25. *Some Derivatives of Glucosaccharic Acid.*

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The preparation of derivatives of glucosaccharic acid in which some or all of the hydroxyl groups are engaged in acetal formation with formaldehyde, benzaldehyde, acetaldehyde or acetone is described, together with their inter-relationships.

It recently became necessary to prepare derivatives of glucosaccharic acid in which part or complete substitution of the hydroxyl groups has been effected. The experiments below described indicate how this has been accomplished with the introduction into the glucosaccharic acid molecule of methylene, ethylidene, benzylidene, and acetone groups.

Methylene derivatives of glucosaccharic acid have been described by Henneberg and Tollens (*Annalen*, 1896, **292**, 40) and by Lobry de Bruyn and Van Ekenstein (*Rec. Trav. chim.*, 1901, **20**, 331; 1902, **21**, 316). The former authors prepared monomethylene glucosaccharolactone and provisionally assigned to it the structure 4 : 5-monomethylene glucosaccharo-3 : 6-lactone; the latter authors claim to have prepared dimethylene and trimethylene derivatives of glucosaccharic acid. All of their results have not, however, been confirmed in this laboratory.

In the preceding communication (Haworth, Jones, Stacey, and Wiggins) the preparation of a dimethylene derivative of glucosaccharic acid has been described, together with the changes in molecular configuration which result when the compound is treated with alkali. An alternative method of preparation of this derivative is described below, together with the relationships which have been found to exist between it and the monomethylene derivatives of glucosaccharolactone, referred to above.

Acid potassium glucosaccharate was used as the starting material for the preparation of the methylene derivatives of glucosaccharic acid. It has been found that potassium glucosaccharate is readily converted, in part, into the corresponding lactone when its aqueous solution is heated. The lactone does not crystallise, and moreover, its presence prevents the complete crystallisation of potassium glucosaccharate from an aqueous solution. Having regard to these facts, it has been found possible to modify the method of preparation of the acid salt by the nitric acid oxidation of glucose (Gans and Tollens, *Annalen*, 1888, **249**, 215) so as to result in an improvement in the yield. A suspension of potassium glucosaccharate in 40% aqueous formaldehyde solution on treatment with hydrogen chloride gave the monomethylene glucosaccharolactone of Henneberg and Tollens, in 80% yield. Whereas *monomethylene glucosaccharolactone ethyl ester* was the product of reaction of this material with ethyl alcohol containing a trace of mineral acid, we found that treatment with a more concentrated acid solution (4% methyl-alcoholic hydrogen chloride) caused the lactone ring to be opened with the consequent formation of *dimethyl monomethylene glucosaccharate* in 85% yield. The crystalline *diamide* of this compound is described. The reverse conversion was readily brought about, for dimethyl monomethylene glucosaccharate, on being heated above its melting point for a short time, was quantitatively converted into *monomethylene glucosaccharolactone methyl ester.*

The introduction of a second methylene group into the molecule of monomethylene glucosaccharic acid was brought about by treating the dimethyl ester of this compound with paraformaldehyde and sulphuric acid. Dimethyl dimethylene glucosaccharate (described in a previous communication) was produced in 60% yield. The following inter-relationships are thus seen to exist between the methylene derivatives of glucosaccharic acid.

$$\begin{array}{ccccc}\text{Monomethylene glucosaccharo-} & \underset{\text{Heat above m. p.}}{\overset{4\%\ \text{MeOH–HCl}}{\rightleftarrows}} & \text{Dimethyl monomethylene} & \xrightarrow{\text{Paraformaldehyde–}\mathrm{H_2SO_4}} & \text{Dimethyl dimethylene}\\ \text{lactone methyl ester} & & \text{glucosaccharate} & & \text{glucosaccharate}\\ \text{(I.)} & & \text{(II.)} & & \text{(III.)}\end{array}$$

If it be assumed that the conversion of (II) into (III) involves simply the introduction of a second methylene group into the molecule without hydrolysis and possible consequent re-orientation of the methylene group already present, it follows that the structure of monomethylene glucosaccharolactone, which it is hoped shortly to establish, will provide the key to the structure of the dimethylene acid and the related dimethylene sorbitol and mannitol derivatives described by Haworth and Wiggins (this vol., p. 58).

Lobry de Bruyn and Van Ekenstein (*Rec. Trav. chim.*, 1899, **18**, 305) have described a benzaldehyde compound of glucosaccharic acid, and more recently Reeves (*J. Amer. Chem. Soc.*, 1939, **61**, 664) has prepared a monobenzylidene derivative of glucosaccharo-3 : 6-lactone methyl ester. In the preparation of benzylidene, ethylidene and acetone derivatives of glucosaccharic acid use has been made of the calcium chloride compound of diethyl glucosaccharate, first described by Heintz (*Ann. Phys. Chem.*, 1858, **105**, 233). We have also succeeded in preparing the corresponding calcium chloride compound of dimethyl glucosaccharate.

Treatment of Girard's compound with benzaldehyde in the presence of zinc chloride gave a crystalline *monobenzylidene* derivative of diethyl glucosaccharate, and a corresponding *diethyl monoethylidene glucosaccharate* was prepared by similar treatment with paraldehyde. The latter derivative was a syrup which gave by the usual methods a crystalline *diamide* and crystalline acid, the analytical figures for which were those required by *monoethylidene glucosaccharolactone.* Treatment of the calcium chloride compound of diethyl glucosaccharate with acetone and zinc chloride gave a *monoacetone* derivative of diethyl glucosaccharate as a syrup, from which a crystalline *diamide* was prepared.

One derivative of glucosaccharic acid was prepared in which different groups were engaged in acetal formation with each of the two pairs of hydroxyl groups: *dimethyl monomethylene monoethylidene glucosaccharate* was prepared by treating dimethyl monomethylene glucosaccharate with paraldehyde and sulphuric acid. It was not found possible, however, to introduce a methylene group into the molecule of diethyl monoethylidene glucosaccharate, this being due most probably to the instability of the ethylidene group under the acid conditions of the reaction. Furthermore an acetone group could not be introduced into the molecule of dimethyl monomethylene glucosaccharate. An attempted condensation of this compound with acetone in the presence of sulphuric acid yielded only monomethylene glucosaccharolactone methyl ester. Again, it was not found possible to introduce a second ethylidene group into the molecule of diethyl monoethylidene glucosaccharate by treatment of this compound in chloroform solution with paraldehyde and sulphuric acid.

EXPERIMENTAL.

Potassium Hydrogen Glucosaccharate.—Glucose (150 g.) was dissolved in nitric acid (*d* 1·15; 900 c.c.) and heated on a boiling water-bath. After the initial vigorous oxidation the solution was evaporated to small volume, and nitric acid in excess removed as completely as possible by repeated evaporation with water. The solution (150 c.c.) was kept for 12 hours and oxalic acid which crystallised was removed. The filtrate was diluted to 250 c.c., neutralised at 70° with concentrated aqueous potassium hydroxide, rendered faintly alkaline (brilliant-yellow), cooled in ice, and acidified with a moderately large excess of glacial acetic acid. The potassium hydrogen glucosaccharate which crystallised was collected and purified in the above manner by precipitation from a solution of its neutral potassium salt, by the addition of glacial acetic acid. Yield, 93 g. (45% of the theoretical); $[\alpha]_D^{20°}$ + 5·1° (*c*, 0·782 in water) [Found: C, 29·35; H, 3·75; K, 15·65; equiv. (direct titration with 0·1N-sodium hydroxide), 252. Calc. for $C_6H_9O_8K$: C, 29·0; H, 3·6; K, 15·7%; equiv., 248]. An aqueous solution (*c*, 1·1) of potassium hydrogen glucosaccharate showed the following changes in specific rotation on heating at 100°: $[\alpha]_D^{20°}$ + 5·5° (initial); + 12·0° (5 mins.); + 15·5° (10 mins.); + 20·0° (20 mins.); + 23·0° (50 mins.); + 25·0° (80 mins.; final value).

The resulting solution on titration against N/10-caustic soda behaved as a mixture of lactone and acid. A rapid titration showed that, if it be assumed that the solution contains a mixture of potassium hydrogen glucosaccharate and the potassium salt of glucosaccharolactone only, very approximately the ratio of the former to the latter is 9 : 13.

Monomethylene Glucosaccharolactone.—Hydrogen chloride was passed through a suspension of potassium glucosaccharate (25 g.) in 40% aqueous formaldehyde (60 c.c.) at 0° for 4 hours. Potassium chloride was removed, and the filtrate kept at 0° for several days. The solution was concentrated in a vacuum over sodium hydroxide, and the crystalline monomethylene glucosaccharolactone hydrate collected. A further quantity was obtained on evaporation of the filtrate. Yield, 13 g.; m. p. 144—146° (hydrate), 165° (anhydrous); $[\alpha]_D^{17°}$ + 118° (*c*, 1·0 in water) (Found: C, 38·2; H, 4·5. Calc. for $C_7H_8O_7,H_2O$: C, 37·8; H, 4·5%).

Monomethylene Glucosaccharolactone Ethyl Ester.—A solution of monomethylene glucosaccharolactone hydrate (1 g.) in absolute alcohol (10 c.c.) containing one drop of concentrated hydrochloric acid was refluxed for 6 hours. The *ethyl* ester crystallised on cooling and was recrystallised from water. The yield was quantitative; m. p. 195—197° (Found: C, 46·8; H, 5·5; OEt, 18·5. $C_9H_{12}O_7$ requires C, 47·0; H, 5·2; OEt, 19·4%).

Dimethyl Monomethylene Glucosaccharate.—A solution of monomethylene glucosaccharolactone (20 g.) in 4% methyl-alcoholic hydrogen chloride (350 c.c.) was refluxed for several hours and then kept at room temperature; dimethyl glucosaccharate gradually crystallised in large colourless prisms. The mother-liquor was decanted, diluted with ether, and again kept at room temperature. A further crop of crystals was thus obtained and by a repetition of this process, *dimethyl monomethylene glucosaccharate* was obtained (19 g.), m. p. 166°, $[\alpha]_D$ + 22·6° (*c*, 1·77 in water) (Found : C, 43·25; H, 5·4; OMe, 24·7. $C_9H_{14}O_8$ requires C, 43·2; H, 5·6; OMe, 24·8%).

Monomethylene Glucosaccharodiamide.—Monomethylene glucosaccharolactone ethyl ester (5 g.) dissolved immediately in concentrated aqueous ammonia (30 c.c.) and the *diamide* crystallised completely after 5 minutes. It was recrystallised from water. Yield, 4·5 g.; m. p. 235° (Found : C, 38·5; H, 5·6; N, 11·7. $C_7H_{12}O_6N_2$ requires C, 38·2; H, 5·5; N, 12·7%).

Conversion of Dimethyl Monomethylene Glucosaccharate into Monomethylene Glucosaccharolactone Methyl Ester.—The dimethyl ester was heated in an oil-bath at 175° for a few minutes. *Monomethylene glucosaccharolactone methyl ester* crystallised on cooling and trituration with acetone; after recrystallisation from water it melted at 214° (Found : C, 44·6; H, 4·7; OMe, 14·2. $C_8H_{10}O_7$ requires C, 44·1; H, 4·6; OMe, 14·2%).

Dimethyl Dimethylene Glucosaccharate.—Dimethyl monomethylene glucosaccharate (4·0 g.) was mixed with paraformaldehyde (3·0 g.), sulphuric acid (1·5 c.c.) added, and the mixture ground into a thick paste and kept at room temperature for 30 minutes. It was thereafter shaken with chloroform (40 c.c.) for 3 hours, the chloroform extract decanted, and the syrupy residue extracted three times with chloroform. Distillation of the combined extracts gave a solid residue, m. p. 157° after recrystallisation from methyl alcohol, which was identical with the dimethyl dimethylene glucosaccharate previously described.

A further quantity of the product was obtained by dissolving the chloroform-insoluble residues in a small volume of methyl alcohol and keeping the solution at 0°; the ester crystallised in long needles (2·3 g.) (Found : C, 45·8; H, 5·2; OMe, 23·8. Calc. for $C_{10}H_{14}O_8$: C, 45·8; H, 5·3; OMe, 23·6%).

Diethyl Monobenzylidene Glucosaccharate.—A mixture of the calcium chloride compound of diethyl glucosaccharate (Girard, *loc. cit.*) (5 g.) and zinc chloride (5 g.) was shaken with benzaldehyde (40 c.c.) for 12 hours, and the product then poured into light petroleum (b. p. 40—60°). The syrup which separated was washed with light petroleum, dissolved in ether, and washed with water until the aqueous extract gave no chloride reaction. The ethereal solution was dried, the ether removed, and the residue further extracted with light petroleum, which resulted in the crystallisation of the product. It was recrystallised from ether–methyl alcohol–light petroleum. Yield, 2·5 g.; m. p. 124°; $[\alpha]_D$ + 36·6° (*c*, 4·04 in chloroform) (Found : C, 57·6; H, 6·3; OEt, 24·3. $C_{17}H_{22}O_8$ requires C, 57·6; H, 5·9; OEt, 24·2%).

Diethyl Monoethylidene Glucosaccharate.—A mixture of the calcium chloride compound of diethyl glucosaccharate (6 g.) and zinc chloride (6 g.) was shaken with paraldehyde (25 c.c.) for 12 hours. A syrupy product separated, which was dissolved in chloroform, and zinc chloride and calcium chloride removed by repeated extraction with water. The chloroform solution was dried, and the chloroform distilled to leave a syrupy residue (3·1 g.), which distilled at 165° (bath temp.)/0·023 mm. The product was *diethyl monoethylidene glucosaccharate*, $n_D^{18^\circ}$ 1·4636 (Found : OEt, 30·2. $C_{12}H_{20}O_8$ requires OEt, 30·8%).

Monoethylidene Glucosaccharodiamide.—A solution of the preceding ester in dry methyl alcohol was saturated with dry ammonia at 0° and kept at 0° for some time; methyl alcohol was then distilled in a vacuum at room temperature, and the syrupy residue triturated with ether. The crystalline product was recrystallised from acetone–ether. Yield, 90%; m. p. 187° (Found : C, 41·7; H, 6·4. $C_8H_{14}O_6N_2$ requires C, 41·0; H, 6·0%).

Monoethylidene Glucosaccharolactone.—A solution of diethyl monoethylidene glucosaccharate (1·0 g.) in water (100 c.c.) was heated at 60° with hydrated barium hydroxide (1·2 g.) for 1 hour, and the barium completely precipitated with 0·1N-sulphuric acid. After filtration the solution was concentrated, the syrupy residue extracted with acetone, and the acetone distilled. The product crystallised on trituration with methyl alcohol and was recrystallised from acetone–ether. Yield, 0·4 g.; m. p. 213°; $[\alpha]_D^{18^\circ}$ − 5·3° (*c*, 1·31 in water) (Found : C, 44·3; H, 4·6. $C_8H_{10}O_7$ requires C, 44·0; H, 4·6%). The material behaved as a lactone acid on titration with 0·1N-caustic soda.

Diethyl Monoacetone Glucosaccharate.—The calcium chloride compound of diethyl glucosaccharate (6 g.) was shaken with acetone (30 c.c.) for 12 hours, a vigorous reaction occurring immediately. The solution was diluted with chloroform and extracted with water until the aqueous extracts no longer gave a chloride ion reaction. The chloroform solution was dried, and the chloroform distilled. The syrupy residue distilled at 150° (bath temp.)/0·005 mm. The product showed $n_D^{17^\circ}$ 1·4627; $[\alpha]_D$ + 21·5° (*c*, 3·904 in chloroform) and was *diethyl monoacetone glucosaccharate* (Found: OEt, 29·3. $C_{13}H_{22}O_8$ requires OEt, 29·4%).

Monoacetone Glucosaccharodiamide.—The preceding ester in methyl alcohol was treated with ammonia in the way described for the corresponding monoethylidene compound. The *diamide* was recrystallised from acetone–methyl alcohol–light petroleum and obtained in long needles, which lost solvent of crystallisation at 100° and melted at 184° (Found : C, 43·5; H, 6·45; N, 11·3. $C_9H_{16}O_6N_2$ requires C, 43·55; H, 6·45; N, 11·3%).

Dimethyl Monomethylene Monoethylidene Glucosaccharate.—A mixture of dimethyl monomethylene glucosaccharate (3 g.) and paraldehyde (50 c.c.) containing two drops of concentrated sulphuric acid was shaken for 12 hours. Solution of the ester gradually took place and an insoluble product separated. It was recrystallised from methyl alcohol and obtained in slender needles (1·98 g.), m. p. 153°, $[\alpha]_D$ + 25·5° (*c*, 2·04 in chloroform) (Found : C, 48·0; H, 5·9; OMe, 23·6. $C_{11}H_{16}O_8$ requires C, 47·8; H, 5·8; OMe, 22·4%).

The authors thank I.C.I. (Dyestuffs) Ltd. for a grant in support of this work.

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[*Received, November 2nd*, 1943.]