LXV. — *Partially Methylated Glucoses. Part II.*
βγ-Dimethyl α-Glucose and βγ-Dimethyl β-Glucose.

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IN continuation of the work described in the preceding paper, we have applied similar principles to introduce two methyl groups into glucose so as to give a reducing sugar. For the preparation of a dimethyl glucose of this nature, two of the hydroxyl groups in glucose, in addition to the reducing group, must be protected from methylation by the introduction of hydrolysable residues. Few substances of this type are available, but we have found that the benzylidene α -methylglucoside described by Alberda van Ekenstein (*Rec. trav. chim.*, 1906, **25**, 153) is well adapted for the purpose.

It will afterwards be shown that the most probable structure for the latter compound is that given below:

According to this view of the constitution, the formation of the compound involves the introduction of a new asymmetric system into the molecule, and thus benzaldehyde should condense with α -methylglucoside so as to produce two isomeric products. This possibility seems to have been overlooked by Alberda van Ekenstein, but has been referred to by Fischer (*Ber.*, 1894, **27**, 1524). We have succeeded in isolating the hitherto unknown isomeride by cautious crystallisation of the accumulated mother liquors obtained in large scale preparations of the condensation compound. The new stereoisomeride crystallises in short prisms, melting at 148—149°, and shows $[\alpha]_D + 96.0^\circ$ in aqueous solution. This compound, which is produced in very small amount, is regarded as $\epsilon\zeta$ -*d*-benzylidene α -methyl-*d*-glucoside.

The methylation of $\epsilon\zeta$ -*l*-benzylidene α -methylglucoside was carried out by the silver oxide reaction. No other process is, in fact, available, as the compound is exceedingly easily hydrolysed by acids, and also to some extent by alkalis. The alkylation proceeded with unusual smoothness. The product, which was readily obtained in the crystalline state, melted at 122—123°, and showed $[\alpha]_D + 97.03^\circ$ in acetone solution.

It was possible, by carefully regulated hydrolysis, to remove the aromatic residue without affecting the glucosidic group, the product of this reaction being β -dimethyl α -methylglucoside, which was isolated in the usual manner. The alkylated glucoside melted at 80—82°, and showed practically the same specific rotation (142.6°) in aqueous and in acetone solution. When boiled with dilute hydrochloric acid, the glucosidic group was removed with the formation of dimethyl glucose, which was isolated in the form of a crystalline solid. After crystallisation from ethyl acetate, the sugar separated in well-developed prisms, which gave satisfactory analytical figures, but which melted very indefinitely. This behaviour was shown to be due to the presence of the stereoisomeric α - and β -forms, both of which were ultimately isolated.

When the crystallisation from ethyl acetate was carried out from solutions containing not more than 5 per cent. of the solute, the sugar separated in clusters of delicate, pointed prisms. This proved to be the pure β -form (m. p. 108—110°), and thus showed upward mutarotation when dissolved in water, alcohol, or acetone. The details of these optical changes are given in the experimental part. The sugar exhibited suspended mutarotation in acetone solution, and it was therefore possible to obtain an exact record of the whole range of the change in this solvent.

The α -form of the sugar crystallised, along with the β -isomeride, from solutions in ethyl acetate containing from 7 to 10 per cent. of the solute. Separation of the two varieties was, however, best effected by cautious precipitation, from the equilibrium solution in alcohol, by the gradual addition of ether. The first crops to separate consisted, as before, of the β -form, but, from the mother liquors, the α -isomeride (m. p. 85—87°) was deposited in warty aggregates of microscopic prisms. This form showed extensive downward mutarotation in acetone solution.

Dimethyl glucose is thus well adapted for the study of mutarotation, as both stereoisomeric forms are available, and the ready solubility of the sugar, in solvents in which the change is slow, permits of the initial values being determined with much greater accuracy than in the case of an unsubstituted sugar.

Discussion of Optical Results.

The specific rotations of dimethyl glucose and its derivatives are only very slightly affected by the nature of the solvent employed. This is seen from the examples quoted below:

Solvent.	$\beta\gamma$ -Dimethyl β -Glucose.	$\beta\gamma$ -Dimethyl α -Methylglucoside.
Water.....	+ 5.7°	+ 142.64°
Alcohol	5.7	143.08
Acetone	5.9	143.49

In this respect the compound resembles tetramethyl glucose, but the uniformity of the rotations in the different solvents is here even more marked. The nature of the solvent has, however, in the case of dimethyl glucose, a pronounced effect in altering the proportions of the mutarotatory α - and β -forms which exist in equilibrium in solution. Thus, the equilibrium mixture in aqueous solution contains 77 per cent. of the α -form and 23 per cent. of the β -isomeride. In acetone solution, on the other hand, the proportions are altered to 59 and 41 per cent. respectively.

Owing to the facility with which the true initial specific rotations of the α - and β -forms of dimethyl glucose may be determined in acetone solution, the compound is a convenient one for testing the application of Hudson's rule (see preceding paper). The choice of acetone as a solvent for this purpose was determined by the facts, mentioned above, that the specific rotation of the sugar is practically unaffected by the nature of the solvent, and that the compound shows suspended mutarotation in this solvent. With regard to the accuracy of the optical values which we ascribe to the α - and β -forms, there is little doubt that the latter isomeride was obtained in a pure condition, unmixed with the α -form. On the other hand, the experimental difficulties encountered in isolating the α -form were very great, and there is thus a possibility that the recorded specific rotation is lower than the true maximum. The discrepancy is, however, probably small.

Applying Hudson's principle, that the proportion of the molecular rotation of a sugar contributed respectively by the reducing group and the remainder of the molecule may be represented by A and B , the following equations are derived:

$$\begin{array}{ll} \beta\gamma\text{-Dimethyl } \alpha\text{-glucose.....} & [M]_D = 17041 = + A + B \\ \beta\gamma\text{-Dimethyl } \beta\text{-glucose} & [M]_D = 1227 = - A + B \end{array}$$

The sum of the molecular rotations ($2B$) thus equals 18268, and the difference ($2A$) equals 15814. The particular case now under consideration resembles that of monomethyl glucose, in that the value of $2B$ should differ from that determined for glucose, whilst,

if Hudson's rule applies to substituted sugars, 2A should be a constant irrespective of the methylation of the non-reducing hydroxyl groups. These values are compared below:

	Sum of Molecular Rotations (2B).	Difference of Molecular Rotations (2A).
Glucose.....	23040	16200
Dimethyl glucose..	18268	15814

It will thus be seen that the value actually found for 2A differs only by slightly over 2 per cent. from that calculated according to Hudson's method. Taking into consideration the fact that extreme accuracy cannot be claimed for the specific rotation of the α -form, the conclusion may reasonably be drawn that the generalisation is supported by this result. An alteration of the initial rotation of α -dimethyl glucose from $[\alpha]_D + 81.93^\circ$ to 83.80° would, in fact, give the calculated value (16200) for 2A.

It may be mentioned that Hudson's method of calculation does not seem applicable to the case of the α - and β -forms of benzylidene methylglucoside, where the difference (2A) should equal that calculated from the activities of the methylglucosides. The values actually found are, however, far apart.

	Sum (2B).	Difference (2A).
Methylglucosides	24371	36729
Benzylidene methylglucosides	2820	45120

The introduction of the new asymmetric ring system into the molecule seems to exclude the application of Hudson's rule, but a definite decision on this point must be withheld until both stereoisomeric forms of benzylidene β -methylglucoside have been isolated. From the comparatively small difference in rotation shown by *d*- and *l*-benzylidene α -methylglucoside, it is, however, most unlikely that any agreement will be found.

Constitution of Dimethyl Glucose.

Considerable difficulty was experienced in determining the constitution of the sugar, as there are six possible isomeric dimethyl glucoses possessing reducing properties, and each should exist in two stereoisomeric modifications. Experimental methods for determining the position of substituting groups in the sugar molecule are far from satisfactory, but the bulk of the evidence points to the following structure as the most probable:

As the compound is a reducing sugar and shows mutarotation, no methyl groups can be attached to the carbon atoms indexed α and δ . The sugar, moreover, formed no osazone, but a dimethyl glucosylphenylhydrazone was produced under conditions favourable to osazone formation. One methyl group must therefore be attached in position β . The allocation of the remaining methyl group can only be arrived at indirectly by consideration of the possible structures for benzylidene methylglucoside. From the evidence quoted above, the possible formulæ for this substance are limited to three, of which the two most probable are the following:

(I).

(II.)

The remaining possibility, in which the benzylidene residue couples the carbon atoms γ and ζ , may be reasonably left out of consideration, as it includes a seven-membered ring. Comparing the two structures shown above, it will be seen that the formation of a substance possessing formula II would not only involve the production of a six-membered ring, but the condensation of the benzaldehyde would in such case take place with hydroxyl groups situated in the *trans*-position with reference to the plane of the γ -oxidic ring.* Arguments have already been given (T., 1910, 97, 1277) to show that this stereochemical arrangement results in considerable molecular strain, and is unlikely to occur when more stable positions are available for condensation. On the other hand, the hydroxyl groups attached to the carbon atoms ϵ and ζ are in the most favourable position for ring formation, and consequently we have selected formula I as the most suitable. This conclusion receives strong support from the following considerations. In methylglucoside, methylmannoside, and methylgalactoside, the same number of hydroxyl groups are in each case available for condensation with benzaldehyde, but their stereochemical arrangement is different:

* See footnote to title of preceding paper, p. 564.

In methylmannoside, the pairs of hydroxyl groups attached to the carbon atoms β , γ , and ϵ , ζ , are in the most suitable position for ring formation admitted by the configuration. In methylglucoside and methylgalactoside, this is only true of the pair ϵ , ζ . It can scarcely be a mere coincidence that methylmannoside readily forms both a mono- and a di-benzylidene compound, whilst methylglucoside and methylgalactoside, irrespective of the conditions of the reaction, give only monobenzylidene derivatives.

We thus conclude that in benzylidene methylglucoside, positions ϵ and ζ are protected from methylation, and that the methyl groups in dimethyl glucose occupy positions β and γ . This structure is in strict agreement with all the properties of the sugar, including its behaviour towards phenylhydrazine. The above considerations, which indicate that the condensation reactions of all the hydroxyl groups in sugars and glucosides are controlled by stereochemical arrangement, are capable of considerable application, and work in this direction is being continued.

EXPERIMENTAL.

Preparation of $\epsilon\zeta$ -1-Benzylidene α -Methylglucoside.

Methylglucoside was condensed with benzaldehyde by the process described by Alberda van Ekenstein (*loc. cit.*). It is, however, quite unnecessary to use sodium sulphate in the reaction, or to take any other precaution to remove the water formed in the condensation; the benzaldehyde used should be very carefully fractionated. The best yields were obtained when the glucoside (50 grams) was finely powdered and sifted through muslin, mixed with a large excess of the aldehyde (300 c.c.), and heated for three hours at 145° . Thereafter, the temperature was maintained at 160° for nine hours. The product was precipitated by the addition of light petroleum, and crystallised from hot water. Yield = 25 per cent. of the glucoside used.

Isolation of $\epsilon\zeta$ -d-Benzylidene α -Methylglucoside.

In the course of several consecutive preparations of benzylidene methylglucoside, the crude product was precipitated as usual by the addition of light petroleum to the solution in benzaldehyde. The united mother liquors were put aside for several hours, when a small second crop of crystals was gradually deposited. On recrystallising this product from hot water, it was at once seen that the material did not consist of Alberda van Ekenstein's compound, as the latter separates in long, flexible needles, which form on the surface of the solution. In this case, the product crystallised on the bottom of the basin in small, warty aggregates of stout prisms, which were analysed after a second crystallisation:

Found, C=59.35; H=6.54; OMe=11.6.

$C_{13}H_{15}O_5(OMe)$ requires C=59.55; H=6.38; OMe=11.0 per cent.

The constants of the two isomerides are compared below:

Alberda van Ekenstein's Compound.

l-Benzylidene α -Methyl-*d*-glucoside.

M. p. 161–162°

$[\alpha]_D^{50} + 85.0^\circ$

Crystalline form: needles.

Less soluble form.

New Isomeride.

d-Benzylidene α -Methyl-*d*-glucoside.

148–149°

+ 96.01°

prisms.

More soluble form.

Methylation of l-Benzylidene α -Methylglucoside.

The material used in the alkylation was the isomeride melting at 161–162°. A solution of 30 grams of the benzylidene compound (1 mol.), in 80 c.c. of acetone, was mixed with 150 grams of methyl iodide (10 mols.), and 123 grams of silver oxide (5 mols.) were gradually added. The reaction was completed by heating on a water-bath for six hours. Next morning, large crystals of the product, measuring several centimetres, were found imbedded in the silver iodide. These were readily soluble in boiling acetone, and crystallised from the solution on concentration and cooling. After recrystallisation from light petroleum, the pure compound weighed 32.5 grams, so that the yield was practically quantitative:

Found, C=61.93; H=7.21; OMe=28.2.

$C_{13}H_{13}O_3(OMe)_3$ requires C=61.93; H=7.10; OMe=30.0 per cent.

$\epsilon\zeta$ -Benzylidene $\beta\gamma$ -dimethyl α -methylglucoside crystallises in prisms, melting at 122–123°. It is very sparingly soluble in water, but is readily dissolved by organic solvents.

Solvent: acetone; $c=1.640$; $[\alpha]_D^{20} + 97.03^\circ$.

Partial Hydrolysis of Benzylidene Dimethyl Methylglucoside.

A 10 per cent. solution of the above compound in 1 per cent. aqueous hydrochloric acid was heated, with frequent shaking, at 95° for one hour. The reaction was conducted under a condenser, through which a current of carbon dioxide was passed. The benzaldehyde formed was removed by extraction with ether, the aqueous liquor neutralised with barium carbonate, and the filtrate evaporated to dryness at 45°/15 mm. The residue was then extracted with acetone, and the filtrate concentrated to a syrup, which solidified on cooling. Purification of the crude product was effected by several recrystallisations from benzene, a large excess of the solvent being employed. During the purification, an oil separated in the first instance from the dilute benzene solution; this was allowed to settle, after which the decanted solution was concentrated to the crystallising point. Throughout these operations moisture must be rigidly excluded until all hygroscopic by-products have been eliminated. Thirteen grams of pure dimethyl methylglucoside, melting at 80—82°, were thus obtained from 20 grams of benzylidene dimethyl methylglucoside:

Found: C=48·46; H=8·26; OMe=39·8.

$C_6H_9O_3(OMe)_3$ requires C=48·65; H=8·11; OMe=41·9 per cent.

$\beta\gamma$ -Dimethyl α -methylglucoside is readily soluble in water and organic solvents generally, sparingly so in ether or benzene, insoluble in hydrocarbon solvents. The compound reduced Fehling's solution only after hydrolysis, and displayed no mutarotation in solution:

Solvent.	c.	l.	α^{20° .	$[\alpha]_D^{20^\circ}$.
Water.....	5·08	1	+7·25	+142·64°
Ethyl alcohol..	5·07	1	7·26	143·08
Acetone	4·25	2	12·21	143·49

Hydrolysis of $\beta\gamma$ -Dimethyl α -Methylglucoside.

The conversion into dimethyl glucose was carried out by boiling a solution of dimethyl methylglucoside, in 10 per cent. hydrochloric acid, for twenty minutes under a condenser. During the hydrolysis, the specific rotation altered from 142·4° to the constant value +58·5°, and recalculation of the latter figure for the concentration of dimethyl glucose formed on hydrolysis gives +62·4°. This agrees with the equilibrium value subsequently found for the sugar, so that the reaction is quantitative.

After removal of the acid with barium carbonate, evaporation to dryness at 45°/15 mm., extraction with boiling acetone and concentration, a syrup was obtained which gradually deposited a

crop of minute prisms. The bulk of the sugar was, however, only obtained in the crystalline state after removal of the acetone and drying of the residue at 60°/15 mm. until constant in weight. Thereafter the compound was crystallised several times from dry ethyl acetate. Yield=63 per cent. of the weight of glucoside used:

Found, C=46.19; H=7.83; OMe=30.2.

$C_6H_{10}O_4(OMe)_2$ requires C=46.15; H=7.69; OMe=29.8 per cent.

By the process described above, dimethyl glucose was obtained in the form of minute prisms readily soluble in water, the lower alcohols, and acetone, sparingly soluble in ethyl acetate, insoluble in ether or hydrocarbon solvents. The melting point observed was very indefinite (70—105°), and this behaviour was shown to be due to the presence of the stereoisomeric α - and β -forms.

β -Dimethyl β -Glucose.

When the mixture of the α - and β -isomerides was crystallised from solutions in ethyl acetate containing from 10 to 20 per cent. of the solute, the sugar separated in brittle, warty aggregates. The initial specific rotations of successive crops varied from +29° to 58°, and the melting points similarly ranged from 80° to 104°. No separation of the two forms could thus be carried out.

On the other hand, crystallisation from a dilute solution in ethyl acetate (not more than 5 per cent.) gave a crop of pointed prisms which showed a tendency to arrange themselves in clusters. With a solution of intermediate concentration (about 7 per cent.), the crop consisted partly of the prisms referred to above, and partly of opaque, spherical aggregates, which were easily distinguished from the prismatic crystals, and could be mechanically separated from them.

The prisms proved to be the β -form of the sugar, and the spherical aggregates the α -isomeride, but only the former could be obtained in quantity by crystallisation from ethyl acetate. In preparing the material used in the rotations, the concentration of the solution was limited to 5 per cent., and the uniformity of each crystalline crop was confirmed by microscopic examination. The β -isomeride thus isolated was practically pure, but melted indefinitely at about 100°. The final purification consisted in preparing a 30 per cent. solution of the sugar in anhydrous alcohol, and precipitating the dissolved material in two crops by the addition of dry ether. The first portion to separate melted at 108—110°, and consisted of the pure β -form.

Mutarotation of $\beta\gamma$ -Dimethyl β -Glucose.

Solvent.	c.	l.	Initial α^{20° .	Final α .	Initial $[\alpha]_D$.	Final $[\alpha]_D$.
Water.....	5.00	1	+0.53° $\rightarrow$	+3.22°	+10.60 $\rightarrow$	+64.4°
Alcohol.....	5.02	2	0.57 $\rightarrow$	4.96	5.68 $\rightarrow$	49.41
Acetone.....	3.84	2	0.50 $\rightarrow$	3.91	6.52 $\rightarrow$	50.9

The speed with which equilibrium was attained in the three solvents differed in a marked degree. Thus, the aqueous solution assumed a constant rotation in about six hours. On the other hand, in alcoholic solution the change was exceedingly slow, while in acetone the sugar showed suspended mutarotation. In one experiment, in which anhydrous acetone, freshly prepared from the bisulphite compound, was used as a solvent, the alteration in specific rotation observed in fifteen days was only +6.5° $\rightarrow$ +8.2°. The permanent value of +49° was, however, reached in a few minutes on the addition of a catalyst. In each case, the curves representing the rotation changes were plotted, and, by extrapolation, the following initial values were indicated:

Solvent.	Water.	Alcohol.	Acetone.
$[\alpha]_D^{20^\circ}$	+5.7°	+5.68°	+5.9°

In the case of the alcoholic and acetone solutions, these values are, of course, very little removed from those determined experimentally.

 $\beta\gamma$ -Dimethyl α -Glucose.

Nuclei of dimethyl α -glucose were obtained, as described, by crystallisation of the equilibrium mixture of the sugar from 7 per cent. solutions in ethyl acetate. These nuclei proved of service in the following preparation of the α -form of the sugar. A 30 per cent. solution of dimethyl β -glucose in ethyl alcohol was heated at 100° for thirty minutes so as to establish equilibrium. Sufficient dry ether was then added to precipitate about one-half of the dissolved material in the first crop. This fraction was essentially the pure β -form. The filtrate was further diluted with ether, nucleated with the α -isomeride, and preserved in a freezing mixture for two days, when a second crop, consisting of the α -form, gradually separated. A third crop, which on microscopic examination appeared to be free from the prismatic β -form, was obtained on similarly nucleating the mother liquor.

$\beta\gamma$ -Dimethyl α -glucose crystallises in dense spherical aggregates, which are quite opaque, so that no exact description of the crystalline form can be given. The crystals melted at 85–87°, and the compound showed downward mutarotation. Owing to the laborious nature of the separation of this isomeride, very little pure

material was obtained, and the mutarotation was only determined in acetone solution, so as to obtain an accurate value for the initial point. The change thus observed, for $c=1$, was $+81.93^\circ \rightarrow 48.3^\circ$.

Proportion of α - and β -Forms present in Equilibrium in Solution.

The necessary data for the above calculation are only available where acetone was used as the solvent.

$$\begin{array}{l} \text{Initial } [\alpha]_D \text{ for } \alpha\text{-form} = +81.93^\circ \\ \text{,, ,, } \beta\text{-form} = +5.90^\circ \end{array} \quad \text{Equilibrium } [\alpha]_D = +50.9^\circ.$$

From these results, it will be seen that the equilibrium mixture contains 59 per cent. of the α -form and 41 per cent. of the β -isomeride. Owing to lack of material, the rotation of the α -form was not taken in aqueous solution, but it may be reasonably assumed that it does not differ notably from the value found in acetone solution. This is justified by the practical coincidence of the initial specific rotations of the β -form in these solvents, as determined by extrapolation. Further, the activity of dimethyl methylglucoside, which is an α -form, is likewise unaffected by the nature of the solvent. The data for the calculation thus becomes:

$$\begin{array}{l} \text{Initial } [\alpha]_D \text{ for } \alpha\text{-form} = +81.93^\circ \\ \text{,, ,, } \beta\text{-form} = +5.7^\circ \end{array} \quad \text{Equilibrium } [\alpha]_D = +34.4^\circ.$$

This corresponds with a mixture consisting of 77 per cent. of the α -form and 23 per cent. of the β -modification, values which are widely different from those found in the case of glucose.

Effect of Heat in Altering the Equilibrium.

On recovering the sugar from an aqueous solution, which had attained equilibrium, by evaporation of the solvent at $30^\circ/12$ mm., the product showed practically no mutarotation. The equilibrium thus appears to be only slightly affected by change of concentration. A specimen of the sugar, isolated in the manner described above, was kept in the fused condition at 120° for an hour, after which, on dissolving the product in water, extensive upward mutarotation was observed. This treatment is known to alter equilibria in methylated sugars in the direction $\alpha \rightarrow \beta$, and the result thus justifies the stereochemical nomenclature we have applied to the two forms of this sugar.

$\beta\gamma$ -Dimethyl Glucosephenylhydrazone.

Several attempts were made to prepare an osazone from dimethyl glucose, but, although the process was modified in various ways, no sparingly soluble product was obtained, and the sugar was resinified.

Condensation with phenylhydrazine was, however, effected under the following conditions. A solution of the sugar (1 mol.), in an equal weight of water, was mixed with phenylhydrazine (3 mols.), and after thorough mixing, the liquid was preserved in the dark for six weeks in a sealed tube. A homogeneous syrup was thus obtained, which was dissolved in ether, the solution shaken successively with dilute acetic acid and water, dried over sodium sulphate, and evaporated. This treatment removed excess of the base, together with any free sugar. The product was a pale yellow syrup, which crystallised completely on keeping. No suitable recrystallising medium could be found, and the compound, which possessed the usual properties of a hydrazone, was analysed after heating gently in a vacuum until constant in weight:

Found, $N=9.80$.

$C_{14}H_{22}O_5N_2$ requires $N=9.40$ per cent.

This nitrogen content is in itself sufficient proof that the compound is a hydrazone, and not an osazone. In a duplicate experiment, in which glucose was used, the sugar was completely converted into glucosphenylosazone.

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