145. *Addition Compounds of the Carbohydrates. Part II. Potassium Hydroxide–Sucrose.*

By Edmund G. V. Percival.

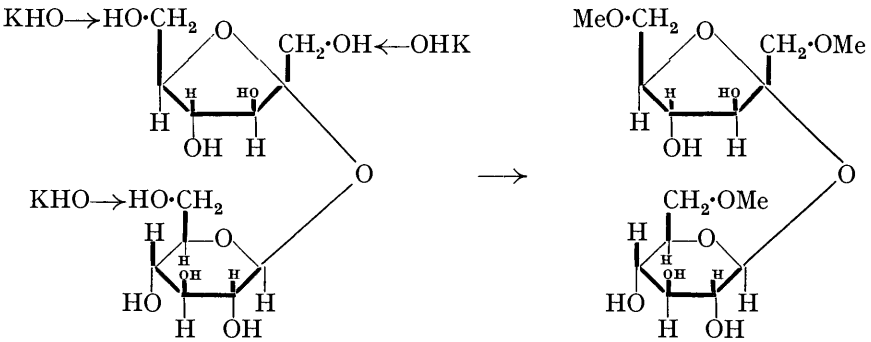
Sucrose forms a large number of compounds with metallic oxides and hydroxides, the compounds with strontium hydroxide indeed forming a basis of sugar refining. From a survey of the literature, it seems clear that, although various molecular proportions of metallic hydroxides may be associated with one molecule of sucrose, no trustworthy evidence exists pointing to the occurrence of compounds containing more than three molecules of the inorganic components as in $C_{12}H_{22}O_{11},3CaO,3H_2O$ (v. Lippmann, **1904**, " Chemie der Zuckerarten," 3 Aufl., 1338; Mackenzie and Quin, J., 1929, 951).

Physicochemical methods such as the phase-rule studies of Reinders and Klinkenberg (*Rec. trav. chim.*, 1929, **48**, 1227), the examination of the decline in specific rotation of sucrose solutions in the presence of alkali (Thomsen, *Ber.*, 1881, **14**, 1647), or the conductometric analyses of Hirsch and Schlags (*Z. physikal. Chem.*, 1929, *A*, **141**, 387) are valuable in indicating that compound formation between sucrose and alkalis does occur. The last authors point out that in aqueous solution sucrose behaves as a weak dibasic acid,

$K_1 = 3{\cdot}1 \times 10^{-13}$, $K_2 = 3{\cdot}0 \times 10^{-14}$ at 25°. It is significant that the second stage of ionisation is about twice as great as for glucose, which may account for the fact that the sucrose derivatives are more complex.

In Part I of this series (J., 1934, 1160) it was concluded that the probable formulation of compounds of this type was similar to that of the stable monohydrates of the alkali-metal hydroxides and involved co-ordination between the hydroxyl ion of the hydroxide and the most active hydrogen atoms of the sugar concerned, notably in the case of glucose the mobile hydrogen atom in the reducing group associated with the pyranoid ring formation.

The results of the present investigation are in harmony with these conclusions, although, in the absence of a reducing group, the primary alcoholic residues in sucrose appear to be the centres of acidity and each of the three appears to be associated with the potassium hydroxide in the compound $C_{12}H_{22}O_{11}$,3KOH studied. The basis of this conclusion rests on the isolation, on treatment with methyl sulphate under mild conditions, of a trimethyl sucrose in which the primary alcohol residues alone are substituted.



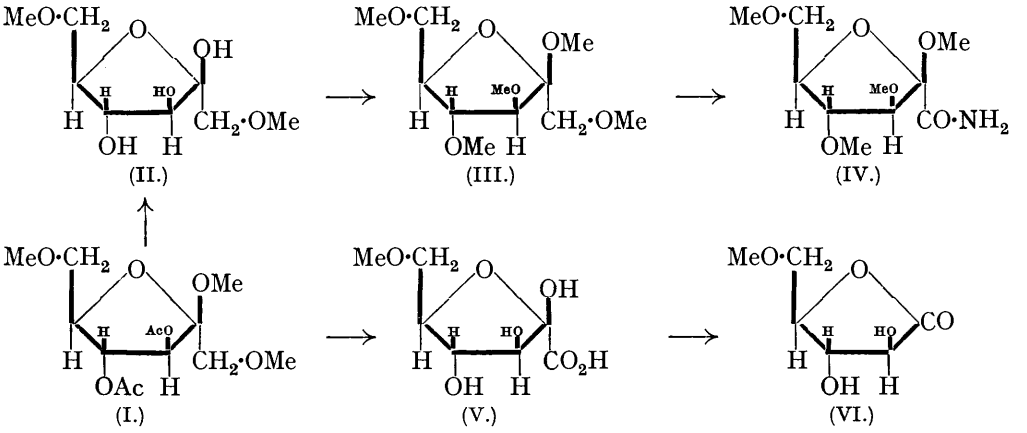
Addition compounds of sucrose and potassium hydroxide were prepared by the action of concentrated alcoholic potassium hydroxide both on sucrose octa-acetate and on an aqueous-alcoholic solution of the free sugar. By the indirect method of analysis (see Part I) it was established that three potassium hydroxide residues were the maximum number which one sucrose molecule would hold in combination, although in ordinary preparations, after washing with alcohol and ether, direct analysis revealed compositions ranging from $C_{12}H_{22}O_{11}$,KOH to $C_{12}H_{22}O_{11}$,3KOH, which explains the isolation by Pfeiffer and Tollens (*Annalen*, 1881, **210**, 296) of a monopotassium derivative after continued washing with alcohol. Whether the tripotassium compound is decomposed completely into the free sugar and potassium hydroxide in contact with alcohol or whether in contact with more dilute alkaline solutions only mono- and di-potassium hydroxide derivatives can exist is not clear, although the latter conclusion would seem more probable.

Products approximating in composition to $C_{12}H_{22}O_{11}$,3KOH were treated with methyl sulphate for a brief period and after removal of unchanged sucrose (90%), followed by acetylation, a glass was obtained which on analysis was shown to be a trimethyl penta-acetyl sucrose. Hydrolysis produced no optical inversion, so it was clear that the resulting methylated fructose was of the furanose type as in the case of the hydrolysis of octamethyl sucrose by Haworth and Law (J., 1916, **109**, 1314). By the formation of the furanosides, followed by acetylation and distillation in a high vacuum, it was found possible to separate these hydrolysis products into a methyl tetra-acetyl methylgluco-furanoside and a dimethyl triacetyl methylfructofuranoside.

The former after hydrolysis was recognised as a genuine derivative of glucopyranose, since methylation yielded 2 : 3 : 4 : 6-tetramethyl methylglucoside giving on hydrolysis crystalline 2 : 3 : 4 : 6-tetramethyl glucopyranose, and that the methyl group occupied the primary alcohol residue was proved by the isolation of crystalline 6-methyl glucose phenylosazone.

On account of the positive specific rotation of the dimethyl fructose (II) obtained on

hydrolysis of the fructofuranoside (I) it was suspected that a derivative of fructofuranose was concerned. This would imply the presence of one methoxyl group in the 6-position to prevent reversion to the more stable pyranose form. Complete methylation of (II) to a tetramethyl methylglycoside (III), followed by oxidation with nitric acid (Avery, Haworth, and Hirst, J., 1927, 2313), gave rise to a tetramethyl lactol acid which on appropriate treatment yielded crystalline 2 : 3 : 4 : 6-tetramethyl fructofuronamide (IV) identical with that obtained from tetramethyl fructofuranose, thus establishing the furanose ring and the participation of the primary alcohol residue at the 6-position in the original methylation.



It remained to indicate the position of the second methoxyl residue. Because the free dimethyl sugar failed to form an osazone, substitution in the 1-position was indicated, and this was confirmed as follows. By direct oxidation of the diacetyl dimethyl fructofuranoside under similar conditions to those employed for the tetramethyl derivative, a lactol acid was obtained (V) containing only one methoxyl residue. This was converted into the monomethyl arabonolactone (VI) by treatment with the calculated quantity of acid permanganate (Haworth and Learner, J., 1928, 619), and this lactone was found to have the properties of a γ-lactone, confirming the view that the terminal position is occupied. The position of the second methoxyl group in the dimethyl fructofuranose (II) on the secondary alcohol residues is obviously excluded, since only a monomethyl γ-arabonolactone resulted on oxidation (VI), the methyl group at the first carbon atom having disappeared on oxidation at that point.

Evidence is thus provided that the trimethyl sucrose obtained by direct methylation of $C_{12}H_{22}O_{11}$,3KOH is substituted only at the three primary alcohol groups present in the molecule. If, therefore, it is considered, as in Part I (*loc. cit.*), that the methyl groups have entered at the points of maximum acidity in the sucrose molecule, it is probable that these primary alcohol residues are involved in the addition compounds of sucrose with alkaline hydroxides. Since the association of sugar and alkali is an unstable one as indicated by the large amount of unconverted sucrose which is recovered from the methylation, there is no evidence that the compounds considered are substitution products, although Pfeiffer and Tollens (*loc. cit.*) described a monosodium derivative which was prepared in a similar manner to $C_{12}H_{21}O_{11}Na$ on the basis of a direct analysis. Their results are, however, just as readily interpreted on the theory of the formation of an addition compound.

Lest it should be considered that the methylation of addition compounds of the type under discussion is due merely to the presence of a certain amount of free potassium hydroxide which, reacting with methyl sulphate, makes possible a substitution in the sugar molecule concerned, although the points of maximum acidity might thereby be indicated, mixtures of dry, finely powdered potassium hydroxide and glucose in molecular proportion were subjected to the methylation process under the conditions used when treating the addition compounds. Careful study of the products of the reaction revealed that the highest yield of methylglucoside obtained by this method was never greater than 0·5%

of the weight of glucose taken, as compared with a conversion of 20% when the addition compound $C_6H_{12}O_6$,KOH was treated under the same conditions (Part I, *loc. cit.*).

Experimental.

Typical Preparations of Potassium Hydroxide–Sucrose.—(1) *From octa-acetyl sucrose.* Octa-acetyl sucrose (5 g.) was moistened with absolute alcohol (10 c.c.), and a solution of potassium hydroxide (10 g.) in alcohol (50 c.c.) added. After 2 hours, the insoluble product was filtered off, washed quickly with alcohol and ether, and dried in a vacuum over phosphoric oxide (Found: KOH, by titration with $N/10$-H_2SO_4 to phenolphthalein, 31·0. $C_{12}H_{22}O_{11}$,3KOH requires KOH, 32·9%).

(2) *From sucrose.* Sucrose (5 g.), dissolved in water (7 c.c.), was mixed with alcohol until the precipitation point was almost reached; alcoholic potassium hydroxide (50 c.c., 10%) was then rapidly added, and the precipitated derivative treated as in (1) (Found: KOH, 28·1%).

The Formation of Potassium Hydroxide–Sucrose under Different Conditions.—Some indication of the amounts of potassium hydroxide taken up by sucrose under various conditions was obtained as in Part I (*loc. cit.*). A known volume of a sucrose solution in 80% alcohol was treated with a definite volume of alcoholic potassium hydroxide solution of known strength. Removal of the precipitated compound by filtration through a Gooch crucible and titration of the equilibrium solution then indicated the quantity of alkali that had been removed by the sucrose. In the case of large excesses of sucrose relative to the amount of alcoholic potassium hydroxide solution, all the alkali was removed. Therefore the solubility of the addition compounds under the conditions studied was insufficient to affect the results appreciably. Typical results are as follows:

Total concn. of sucrose, %	1·2	1·25	2·1	4·0	4·5
Concn. of KOH, N { Initial	1·24	1·33	0·96	0·22	0·08
Concn. of KOH, N { Final	1·14	1·22	0·80	0·03	nil.
KOH combined, % { Method (1).....	46·8	49·3	42·7	26·6	10·0
KOH combined, % { ,, (2).....	45·0	45·0	40·8	20·5	10·5

The results are similar to those previously recorded in the case of maltose (see Part I), for, whilst in the more concentrated alkaline solutions the composition approximates to $C_{12}H_{22}O_{11}$,3KOH (100 g. of the disaccharide require 49·2 g. of potassium hydroxide), under less rigorous conditions $C_{12}H_{22}O_{11}$,2KOH and even $C_{12}H_{22}O_{11}$,KOH appear to exist, indicating the instability of the tripotassium derivative. It is at present impossible to decide by analytical methods whether decomposition to a mixture of sucrose and potassium hydroxide or to the lower types of addition compound takes place on washing with alcohol.

Potassium Hydroxide–Sucrose and Methyl Sulphate.—The dry compound (45 g.) prepared as in (2) was stirred with dry, neutral methyl sulphate (90 c.c.) for 10 minutes at 60° and for 5 minutes at 70—75°, at the end of which time the mass coagulated. At this point the flask was cooled, the liquid removed, and the product washed with acetone and dissolved in hot methyl alcohol (200 c.c.). On cooling, potassium methyl sulphate separated, which was filtered off, and excess of alcoholic potassium hydroxide was added, followed by ether (1000 c.c.). The potassium hydroxide derivative so isolated weighed 40 g.

Isolation of a Trimethyl Sucrose Penta-acetate.—After acidification with acetic acid and removal of the solvent, the syrup was acetylated by treatment for 2·5 hours with acetic anhydride (50 c.c.) and anhydrous sodium acetate (8 g.). The mixture was poured into water, neutralised by sodium bicarbonate, and extracted with chloroform. Removal of the solvent after drying with sodium sulphate yielded a non-reducing glass (4·8 g.). $[\alpha]_D^{20°} = +52°$ in acetone (*c*, 1) (Found: C, 50·3; H, 6·5; OMe, 15·4; CH_3·CO, 37·0. Calc. for $C_{25}H_{38}O_{16}$: C, 50·6; H, 6·4; OMe, 15·6; CH_3·CO, 36·2%).

Deacetylation and Hydrolysis of Trimethyl Sucrose Penta-acetate.—Deacetylation after Zemplén (*Ber.*, 1923, **56**, 1705) yielded a solution (60 c.c.), which was hydrolysed with oxalic acid (1 g.) at 90—100° until a constant rotation was reached (3 hours). $[\alpha]_D^{20°}$ approx. + 20° (*c*, 4). After neutralisation with calcium carbonate, filtration, and concentration, the syrupy mixture of methylated sugars showed $[\alpha]_D^{20°} = +19°$ in water (*c*, 1) [Found: OMe, 23·2. Calc. for $C_6H_{11}O_5(OMe) + C_6H_{10}O_4(OMe)_2$: OMe, 23·1%].

Alternative Method for isolating the Mixture of Methylated Sugars.—A more rapid method was used with success as follows. Following methylation of the dry potassium hydroxide derivative (70 g.) and the precipitation of the unchanged sucrose, the excess of potassium hydroxide was removed by the passage of carbon dioxide through the alcohol–ether solution. After removal of the precipitated potassium carbonate and evaporation of the solvent, a syrup (5 g.)

was obtained. Hydrolysis under the same conditions as before yielded the mixed methylated sugars. It was sometimes observed that, unless very large quantities of ether were employed to complete the precipitation of the potassium hydroxide addition compounds during the removal of unchanged sucrose, a small quantity of sucrose avoided precipitation, with the result that the syrup had a low methoxyl content (17%) and a low specific rotation after hydrolysis. This appeared to be due to the greater solubility of the derivatives in mixtures of methyl with ethyl alcohol. After hydrolysis, however, further treatment of the mixed sugars in ethyl-alcoholic solution with potassium hydroxide served to remove any glucose or fructose formed by the hydrolysis.

Separation of the Glucose and Fructose Fractions.—Mixtures of methylated sugars prepared as described above of methoxyl content 23% (5 g.) were dissolved in dry methyl alcohol containing hydrogen chloride (0·5 g.) and kept at 15° for 48 hours. Acid was removed with barium carbonate and after filtration the solution was evaporated. Acetylation was carried out by dissolving the product in pyridine (20 c.c.) and treating the solution with a mixture of pyridine (25 c.c.) and acetic anhydride (25 c.c.) at 70° for 20 minutes, followed by standing at 15° for 2 days. The solution was poured into water and extracted with chloroform, from which dissolved pyridine was removed by washing with dilute sulphuric acid. After removal of solvent the syrup (6·5 g.) was subjected to distillation under 0·03 mm. pressure: (1) 2·1 g. (bath temp. 145—160°), $n_D^{20°}$ 1·4470; (2) 0·5 g. (bath temp. 160—170°), $n_D^{20°}$ 1·4475; (3) 2·0 g. (bath temp. 170—180°), $n_D^{20°}$ 1·4510; (4) 0·3 g. (bath temp. 170—200°), $n_D^{16°}$ 1·4550; residue 1·7 g. Redistillation of fractions (1) and (2) appeared to yield a homogeneous product, practically the whole distilling at a bath temp. of 146°/0·04 mm.; $n_D^{18°}$ 1·4475, $[\alpha]_D^{21°}$ +24° in chloroform (*c*, 1) (Found: OMe, 30·6; CH_3·CO, 28·4. Calc. for $C_{13}H_{22}O_8$: OMe, 30·4; CH_3·CO, 28·1%). The compound would thus appear to be a dimethyl methylglycoside diacetate. On the other hand, fraction (3) showed $[\alpha]_D^{21°}$ + 33·0° in chloroform (*c*, 1·5) (Found: OMe, 19·0; CH_3·CO, 38·9. Calc. for $C_{14}H_{22}O_9$: OMe, 18·6; CH_3·CO, 38·6%). This was evidently a monomethyl glycoside triacetate.

Identification of the Fraction of High Methoxyl Content as a Derivative of 1 : 6-*Fructofuranose.*—1·0 G. was deacetylated according to Zemplén (*loc. cit.*) and this was followed by hydrolysis in contact with *N*/10-sulphuric acid for 2 hours at 90°, during which period the rotation only fell slightly but the solution rapidly became strongly reducing. No crystalline osazone could be isolated on heating with phenylhydrazine and acetic acid in the usual manner. Two methylations with methyl sulphate (10 c.c.) and sodium hydroxide (25 c.c., 30%) (Haworth, J., 1915, **107**, 8) followed and the full methoxyl content was introduced by one treatment with methyl iodide (25 c.c.) and silver oxide (4 g.) at 43° during 6 hours. After being worked up in the usual way, the product was distilled and yielded 0·6 g. of a fraction at a bath temp. of 100°/0·03 mm., $n_D^{15°}$ 1·4430, and having all the properties of tetramethyl methylfructofuranoside. This derivative was characterised by its conversion into crystalline 2 : 3 : 4 : 6-tetramethyl fructofuronamide by direct oxidation with nitric acid. The fructofuranoside (0·4 g.) was treated with nitric acid (3 c.c., *d* 1·42) for 90 minutes at 70—90°. When all action had ceased, an excess of water was added and continuous distillation with the addition of water was carried out during 6 hours. The residue was dried with benzene and esterified with methyl-alcoholic hydrogen chloride (20 c.c., 3%) for 3·5 hours. The solution was neutralised with silver oxide and after filtration and removal of the solvent was methylated with silver oxide and methyl iodide. Distillation from a bath at 135°/0·03 mm. yielded a non-reducing ester (0·3 g.), $n_D^{18°}$ 1·4430, which was converted into the amide by contact for 3 days with methyl-alcoholic ammonia. On removal of solvent the characteristic long needles appeared of the 2 : 3 : 4 : 6-tetramethyl fructofuronamide (0·2 g.) described by Avery, Haworth, and Hirst (J., 1927, 2313). $[\alpha]_D^{20°}$ − 81° in water (*c*, 0·5), m. p. 100—101° alone or in admixture with a specimen prepared directly from tetramethyl fructofuranose (Found: OMe, 48·1; N, 5·6. Calc. for $C_{10}H_{19}O_6N$: OMe, 49·8; N, 5·6%).

Direct Oxidation of the Diacetyl Dimethyl Methylfructofuranoside.—A second portion (1·4 g.) was oxidised with nitric acid (5 c.c., *d* 1·42) for 2 hours at 70—95° and the excess of nitric acid was removed by continuous distillation with the addition of water for 24 hours. The reducing syrup obtained appeared to be the monomethyl analogue of the trimethyl lactol acid described above (Found: OMe, 14·4. Calc. for $C_7H_{12}O_7$: OMe, 14·9%).

Oxidation of the Monomethyl Lactol Acid.—A solution of the above syrup in water was acidified with *N*-sulphuric acid (11 c.c.), and the volume made up to 40 c.c. by the addition of water. This solution was titrated with 6·7 c.c. of *N*-barium permanganate. Excess of barium hydroxide was added and after some hours this was neutralised with carbon dioxide.

Filtration yielded a solution, which was evaporated (diminished pressure) to yield a barium salt (0·8 g.) [Found: OMe, 11·1; Ba, 30·3. Calc. for $(C_6H_{11}O_6)_2Ba$: OMe, 12·5; Ba, 27·7%].

Isolation of 5-Methyl γ-Arabonolactone.—Barium was removed by the addition of the calculated quantity of *N*/10-sulphuric acid and the aqueous solution was evaporated under diminished pressure to yield a glass (0·5 g.), which was heated at 90—100° for some hours (Found: C, 44·0; H, 6·4; OMe, 19·3. Calc. for $C_6H_{10}O_5$: C, 44·4; H, 6·2; OMe, 19·1%). It showed $[\alpha]_D^{18°}$ + 40° (30 mins.); + 35° (1 day); + 31° (2 days); + 29° (8 days); + 27° (17 days, constant value); in water (*c*, 0·4). This slow hydrolysis is in harmony with the presence of a γ-lactone.

Identification of the Fraction of Low Methoxyl Content as a Derivative of 6-Methyl Glucose.—A portion of the fraction showing $n_D^{20°}$ 1·4510 (0·7 g.) was hydrolysed with *N*/6-sulphuric acid for 2 hours after deacetylation by the method of Zemplén (*loc. cit.*). Neutralisation with barium carbonate, filtration, concentration, and acetylation with pyridine and acetic anhydride yielded a syrup, which, dissolved in acetic acid (1 c.c.), was converted into the acetobromo-compound by contact for 2 hours with acetic acid saturated with hydrogen bromide (1·2 c.c.). The product was mixed with chloroform, and the chloroform solution washed with water and sodium bicarbonate solution, dried, and concentrated to a syrup under diminished pressure. Solution in dry methyl alcohol, followed by shaking with dry silver carbonate for 24 hours, gave rise to a non-reducing syrup, which failed to crystallise, $[\alpha]_D^{18°}$ + 73° in chloroform (*c*, 2·2) (Found: OMe, 17·4. Calc. for $C_{14}H_{22}O_9$: OMe, 18·6%). Nucleation with a specimen of 4-methyl 2 : 3 : 6-triacetyl β-methylglucoside failed to induce crystallisation.

Isolation of 2 : 3 : 4 : 6-Tetramethyl Glucopyranose.—This syrup was methylated once with methyl sulphate (30 c.c.) and sodium hydroxide (70 c.c. of 30%) in the usual way, followed by treatment with silver oxide (5 g.) and methyl iodide (20 c.c.). The syrup obtained was distilled under 0·03 mm. from a bath at 100° and had all the properties of tetramethyl methylglucopyranoside. By hydrolysis for 8 hours with hydrochloric acid (5%), neutralisation with barium carbonate, concentration, and extraction with ether, crystalline 2 : 3 : 4 : 6-tetramethyl glucopyranose was obtained, m. p. 82·3° alone or in admixture with an authentic specimen. $[\alpha]_D^{18°}$ + 83° (equil.) in water (*c*, 0·6) (Found: OMe, 51·8. Calc. for $C_{10}H_{20}O_6$: OMe, 52·5%).

The Reaction with Phenylhydrazine and the Isolation of 6-Methyl Glucosazone.—The remainder of the glucose fraction (1·0 g.) was deacetylated and hydrolysed as above to yield the syrupy monomethyl glucose. It was attempted to prepare 2-methyl glucose phenylhydrazone by the method of Brigl and Schinle (*Ber.*, 1929, **62**, 1716). The product, dissolved in methyl alcohol (1 c.c.), was treated with phenylhydrazine (0·6 c.c.) and a drop of glacial acetic acid at 15° for 24 hours. Removal of solvent in a vacuum, followed by nucleation with authentic 2-methyl glucose phenylhydrazone, gave rise to no crystals. A further quantity of phenylhydrazine (2 c.c.), acetic acid (3·0 c.c.), sodium acetate (10 g.), and water (30 c.c.) were added together with sodium bisulphite (1·0 g.). This mixture was heated for 3 hours at 90—100°; on cooling, an osazone separated, which was removed. A further quantity was precipitated on dilution, followed by further heating (8 hours). Total yield of crude product (0·5 g.) (cf. Helferich and Günther, *Ber.*, 1931, **64**, 1276). Several recrystallisations from aqueous pyridine raised the m. p. from 172° to 183—186°, the osazone when pure appearing in pale yellow needles. The m. p. showed no depression in admixture with a specimen of 6-methyl glucosazone prepared by the method of Helferich and Günther (*loc. cit.*), but with 3-methyl glucosazone (m. p. 179°) the m. p. was depressed to 163°. $[\alpha]_D^{20°}$ − 69° in ethyl alcohol (*c*, 0·4) (Found: OMe, 8·1; N, 14·75. Calc. for $C_{19}H_{24}O_4N_4$: OMe, 8·3; N, 15·0%). The properties were thus in accord with those of 6-methyl glucosazone.

The Reaction of a Mixture of Glucose and Potassium Hydroxide with Methyl Sulphate.—Glucose (10 g.) and powdered potassium hydroxide (3 g.) which had been dried in a vacuum over phosphoric oxide were mixed with dry neutral methyl sulphate (50 c.c.) and stirred at 45° (5 mins.) and 70° (5 mins.). After the separation of the excess of glucose and acetylation (see Part I, *loc. cit.*) a syrupy acetate (0·3 g.) was obtained which was still reducing (Found: OMe, 3·0%, corresponding to 0·05 g. of methylglucoside). This was the highest yield obtained in three experiments.

Thanks are expressed to Professor W. N. Haworth, F.R.S., and Dr. E. L. Hirst, F.R.S., for the gift of specimens of a number of the reference compounds used in this investigation and to the Earl of Moray Endowment for a grant in aid of these researches.

KING'S BUILDINGS, UNIVERSITY OF EDINBURGH. [*Received, March 19th*, 1935.]