24. *The Epimerisation of some Dimethylene Saccharic Acids and their Derivatives.*

By W. N. Haworth, W. G. M. Jones, M. Stacey, and L. F. Wiggins.

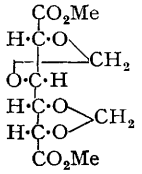
The preparation of *dimethylene glucosaccharic acid* and its derivatives is described. These substances epimerise with remarkable ease on treatment with barium hydroxide solution with the formation of *dimethylene* l-*idosaccharic acid*, derivatives of which are described. The epimerisation is brought about by both methyl-alcoholic and aqueous solutions of ammonia, and also methyl-alcoholic ammonia epimerises *dimethyl dimethylene glucosaccharate* to the corresponding derivative of *l*-idosaccharic acid without amide formation. Dimethyl dimethylene mannosaccharate also is epimerised by means of barium hydroxide solution to give the same dimethylene *l*-idosaccharic acid.

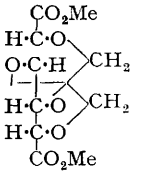
We have been concerned with the preparation of derivatives of hexahydric alcohols and of saccharic acids * in which the four central hydroxyl groups of these compounds have been fully substituted. We have utilised

* Throughout this communication we have used the term saccharic acid to indicate the dibasic acids derived from hexoses generally. The specific nature of the saccharic acid has been designated by prefixing the name of the sugar from which it was derived. Thus for the dibasic acid derived from galactose we should write galactosaccharic acid, or again that from idose, idosaccharic acid.

formaldehyde in acetal combination with the two central pairs of hydroxyl groups of mannitol and sorbitol and obtained crystalline dimethylene derivatives. Similarly fully methylenated derivatives of saccharic acids have been prepared.

The only well-authenticated methylene derivative of glucosaccharic acid previously recorded is the monomethylene glucosaccharolactone of Henneberg and Tollens (*Annalen*, 1896, **292**, 40). A dimethylene derivative is now described. Potassium hydrogen glucosaccharate, prepared by the oxidation of glucose with nitric acid (Kiliani, *Ber.*, 1925, **58**, 2344), was warmed with paraformaldehyde and concentrated sulphuric acid. After esterification of the reaction mixture, *dimethyl dimethylene glucosaccharate* was obtained in 18% yield. The exact position of the linkages between the hydroxyl groups and formaldehyde has not yet been determined. It is clear, however, that there are three possibilities. The acetal formation might involve linkage of formaldehyde either with the hydroxyl groups attached to adjacent carbon atoms (I) or with those attached to alternate carbon atoms (II). The third possibility involves linkage of formaldehyde with the hydroxyl groups attached


(I)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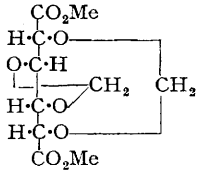
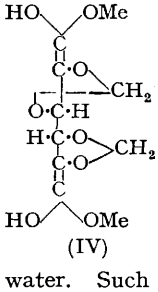

(III)

to carbon atoms C_2 and C_5, and C_3 and C_4 (III) and is regarded as improbable. Experiments to differentiate between these possible structures are now in progress. Throughout this paper the dimethylene derivatives of the saccharic acids have been formulated according to the first possibility, but this is for convenience only and does not imply a preference for this particular formulation.

A most interesting phenomenon was discovered when attempts were made to prepare *dimethylene glucosaccharic acid* by hydrolysis of the dimethyl ester with excess of barium hydroxide solution at 100°. The dimethyl dimethylene glucosaccharate, on such treatment, gave a mixture of dimethylene saccharic acids, from which was isolated a dimethylene saccharic acid (m. p. 292°) in 33% yield. The syrupy residue on re-esterification gave dimethyl dimethylene glucosaccharate in 30% yield. When dimethyl dimethylene glucosaccharate was treated with the theoretical amount of barium hydroxide at 60°, however, a different dimethylene saccharic acid (m. p. 223°) was obtained in good yield. It crystallised from acetone with one molecule of the solvent. This acid gave dimethyl dimethylene glucosaccharate (m. p. 157°) on esterification with methyl-alcoholic hydrogen chloride. On the other hand the high-melting dimethylene saccharic acid (m. p. 292°), when treated similarly, immediately gave a crystalline precipitate of a dimethyl ester (m. p. 297°) which was different from the original dimethyl ester of dimethylene glucosaccharic acid. In a similar manner dimethyl dimethylene mannosaccharate (V) (m. p. 109°), prepared by the chromic anhydride oxidation of 2 : 3 : 4 : 5-dimethylene mannitol (Haworth and Wiggins, preceding paper), gave on treatment with a solution of excess of barium hydroxide at 100° the same dimethylene saccharic acid (m. p. 292°) in 32% yield as was obtained from dimethyl dimethylene glucosaccharate.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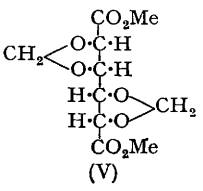
It is well known that hexonolactone and acids of the sugar group generally undergo a change of configuration on carbon atom C_2 when treated with alkaline reagents; *e.g.*, Fischer (*Ber.*, 1890, **23**, 799) effected the interconversion of gluconic acid and mannonic acid in pyridine solution. Fischer (*Ber.*, 1891, **24**, 2136) observed a similar change when galactosaccharic acid was heated under pressure with aqueous quinoline. It seemed probable that here we had encountered a similar phenomenon. Thus under the influence of alkali rearrangement takes place, giving rise to the enolic substance (IV), for when either dimethyl dimethylene glucosaccharate or dimethylene glucosaccharic acid is plunged into boiling Fehling's solution reduction takes place. Moreover, when either of these compounds is warmed with dilute sodium hydroxide solution, the resulting solution, after acidification, exhibits properties of unsaturation towards acid permanganate and bromine water. Such behaviour can only be explained by postulating the existence of enolic substances of type (IV).

Such a substance on reverting to the carboxylic form could give rise to the following epimeric esters: dimethyl dimethylene glucosaccharate (I), dimethyl dimethylene mannosaccharate (V), dimethyl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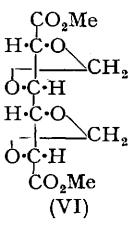
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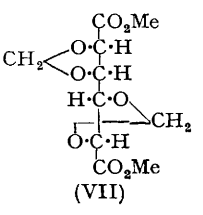
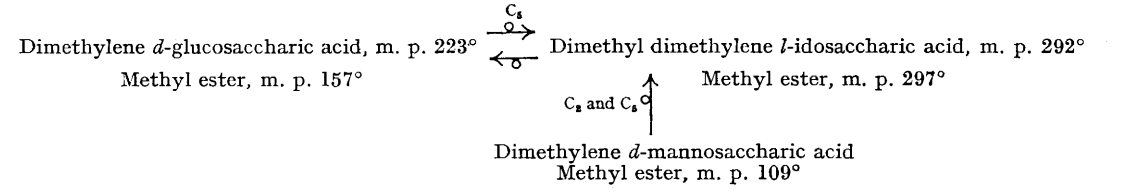

(VII)

dimethylene *l*-idosaccharate (VI), and dimethyl dimethylene *l*-gulosaccharate (VII). Since (I) and (VII) are identical, it is clear that three epimers (I), (V) and (VI) are theoretically possible. The configuration

of the dimethyl ester of dimethylene saccharic acid (m. p. 157°) as a glucosaccharic acid derivative is established from its preparation in an acid medium from potassium hydrogen saccharate and also from 2 : 3 : 4 : 5-dimethylene sorbitol by oxidation both with chromic anhydride (Haworth and Wiggins, *loc. cit.*) and with potassium permanganate. Again the dimethyl dimethylene saccharate of m. p. 109° must have the configuration of mannosaccharic acid, since it has been prepared from 2 : 3 : 4 : 5-dimethylene mannitol by oxidation with chromic anhydride (Haworth and Wiggins, *loc. cit.*) and also from mannose itself, by oxidation with nitric acid to give mannosaccharic acid, isolated as its potassium salt, which on methylenation and esterification gave the dimethyl ester, m. p. 109°. These substances have been prepared under conditions which avoided alkalinity and therefore the possibility of epimerisation. It follows that the third, the high-melting ester which was obtained from both of these saccharic acids, by treatment with excess of alkali, must have the configuration of the third possible isomer, *l*-idosaccharic ester (VI). Epimerisation under mild alkaline conditions is not confined to the esters, but is shown also by the free dimethylene saccharic acids. Thus dimethylene glucosaccharic acid epimerises to *dimethylene* l-*idosaccharic acid*. In addition the reverse change from pure dimethylene *l*-idosaccharic acid to dimethylene glucosaccharic acid takes place. The epimerisation took place with remarkable ease and rapidity, the presence of the epimer being evident from the large mass of flocculent barium salt which separated on temporary cooling of the reaction mixture to 80°, after boiling for a few minutes only. The barium salt of dimethylene *l*-idosaccharic acid was much less soluble than that of either of the epimeric dimethylene saccharic acids. A comparative experiment was carried out with tetramethyl dimethyl glucosaccharate under the conditions that were used for the dimethyl dimethylene saccharates. No indication of any epimerisation was observed and the original ester was recovered in excellent yield. It is a curious fact that we have been unable to isolate hitherto any dimethylene mannosaccharic acid or its derivatives from the epimerisation of either dimethylene glucosaccharic acid or dimethylene *l*-idosaccharic acid or their derivatives. Moreover no dimethylene glucosaccharic acid has been found amongst the products of epimerisation of dimethyl dimethylene mannosaccharate. Our observations on the epimerisation of the dimethylene saccharic acids and their esters may be summarised diagrammatically as follows :



It would seem that the methylene groups in the saccharic acid molecule have facilitated the migration of the hydrogen atoms attached to carbon atoms C_2 and C_5 to the carboxyl groups. The methylene groups have certainly enhanced the ability of the saccharic acids to epimerise. More drastic conditions were necessary in the epimerisations carried out by Fischer (*loc. cit.*), namely, heating the acids in aqueous quinoline or pyridine solution under pressure at 140°. Similarly Hedenberg and Cretcher (*J. Amer. Chem. Soc.*, 1927, **49**, 478), in epimerising *d*-galactonic acid to *d*-talonic acid, heated the acid with aqueous pyridine for 115 hours at 100° under pressure, and like conditions were used by Haworth and Long (J., 1929, 345) to epimerise tetramethyl γ- and δ-gluconolactones.

The epimerisation of dimethyl dimethylene glucosaccharate was found to take place under other conditions of mild alkalinity. For instance, when this glucosaccharic acid derivative was treated with methyl-alcoholic ammonia at 0°, the *diamide* of dimethylene *l*-idosaccharic acid was obtained in 13·3% yield together with the *diamide* of dimethylene glucosaccharic acid, isolated in 85·3% yield. Again, when this treatment was carried out at 60° by passing a stream of dry ammonia through a methyl-alcoholic solution of the dimethyl ester of dimethylene glucosaccharic acid, the product was *dimethyl dimethylene* l-*idosaccharate* in 50% yield and not the diamide of this saccharic acid. Incidentally this provides the best method of preparation of *l*-idosaccharic acid derivatives. The epimerisation was also brought about very easily when dimethyl dimethylene glucosaccharate was kept at room temperature with a saturated aqueous solution of ammonia for 2 hours, a 70% yield of the diamide of dimethylene *l*-idosaccharic acid being obtained.

Experimental.

Dimethyl Dimethylene Glucosaccharate.—An intimate mixture of potassium hydrogen glucosaccharate (40 g.), paraformaldehyde (20 g.), and sulphuric acid (10 c.c.) is heated gently over a gauze for 30 minutes. The melt is allowed to cool and extracted with dry methyl alcohol (150 c.c.). Undissolved potassium sulphate and formaldehyde polymer are removed, and the filtrate refluxed for 6 hours, concentrated to 80 c.c., and diluted with an equal volume of ether. The crystalline product obtained on keeping at 0° is collected and extracted with chloroform in the cold. Distillation of the chloroform gives the *ester*, which forms fine needles (7·5 g.), m. p. 157·5°, on recrystallisation from methyl alcohol (Found : C, 45·8; H, 5·2; OMe, 23·75. $C_{10}H_{14}O_8$ requires C, 45·8; H, 5·3; OMe, 23·6%). When a few crystals are plunged into boiling Fehling's solution, reduction takes place. Again, when a small amount of the substance is warmed with a little bench caustic soda and acidified with hydrochloric acid, the resulting solution decolourises acid potassium permanganate solution and also dilute bromine water.

Oxidation of Dimethylene Sorbitol.—Dimethylene sorbitol (0·45 g.) (Haworth and Wiggins, *loc. cit.*) is dissolved in water (15 c.c.) containing potassium hydroxide (0·25 g.), and potassium permanganate (1 g.) in water (40 c.c.) run in until the solution acquires a permanent pink colour. Manganese dioxide is removed and washed with hot water, and filtrate and

washings are combined and neutralised with N-sulphuric acid and then rendered just acid to litmus with 0·1N-sulphuric acid. The solution is concentrated, and the solid residue boiled under reflux for 6 hours with 1% methyl-alcoholic hydrogen chloride. Insoluble potassium salts are removed, the filtrate neutralised with silver carbonate, and the methyl alcohol distilled. The crystalline residue (0·48 g.) is fractionally recrystallised from methyl alcohol, giving two fractions: (i) less soluble in methyl alcohol, identified as dimethyl dimethylene glucosaccharate, m. p. 157°, identical with the sample described above; (ii) more soluble in methyl alcohol, m. p. 147°, probably a dimethylene derivative of a hexonic acid, identical with the product obtained by the chromic anhydride oxidation of dimethylene sorbitol (Haworth and Wiggins, *loc. cit.*).

Dimethylene Glucosaccharodiamide.—Into dimethyl dimethylene glucosaccharate (17 g.), suspended in dry methyl alcohol (250 c.c.), dry ammonia is passed at 0° until complete solution of the ester takes place. After standing at 0° for 12 hours, the solution is filtered, to remove dimethylene *l*-idosaccharodiamide (2·0 g.; 13·3%), and the filtrate diluted with light petroleum (1 l.). The light flocculent precipitate is collected, washed with ether, and recrystallised from methyl alcohol, forming prisms containing methyl alcohol of crystallisation. The anhydrous *dimethylene glucosaccharodiamide* melts at 215° and is soluble in water and methyl alcohol. Yield (material containing methyl alcohol of crystallisation) 14·5 g.; 85·3% (Found: C, 41·4; H, 5·4; N, 12·1. $C_8H_{12}O_6N_2$ requires C, 41·4; H, 5·2; N, 12·1%).

Dimethylene Glucosaccharic Acid.—Dimethyl dimethylene glucosaccharate (2 g.) is heated with hydrated barium hydroxide (2·6 g.) in water (65 c.c.) at 60° for 1 hour. The barium salt is decomposed with dilute sulphuric acid, barium sulphate removed, the filtrate concentrated, and the solid residue extracted with hot acetone. *Dimethylene glucosaccharic acid* crystallises from a concentrated solution in prisms containing acetone of crystallisation, which is expelled in a vacuum at 65° or on long standing in air. Yield (material containing acetone of crystallisation), 1·7 g. It crystallises from water as a hydrate and is soluble in alcohol and dioxan; m. p. (anhydrous material) 223°, $[\alpha]_D^{21°}$ + 42·5° (water; *c*, 10·0) (Found: C, 41·15; H, 4·3. $C_8H_{10}O_8$ requires C, 41·0; H, 4·3%. Found for the product containing acetone of crystallisation: C, 44·7; H, 5·5. $C_8H_{10}O_8,C_3H_6O$ requires C, 45·2; H, 5·5). The anhydrous material reduces boiling Fehling's solution and shows unsaturated properties towards acid permanganate solution and to bromine water after being warmed with caustic alkali solution and then acidified.

Re-esterification of Dimethylene Glucosaccharic Acid.—The acid (1 g.) is boiled with 2% methyl-alcoholic hydrogen chloride (100 c.c.) for 4 hours and after neutralisation with silver carbonate and filtration the silver residues are washed with hot methyl alcohol. The alcoholic solution is evaporated to dryness, and the residue recrystallised from ethyl alcohol. Yield, 0·95 g. The product is dimethyl dimethylene glucosaccharate, m. p. and mixed m. p. 157°.

Epimerisation of Dimethylene Glucosaccharic Acid.—(a) *Dimethylene* l-*idosaccharic acid.* Dimethylene glucosaccharic acid (0·900 g.) is dissolved in water (30 c.c.), hydrated barium hydroxide (2 g.) added, and the solution refluxed for 6 hours. The barium salt of the acid product separates as a gelatinous mass on cooling, and barium is completely precipitated with dilute sulphuric acid. After removal of barium sulphate the filtrate is concentrated in a vacuum. The crystalline product is extracted with hot acetone, and the residue recrystallised from hot water. The product is *dimethylene* l-*idosaccharic acid*, m. p. 292° (decomp.), $[\alpha]_D^{16°}$ + 73·7° (water; *c*, 1·817). Yield, 0·3 g.; 33·3% (Found: C, 41·3; H, 4·6. $C_8H_{10}O_8$ requires C, 41·0; H, 4·3%). The acetone solution is concentrated to give a syrupy residue. This is dissolved in 1% methyl-alcoholic hydrogen chloride (5 c.c.) and refluxed for 5 hours. On cooling, needle-shaped crystals (0·3 g.; 29·7%) are deposited, m. p. 157° after recrystallisation from methyl alcohol, not depressed by authentic dimethyl dimethylene glucosaccharate. The filtrate, after neutralisation with silver carbonate, is concentrated; the brown syrupy residue (0·28 g.) does not crystallise on long standing at 0°.

(b) *Dimethyl dimethylene* l-*idosaccharate.* Dimethylene idosaccharic acid (0·25 g.) is suspended in dry methyl alcohol (5 c.c.) and one drop of hydrochloric acid. Solution takes place immediately on warming, and after 5 minutes' refluxing, *dimethyl dimethylene* l-*idosaccharate* crystallises. Recrystallised once from water, the ester is obtained in fine needles (0·27 g.), m. p. 297° (Found: C, 46·2; H, 5·4; OMe, 22·0. $C_{10}H_{14}O_8$ requires C, 45·8; H, 5·3; OMe, 23·6%).

(c) *Dimethylene* l-*idosaccharodiamide.* Into a suspension of dimethyl dimethylene idosaccharate (90 mg.) in concentrated aqueous ammonia (7 c.c.), ammonia is passed at room temperature for 2 hours. The product is kept at 0° for several hours, and the crystalline material then collected and recrystallised once from water. *Dimethylene* l-*idosaccharodiamide* (50 mg.) decomposes without melting at *ca.* 350° (Found: C, 41·6; H, 5·3; N, 12·0. $C_8H_{12}O_6N_2$ requires C, 41·4; H, 5·2; N, 12·1%).

Epimerisation of Dimethyl Dimethylene Glucosaccharate.—(a) *Dimethylene* l-*idosaccharic acid.* Dimethyl dimethylene glucosaccharate (4 g.) is added gradually to a boiling solution of hydrated barium hydroxide (9 g.) in water (70 c.c.). After 2 hours' refluxing, the gelatinous barium salt of the acidic product which separates on cooling is collected and treated with dilute sulphuric acid, and the filtered solution concentrated in a vacuum at 50°. The crystalline residue, recrystallised from water, gives dimethylene *l*-idosaccharic acid, m. p. 292°. Yield, 1·4 g.; 39·2%.

(b) *Dimethyl dimethylene* l-*idosaccharate.* Into a solution of dimethyl dimethylene glucosaccharate (2·8 g.) in dry methyl alcohol (50 c.c.) at 60°, dry ammonia is rapidly passed; dimethyl dimethylene *l*-idosaccharate soon crystallises, m. p. 297° after recrystallisation from water. Yield, 1·4 g.

(c) *Dimethylene* l-*idosaccharodiamide.* Into a suspension of dimethyl dimethylene glucosaccharate (2·6 g.) in concentrated aqueous ammonia (25 c.c.) at room temperature, ammonia is passed for 2 hours. The solution thus obtained is kept at 0° for 2 days, and the crystalline product then collected and recrystallised from water, giving dimethylene *l*-idosaccharodiamide in feathery needles, decomposing at 350°. A further quantity is obtained by diluting the filtrate with methyl alcohol and keeping the solution at 0° for 2 days. Total yield, 1·6 g.

Epimerisation of Dimethylene l-*Idosaccharic Acid.*—The acid (0·9 g.), dissolved in water (30 c.c.), is refluxed with hydrated barium hydroxide (2 g.) for 6 hours. The insoluble salt first formed gradually dissolves, and the gelatinous barium salt of the acid product separates on cooling. The acid is liberated with dilute sulphuric acid and after filtration the solution is concentrated, and the solid residue extracted with acetone. The syrupy product obtained on distillation of the acetone (0·5 g.) is triturated with acetone, and the insoluble product is identified as dimethylene *l*-idosaccharic acid, m. p. 292°. Yield, 0·3 g. The acetone solution on distillation of the acetone gives a syrupy product, which is refluxed for 8 hours with 1% methyl-alcoholic hydrogen chloride (5 c.c.). On cooling, needle-shaped crystals separate, m. p. 157·5° after one recrystallisation from methyl alcohol. The product is dimethyl dimethylene glucosaccharate. Yield, 0·2 g. The filtrate is neutralised with silver carbonate, and methyl alcohol distilled. The residue, a brown syrupy product, does not crystallise on long standing at 0°.

Preparation of Dimethyl Dimethylene Mannosaccharate from Mannose.—Mannose (4 g.) is dissolved in concentrated nitric acid and cautiously heated over a gauze until a vigorous reaction commences. When this subsides (10 minutes), water (10 c.c.) is added, and the solution kept at 90° for 15 minutes and then overnight at room temperature. The liquid is distilled, and the nitric acid removed by continuous distillation with water for 8 hours. The residual syrup is cautiously dissolved at 0° in dilute aqueous potassium hydroxide, and the solution kept at pH 8 for 6 hours and then adjusted to pH 7 with a few drops of dilute acetic acid. The solution is poured into absolute alcohol, giving a precipitate consisting mainly of potassium mannosaccharate. This is reprecipitated again from aqueous solution by alcohol, washed with alcohol and ether, and dried. The product is a cream-coloured powder (2·5 g.) (Found: K, 27·1%). The potassium

salt (2·0 g.) is mixed with paraformaldehyde (2 g.), and concentrated sulphuric acid (1·5 c.c.) slowly stirred in to form a pasty mass, which, on cautious heating, liquefies. It is heated for a further 5 minutes until the paraformaldehyde begins to sublime; it is then allowed to cool slowly. When cold it is thinned with methyl alcohol and refluxed for 3 hours. Most of the methyl alcohol is distilled off, and the residual syrup dissolved in chloroform, which is washed with water until free from acid, dried with magnesium sulphate, and the chloroform distilled off. The viscid brown product (2·0 g.) is distilled, a fraction (0·55 g.) being collected at 170—180°/0·05 mm. This, when nucleated with dimethyl dimethylene mannosaccharate, slowly crystallises to a semi-solid mass. The crystals (0·24 g.) are drained on a tile and recrystallised (twice) from methyl alcohol; m. p. 107° alone or mixed with the dimethyl dimethylene mannosaccharate (Haworth and Wiggins, *loc. cit.*) (Found: C, 46·1; H, 5·6; OMe, 24·0. Calc. for $C_{10}H_{14}O_8$: C, 45·7; H, 5·3; OMe, 23·6%).

Epimerisation of Dimethyl Dimethylene Mannosaccharate.—The ester (0·14 g.) is boiled with excess of barium hydroxide (octahydrate) (0·45 g. in 5 c.c. of water) over a gauze for 2 hours. On cooling to about 85°, the clear solution becomes solid with a mass of gelatinous crystals. The mixture is dissolved in a larger volume of water, the barium exactly removed by titration with N-sulphuric acid, the barium sulphate washed with water, and the filtrate evaporated to dryness. The solid residue is dissolved in 1 c.c. of hot water; from the filtered solution, thin plates separate, m. p. 292° (decomp.), not depressed by the compound obtained by the epimerisation of dimethyl dimethylene glucosaccharate. Therefore the product is dimethylene *l*-idosaccharic acid. The mother-liquors deposit a few more crystals on cooling to 0°. Total yield, 40 mg.; 32% (Found: C, 41·0; H, 4·3. Calc. for $C_8H_{10}O_8$: C, 41·0; H, 4·3%). The mother-liquors are evaporated to dryness; hot acetone extracts nothing from the residue, which indicates the absence of dimethylene glucosaccharic acid, which is soluble in hot acetone. The residue cannot be crystallised and probably contains dimethylene mannosaccharic acid.

Attempted Epimerisation of Tetramethyl Glucosaccharic Acid. Treatment of Dimethyl Tetramethyl Glucosaccharate with Barium Hydroxide.—The ester (2 g.), prepared by methylation of potassium hydrogen glucosaccharate with methyl sulphate and caustic soda, and subsequent esterification of the tetramethyl glucosaccharic acid thus formed with methyl iodide and silver oxide, is dissolved in water (60 c.c.), hydrated barium hydroxide (3·5 g.) added, and the solution refluxed for 9 hours. Barium hydroxide in excess is neutralised with carbon dioxide, and the acid product liberated from the barium salt with dilute sulphuric acid. Barium sulphate is removed, and the filtrate concentrated in a vacuum at 50°. The acid syrupy residue (1·7 g.) is esterified by refluxing for 7 hours with 1% methyl-alcoholic hydrogen chloride (25 c.c.). The solution is neutralised with silver carbonate, and the methyl alcohol distilled. The crystalline product (1·8 g.) is dimethyl tetramethyl glucosaccharate, m. p. 71—73°.

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