.)

Proof, additional to that of Soltzberg, Goepp, and Freudenberg (*loc. cit.*), that this is indeed 1 : 4-anhydrosorbitol would be afforded if it could be converted into the dianhydride, *iso*sorbide, since this has been shown unequivocally to be 1 : 4-3 : 6-dianhydrosorbitol (IV) (Montgomery and Wiggins, *Nature*, 1946, **157**, 372; *J.*, 1946, 390; Hockett, Fletcher, Sheffield, and Goepp, *J. Amer. Chem. Soc.*, 1946, **68**, 927). This conversion has now been effected in the following way. The anhydrosorbitol obtained on the deamination of glucamine gave, on selective tosylation followed by acetylation, liquid 6-tosyl 2 : 3 : 5-triacetyl 1 : 4-anhydrosorbitol (III). The presence of a tosyl group at either C_1 or C_6 was proved by the observation that treatment of

(III) with sodium iodide in acetone at 100° afforded a 90% yield of sodium *p*-toluenesulphonate. Treatment of (III) with four mols. of sodium in methyl alcohol effected simultaneous deacetylation and anhydro-ring formation with the production of 1 : 4-3 : 6-dianhydrosorbitol (IV), recognised by its conversion into the characteristic crystalline 2 : 5-*bismethanesulphonyl* 1 : 4-3 : 6-*dianhydrosorbitol*. The isolation of the latter proves that the anhydrosorbitol must be either 1 : 4- or 3 : 6-anhydrosorbitol. Since the 3 : 6-anhydro-derivative has been previously prepared by Fischer and Zach (*Ber.*, 1912, **45**, 2069) and has constants different from those of the anhydride under discussion, it is clear that the latter must contain the 1 : 4-anhydro-ring. The structure (II) assigned to the anhydrosorbitol obtained by the deamination of glucamine or by the restricted dehydration of sorbitol is therefore correct.

The action of methanesulphonyl chloride on the product of detosylation and deacetylation of 6-tosyl triacetyl 1 : 4-anhydrosorbitol gave, in addition to 2 : 5-bismethanesulphonyl 1 : 4-3 : 6-dianhydrosorbitol, 2 : 5-bismethanesulphonyl 1 : 4-3 : 6-dianhydro-L-iditol (VIII) (Wiggins, *Nature*, 1947, **157**, 372), as well as a methanesulphonyl derivative, m. p. 82—83°, not yet identified. The formation of (VIII) lends support to the view that the anhydrosorbitol obtained by deamination of glucamine is indeed (II).

The isolation of a derivative of 1 : 4-3 : 6-dianhydro-L-iditol is of interest not only from the constitutional point of view but also from its mode of formation; the following represents one possible mechanism. Tosylation of 1 : 4-anhydrosorbitol probably gives some 5-tosyl 1 : 4-anhydrosorbitol (V) in addition to the 6-tosyl isomer which must be the main product. Detosylation of the 5-tosyl isomer (V) might then give rise to 1 : 4-5 : 6-dianhydro-L-iditol (VI); that is to say, the removal of the tosyl group at C_5 would be accompanied by Walden inversion. Rearrangement of this product through (VII) as a possible intermediate could then give the more stable bicyclic structure, 1 : 4-3 : 6-dianhydro-L-iditol (VIII).



In seeking to obtain characteristic derivatives of 1 : 4-anhydrosorbitol we obtained crystalline 2 : 3 : 5 : 6-*tetrakismethanesulphonyl* 1 : 4-*anhydrosorbitol*, liquid 2 : 3 : 5 : 6-*tetra-acety* 1 : 4-*anhydrosorbitol*, and a crystalline monobenzylidene 1 : 4-anhydrosorbitol of m. p. 154—155° and $[\alpha]_D$ + 15·4° which appears to be different from the monobenzylidene derivatives {(*a*) m. p. 136—140°, $[\alpha]_D$ — 33·7°; (*b*) m. p. 121—122°, no $[\alpha]_D$ recorded} obtained by Soltzberg, Goepp, and Freudenberg (*loc. cit.*) by a different method. Thus (*a*) may be an impure form of the compound described herein, which is shown to be 3 : 5-*benzylidene* 1 : 4-*anhydrosorbitol* (IX) by the following facts.

Ultimate analysis gave results in agreement with those required by benzylidene 1 : 4-anhydrosorbitol. On treament of its *monotosyl* derivative with sodium iodide in acetone at 100°, sodium *p*-toluenesulphonate was isolated (90% yield). Thus the original monobenzylidene 1 : 4-anhydrosorbitol must have an unsubstituted hydroxyl at C_6. It was also found that this 6-tosyl derivative was stable to cold sodium methoxide. Since a 6-tosyl compound possessing a hydroxyl group adjacent to the tosyl residue would readily afford a 5 : 6-ethylene oxide anhydro-ring, it is concluded that the hydroxyl group at C_5 is engaged in union with the benzylidene group. It follows therefore that this must engage either $C_2 : C_5$ or $C_3 : C_5$. A study of models shows that of the two possibilities the former is sterically highly unlikely. The tentative conlusion is therefore reached that the benzylidene group engages

C_3 and C_5 as in (IX). Confirmation of this structure is provided through the product of chlorination of the monobenzylidene 1 : 4-anhydrosorbitol. This was identical with that obtained by chlorination of 6-chloro 3 : 5-benzylidene 1 : 4-anhydrosorbitol, the structure of which has been established (see Part IX, this vol., p. 237).

The 3 : 5-benzylidene derivative of 1 : 4-anhydrosorbitol provides a means whereby a more selective tosylation at C_6 can be made to take place; thus we have prepared crystalline 6-*tosyl* 3 : 5-*benzylidene* 1 : 4-*anhydrosorbitol*, in which the tosyl group is readily exchanged for iodine giving 6-*iodo* 3 : 5-*benzylidene* 1 : 4-*anhydrosorbitol*. The tosyl compound on debenzylidenation gave liquid 6-tosyl 1 : 4-anhydrosorbitol, which after detosylation with sodium methoxide gave mainly 1 : 4-3 : 6-dianhydrosorbitol, isolated as its bismethanesulphonyl derivative, together with the unknown methanesulphonyl compound, m. p. 82—83°. No derivative of dianhydro-L-iditol was isolated.

Treatment of 3 : 5-benzylidene 1 : 4-anhydrosorbitol with thionyl chloride and pyridine would be expected to yield 2 : 6-dichloro 3 : 5-benzylidene 1 : 4-anhydrosorbitol; in fact, however, the product (m. p. 108—109°) contained only one chlorine atom per molecule of sorbitol and also contained sulphur and combined benzaldehyde; moreover, its molecular weight showed it to be bimolecular with respect to 1 : 4-anhydrosorbitol. This product was hydrolysed to 6-chloro 1 : 4-anhydrosorbitol. It was also obtained from thionyl chloride, pyridine, and 6-chloro 3 : 5-benzylidene 1 : 4-anhydrosorbitol (see Part IX, *loc. cit.*), in which the C_2 is the only position available for substitution. For these reasons it is tentatively suggested that the product is *bis*-(6-*chloro* 3 : 5-*benzylidene* 1 : 4-*anhydrosorbitol*) 2 : 2′-*sulphite* (X).

Experimental.

Deamination of Glucamine.—Glucamine (Adkins and Wayne, *loc. cit.*) (10 g.) was dissolved in water and the solution acidified with glacial acetic acid. Sodium nitrite (4·7 g.) was then added in small portions. The solution was well stirred and then left at room temperature overnight; thereafter it was neutralised with sodium hydrogen carbonate and evaporated to dryness under reduced pressure. The residue was extracted with dry ethyl acetate in a Soxhlet apparatus. On standing, crystals of 1 : 4-anhydrosorbitol were formed and were recrystallised from ethyl alcohol–ethyl acetate. Yield, 5·15 g.; m. p. 114—116°, $[\alpha]_D^{16°}$ − 22·21° (*c*, 1·5 in water). Soltzberg, Goepp, and Freudenberg (*loc. cit.*) described 1 : 4-anhydrosorbitol as having m. p. 115—116°, $[\alpha]_D$ − 21·9°.

2 : 3 : 5 : 6-*Tetra-acetyl* 1 : 4-*Anhydrosorbitol.*—(*a*) 1 : 4-Anhydrosorbitol (0·4 g.) was dissolved in dry pyridine, acetic anhydride (2·0 c.c.) added, and the mixture kept at room temperature for 4 days. The solution was then poured into ice–water and extracted with chloroform. The chloroform extracts were washed with N-sulphuric acid, sodium hydrogen carbonate solution, and twice with water, dried ($MgSO_4$), and evaporated to dryness. The residue of 2 : 3 : 5 : 6-*tetra-acetyl* 1 : 4-*anhydrosorbitol* distilled at 195—200° (bath temp.)/0·01 mm. as a colourless liquid (0·604 g.), $n_D^{18°}$ 1·4549, $[\alpha]_D^{14·5°}$ + 46·4° (*c*, 2·995 in chloroform).

(*b*) 1 : 4-Anhydrosorbitol (0·59 g.), fused sodium acetate (0·6 g.), and acetic anhydride were refluxed for 1½ hours and the mixture poured into ice–water. The solution was neutralised with sodium hydrogen carbonate and extracted several times with chloroform. The combined extracts were dried ($MgSO_4$) and evaporated to dryness. The residue distilled at 195—200° (bath temp.)/0·01 mm. as a colourless syrup (1·228 g.), $n_D^{20°}$ 1·4559, $[\alpha]_D^{16°}$ + 47·6° (*c*, 2·395 in chloroform) (Found : C, 50·7; H, 6·6; Ac, 51·2. $C_{14}H_{20}O_9$ requires C, 50·6; H, 6·0; Ac, 51·8%).

2 : 3 : 5 : 6-*Tetrakismethanesulphonyl* 1 : 4-*Anhydrosorbitol.*—1 : 4-Anhydrosorbitol (0·103 g.) and methanesulphonyl chloride (0·3 c.c.) were mixed in dry pyridine (5·0 c.c.) and kept at room temperature for 3 days. The mixture was poured into ice–water and the aqueous solution extracted several times with chloroform, and the combined extracts dried ($MgSO_4$) and evaporated to dryness. The residue crystallised after treatment with acetone–ethyl alcohol. The *compound* (0·17 g.) recrystallised from the same solvents and showed m. p. 122°. Further recrystallisation raised the m. p. to 122·5°, $[\alpha]_D^{19·5°}$ − 3·46° (*c*, 2·3 in acetone) (Found : C, 25·7; H, 4·5. $C_{10}H_{20}O_{13}S_4$ requires C, 25·2; H, 4·2%).

3 : 5-*Benzylidene* 1 : 4-*Anhydrosorbitol.*—1 : 4-Anhydrosorbitol (5·0 g.), benzaldehyde (redistilled, 25 c.c.), and anhydrous finely-ground zinc chloride (6·0 g.) were shaken for 16 hours. Sodium carbonate (12·0 g.), dissolved in water, was added to the mixture which was then evaporated to dryness. The residue was extracted with chloroform in a Soxhlet apparatus, and the chloroform solution dried ($MgSO_4$) and evaporated under reduced pressure. The crystals of 3 : 5-*benzylidene* 1 : 4-*anhydrosorbitol* which separated were triturated with ether, collected, and recrystallised from alcohol–light petroleum. Yield, 1·78 g., m. p. 154—155°, $[\alpha]_D^{19°}$ + 15·4 (*c*, 3·9 in acetone). A further crop (0·45 g.) was obtained from the mother liquors (Found : C, 62·6; H, 6·3. $C_{13}H_{16}O_5$ requires C, 61·9; H, 6·35%).

6-*Tosyl* 3 : 5-*Benzylidene* 1 : 4-*Anhydrosorbitol.*—To a solution of 3 : 5-benzylidene 1 : 4-anhydrosorbitol (1·679 g.) in dry pyridine (10 c.c.) cooled to 0°, *p*-toluenesulphonyl chloride (1·395 g.) was added gradually with shaking, and the solution was left at room temperature for 2 days and then poured into ice–water. A white solid was deposited which was filtered off, washed with water, and recrystallised from alcohol–water. 6-*Tosyl* 3 : 5-*benzylidene* 1 : 4-*anhydrosorbitol* had m. p. 125·5°, $[\alpha]_D^{22°}$ + 9·1° (*c*, 2·2 in chloroform). Yield, 0·86 g. (Found : C, 59·2; H, 5·6. $C_{20}H_{22}O_7S$ requires C, 59·2; H, 5·4%).

Bis-(6-*chloro* 3 : 5-*benzylidene* 1 : 4-*anhydrosorbitol*) 2 : 2′-*Sulphite.*—3 : 5-Benzylidene 1 : 4-anhydrosorbitol (0·5 g.), thionyl chloride (0·36 c.c.), and dry pyridine (1·5 c.c.) were mixed and left at 0° for ½ hour. The solution was then brought to room temperature, anhydrous magnesium sulphate (0·1 g.) added, and the whole heated on the water-bath for 45 minutes; the mixture was then cooled and poured into

ice–water. After trituration the solid was filtered off and recrystallised from alcohol–water. Yield, 0·2 g.; m. p. 96—98°. On further recrystallisation from alcohol, the *compound* had m. p. 106—107°, alone or in admixture with the product obtained on similar treatment of 6-chloro 3 : 5-benzylidene 1 : 4-anhydrosorbitol (see Part IX, *loc. cit.*); $[\alpha]_D^{16.2°}$ + 46·8° (*c*, 2·2 in chloroform) [Found: C, 53·2; H, 5·1; Cl, 13·5; S, 5·8; *M* (Rast), 550. $C_{26}H_{28}O_9Cl_2S$ requires C, 53·2; H, 4·8; Cl, 12·1; S, 5·5%; *M*, 582].

The compound (0·98 g.) in acetone (40 c.c.) was heated under reflux with oxalic acid (1·5 g.) in water (5 c.c.) for 18 hours. The acid was neutralised with barium carbonate, and the solution filtered and evaporated to dryness. The dry residue was extracted several times with boiling chloroform. On standing, the chloroform extracts deposited crystals (0·26 g.) which had m. p. 108—109° alone or in admixture with 6-chloro 1 : 4-anhydrosorbitol (see Part IX, *loc. cit.*). It showed $[\alpha]_D$ − 13·8° (*c*, 2·33 in acetone) in agreement with that previously recorded. The chloroform mother liquors deposited a further amount of the same material (0·06 g.) on evaporation.

6-*Iodo* 3 : 5-*Benzylidene* 1 : 4-*Anhydrosorbitol*.—A solution of 6-tosyl 3 : 5-benzylidene 1 : 4-anhydrosorbitol (0·5 g.) and dry sodium iodide (0·75 g.) in dry acetone (50 c.c.) was heated in a sealed tube at 110° for 4 hours. Crystals of sodium *p*-toluenesulphonate separated during the reaction. When the tube had cooled these crystals were filtered off. Yield, 0·23 g. (89·9%). The acetone filtrate was evaporated and the residue extracted with chloroform. The chloroform was dried ($MgSO_4$) and concentrated, and the crystals of 6-*iodo* 3 : 5-*benzylidene* 1 : 4-*anhydrosorbitol* were filtered off and washed with ether; m. p. 144° (Found: C, 42·7; H, 4·5. $C_{13}H_{15}O_4I$ requires C, 43·2; H, 4·2%).

6-*Tosyl* 1 : 4-*Anhydrosorbitol*.—6-Tosyl 3 : 5-benzylidene 1 : 4-anhydrosorbitol (6·68 g.), oxalic acid (10·0 g.), water (31·0 c.c.) and acetone (250 c.c.) were refluxed for 18 hours, during which $[\alpha]_D$ changed from + 5·05° to + 13·46°. The solution was cooled and neutralised with barium carbonate. The insoluble salts were removed by centrifuging and the remaining clear solution evaporated to dryness under reduced pressure. The residue was extracted with chloroform and the chloroform extracts evaporated; the *compound* was a syrup which failed to crystallise. Yield, 3·07 g., $[\alpha]_D^{17.8°}$ + 10·5 (*c*, 2·095 in chloroform) (Found: S, 10·3. $C_{15}H_{18}O_7S$ requires S, 10·05%).

2 : 5-*Bismethanesulphonyl* 1 : 4-3 : 6-*Dianhydrosorbitol*.—1 : 4-3 : 6-Dianhydrosorbitol (10 g.) was dissolved in dry pyridine (50 c.c.), and methanesulphonyl chloride (23 g.) added slowly at 0° with occasional shaking. Thereafter the mixture was kept overnight and then poured into ice–water. The precipitated *bismethanesulphonyl* derivative, after being collected and washed with water, was recrystallised from alcohol; m. p. 122—123°, $[\alpha]_D$ + 77·7° (*c*, 1·416 in chloroform) (Found: C, 31·9; H, 4·6. $C_8H_{14}O_8S_2$ requires C, 31·8; H, 4·7%).

Action of Sodium Methoxide on 6-*Tosyl* 1 : 4-*Anhydrosorbitol*.—6-Tosyl 1 : 4-anhydrosorbitol (3·06 g.) was dissolved in chloroform and cooled to 0°. Sodium (0·24 g.) was dissolved in dry methanol and cooled to 0°. The two solutions were mixed and left overnight at room temperature. More chloroform was added and the solution extracted with water. The combined aqueous extracts were neutralised with N-sulphuric acid and evaporated to dryness in the presence of barium carbonate (1·0 g.). The residue was extracted 3 times with hot ethyl acetate and the extracts evaporated to dryness under reduced pressure. The resulting syrup (1·527 g.) was dried, dissolved in dry pyridine at 0°, methanesulphonyl chloride (3·4 c.c.) added, and the solution left at room temperature overnight. The solution was then poured into water, and a flocculent precipitate and a gum were deposited. The precipitate was filtered off, dissolved in acetone, charcoaled, filtered off, and treated with ethyl alcohol; crystals (0·24 g.) of 2 : 5-bismethanesulphonyl 1 : 4-3 : 6-dianhydrosorbitol were obtained, m. p. 123° alone or in admixture with an authentic specimen; $[\alpha]_D^{18°}$ + 78·5° (*c*, 1·412 in chloroform).

The gum was dissolved in chloroform and the chloroform solution washed with N-sulphuric acid, sodium hydrogen carbonate solution, and water, and dried ($MgSO_4$). The solution was evaporated to dryness and treated with acetone–ethyl alcohol, giving a compound, m. p. 82—83°, $[\alpha]_D$ + 25·1° (*c*, 2·215 in chloroform), which has not yet been identified.

Conversion of 1 : 4-*Anhydrosorbitol into the* 2 : 5-*Bismethanesulphonyl Derivatives of* 1 : 4-3 : 6-*Dianhydrosorbitol and of* 1 : 4-3 : 6-*Dianhydro*-L-*iditol*.—1 : 4-Anhydrosorbitol (1·0 g.) was dissolved in dry pyridine, cooled to 0°, and treated with *p*-toluenesulphonyl chloride (1·2 g.) with cooling and shaking. Thereafter it was left at room temperature for 52 hours. The solution was then cooled again to 0° and acetic anhydride (4·6 c.c.) added, and the mixture left at room temperature for 48 hours. The solution was then poured on ice–water and the deposited oil extracted with chloroform. The chloroform extracts were washed with N-sulphuric acid, sodium hydrogen carbonate solution, and water, dried ($MgSO_4$), and evaporated to dryness. The resulting syrup (2·095 g.) was mainly 6-tosyl 2 : 3 : 5-triacetyl 1 : 4-anhydrosorbitol, contaminated with the corresponding 5-tosyl derivative. It had $[\alpha]_D^{16.5°}$ + 25·3° (*c*, 1·2 in chloroform). To a solution of the syrup (1·99 g.) in chloroform, a solution of sodium (0·428 g.) in absolute methyl alcohol was added at 0° and the mixture kept at room temperature overnight. Thereafter more chloroform was added and the solution extracted several times with water. The aqueous extracts were neutralised with N-sulphuric acid and evaporated to dryness in the presence of barium carbonate (0·5 g.). The residue was extracted with chloroform and the chloroform solution evaporated to a syrup, which was distilled at 220° (bath temp.)/10 mm., and separated into two fractions: (i) 0·153 g., $n_D^{18°}$ 1·4982, $[\alpha]_D^{14°}$ + 18·4° (*c*, 5·1 in chloroform); (ii) 0·15 g., $n_D^{18°}$ 1·4982 ($[\alpha]_D$ could not be determined owing to opacity).

Both fractions were treated with methanesulphonyl chloride (0·4 c.c.) in dry pyridine at 0°. When the solution from (i) was poured into water a solid was obtained which, recrystallised from ethyl alcohol, had m. p. 109°. Two further recrystallisations raised the m. p. to 112°, and after several more recrystallisations a product was obtained (0·0107 g.) of m. p. 119—122°, $[\alpha]_D^{18°}$ + 71·0 (*c*, 0·5 in chloroform). This was doubtless impure 2 : 5-bismethanesulphonyl 1 : 4-3 : 6-dianhydrosorbitol.

The mother liquors were evaporated to dryness and dissolved in acetone–ethyl alcohol, from which solution a few crystals of m. p. 155—156° were obtained together with some material, m. p. 82°. The former showed no depression of m. p. in admixture with 2 : 5-bismethanesulphonyl 1 : 4-3 : 6-dianhydro-L-iditol, and had the identical $[\alpha]_D^{15°}$ + 41·4° (*c*, 1·98 in acetone). The material, m. p. 82°, was identical

with the compound of the same m. p. obtained by Montgomery and Wiggins (Part IX, *loc. cit.*) from the product of the action of sodium methoxide on 6-chloro 1 : 4-anhydrosorbitol. The solution from fraction (ii) was poured into water and the product extracted with chloroform. The chloroform extracts were washed with sulphuric acid, sodium hydrogen carbonate, and water, dried ($MgSO_4$), and evaporated to dryness. The residual syrup eventually crystallised and after two recrystallisations had m. p. 81—82°. As the amount of this compound was small (0·0043 g.) its optical rotation could not be determined. It was identical with the compound of the same m. p. obtained from fraction (i).

The mother liquors from the recrystallisation were combined and concentrated; crystals were obtained (0·018 g.) showing m. p. 122° (alone or in admixture with 2 : 5-bismethanesulphonyl dianhydrosorbitol) and $[\alpha]_D^{20°}$ + 80·85° (*c*, 0·94 in chloroform).

The experiment was repeated on a larger scale, with the same result.

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