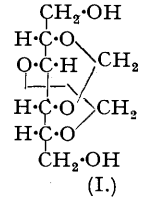
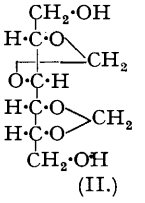
96. *The Structure of Monomethylene* d-*Glucosaccharolactone.*

By W. G. M. Jones and L. F. Wiggins.

Monomethylene glucosaccharolactone has been oxidatively degraded to monomethylene xylotrihydroxyglutaric acid, shown to be identical with the product of methylenation of xylotrihydroxyglutaric acid. The methylene group is therefore engaged in acetal formation with the hydroxyl groups at C_2 and C_4 of the carbon chain, and the substance is to be assigned the structure of 2 : 4-monomethylene glucosaccharic acid 3 : 6-lactone. Structures are assigned to the dimethylene derivatives of the saccharic acids and hexahydric alcohols described in previous communications. Methylated derivatives of monomethylene glucosaccharic acid are also described.

In a description of the methylene compounds of saccharic acids and hexahydric alcohols (this vol., pp. 58, 61) we have been confronted with several possibilities for the configuration of the methylene groups in these compounds. For instance, in the dimethylene sorbitol prepared by methylenation of 1 : 6-dibenzoyl sorbitol (Haworth and Wiggins, this vol., p. 58) there are three possible allocations of the methylene groups, involving the hydroxyl groups at $C_2 : C_4$ and $C_3 : C_5$ (I), at $C_2 . C_3$ and $C_4 : C_5$ (II), and at $C_2 : C_5$ and $C_3 : C_4$ (III).


(I.)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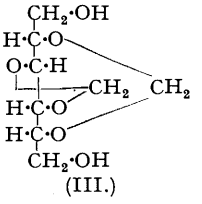
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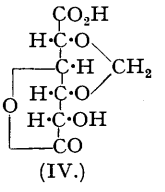
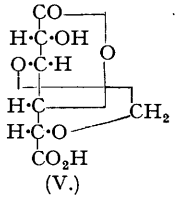

(IV.)

It has been shown that it is possible to oxidise both dimethylene sorbitol and dimethylene mannitol to the corresponding saccharic acids and that, furthermore, these acids epimerise on treatment with hot alkali, giving a common product, dimethylene *l*-idosaccharic acid (Haworth, Jones, Stacey, and Wiggins, this vol., p. 61). Hence, it is to be concluded that all these dimethylene derivatives of the hexahydric alcohols and saccharic acids have the same arrangement of the formaldehyde residues. It has been shown by Haworth and Jones (this vol., p. 65) that monomethylene glucosaccharolactone reacts with methyl-alcoholic hydrogen chloride to give dimethyl monomethylene glucosaccharate, which can be completely methylenated to give dimethyl dimethylene glucosaccharate. If the disposition of the methylene groups in monomethylene glucosaccharolactone can be ascertained, and if it is assumed that no change in position of the methylene group occurs on further treatment with formaldehyde, then the orientation of the methylene groups in all the dimethylene hexahydric alcohols and saccharic acids mentioned previously will have been determined.

Monomethylene glucosaccharolactone has in fact been shown to be the 2 : 4-methylene compound (IV). Hence, since C_4 is involved in acetal formation with formaldehyde, the γ-lactone ring of monomethylene glucosaccharolactone must involve C_3 and C_6. As the only free alcoholic hydroxyl groups in monomethylene glucosaccharic acid are at C_3 and C_5, it follows that dimethylene glucosaccharic acid formed from it by further methylenation is 2 : 4-3 : 5-dimethylene glucosaccharic acid. It is concluded therefore that the structures of dimethylene glucosaccharic acid and its epimers, and of the dimethylene hexahydric alcohols from which they have been derived, are such that the methylene groups in each are attached to alternate carbon atoms C_2 and C_4, and C_3 and C_5.

Monomethylene glucosaccharolactone may have one of the structures shown in (IV)—(IX). In these the methylene group joins C_2 and C_4 (IV), C_3 and C_5 (V), C_2 and C_3 (VI), C_4 and C_5 (VII), C_3 and C_4 (VIII), C_2 and C_5 (IX). Formula (VIII) is eliminated because monomethylene glucosaccharolactone is a γ- and not a δ-lactone,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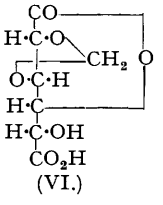
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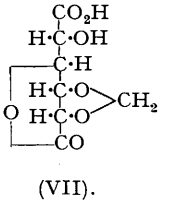
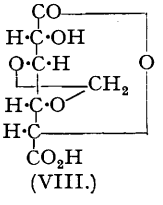
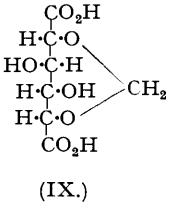

(VII).

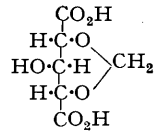

(VIII.)

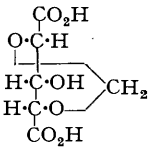

(IX.)

and (IX) is improbable because lactone ring formation would be expected to be sterically hindered by the methylene grouping. The rate of oxidation with lead tetra-acetate of the dimethyl monomethylene glucosaccharate derived from the lactone (Haworth and Jones, *loc. cit.*), determined by Hockett and McClenahan's method (*J. Amer. Chem. Soc.*, **1939**, **61**, **1667**), was extremely slow, a fact which eliminates structures containing glycollic acid groups, *viz.*, (VI) and (VII). A decision between the remaining possibilities (IV) and (V) was made on the basis of an examination of the products of oxidative degradation of monomethylene glucosaccharolactone.

The oxidative degradation was carried out by means of chromic anhydride in glacial acetic acid solution and a substance corresponding in composition to a dimethyl monomethylene trihydroxyglutarate was isolated. The product was optically inactive and was therefore more probably the *dimethyl* ester of monomethylene

xylotrihydroxyglutaric acid. On hydrolysis, the free acid, m. p. 254°, was obtained. Authentic monomethylene xylotrihydroxyglutaric acid (X), prepared by the procedure described below, had the same m. p. and a mixture

(X.) 

 (XI.

of the two showed no depression of m. p. This xylotrihydroxyglutaric acid could only have arisen from (IV) : (V) would yield an acid with the arabinose configuration (XI). A Weerman test on the diamide derived from (X) showed the absence of α-hydroxy-groups, thus confirming the allocation of the methylene linkages to C_2 and C_4. Monomethylene glucosaccharolactone, therefore, has the structure represented by (IV). In the preparation of the reference compound, calcium xylotrihydroxyglutarate, prepared from *d*-xylose by Fischer's method (*Ber.*, 1891, **24**, 1836), was methylenated with paraformaldehyde and concentrated sulphuric acid, and the product isolated as its dimethyl ester. This was identical with the product obtained from the oxidation of monomethylene glucosaccharolactone. Hydrolysis gave the monomethylene xylotrihydroxyglutaric acid. This acid had m. p. 254°, whereas Lobry de Bruyn (*Rec. Trav. chim.*, 1900, **19**, 180) gives m. p. 242°.

By the methylation of dimethyl monomethylene glucosaccharate with silver oxide and methyl iodide, two crystalline products were obtained, *viz.*, *dimethyl* 3 : 5-*dimethyl* 2 : 4-*monomethylene glucosaccharate* and 5-*methyl* 2 : 4-*monomethylene glucosaccharolactone methyl* ester. Oxidation of the former afforded crystalline products which are still under investigation.

In the course of this work the following new crystalline compounds were also prepared : *dimethyl* 3-*methyl* 2 : 4-*monomethylene xylotrihydroxyglutarate* and the *diamide* of the acid.

Experimental.

Oxidation of Dimethyl Monomethylene Glucosaccharate with Lead Tetra-acetate.—The ester (0·0005 mol.) was dissolved in glacial acetic acid (49 c.c.), lead tetra-acetate solution (50 c.c.) [prepared by dissolving lead tetra-acetate (15 g.) in glacial acetic acid (500 c.c.)] added, and the solution made up to 100 c.c. 10-C.c. portions were withdrawn from time to time, run into potassium iodide–sodium acetate buffer, and the liberated iodine titrated with 0·02N-sodium thiosulphate. Hence, the number of g.-atoms of oxygen used per mol. of ester could be calculated : 3 mins., nil; 40 mins., 0·02; 119 mins., 0·02; 257 mins., 0·04. There is, therefore, no rapid oxidation of dimethyl monomethylene glucosaccharate with this reagent.

Oxidation of Monomethylene Saccharolactone with Chromic Anhydride.—The lactone monohydrate (2 g.) was suspended in glacial acetic acid (75 c.c.) (the prismatic changed into feathery crystals, corresponding to conversion into the anhydrous form), the suspension stirred vigorously at room temperature, and a solution of chromic anhydride (1·5 g.) in glacial acetic acid (50 c.c.) added dropwise during 2 hours, stirring being continued overnight; the clear green solution was then evaporated under diminished pressure, and water evaporated over the residue in order to remove all the acetic acid. The residue was then dissolved in water, and a slight excess of barium hydroxide solution added to precipitate chromium hydroxide, which was centrifuged off and washed well with cold water. Barium was removed from the combined filtrate and washings by addition of the correct amount of N-sulphuric acid, and after the barium sulphate had been centrifuged off, the filtrate was evaporated to dryness. The residue was esterified by boiling for 6 hours with 2% methyl-alcoholic hydrogen chloride. The acid was then neutralised with silver carbonate, the silver residues filtered off and washed with methyl alcohol, and the filtrate and washings evaporated to dryness. This residue deposited crystals (0·06 g.) after dissolving in a little warm alcohol. The crystals were moderately soluble in water but could be crystallised from a concentrated solution. The substance showed m. p. 203—204° and was optically inactive. A repeat preparation from 5 g. of monomethylene saccharolactone monohydrate gave 0·4 g. of the crystalline product, m. p. 204°, which was *dimethyl monomethylene xylotrihydroxyglutarate* (Found : C, 44·3; H, 5·5; OMe, 27·1; *M*, by titration, 216. $C_8H_{12}O_7$ requires C, 43·7; H, 5·5; OMe, 28·2%; *M*, 220).

2 : 4-*Monomethylene* i-*Xylotrihydroxyglutaric Acid.*—Dimethyl monomethylene *i*-xylotrihydroxyglutarate (27 mg.) was suspended in water and heated with 0·064N-baryta solution (4 c.c.) at 60° for 1½ hours. The correct amount of N/100-sulphuric acid was added, and the solution filtered and evaporated to dryness. Recrystallisation from aqueous alcohol gave monomethylene *i*-xylotrihydroxyglutaric acid as prismatic crystals, m. p. 253—254° (Found : C, 37·8; H, 3·8. Calc. for $C_6H_8O_7$: C, 37·5; H, 4·1%).

2 : 4-*Monomethylene* i-*Xylotrihydroxyglutarodiamide.*—The dimethyl ester (33 mg.) was suspended in dry methyl alcohol (5 c.c.), and the solution saturated with ammonia at 0°. The ester rapidly dissolved and crystals separated. After being kept for 72 hours, these were filtered off and recrystallised from methyl alcohol; yield, 27 mg., m. p. 286° (Found : C, 37·7; H, 5·0. $C_6H_{10}O_5N_2$ requires C, 38·0; H, 5·3%). A Weerman test for an α-hydroxy-group gave a negative result.

Dimethyl 3-*Methyl* 2 : 4-*Monomethylene Xylotrihydroxyglutarate.*—Dimethyl 2 : 4-monomethylene xylotrihydroxyglutarate (33 mg.) was methylated by three treatments with silver oxide and methyl iodide. The product was extracted after each treatment several times with boiling chloroform. A crystalline residue was finally obtained which was recrystallised from ethyl alcohol; yield, 20 mg., m. p. 157° (Found : C, 46·3; H, 6·1. $C_9H_{14}O_7$ requires C, 46·1; H, 6·0%).

Dimethyl 3-*Methyl* 2 : 4-*Monomethylene Xylotrihydroxyglutarodiamide.*—The above *ester* (12 mg.) was dissolved in dry methyl alcohol, and the solution saturated with ammonia gas at 0°, whereupon the solution was set aside at 0° for 74 hours. Evaporation at room temperature in a vacuum gave a crystalline *diamide*, which recrystallised from methyl alcohol in the form of prisms (8 mg.), m. p. 295° (decomp.) (Found : C, 41·9; H, 5·8. $C_7H_{12}O_5N_2$ requires C, 41·7; H, 5·9%).

Dimethyl Monomethylene Xylotrihydroxyglutarate from d-*Xylose.*—*d*-Xylose (10 g.) was heated with nitric acid (30 c.c.; *d* 1·2) at 40° for 8 hours with occasional stirring (see Fischer, *loc. cit.*). The liquid was then evaporated in an open dish with the addition of water from time to time until most of the nitric acid had evaporated. The solution was then neutralised at the boil with calcium carbonate, filtered, and evaporated to 70 c.c.; the calcium salts then separated; yield, 9 g. A portion (1 g.) of the calcium salt of xylotrihydroxyglutaric acid was mixed with paraformaldehyde (1 g.)

and concentrated sulphuric acid (0·8 c.c.), and the mixture gently warmed for 20 mins.; it was then diluted with dry methyl alcohol (80 c.c.) and refluxed for 4 hours. After neutralisation with barium carbonate, filtration, and evaporation, a semi-solid residue was obtained which yielded crystals of dimethyl monomethylene xylotrihydroxyglutarate, m. p. 203—204°, not depressed in admixture with the product obtained by oxidation of monomethylene glucosaccharolactone. The lactone again showed no optical activity.

Methylation of Dimethyl Monomethylene Glucosaccharate.—The ester (10 g.) was dissolved in acetone–methyl iodide (70 c.c.; 1 : 1), and silver oxide (20 g.) added during 10 hours at 50°. Some crystals were formed, and the product was isolated by extraction with acetone. This operation was repeated five times without any attempt at fractionation of the product. The syrupy product finally obtained by distillation of the acetone extract was dissolved in a small amount of acetone and diluted with ether. Crystallisation occurred immediately, and the crystals were filtered off, washed with acetone and ether, and recrystallised from water. *Methyl 5-monomethyl 2 : 4-monomethylene glucosaccharo-3 : 6-lactone* was obtained as long needles (1·2 g.), m. p. 149° (Found : C, 45·9; H, 5·5. $C_9H_{12}O_7$ requires C, 46·0; H, 5·2%).

The mother-liquors were concentrated, the syrupy residue dissolved in the minimum of ether, and the solution set aside. Crystallisation occurred, and the crystals which separated were collected and recrystallised from acetone–ether, forming long needles (3·0 g.), m. p. 96—97° (Found : C, 48·2; H, 6·5; OCH_3, 44·7. $C_{11}H_{18}O_8$ requires C, 47·5; H, 6·5; OCH_3, 44·6%); these were *dimethyl 3 : 5-dimethyl 2 : 4-monomethylene glucosaccharate.* The mother-liquors on concentration gave a yellow, fairly viscid syrup which has not been further examined.

Oxidation of Dimethyl 3 : 5-Dimethyl 2 : 4-Monomethylene Glucosaccharate.—The ester (1·0 g.) was dissolved in nitric acid (10 c.c.; *d* 1·42), and the solution gradually heated to 90° by warming in a water-bath, being kept at that temperature for 1 hour; thereafter nitric acid was removed in the usual way. The syrupy residue was boiled with 2% methyl-alcoholic hydrogen chloride (50 c.c.) for 7 hours, the solution neutralised with silver carbonate, and the ester product isolated. It distilled at 165°/0·06 mm. (bath temp.), $n_D^{16\cdot5°}$ 1·4642, yield 0·34 g. The amide was prepared by dissolving a portion of the ester in dry methyl alcohol (2 c.c.) and saturating the solution with ammonia at 0°; m. p. 176° after recrystallising from methyl alcohol (Found : C, 41·3; H, 6·7%).

Methylation of Esterified Oxidation Product.—This was methylated by three treatments with methyl iodide (3 c.c.) and silver oxide (1 g.), the product being extracted with chloroform. A fairly viscid syrup was obtained, distilling at 130°/0·02 mm. (bath temp.), $n_D^{20°}$ 1·4457, $[\alpha]_D^{20°}$ + 8·08°.

The amide was prepared by means of methyl-alcoholic ammonia in the usual manner, and appeared to be a mixture of two products : (*a*) recrystallised from water, m. p. 261° (Found : C, 41·8; H, 7·5%), and (*b*) recrystallised from methyl alcohol, m. p. 205° (Found : C, 42·6; H, 7·2%). Neither of these amides, however, has been identified.

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