

82. *Anhydrides of Polyhydric Alcohols. Part XIII. The Amino-derivatives of 1 : 4-3 : 6-Dianhydro-mannitol, -sorbitol, and -L-Iditol, and their Behaviour towards Nitrous Acid.*

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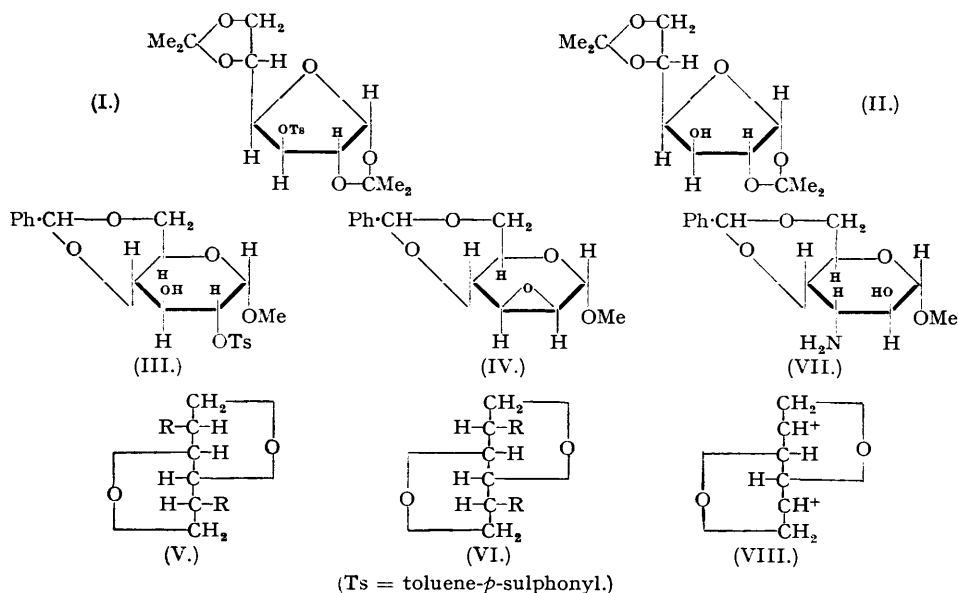
The behaviour of 2 : 5-diamino-1 : 4-3 : 6-dianhydro-2 : 5-dideoxy-mannitol and -sorbitol towards nitrous acid has been investigated. It has been found that in both cases the only product isolated was 1 : 4-3 : 6-dianhydro-L-Iditol, the formation of which must have involved Walden inversion at C_(a) and C_(s), and C_(s), respectively. The similarity between this phenomenon and that occurring when 2 : 4-3 : 5-dimethylene D-gluco- and -D-manno-saccharic acids are epimerised is emphasised. Although the replacement of the toluene-*p*-sulphonyl groups in 2 : 5-ditoluene-*p*-sulphonyl 1 : 4-3 : 6-dianhydro-mannitol and -sorbitol proceeds smoothly with the formation of the corresponding diamines, the attempt to prepare the diamine from 1 : 4-3 : 6-dianhydro-L-Iditol by the same procedure failed; in this case a secondary amine was formed which on the basis of its physical and chemical properties and, as a result of scale-model studies, is tentatively allocated the structure, 2 : 5-imino-1 : 4-3 : 6-dianhydro-2 : 5-dideoxy-D-mannitol. Further work designed to confirm or reject this conjecture is in progress.

IN view of the interesting facts that have come to light during study of the deamination of amino-derivatives of partly substituted sugar derivatives containing hydroxyl groups situated *trans* to the amino-groups (Wiggins, *Nature*, 1946, **157**, 300) it was held worth while to investigate the deamination of the diamino-derivatives of the 1 : 4-3 : 6-dianhydrides of the epimerically related hexitols, D-mannitol, D-sorbitol, and L-Iditol in which no free hydroxyl groups exist. A preliminary account of this work has already appeared (Bashford and Wiggins, *Nature*, 1949, **164**, 573). The deamination of amino-sugars such as 4 : 6-benzylidene 3-amino- α -methyl-3-deoxyaltroside led to the formation of ethylene oxide anhydro-rings, this particular amine giving 4 : 6-benzylidene 2 : 3-anhydro- α -methylmannoside. The same phenomenon has been observed not only with appropriate glycoside derivatives, but also with those of 1 : 6-anhydro-sugars and sugar alcohols (Bashford and Wiggins, forthcoming publication).

If 2 : 5-diamino-dianhydro-2 : 5-dideoxyhexitols were deaminated, no such anhydro-ring formation could take place. Deamination of these substances might be expected to occur without Walden inversion, by analogy with the behaviour, towards alkaline reagents, of toluene-*p*-sulphonyl derivatives of sugars which contain no free hydroxyl group, or no hydroxyl group situated *trans* to the toluene-*p*-sulphonyloxy residue. Thus, 3-toluene-*p*-sulphonyl 1 : 2-5 : 6-diisopropylidene glucose (I) was hydrolysed by alkaline reagents without Walden inversion, to give diisopropylidene glucose (II). This contrasts with behaviour of compounds such as 2-toluene-*p*-sulphonyl 4 : 6-benzylidene α -methylglucoside (III), the alkaline hydrolysis of which is accompanied by Walden inversion: for from (III), 4 : 6-benzylidene 2 : 3-anhydro- α -methylmannoside (IV) is formed.

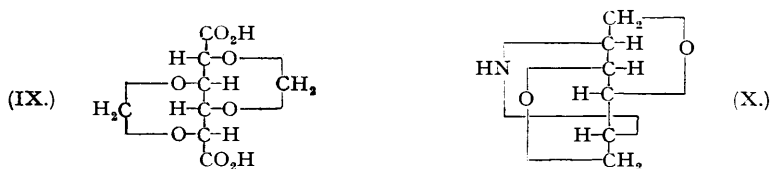
Deamination of 2 : 5-diamino-1 : 4-3 : 6-dianhydro-2 : 5-dideoxymannitol (V; R = NH₂) and -sorbitol (VI; R = NH₂) might be expected to lead only to the parent hexitols, 1 : 4-3 : 6-dianhydro-mannitol, (V; R = OH) and -sorbitol (VI; R = OH) respectively, especially since deamination of 4 : 6-benzylidene 3-amino- α -methyl-3-deoxyaltroside (VII) follows the same course as alkaline hydrolysis of 2-toluene-*p*-sulphonyl 4 : 6-benzylidene α -methylglucoside and gives rise to 4 : 6-benzylidene 2 : 3-anhydro- α -methylmannoside (IV). When, however, 2 : 5-diamino-1 : 4-3 : 6-dianhydro-2 : 5-dideoxymannitol was treated with sodium nitrite in acid solution and the liquid product treated with methanesulphonyl chloride, the dimethanesulphonate, m. p. 156°, of 1 : 4-3 : 6-dianhydro-L-Iditol (Wiggins, *J.*, 1948, 1403) was obtained. This product was also isolated after similar treatment of 2 : 5-diamino-1 : 4-3 : 6-dianhydro-2 : 5-

dideoxysorbitol. Although in neither case was any other dianhydrohexitol derivative isolated, the small yield of the L-iditol derivative indicated that it was not the only product. The fact that



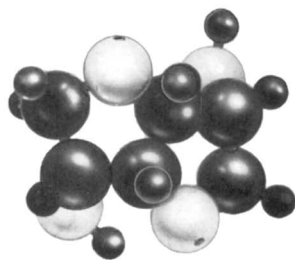
an L-iditol derivative has been obtained from both diamino-dianhydrodideoxyhexitols means that the deamination has been accompanied by Walden inversion, in the case of sorbitol at C₍₅₎, and in that of mannitol at both C₍₂₎ and C₍₅₎. This is explicable since deamination must involve the transitory formation of the carbonium cation (VIII) and this, on hydroxylation may take up the configuration of D-mannitol, D-sorbitol, or L-iditol. That in fact it takes up that of L-iditol to the apparent exclusion of the other two seems to indicate a configurational stability peculiar to this hexitol. The behaviour of the diamino-dianhydrohexitols towards deamination is in marked contrast to the alkaline hydrolysis of 3-toluene-*p*-sulphonyl diisopropylidene glucose, where Walden inversion, although possible because of the likelihood of the transitory formation of a carbonium cation (at C₍₃₎), does not take place.

This conversion of dianhydro-mannitol and -sorbitol into the corresponding derivative of L-iditol is paralleled by the epimerisation of 2 : 4-3 : 5-dimethylene D-manno- and D-glucosaccharic acid. When a solution of the dimethyl ester of either of these acids is boiled with barium hydroxide solution, epimerisation occurs with the formation of 2 : 4-3 : 5-dimethylene L-ido-saccharic acid (IX) (Haworth, Jones, Stacey, and Wiggins, *J.*, 1944, 61). In this case,

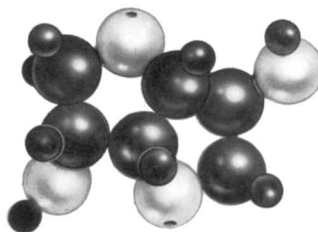


however, the ready isolation of dimethylene L-idosaccharic acid may be caused merely by the ease with which this substance crystallises or to its lower solubility. In fact the alkaline hydrolysis of dimethyl dimethylene D-glucosaccharate did afford some dimethylene D-glucosaccharic acid as well as the L-idosaccharic acid derivative. On the other hand, similar treatment of the corresponding mannosaccharic acid derivative gave only (IX).

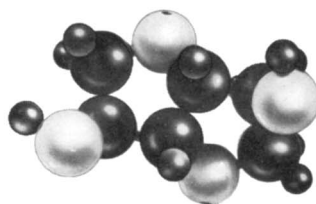
Another example of the conversion of 1 : 4-3 : 6-dianhydro-mannitol and -sorbitol into dianhydro-L-iditol is given by Fletcher and Goepf (*J. Amer. Chem. Soc.*, 1946, 68, 939), who treated each of these derivatives with Raney nickel and then hydrogenated them in the presence of that catalyst. Again dianhydro-L-iditol was the only product isolated in quantity. Lew, Wolfrom, and Goepf (*J. Amer. Chem. Soc.*, 1945, 67, 1865) however claim to have demonstrated the presence of all three dianhydrides in the reaction product, by chromatographic methods.



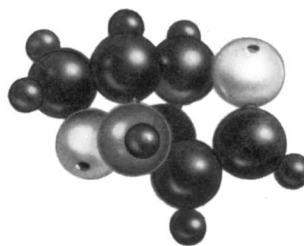
(1)



(2)



(3)



(4)

- (1) 1 : 4-3 : 6-*Dianhydro-D-mannitol*.
 (2) 1 : 4-3 : 6-*Dianhydro-D-sorbitol*.
 (3) 1 : 4-3 : 6-*Dianhydro-D-iditol*.
 (4) 2 : 5-*Imino*-1 : 4-3 : 6-*dianhydro*-2 : 5-*dideoxy-D-mannitol* (inverted to show the imine bridge).

In order to test whether the deamination of 2:5-diamino-1:4-3:6-dianhydro-2:5-dideoxy-L-*iditol* would lead solely to the formation of dianhydro-L-*iditol* the attempt was made to prepare this diamine. 1:4-3:6-Dianhydro-L-*iditol* was converted into the 2:5-*ditoluene-p-sulphonate* and this treated with methyl-alcoholic ammonia in the manner found successful for the preparation of the diamines of dianhydro-mannitol and -sorbitol (Montgomery and Wiggins, *J.*, 1946, 393). No diamine was obtained however; instead a substance having only one nitrogen atom per six carbon atoms was isolated. This was a base, $C_6H_9O_2N$, which had m. p. 99–100°, $[\alpha]_D +90.5^\circ$, and formed a crystalline *oxalate*, *picrate*, and *hydrochloride*. It gave no Schiff base with salicylaldehyde; it lost no nitrogen on treatment with nitrous acid, but afforded a crystalline *N*-nitroso-derivative giving the characteristic Liebermann colour reaction with phenol and sulphuric acid. The compound $C_6H_9O_2N$ is therefore a dianhydro-hexitol containing a secondary amino-group, and the only way in which this can be reconciled with the analytical data of the compound and its derivatives is to assume the formation of an imine bridge between $C_{(2)}$ and $C_{(5)}$. An immediate difficulty arises as scale models show that it is impossible so to join $C_{(2)}$ to $C_{(5)}$ of the 1:4-3:6-dianhydro-L-*iditol*. The imino-compound $C_6H_9O_2N$ must therefore possess a different configuration. Since the reaction conditions preclude the likelihood of there being any alteration to the ring structure and hence of the configuration about $C_{(3)}$ and $C_{(4)}$ the only possible configurations are those of *D*-mannitol and *D*-sorbitol. Configurational changes about $C_{(2)}$ and $C_{(5)}$ are certainly possible because the removal of toluene-*p*-sulphonyloxy-groups by alkaline reagents must involve the transitory formation of the carbonium cation (VIII). From scale models of the three epimerically related 1:4-3:6-dianhydrohexitols (shown in the figure) it is clear that the only one in which $C_{(2)}$ and $C_{(5)}$ could be bridged by an imine group is 1:4-3:6-dianhydro-*D*-mannitol. Hence it is tentatively suggested that the compound $C_6H_9O_2N$ obtained by the action of ammonia on 2:5-di-toluene-*p*-sulphonyl 1:4-3:6-dianhydro-L-*iditol* is 2:5-*imino*-1:4-3:6-*dianhydro*-2:5-*dideoxy-D-mannitol* (X).

EXPERIMENTAL.

Deamination of 2:5-Diamino-1:4-3:6-dianhydro-2:5-dideoxysorbitol.—The diamine (3.95 g., prepared according to Montgomery and Wiggins *J.*, 1946, 393) was dissolved in water (25 c.c.) and acidified with dilute hydrochloric acid. Sodium nitrite (4.5 g.) dissolved in water (25 c.c.) was then added and the mixture kept overnight. Thereafter the solution was neutralised with barium carbonate, filtered, and evaporated to dryness under reduced pressure. The dry residue was extracted exhaustively with hot ethyl acetate, and the extracts were evaporated to a syrup (1.68 g.). This distilled at 115–130° (bath temperature)/0.05 mm. as a light-yellow oil (1.27 g.), $[\alpha]_D +46.7^\circ$ (*c*, 1.9 in acetone). A portion (0.9 g.) of this distillate was dissolved in dry pyridine (15 c.c.), and methanesulphonyl chloride (1.6 c.c.) added at 0°. After being kept overnight at room temperature, the mixture was poured into water and extracted therefrom with chloroform. The chloroform extract was washed successively with dilute sulphuric acid, sodium hydrogen carbonate solution, and with water, dried ($MgSO_4$), filtered (charcoal), and evaporated to dryness. The residue, crystallised and recrystallised from alcohol, gave needles of 2:5-dimethanesulphonyl 1:4-3:6-dianhydro-L-*iditol*, m. p. 156.5° alone or on admixture with authentic material, and had $[\alpha]_D +48.0^\circ$ (*c*, 2.1 in acetone). Further crops of crystals were obtained from the mother-liquors but no other pure substance could be isolated.

Deamination of 2:5-Diamino-1:4-3:6-dianhydro-2:5-dideoxymannitol.—The diamine (1.29 g.) (Montgomery and Wiggins, *loc. cit.*) was dissolved in water (30 c.c.), acidified with glacial acetic acid (3 c.c.), and treated with sodium nitrite (1.3 g.). The solution was kept overnight at room temperature and worked up as above. The resultant syrup distilled at 175–180° (bath temperature)/0.001 mm. By repetitions 3.52 g. of the distillate were accumulated. This was treated in dry pyridine (40 c.c.) with methanesulphonyl chloride (9.33 c.c.) at 0°. Thereafter the mixture was kept at room temperature overnight and then poured into water (300 c.c.). A solid (0.76 g.) was deposited and after being recrystallised from methyl alcohol had m. p. 156–157° alone or on admixture with 2:5-dimethanesulphonyl 1:4-3:6-dianhydro-L-*iditol*, and $[\alpha]_D +48.0^\circ$ (*c*, 2.1 in acetone). For the isomers of this product see Montgomery and Wiggins (*J.*, 1948, 2204) and Bashford and Wiggins (*J.*, 1948, 299).

2:5-Ditoluene-p-sulphonyl 1:4-3:6-Dianhydro-L-iditol.—To 1:4-3:6-dianhydro-L-*iditol* (17.3 g.; Wiggins, *J.*, 1948, 1403) in dry pyridine (75 c.c.) toluene-*p*-sulphonyl chloride (50 g.) was added a little at a time at 0°. The mixture was kept at room temperature for 72 hours and thereafter poured into water. The solid which separated was filtered off, washed, and dried; recrystallised from ethyl alcohol, 2:5-*ditoluene-p-sulphonyl* 1:4-3:6-*dianhydro-L-iditol* (44 g.) formed needles, m. p. 90°, $[\alpha]_D +38.2^\circ$ (*c*, 2.0, in chloroform) (Found: C, 52.8; H, 5.1. $C_{20}H_{22}O_8S_2$ requires C, 52.8; H, 4.85%).

Reaction of 2:5-Di-toluene-p-sulphonyl 1:4-3:6-Dianhydro-L-iditol with Methyl-alcoholic Ammonia.—The compound (42 g.) was mixed with dry methyl alcohol (900 c.c.), saturated at 0° with dry ammonia gas, and heated in an autoclave for 30 hours at 160–170°. Thereafter the solution was evaporated to dryness, and the residue heated at 100° with barium hydroxide (50 g.) in water (400 c.c.) (this and all subsequent operations were carried out in an atmosphere of nitrogen). The solution was then evaporated to a syrup under reduced pressure, the water being completely removed by distillation with benzene. The residue was extracted several times with boiling chloroform, and the combined extracts were filtered and evaporated to dryness. The residue, recrystallised from ethyl acetate, formed needles, m. p. 99–100°, $[\alpha]_D +90.5^\circ$ (*c*, 2.56 in chloroform) (2.0 g.). This substance was very volatile and

readily sublimed, and it is probable that a large amount of the material was lost during the isolation. It did not form a Schiff base with salicylaldehyde and a trace of alkali. It was 2 : 5-*imino*-1 : 4-3 : 6-*dianhydro*-2 : 5-*dideoxy*-D-*mannitol* [Found : C, 56.4; H, 6.9; N, 10.7%; *M* (Rast), 136.5. $C_6H_9O_2N$ requires C, 56.6; H, 7.1; N, 11.0%; *M*, 127]. The imine (0.05 g.) was dissolved in alcohol (2 c.c.), and picric acid (0.1 g.), also dissolved in alcohol (2 c.c.), was added. Recrystallised from alcohol the *picrate* which separated formed yellow needles (0.11 g.), m. p. 219–220° (decomp.) (Found : N, 16.3. $C_{12}H_{12}O_9N_4$ requires N, 15.8%). The imine (0.07 g.) was dissolved in chloroform (4 c.c.), and the solution saturated with dry hydrogen chloride. After a few seconds a white precipitate separated. The *hydrochloride*, recrystallised from alcohol containing a trace of water, had m. p. 280–290° (decomp.) (Found : C, 44.1; H, 6.0; N, 8.3. $C_6H_9O_2N.HCl$ requires C, 44.3; H, 6.1; N, 8.6%). The imine (0.05 g.) in alcohol (2 c.c.) was treated with an equivalent amount of oxalic acid also dissolved in alcohol. A white solid separated. The mixture was heated to the b. p., and water added drop by drop until complete dissolution was effected. On cooling, the *oxalate* separated; it had m. p. 243° (Found : C, 48.6; H, 5.5. $C_{14}H_{20}O_8N_2$ requires C, 48.8; H, 5.81%).

The mother-liquors after the separation of the imino-compound were concentrated and distilled in two portions: (a) b. p. 100° (bath temperature)/0.1 mm. (0.3 g.), and (b) b. p. 120–140° (bath temperature)/0.1 mm. (1.52 g.). Fraction (a) yielded a further amount of 2 : 5-*imino*-1 : 4-3 : 6-*dianhydro*-2 : 5-*dideoxy*-D-*mannitol*, but fraction (b) was a liquid which has not been identified.

N-Nitroso-derivative of 2 : 5-Imino-1 : 4-3 : 6-dianhydro-2 : 5-dideoxy-D-mannitol.—The imine (0.5 g.) was dissolved in water, acidified with acetic acid, and treated with sodium nitrite (0.5 g.) dissolved in water, and the mixture kept at room temperature overnight. No evolution of nitrogen was apparent. The solution was neutralised with sodium hydrogen carbonate and evaporated to dryness, and the dry residue exhaustively extracted with hot ethyl acetate. The combined extracts on being evaporated afforded a solid which, recrystallised from ethyl acetate, furnished the *N-nitroso-derivative*, m. p. 121.5°, $[\alpha]_D - 323^\circ$ (c, 2.43 in chloroform), which gave the characteristic Liebermann test for *N-nitroso*-compounds (Found : C, 45.6; H, 5.1. $C_6H_8O_3N_2$ requires C, 46.2; H, 5.1%).

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