

CIX.—*The Stereoisomeric Tetramethyl Methylglucosides and Tetramethyl Glucose.*

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WE have shown in a former communication (Trans., 1903, 83, 1021) that a dextrorotatory liquid pentamethylated glucose is obtained by methylating α -methylglucoside with methyl iodide and silver oxide. As the compound had no action on Fehling's solution, and on being hydrolysed gave a tetramethyl glucose which possessed the characteristic properties of a reducing sugar, it was evidently a tetramethyl ether of α -methylglucoside. By remethylating the tetramethyl glucose with methyl iodide and silver oxide, a levorotatory, crystalline pentamethyl glucose (m. p. 42—43°) was obtained, but, on account of the

small quantity of material available for examination, it remained uncertain whether this substance was the stereoisomeride of the liquid compound referred to, that is to say, tetramethyl β -methylglucoside, or the pentamethyl glucose of aldehydic structure.

The present research was undertaken with the object of deciding this point, and also of supplementing our previous observations on the optical activity of tetramethyl glucose. This compound, as stated, was found to possess the ordinary properties of an aldose. It was without doubt an etheric derivative of glucose, and its solutions, like those of glucose and aldoses in general, should therefore exhibit multirotation, but this phenomenon, however, could not be detected. As the total lack of this property in a compound of its class seemed very improbable, we thought it necessary to repeat and extend our observations on the rotatory power of the substance.

We find that the crystalline pentamethyl glucose is, as we surmised (*loc. cit.*), tetramethyl β -methylglucoside. The substance crystallises readily on nucleating the crude, syrupy product of the methylation of tetramethyl glucose by the silver oxide method, previous purification by distillation being unnecessary. When this method of alkylation is applied to glucose, the sugar undergoes extensive oxidation, but the methylated glucose resists entirely the oxidising action of the silver oxide. The identification of the crystalline pentamethyl glucose as tetramethyl β -methylglucoside is based on the fact that it behaves like a glucoside towards Fehling's solution, and on its ready hydrolysis by dilute acids, with the production of the same tetramethyl glucose which is obtained by the hydrolysis of the α -glucoside. The relation of the tetramethyl α - and β -methylglucosides with respect to rotatory power is the same as that of the corresponding methylglucosides, the α -compound being dextro-, the β -compound laevo-rotatory; the specific rotations of the former in water were found to be $+147.4^\circ$ and -11.6° ,* those of the latter being $+157.5^\circ$ and -31.85° respectively. The means of these values, namely, 67.9° and 62.83° , do not differ very much. The two compounds, like other stereoisomeric glucosides, are also characterised by their behaviour towards emulsin, the β -glucoside being readily hydrolysed by the enzyme, whilst the α -isomeride is little, if at all, affected even after prolonged heating. Further, we find that in the methylation of tetramethyl glucose by the silver oxide method, the liquid α -glucoside is produced simultaneously with the crystalline β -compound. We were unable to isolate the former in the pure state, as it retains a large proportion of the latter in solution, and only a partial separation is effected by distillation. The evidence

* This observation was made in alcoholic solution, but we have reason to believe that the rotatory power in water has nearly the same value.

for the presence of the α -glucoside in this uncrystallisable mixture is detailed in the experimental part.

The unalkylated hydroxyl group of tetramethyl glucose being in the γ -position, and the compound able, therefore, to assume the tautomeric γ -oxido-forms, methylation should be possible not only by the silver oxide method, but also by Fischer's method (*Ber.*, 1895, 28, 1145) by heating with a dilute solution of hydrogen chloride in methyl alcohol. Tetramethyl glucose is, in fact, methylated by this process more readily than glucose, the action being easily completed at 40°, and here, as in the other method of alkylation, both the isomeric glucosides are produced simultaneously. It is, however, worthy of notice that by the silver oxide process the β -glucoside is produced in notably larger proportion than the α -glucoside. The former compound was produced in such large excess by this method that it crystallised at once from the syrupy product of the action, whilst in the case of Fischer's method it was obtained after fractional distillation of the product, and then only in small quantity. Polarimetric observations showed that the product of the former process contained at least 70 per cent. of the β -compound, the product of the latter process being 53 per cent. at most. These facts supply a fresh instance of the familiar phenomenon that the alkylation of a tautomeric substance by a method depending on the agency of a silver compound usually differs in its result from other methods of alkylation. The explanation in the present case may be that the β -form of the aldose is of a more acid nature than its isomeride, and more readily gives the unstable silver derivative on the intermediate formation of which the reaction probably depends.

The methylation of glucose by the hydrochloric acid method, like that of tetramethyl glucose by the same method, appears to favour the production of the α -glucoside (compare Fischer, *loc. cit.*). W. A. van Ekenstein (*Rec. trav. chim.*, 1894, 13, 183—186) found that the glucosides were produced in about equal proportions, but Jungius (*Proc. K. Acad. Wetensch. Amsterdam*, 1903, 6, 99) states that the mixture of methylglucosides obtained by the action of methyl alcohol containing hydrogen chloride on either glucoside contains 77 per cent. of the α -form. The tetramethyl methylglucosides, however, are not so readily interconvertible. On heating the α -compound at 40° for 60 hours in methyl alcohol containing 0.25 per cent. of hydrogen chloride under conditions which suffice for the formation of the glucosides from tetramethyl glucose, no fall of rotatory power was observed, and the conversion into the β -compound, therefore, did not occur.

The tetramethyl methylglucosides show a marked difference in their rates of hydrolysis by dilute hydrochloric acid. Parallel experiments,

in which the progress of the action was ascertained by polarimetric observations, showed that 92 per cent. of the β -glucoside, but only 74 per cent. of the α -compound, was hydrolysed in one hour. The rotatory power of tetramethyl glucose is intermediate with those of the glucosides. As the β -glucoside hydrolyses more rapidly than the α -isomeride, it follows that, during the hydrolysis of a mixture of the two isomerides such as was obtained in the methylation of the aldose, the rotatory power should at first rise above the value for the hydrolysis product, tetramethyl glucose, and finally fall to the value of this compound; this was found to be the case. Tetramethyl β -methylgalactoside, as shown in the succeeding paper, is also more rapidly hydrolysed than the α -isomeride.

Multirotation of Tetramethyl Glucose.

As already mentioned, we detected no distinct signs of multirotation in the course of our previous observations on the rotatory power of tetramethyl glucose. On closer examination, we find that the compound does possess the property in question, and that the phenomena exhibited are in every way comparable with those presented by glucose and other reducing sugars. The substance is capable of assuming three forms corresponding closely in their mutual relations with the three forms of glucose first recognised by Tanret, and designated by him α -, β -, and γ -glucoses.

Of the various theories advanced in explanation of the phenomena of multirotation, as displayed in the sugar group, that of Lowry (Trans., 1899, 75, 213), which attributes the rise or fall of rotatory power to reversible isomeric change, is best in agreement with experimental fact. According to Lowry, Tanret's α - and γ -forms are dynamic isomerides, and the β -form, which is stable in solution, is a mixture of these in equilibrium. It is only recently, however, that definite evidence has been obtained regarding the structure of the isodynamic forms concerned in the phenomena, which makes it possible to formulate the theory more precisely. Fischer's opinion (*Ber.*, 1893, 26, 2403) that the isomerism of the α - and β -glucosides and allied series of derivatives is stereochemical and that the compounds have the constitution of γ -oxides may now be accepted as finally established. E. F. Armstrong (Trans., 1903, 83, 1306) has given an excellent summary of the evidence which supports the view, and to this may be added the experimental evidence for the γ -oxido-structure furnished by us in the study of the tetramethyl methylglucosides (Trans., 1903, 83, 1027). If, as is generally supposed, the lactones of aldonic acids are γ -lactones, then tetramethyl gluconolactone is a γ -lactone, and from this it follows necessarily that tetramethyl

methylglucoside and the parent methylglucoside also possess the γ -oxygen linking.

Armstrong's experiments on the hydrolysis of α - and β -methylglucosides (*loc. cit.*) show conclusively that the products of the action are Tanret's α - and γ -glucoses respectively, and furnish strong evidence for the view that these forms of the sugar have the glucosidic structure and bear the same stereoisomeric relation to each other as the corresponding glucosides. They are therefore more appropriately named α - and β -glucoses, and, according to Lowry, it is the establishment of equilibrium by reversible isomeric change between these labile forms which occasions the phenomena of multirotation. The results of Armstrong's hydrolytic experiments have quite recently found happy confirmation in evidence of a synthetical kind furnished by Behrend and Roth (*Annalen*, 1904, 331, 359), which correlates the isodynamic α - and β -glucoses with the α - and β -penta-acetates. On acetylating glucose in pyridine solution at 0°, they find that α -glucose yields the α -penta-acetate in preponderating quantity, whilst the glucose of permanent rotatory power gives a mixture of the acetates from which the less soluble β -penta-acetate alone could be isolated. The yield of this compound was less than that of the α -isomeride in the previous experiment, and the conclusion is drawn that the glucose of permanent rotatory power is probably a mixture of the α - and β -forms.

The reversible change, α -glucose \rightleftharpoons β -glucose, implies an interchange of the positions of attachment of hydrogen and hydroxyl radicles, and as the view prevails that this cannot occur directly, the interchange has been supposed to be brought about by the breaking of the oxide ring and the subsequent formation of the aldehyde or its hydrate. It is quite possible that the aldehyde plays a part in the establishment of the equilibrium, but the presence of its hydrate as an agent in the process is precluded by the fact recorded below, that anhydrous tetramethyl glucose exhibits all the phenomena of multirotation in organic solvents. Another explanation of the mechanism of the reversible isomeric change in question, advanced by E. F. Armstrong (*loc. cit.*), seems also to be excluded for the same reason.

In describing our observations on the multirotation of tetramethyl glucose, we adopt Lowry's theory provisionally, and assume therefore that the modification of the sugar, which shows a permanent rotatory power, is an equilibrium mixture of the oxide α - and β -forms (Tanret's α - and γ -forms).

Pure tetramethyl α -glucose was obtained from the crude product of the hydrolysis of the α -glucoside by repeated crystallisation from light petroleum containing a very little ether. The product, after one crystallisation from this solvent, is white and crystalline and presents

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all the appearance of a homogeneous substance. Its low and indefinite melting point ($76-80^{\circ}$) and its low initial rotatory power (90.6°) indicate, however, that it is a mixture in varying proportions of the α - and β -forms. With repeated crystallisation, the melting point gradually rises, and finally becomes constant at $88-89^{\circ}$. The initial specific rotatory power in aqueous solution also rises, as the β -form is eliminated, until it attains the value $+100.8^{\circ}$, which is therefore regarded as the specific rotatory power of the α -isomeride; when this solution is allowed to remain, the rotatory power gradually falls, until after 24 hours it reaches the permanent value $+83.3^{\circ}$. The equilibrium mixture of α - and β -forms, now contained in the solution, can be obtained in the crystalline state, with but little alteration in the proportion of the constituents, by evaporation on a water-bath. Prolonged heating of the residual syrup must be avoided, as this transforms the α - into the β -form, and the final drying is conducted under diminished pressure at the ordinary temperature until a constant weight is recorded. The melting point of the substance so obtained is no longer that of the pure α -form, but is again low and indefinite ($75-80^{\circ}$), and when redissolved in water the initial rotation is only slightly higher than the permanent value already quoted, which is soon reached. By repeated crystallisation from light petroleum, the pure α -form is again obtained. The production of the pure α -form from the mixture by crystallisation is apparently due to the transformation of the β - into the α -form, and not merely to its elimination from the mixture by solution. This is shown by the fact that in purifying the original crude compound, whilst the first crystallisation certainly removes a little syrupy matter, in subsequent recrystallisations, although the indefinite melting point and low rotatory power may still betray the presence of the β -form, the mother liquors contain only traces of dissolved matter.

Tetramethyl β -glucose, or more correctly a mixture of this with the α -form, containing a larger proportion of the former than exists in the equilibrium-mixture, is produced when the α -form or this mixture is heated for some time above the melting point and then quickly cooled (compare Lowry, *Proc.*, 1904, 20, 108). A crystalline specimen prepared in this way showed in aqueous solution initially the specific rotation $+73.1^{\circ}$, which gradually rose, until after 18 hours it reached $+83.1^{\circ}$, this being practically the same permanent value as that attained by solutions of the α -form.

Our previous failure in detecting the multirotation of tetramethyl glucose is no doubt attributable to the specimens examined having been distilled and afterwards crystallised only once or twice from light petroleum. The distillation increases the quantity of the β -form, and the subsequent crystallisation was probably only sufficient to

reduce this to the proportion contained in the stable mixture which shows no multirotation.

Excepting Behrend and Roth's recent observations (*loc. cit.*) on pyridine solutions of glucose, the investigation of the rotatory powers of sugars has been hitherto unavoidably confined to aqueous or alcoholic solutions. Owing, however, to the extreme solubility of tetramethyl glucose, we have been able to examine its rotatory power not only in alcohol, but also in non-ionising solvents such as benzene and carbon tetrachloride. Multirotation occurs in each of these solvents, and the changes of rotatory power are in every case in the same sense as in water, the α -glucose showing a fall, the β -glucose, prepared as above, a rise of dextrorotation to a permanent value; the range of the change is also much the same as in water, but the rate is much slower. The observations made in these solvents dispose of all the theories of multirotation which are based on the supposed formation of hydrates or compounds of the acetal class. They also show that ionisation is not essential to its occurrence. The addition of a trace of alcoholic ammonia hastens the change greatly, but our experiments do not suffice to decide whether it ceases to occur in the entire absence of catalytic impurities (compare Lowry, *Trans.*, 1903, 83, 1320).

The rotatory power of ordinary glucose varies greatly according as the solvent is water, methyl alcohol, or pyridine. It is worthy of note that, in the case of tetramethyl glucose, the permanent rotation in alcohol, benzene, toluene, and carbon tetrachloride is approximately the same as in water, and that even the initial rotations in the different solvents do not differ much. The following permanent rotations were found in the solvents mentioned: water, $+83.3^\circ$; ethyl alcohol, 83.1° ; benzene, 84.6° ; toluene, 84.1° ; carbon tetrachloride, 81.6° . The specific rotation of the α -form in benzene (111.1°) is somewhat higher than that found in water (100.8°), but the real difference is less than these numbers indicate, as the rotatory power of the aqueous solution must undergo a fall of several degrees before the observation can be made. The initial specific rotation of the mixture containing an excess of the β -form, obtained by heating the substance at $115-120^\circ$, was 73.1° in water, 73.5° in ethyl alcohol, and 76.3° in benzene. It may be concluded, therefore, that the nature of the solvent has only a slight effect on the permanent state of equilibrium of the isodynamic forms in the solvents mentioned. This result is at variance with the well-known fact that the nature of the solvent has, in general, a marked effect on the composition of the equilibrium-mixtures of dynamic isomerides.

The similarity in the values of the permanent specific rotations in water and in benzene are all the more striking considering that the substance has the normal molecular weight in the former solvent, and

consists of associated double molecules in the latter. Molecular association appears in fact to have no connection with rotatory power (compare Patterson, *Trans.*, 1901, 79, 184; 1902, 81, 1111; also *Trans.*, 1901, 79, 978).

When glucose is crystallised from moderately concentrated solutions in water or alcohol, it is the α -form which is deposited. Similarly, when tetramethyl glucose is crystallised from light petroleum, in which the substance is not very soluble, it separates in the α -form. When, on the other hand, it is quickly recovered by evaporation under diminished pressure at the ordinary temperature from solution in a solvent such as benzene, which can be almost entirely removed before crystallisation sets in, the solid mixture so obtained contains the isodynamic forms in nearly the same proportion as that in which they existed in the solution.

The rotatory power of a solution of the equilibrium mixture, which had been recovered from benzene solution, was found to be much lower in methyl iodide than in the other solvents used, but the observations recorded in the experimental part tend to show that, despite the different rotatory power, the isodynamic forms are here present in the same proportion as in other solutions which have attained the stable state.

Relative Stability of the α - and β -forms of Tetramethyl Glucose.

As tetramethyl α -glucose melts sharply at 88–89°, it may be concluded that the velocity of the isomeric transformation is slow in the immediate neighbourhood of the melting point, and that the α -modification is therefore the stable form at this temperature.

It is also the stable form at lower temperatures, as the change $\beta \rightarrow \alpha$ occurs spontaneously in the solid state. This was proved by the following experiments. A dry, crystalline specimen of the mixture of the two forms, which exhibits at once the permanent specific rotatory power (83.3°), was prepared from an aqueous solution by the method already described, and was heated in a stoppered tube for 50 hours at 50–60°, a temperature about 15° short of the melting point. After this treatment, a 4 per cent. aqueous solution of the substance showed initially the specific rotation +94.7°, falling in 12 hours to 84.8°, approximately the permanent value. A portion of the β -form originally present, therefore, had passed while in the solid state into the α -form. The same transformation takes place at the ordinary temperature. A crystalline mixture containing the β -form in greater proportion than it exists in the equilibrium mixture in solution was prepared, as already indicated, by melting the α -modification (m. p. 87–88°) and keeping it for two hours in the fused state at 120°. The solidified

product now melted indefinitely at a temperature ($51-56^\circ$) still lower than the melting point of the equilibrium-mixture, and a 5 per cent. solution of it in benzene gave the initial specific rotation as 76.3° . A large proportion of the α -form had therefore been converted by the fusion into the β -form. The remaining portion of this specimen was kept in a stoppered tube at the ordinary temperature for 12 days. The melting point of the substance was now found to have risen to about 77° , and in a 4 per cent. benzene solution it showed the initial specific rotation 87.6° . So much of the β -form had passed spontaneously in the solid state into the α -form, that the proportion of the latter now present exceeded the proportion which exists in the mixture of permanent rotatory power. This was confirmed by adding a trace of alcoholic ammonia and letting the solution remain some time, after which the specific rotation was found to have fallen to 83.4° .

At temperatures below the melting point, therefore, the non-reversible change $\beta \rightarrow \alpha$ occurs. The observations on the multirotation of solutions of the fused substance, quoted above, show that at temperatures above the melting point the reverse change sets in, but the final product in this case must necessarily be a mixture of the two forms in equilibrium. A change in the same sense is produced by fusion in the case of glucose, and Tanret (*Bull. Soc. chim.*, 1895, [iii], 13, 733) prepared pure β -glucose (his γ -glucose) by dissolving the mixtures obtained in this manner in water, and then adding alcohol, which caused the deposition of the less soluble β -form. This method is inapplicable in the case of tetramethyl glucose on account of the great solubility of both its forms, and we have not succeeded therefore, in isolating the β -modification in the pure state. Its rotatory power being thus unknown, it is not possible to calculate the composition of mixtures of the two forms.

Tanret examined a series of mixtures of α - and β -glucoses, obtained by allowing fused α -glucose to crystallise at definite temperatures between 75° and 97° , and found that the rotatory powers of the crystalline mixtures decreased from 84° to 39.6° as the temperature of crystallisation rose. From this it is legitimate to conclude that the proportion of β -glucose in the fused mixture increases with the temperature between the limits given. Our observations on the effect of temperature on the equilibrium of the α - and β -forms in fused tetramethyl glucose are not extensive enough to enable one to draw exact conclusions, but they indicate that, whilst at temperatures a little higher than the melting point of the α -form the transformation $\alpha \rightarrow \beta$ proceeds rapidly, at higher temperatures it nearly ceases. The experiments were made by observing the rotatory powers of the three mixtures obtained from the α -form by keeping it in a fused state for two hours at 100° , 120° , and 140° respectively. In each case, the fused mass was solidified by rapid

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cooling and the rotatory power examined at once in about a 5 per cent. benzene solution. The initial specific rotations were respectively $+77.5^\circ$, 76.3° , and 76.6° . It seems probable from these observations that the fused substance at 120° consists mainly of the β -form, and that the rotatory power of this form lies not very far below the values quoted; much higher, therefore, than that of β -glucose, which is $+22.5^\circ$. If it is admissible to assume that the state of equilibrium of the α - and β -forms in aqueous solution is the same for glucose as for its tetramethyl derivative, then, calculating from the known rotatory powers of the compounds, the value 73.5° is obtained for tetramethyl β -glucose.

| | α -Form. | Equilibrium mixture. | β -Form. |
|---------------------------|-----------------|----------------------|----------------|
| Glucose | $+106^\circ$ | 52.5° | 22.5° |
| Tetramethyl glucose | 100.8 | 83.3 | 73.5 |

The real specific rotatory power of tetramethyl α -glucose in water is doubtless some degrees higher than the recorded value, 100.8° , owing to the fall which necessarily occurs before the observation can be taken; this implies that the calculated value for the β -form is somewhat less than the figure quoted. As already stated, the initial specific rotatory power found for an aqueous solution of the fused aldose was 73.1° .

EXPERIMENTAL.

Preparation of Tetramethyl α -Methylglucoside and Tetramethyl Glucose.

Tetramethyl α -methylglucoside was prepared as before (*loc. cit.*) by the methylation of α -methylglucoside by means of dry silver oxide and methyl iodide. A partial alkylation was in the first place carried out in methyl alcoholic solution, and after removal of water and alcohol from the product by heating under diminished pressure, the process was completed in methyl iodide solution. Methylglucoside is more soluble in a mixture of methyl alcohol and the methylated product of the action than in the pure alcohol; accordingly it was found that, by adding not only the oxide and iodide but also the glucoside in successive small instalments, the quantity of solvent alcohol could be much reduced. By this modification of the process, some economy in alkylating material was effected, and the yield of completely methylated glucoside was increased to nearly the calculated quantity. Despite the reduced quantity of methyl alcohol present, however, a large part of the alkylating agent was lost owing to the production of dimethyl ether, and a large excess of the mixture therefore had still to be used. Employing 60 grams of Kahlbaum's methylglucoside (1 mol.), 200 c.c. of methyl alcohol, 680 grams of silver oxide (about 9.5 mols.),

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and 900 grams of methyl iodide, we obtained, after fractional distillation, 75.5 grams of the tetramethylated glucoside boiling at 145—152° under 13 mm. pressure, of which 62.5 grams passed over at 148—150°. The molecular weight of the compound was determined, as this had not been done previously. The value found in aqueous solution by the cryoscopic method was 223.4, the calculated number being 250. As the determinations of specific rotatory power previously made (*loc. cit.*, pp. 1031, 1039) on different specimens of the substance were not concordant, the observations were repeated on the present preparation with the following results. A 2-dm. tube was used for the solutions and a 1-dm. tube for the pure liquid.

| | <i>p.</i> | $d_{20}^{20}/4^{\circ}$. | $\alpha_D^{20^{\circ}}$. | $[\alpha]_D^{20^{\circ}}$. |
|----------------------|-----------|---------------------------|---------------------------|-----------------------------|
| In ethyl alcohol ... | 12.345 | 0.8201 | + 31.17° | + 153.9° |
| In water | 10.024 | 1.0131 | 29.94 | 147.4 |
| Pure liquid | | 1.1082 | 171.10 | 154.4 |

The specific rotation in alcoholic solution approximates to the highest value previously found, namely, 152.6°; as before, the specific rotation of the pure liquid is nearly the same as that of the alcoholic solution, and a few degrees higher than that of the aqueous solution. The preparation being on a larger scale than formerly, more complete fractionation of the distillate was possible, and we regard the constants now given, including the density of the pure liquid, as more accurate than those recorded in our previous paper.

We have to thank Mr. J. C. Bagot for a determination of the refractive index of the compound. The value at 20°, $\mu_D = 1.4464$, approaches closely to that of chloroform.

In our former hydrolyses of the glucoside, the yield of crystalline tetramethyl glucose amounted to only 35 per cent. of the weight of substance taken. If the hydrochloric acid used is too dilute or if the heating is insufficient, the hydrolysis is incomplete, and the unaltered syrupy glucoside prevents crystallisation. If, on the other hand, the hydrolysis is pushed too far, some of the methylated glucose is apparently affected by the prolonged action of the acid, with a similar effect on the yield of crystalline product. By the following modification of the process, the yield of crystallised tetramethyl glucose was raised to 67 per cent. of the weight of glucoside taken. From 7 to 8 grams of glucoside are dissolved in 100 c.c. of about 8 per cent. hydrochloric acid, and the flask containing the solution is heated in boiling water. The progress of the hydrolysis is best followed by frequent polarimetric observations, and the heating is continued just until the observed rotation becomes nearly constant, which occurs in about 3½ hours. The solution, which is usually only slightly coloured, is then neutralised with barium carbonate, filtered, and evaporated to

dryness on a water-bath. The ethereal extract of the residue, after being dried with sodium sulphate and evaporated, gives a syrup which crystallises readily on being nucleated with tetramethyl glucose. A considerable quantity of the syrup, however, fails to crystallise even after a long time, and this has to be removed by spreading the product on a porous tile. The syrup, which is extracted from the tile with ether, gives a further crop of crystals, and the drying on a tile and subsequent extraction of the oil with ether has to be repeated several times in order to obtain the full yield of material. Part of the alkylated sugar may be obtained in a readily crystallisable condition from the neutralised solution of the hydrolysis product by direct extraction with ether in Hagemann's apparatus. Although this method was not found helpful in increasing the yield, it is useful in separating the substance from the gummy by-products which result when the hydrolysis is continued too long.

The melting point of tetramethyl glucose was previously recorded as 81—83°, and in the case of a specimen prepared from cane-sugar as 83—84°. We find that by recrystallisation from light petroleum containing a very little ether the melting point gradually rises, but after five or six crystallisations becomes sharp and constant at 88—89°. This change is due, as explained in the introduction, to the conversion of the α - into the β -form of the sugar.

Determinations of molecular weight were made in water and in benzene, and the values found were respectively 222 and 475, the calculated value being 236. The substance therefore has the normal molecular weight in water, but is associated in double molecules in benzene.

Tetramethyl glucose differs materially from glucose and other reducing sugars with respect to its cupric-reducing power. The oxidising action of the copper solution is not so vigorous, and as the following quantitative determinations show, it does not proceed so far as in the case of unalkylated sugars. When the substance is heated at 100° with Fehling's solution, very little cuprous oxide is produced, and the solution must be boiled before vigorous reduction occurs. The reducing power is nearly exhausted after 10 minutes, but, despite the presence of unreduced copper in the solution, the latter still remains of a dark brown colour, and on more prolonged boiling continues to deposit minute quantities of cuprous oxide. This behaviour applies also to tetramethyl galactose and is probably characteristic of alkylated sugars in general. The quantitative determination of the reducing power was carried out according to O'Sullivan's method (Trans., 1896, 69, 1692), but, for the reasons explained, the Fehling's solution containing the sugar was boiled for 10 minutes instead of being merely heated in boiling water.

I. 0.3120 gave 0.1280 Cu_2O . II. 0.3482 gave 0.1438 Cu_2O . Mean: 0.3301 gave 0.1359 Cu_2O . This weight of cuprous oxide corresponds with 0.0615 gram of glucose, and the reducing power of tetramethyl glucose is therefore only 18.6 per cent. of that of glucose.

Tetramethyl β -Methylglucoside.

Preparation by the Silver Oxide Process.—The compound was prepared in the first instance by the method described in our previous paper, namely, by the action of silver oxide and methyl iodide on tetramethyl glucose. The proportion of materials used and the process in other respects were the same as before, but distillation was avoided, as it was found that the liquid product crystallised readily when it was nucleated with the specimen of the substance previously obtained. The β -glucoside was then deposited in delicate needles over an inch in length, and these were separated from adherent liquor by absorbing the latter in a porous tile. The total product from 5 grams of tetramethyl glucose amounted to 5 grams, whilst the crystals (m. p. 30—35°) weighed 1.85 grams. The examination of the uncrystallisable part, which consisted of a mixture of the isomeric glucosides, is described below.

The crystals proved to be so soluble in all the ordinary solvents that it was impossible to recrystallise them in the usual manner; by evaporating an alcoholic solution under diminished pressure, however, until nearly all the solvent was evaporated, the substance solidified as a fine crystalline meal from which the adherent mother liquor was effectually removed by means of a porous tile. The crystals then melted at 40—42°, a result agreeing closely with the melting point formerly recorded, namely, 42—43°. The substance showed only a very faint action on Fehling's solution after boiling for 5 minutes, and this proved to be due to the presence of a trace of some impurity, as after distillation the compound had no reducing action whatever. The l avorotatory power of the compound was confirmed, but the specific rotation in about a 5 per cent. alcoholic solution, $[\alpha]_D^{20} - 11.6^\circ$, was less than the previously recorded value, namely, -13.99° .

The hydrolysis of the β -glucoside by dilute hydrochloric acid was carried out under the same conditions as that of its liquid isomeride, and the product was isolated in the same manner. The solution at the outset contained 1.483 grams of the glucoside in 20 c.c., and the observed rotation in a 2-dcm. tube was -1.56° . The solution in the course of hydrolysis became quickly dextrorotatory, and after 2 hours the observed rotation became constant at $+11.47^\circ$. The final observed rotation calculated on the assumption that the whole of the substance used was converted into tetramethyl glucose ($[\alpha]_D^{20} + 83.3^\circ$) should be

11.7°, so that the hydrolysis was complete and was not accompanied by other changes.

The syrup obtained from the hydrolysis solidified at once to a hard, crystalline mass readily recognisable as tetramethyl glucose. The weight of the recrystallised substance was 1.04 grams, equal to 74 per cent. of the calculated yield; its melting point was 87–88°, and its permanent specific rotatory power in aqueous solution ($c=4.804$) was $[\alpha]_D^{20} + 82.8^\circ$. The compound was not further purified, but the constants quoted are in agreement with the values found for the tetramethyl glucose produced by the hydrolysis of the α -glucoside, namely, 88–89° and $+83.3^\circ$.

It was to be expected that in alkylating tetramethyl glucose both the stereoisomeric glucosides would be produced. The uncrystallisable part of the product of alkylation therefore consisted presumably of the liquid α -glucoside with a considerable proportion of the dissolved β -isomeride, and it was accordingly examined with the object of proving the presence of the former compound. The uncrystallisable syrup in question, when recovered by extraction with ether from the tile in which it was absorbed, weighed 2.76 grams. It was neutral towards litmus and had no action on Fehling's solution until it was hydrolysed; it was therefore of a glucosidic nature.

As the β -glucoside boils some 20° lower than its isomeride, the liquid was distilled with the view of further eliminating the former compound from the mixture. The more volatile fraction, weighing 1 gram (b. p. 120–125° under 7 mm. pressure), deposited a small additional quantity of the crystalline β -glucoside, whilst the rest of the distillate, collected at 125–130°, remained liquid and had the composition of the glucosides. The results of analysis were C=52.53, H=8.75, the calculated numbers being 52.80 and 8.80 respectively. The view that we were thus dealing with a mixture of the two isomerides was further confirmed by polarimetric observations, and by the result of a quantitative hydrolysis of the liquid. The specific rotatory powers of the α - and β -glucosides in alcoholic solution are $+153.9^\circ$ and -11.6° respectively; the specific rotatory power of the supposed mixture before distillation was found to be, under similar conditions, $+72.9^\circ$, and that of the less volatile fraction obtained from it was $+81.2^\circ$. The mixture before distillation and the less volatile fraction obtained from the distillation contained, therefore, about 51 and 56 per cent. of the α -isomeride respectively. Further separation being found impossible, the mixture was hydrolysed. The hydrolysis was carried out under the same conditions and simultaneously with that of the pure β -glucoside described above, the concentration being nearly the same, namely, 1.498 grams in 20 c.c. The observed rotation became constant after heating for 3 hours, and was then

+5.85° ($l=1$). The rotation, calculated on the assumption that the whole of the original material used was glucosidic and was converted completely by the hydrolysis into tetramethyl glucose, should be 5.89°. The product was isolated, as already described, and was found to be nearly pure tetramethyl glucose. The melting point, 87—88°, the permanent rotatory power in a 5 per cent. aqueous solution, $[\alpha]_D^{20} +82.8^\circ$, and the yield of 1.06 grams were identical with the results of the parallel hydrolysis of the pure β -glucoside. A further proof of the presence of the α -glucoside in the mixture was furnished by the remarkable rise and final fall of rotatory power which occurred during the progress of the hydrolysis; this is alluded to below in connection with the relative rates of hydrolysis of the two glucosides.

We conclude that the product of the alkylation of tetramethyl glucose by means of silver oxide and methyl iodide is a mixture of the two glucosides, and that if the isomeric pentamethylated aldehyde is produced at all in the reaction, it can only be in small quantity. It is evident, also, that the β -glucoside is produced in this reaction in much larger proportion than the α -isomeride. The weight of the former obtained in the crystalline state was 1.85 grams; the weight of the uncrystallisable mixture was 2.76 grams, about one-half of which, as already stated, consisted of the β -glucoside. The total product therefore contained 70 per cent. of this compound and 30 per cent. of the α -glucoside.

Preparation by Fischer's Process (Ber., 1895, 28, 1145).—Tetramethyl glucose (4.752 grams) was dissolved in methyl alcohol containing 0.25 per cent. of hydrogen chloride and the solution was made up to 100 c.c. with the same liquid. To convert glucose completely into the methyl glucosides, prolonged heating at 100° is requisite, but previous experiment having shown that a temperature of 40° sufficed in the case of tetramethyl glucose, the solution was maintained at this temperature in a closed flask. As the heating proceeded, the action on Fehling's solution gradually diminished until 15 hours had elapsed, when the action could no longer be detected. Polarimetric observations indicated that both glucosides were produced, but the β -isomeride was not present in the greatly preponderating proportion found in the silver oxide method of preparation, and this was confirmed by further examination of the product. The specific rotatory power of the solution before being heated was +84°, and this gradually diminished with the decreasing action on Fehling's solution. Finally, after 24 hours, when the action was stopped, the specific rotatory power, calculated on the weight of tetramethyl glucoside equivalent to the tetramethyl glucose used, was +66.5°. The rotatory powers of the glucosides have not been examined in methyl alcohol, but on the basis of their constants in ethyl alcohol, namely, +153.9° and -11.6°;

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the solution then contained 47 per cent. of the α - and 53 per cent. of the β -glucoside.

The hydrogen chloride having been removed by means of silver carbonate, the solution was decolorised with animal charcoal and evaporated to dryness. Owing to the larger proportion of the liquid α -glucoside present, the residual syrup did not deposit β -glucoside on being nucleated, as was the case in the other method of alkylation. On distillation, a fraction weighing 1.26 grams was collected at 126—138° under 12 mm. pressure, and a second, weighing 2.38 grams, at 140—150°. Both fractions were glucosidic, as they had no action on Fehling's solution until hydrolysed; the more volatile fraction deposited the crystalline β -glucoside, which was recognised by its melting point, 38—39°; the less volatile fraction remained liquid. By repeating the fractional distillation, a further small quantity of the crystalline glucoside was obtained, but the total yield of the compound in the crystalline state from 4.752 grams of tetramethyl glucose used amounted to only 1 gram.

The presence of the α -glucoside in the uncrystallisable liquid was proved by its boiling point, by the increased dextrorotation it showed as the β -compound was removed by distillation, and by the composition of the mixture as determined by analysis. The analytical results were C=52.33, H=8.95, the calculated numbers for the glucosides being 52.80 and 8.80 per cent. Further, the same rise and final fall of rotatory power were observed during the progress of the hydrolysis as in the case of the similar mixture of glucosides produced in the silver oxide method of preparation.

Rate of Hydrolysis of Tetramethyl α - and β -Methylglucosides.

Our experience in preparing tetramethyl glucose from these glucosides showed that whilst the β -compound is easily hydrolysed by dilute hydrochloric acid and gives a good yield of aldose, the action in the case of the α -compound proceeds much less readily. The latter compound, indeed, appears to resist the action of dilute sulphuric acid entirely; when it was heated in a sealed tube at 120° for 1 hour with 10 per cent. sulphuric acid, the liquid remained colourless and devoid of action on Fehling's solution.

In order to compare the rates of hydrolysis of the glucosides, weighed quantities of each of the pure compounds and of the uncrystallisable mixture obtained in the methylation of tetramethyl glucoside by the silver oxide method were dissolved separately in 8 per cent. aqueous hydrogen chloride, and the solutions made up to definite volumes with this liquid so that the concentrations of the three should be similar. The rotatory powers of the solutions having

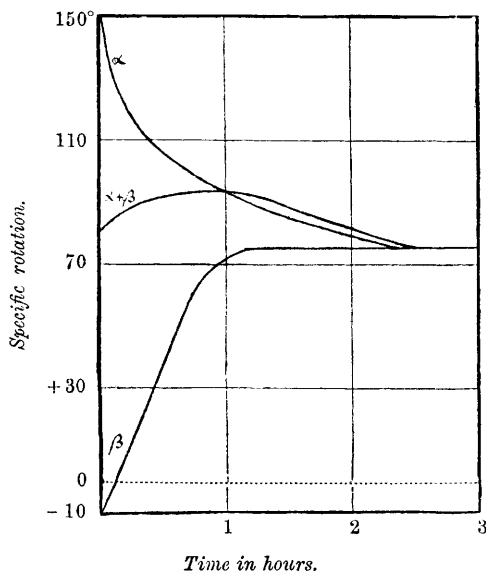
been ascertained immediately after their preparation, they were heated in stoppered flasks in boiling water, and polarimetric observations were made at intervals until the hydrolysis was complete. The results, in the form of specific rotations, calculated on the initial concentrations of the glucosides, are quoted below, and are also plotted as curves. The observations show that after one hour 92 per cent. of the β -glucoside was hydrolysed and only 73.8 per cent. of the α -compound. In the case of the mixture, the rotatory power of the solution could not be determined before heating, owing to its turbidity, and the initial rotatory power quoted is that of the mixture in alcoholic solution, which, for each constituent, does not differ much from the value in water. Owing to the more rapid hydrolysis of the β -glucoside, as pointed out in the introduction, the progress of the action is in this case attended by a rise and subsequent fall of rotation. It will be seen that the specific rotatory powers of the three solutions in the end attain approximately the same value, namely, that of tetramethyl glucose. The final specific rotatory powers, calculated on the concentrations of this compound equivalent to those of the glucosides taken, are $+79.4^\circ$, 81.9° , and 82.7° for the α -glucoside, β -glucoside, and the mixture respectively; the permanent rotatory power of tetramethyl glucose in pure water is 83.3° .

| Time of heating in hours. | α -Glucoside ($c=7.602$). | β -Glucoside ($c=7.415$). | Mixture ($c=7.49$). |
|------------------------------|---------------------------------------|--------------------------------------|--------------------------|
| 0 | $+149.4^\circ$ | -10.5° | $+81.2^\circ$ |
| $\frac{1}{2}$ | 104.5 | — | — |
| 1 | 94.5 | $+70.3$ | 93.6 |
| 2 | 81.3 | 77.2 | 83.8 |
| $2\frac{1}{2}$ | 77.7 | 77.2 | 79.3 |
| 3 | 75.2 | 77.3 | 78.1 |
| $3\frac{1}{2}$ | 75.0 | — | — |

Comparative experiments were also made on the hydrolytic action of emulsin on the glucosides. One gram of tetramethyl β -methylglucoside was dissolved in 10 c.c. of water, and to this was added 0.5 gram of emulsin. The mixture at the outset had no action on Fehling's solution, but after heating at 37° for 4 hours in a thermostat the reducing action was vigorous. The filtered solution was then evaporated to dryness, and the residue was extracted with ether. The liquid left on evaporating the ether reduced Fehling's solution actively, and an alcoholic solution of it showed a dextrorotation. The original glucoside being levorotatory, hydrolysis had therefore been effected. In a comparative experiment with tetramethyl α -methylglucoside, prepared from Kahlbaum's α -methylglucoside, hydrolysis also occurred but much more slowly, decided action on Fehling's solution being

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detected only after 15 hours' heating. As it was found that Kahlbaum's α -methylglucoside was similarly affected by emulsin, the experiment was repeated on a specimen of tetramethyl α -methylglucoside obtained from a specially purified preparation of α -methylglucoside. In this case, the reducing action after 15 hours' heating was very faint, and only after 24 hours was decided action detected. The slight hydrolysis which occurred in this instance may have been due



to some trace of impurity, and our results therefore on the whole bear out Fischer's experience that susceptibility to the hydrolytic action of emulsin is a characteristic of β -glucosides. We purpose making a more extended study of the action of enzymes on alkylated glucosides.

Multirotation of Tetramethyl Glucose.

Aqueous Solutions.—In order to observe the multirotation of the α -form, the crude substance was crystallised five times from light petroleum containing a very little ether until the melting point was constant at 88—89°. An aqueous solution was prepared containing 1.5708 grams in 30 c.c. ($c = 5.236$), and observations in a 2-dcm. tube were taken at intervals until the rotatory power was constant; the first observation was taken 5 minutes after the solid came in contact with the solvent. The temperature during the first hour was maintained at

20°; later, it was that of the room. Some of the observations are appended.

| Time after the preparation of the solution. | $\alpha_D^{20^\circ}$. | $[\alpha]_D^{20^\circ}$. |
|---|-------------------------|---------------------------|
| 5 minutes | + 10·55° | 100·8° |
| 15 „ | 10·27 | 98·1 |
| 45 „ | 9·74 | 93·0 |
| 63 „ | 9·44 | 90·1 |
| 28 hours | 8·65 | 82·6 |
| 52 „ | 8·72 | 83·3 |

The solution of permanent rotatory power was evaporated on a water-bath until on cooling it crystallised and formed a solid mass, which was then completely dried under diminished pressure at the ordinary temperature. An aqueous solution ($c=5\cdot0016$) was quickly prepared and examined at once with the polarimeter. The specific rotatory power was initially only $85\cdot5^\circ$, and it became constant at the same value as before, namely, $83\cdot3^\circ$. The melting point of the nearly stable mixture of the α - and β -forms thus obtained was indefinite (75 — 80°), and considerably lower than that of the pure α -form. The conversion of the α - into the β -form in aqueous solution is accelerated in a striking manner by the addition of alkali. A minute drop of very dilute ammonia caused a fall of 5° in the specific rotation in 30 seconds, and the permanent value was reached in 15 minutes. The faintest trace of ammonia on the cover-glass of the polarimeter produces an immediate effect.

With the view of obtaining the β -form of the sugar, or at least a mixture containing a larger proportion of this form than exists in the aqueous solution of permanent rotatory power, a specimen of the latter form in the dry solid state, obtained as described, was distilled under diminished pressure. The distillate, which crystallised at once, was dissolved in water, and the solution ($c=4\cdot606$) was examined for multirotation without delay. The specific rotation initially was now $+70\cdot8^\circ$, and rose in 2 hours, on a trace of ammonia being added, to $80\cdot7^\circ$, at which value it remained constant. The isomeric change $\alpha \rightarrow \beta$ had therefore been effected by the distillation, and the proportion of the β -form in the mixture had thus been increased; but in solution the reverse transformation was set up, and this proceeded until the mixture had approximately the original composition. As the permanent rotatory power, however, was somewhat short of the limiting value reached by solutions of the pure α -form, it seemed not unlikely that this might be due to decomposition caused by the distillation, which had of necessity to be conducted rapidly, and the experiment was accordingly repeated in a modified form.

The material used was, as before, the solid mixture of permanent rotatory power, but instead of being distilled it was only kept in a state of fusion for 2 hours at 115° , and then quickly cooled. An aqueous solution of the crystalline solid ($c = 5.117$, $l = 2$) showed the following multirotation :

| Time after the preparation of the solution. | $\alpha_D^{20^{\circ}}$. | $[\alpha]_D^{20^{\circ}}$. |
|--|---------------------------|-----------------------------|
| 0 | + 7.49° | 73.1° |
| 1 hour | 7.60 | 74.3 |
| 3 hours | 8.20 | 81.1 |
| 18 " | 8.51 | 83.1 |
| 22 " | 8.51 | 83.1 |

The final state of equilibrium in solution of the mixture obtained by fusion and sudden cooling is therefore the same as that attained by the α -form. The change of rotatory power was also in this case accelerated by adding a trace of ammonia.

Alcoholic Solutions.—A specimen of tetramethyl glucose, which had been crystallised twice from light petroleum and consisted therefore mainly of the α -form, was dissolved in ethyl alcohol. The specific rotation of the solution ($c = 4.985$) was 96.3° initially; this gradually decreased, and, after 48 hours, became constant at 83.1° . A portion of the same specimen used in the preceding experiment was kept in the fused state at 120° for 2 hours in order to shift the state of equilibrium towards the β -form. The substance was crystallised by rapid cooling, and again examined in alcoholic solution ($c = 4.621$). The specific rotation, which was 73.5° initially, rose in 72 hours to almost the same limiting value as before, namely, 82.5° .

Benzene Solutions.—A portion of the same specimen of the pure α -form, which was used for the observations in aqueous solution, showed initially in benzene solution ($c = 5.248$) the specific rotatory power $+111.1^{\circ}$, which decreased in 3 hours to 109.6° , and 17 hours later to 104.9° . The change of rotatory power in this solvent is extremely slow, and the limiting value was not reached in the present instance. That the α -form had, however, undergone partial conversion was proved by evaporating off the benzene completely under diminished pressure at the ordinary temperature, and observing the rotatory power of the recovered crystalline substance in aqueous solution. The initial specific rotation, 98.24° , was less than that of the pure α -form; the permanent value was approximately the same as in previous experiments. If allowance is made for the fact that the initial rotatory power in benzene is greater than that in water, this experiment shows that a mixture which is still in the

unstable state can be isolated from benzene solution without much change of composition.

In order to compare the permanent rotatory power in benzene with that in water, a fresh solution in this solvent was prepared ($c = 5.075$) and observations made at intervals during 4 days in a 2-dcm. tube. Some of these are recorded below :

| Time after the preparation of the solution. | $\alpha_D^{20^\circ}$. | $[\alpha]_D^{30^\circ}$. |
|--|-------------------------|---------------------------|
| 0 | +9.86° | 97.1° |
| 6 hours | 9.52 | 93.8 |
| 24 „ | 9.36 | 92.2 |
| 60 „ | 8.67 | 85.4 |
| 75 „ | 8.59 | 84.6 |
| 100 „ | 8.59 | 84.6 |

The initial rotation recorded here is lower than in the last experiment, as the substance used had been crystallised only twice from light petroleum, and contained therefore a certain proportion of the β -form. The permanent rotatory power does not differ much from that in water, and it may be concluded that the state of equilibrium between the isodynamic forms is nearly the same in the two solvents. To confirm this, a specimen of the equilibrium-mixture was recovered from water and examined in benzene solution, and a specimen of the substance which had been in benzene solution for some days was recovered and examined in water. Multirotation was not observed in either case. The former solution ($c = 5.354$) showed the specific rotation 83.5° , the latter ($c = 5.533$) 83.1° .

The rise of rotatory power due to the conversion of the β - into the α -form was also observed in benzene solution. A mixture, containing a larger proportion of the β -form than exists in the equilibrium-mixture, was prepared as before, by heating a specimen of the latter mixture in the fused state at 140° for 2 hours. The crystalline substance, obtained by rapid cooling, was examined at once in benzene solution ($c = 7.760$); the initial specific rotation was $+76.6^\circ$, the permanent value being practically the same as in aqueous solution, namely, 83.5° . The change of rotation in benzene solutions is greatly accelerated by the addition of a trace of alcoholic ammonia.

Toluene Solution.—A specimen of the aldose recovered from aqueous solution as previously described, and consisting therefore of the mixture of α - and β -forms which is stable in water and gives the specific rotation 83.3° , was dissolved in toluene. The initial specific rotation of the solution ($c = 5.150$) was 84.1° and no multi-rotation was observed. The state of equilibrium in toluene is therefore nearly the same as in water, alcohol, or benzene.

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Experiment having shown that when the substance is distilled or kept in fusion for some time the transformation $\alpha \rightarrow \beta$ occurs, the toluene solution was subjected to prolonged heating in the expectation that a similar change would occur in the solution; the rate of transformation in the solvent being slow, it was to be expected that on rapid cooling the rotatory power would be found to be temporarily lowered. This, however, was not the case. After heating at 60° for 12 hours and at 100° for 2 hours, the rotatory power remained unchanged. After heating to 120° in a sealed tube, the specific rotation was lowered to 82.5° , but this was not followed by any perceptible rise and was probably due to some slight decomposition. The solution, in fact, had become faintly turbid.

Solution in Carbon Tetrachloride.—The aldose used had been kept in the fused state at 115° for 2 hours and was a part of the specimen referred to above, the specific rotation of which in water rose from 73.1° to the permanent value 83.1° . In carbon tetrachloride solution ($c=4.544$) the specific rotation initially was 76.1° ; the value rose in 2 hours to 78.5° , and in 24 hours became permanent at 81.6° . The state of equilibrium therefore does not differ much from that in the other solvents used. The solution after having attained the permanent state was heated at $50-60^\circ$ for 17 hours, quickly cooled, and examined at once; as in the case of the similar experiment in toluene solution, no alteration in the rotatory power had been produced.

Solution in Methyl Iodide.—The crystalline aldose used had been recovered from a solution in benzene, the specific rotatory power of which possessed the permanent value. The substance therefore consisted of the isodynamic mixture which is stable in this and in the other solvents hitherto used. This was confirmed by observing its specific rotatory power in a fresh benzene solution; the value found was 84.4° and no multirotation occurred. A solution of the substance in methyl iodide ($c=4.880$), examined immediately after preparation, showed the specific rotation 74.8° , and this value was permanent. The substance was recovered in the crystalline state by evaporating the methyl iodide under diminished pressure at the ordinary temperature and its specific rotatory power again determined in benzene solution ($c=4.500$), when practically the same initial permanent value as before was found, namely, 84.6° . The rotatory power is therefore much less in methyl iodide than in the other solvents used, but this is not due to the establishment of a different equilibrium by the transformation of α - into β -form, but to a specific effect of the solvent on the rotatory power such as is commonly observed in the case of homogeneous optically active compounds.