

CXLIV.—*The Alkylation of Mannose.*

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THE only alkylated sugars which have so far been examined in detail are trimethyl glucose, tetramethyl glucose, and tetramethyl galactose (Trans., 1903, 83, 1021, and subsequent papers), which have been prepared respectively by the hydrolysis of the corresponding alkylated methylhexosides.

We are at present engaged in this laboratory in the study of other alkylated sugars, and the following paper describes the preparation of tetramethyl mannose and the isomeric  $\alpha$ - and  $\beta$ -tetramethyl methylmannosides. The data collected in the course of the present work are, on the whole, strictly comparable with those already obtained in the study of tetramethyl glucose and tetramethyl galactose, but we reserve any detailed discussion of the results until other types of alkylated sugars have been further examined.

The method of preparing tetramethyl  $\alpha$ -methylmannoside was essentially the same as that already described for the corresponding methylated glucoside and galactoside.  $\alpha$ -Methylmannoside was alkylated in methyl-alcoholic solution by the joint action of silver oxide and methyl iodide. After two such treatments, the product was soluble in methyl iodide, and the final alkylation was therefore carried out in this solvent. Tetramethyl  $\alpha$ -methylmannoside was isolated from the reaction mixture as a colourless, mobile liquid boiling at 148–150° under 15 mm. pressure. The liquid solidified on standing to a crystalline mass of complicated prisms melting at 37–38°, and in this respect the compound differs from the isomeric tetramethyl  $\alpha$ -methylglucoside and the corresponding galactoside. In the latter cases, the fully methylated derivatives having the  $\alpha$ -configuration are liquids, whilst the  $\beta$ -isomerides are solid and crystalline. In the case of the alkylated methylmannosides, the converse holds true. That the foregoing crystalline compound represented the  $\alpha$ -isomeride was shown by the fact that it was unaffected by emulsin and also by the subsequent preparation of a liquid isomeride displaying widely different rotatory powers, but which was readily hydrolysed by this enzyme, and therefore consisted essentially of the  $\beta$ -form.

The optical rotatory powers of tetramethyl  $\alpha$ -methylmannoside in different solvents show on the whole the same relationships as the corresponding glucoside. In water, the specific rotation in the dextro-rotatory sense is much smaller than in alcohol, and in this respect the compound differs sharply from the corresponding galactoside, for which

the converse holds true. The specific rotations of these isomerides are compared in the following table :

	Water. [ $\alpha$ ] <sub>D</sub> <sup>20°</sup> .	Methyl alcohol. [ $\alpha$ ] <sub>D</sub> <sup>20°</sup> .	Ethyl alcohol. [ $\alpha$ ] <sub>D</sub> <sup>20°</sup> .
Tetramethyl $\alpha$ -methylmannoside.....	+42·9°	+70·5°	+75·5°
„ $\alpha$ -methylglucoside .....	+147·4	—	+153·9
„ $\alpha$ -methylgalactoside ...	+143·4	—	+109·9
„ $\beta$ -methylgalactoside ...	+30·7	—	-20·9

When heated with 8 per cent. aqueous hydrochloric acid, the compound loses the glucosidic methyl group and is converted into tetramethyl mannose, the change being accompanied by a marked decrease in rotatory power. The alkylated sugar is a viscid, colourless syrup, boiling without decomposition at 187—189° under 19 mm. pressure. The compound is almost inactive in aqueous solution, and, moreover, on account of its syrupy nature, is not well adapted to the study of multirotation. After heating for some time to 120°, however, its solutions in water or methyl alcohol exhibited slight changes in optical activity. In water, the initial specific rotation of a 5 per cent. solution was -1·7°, and after 15 hours this had attained the constant value of +1·2°. In methyl-alcoholic solution, a similar change was observed, the specific rotation increasing from +14·6° to +17·2°.

In its condensation with methyl alcohol, tetramethyl mannose behaves in an exactly similar manner to the parent sugar mannose. The sole product of the reaction was the crystalline tetramethyl  $\alpha$ -methylmannoside already referred to, and apparently no  $\beta$ -isomeride was produced. Both tetramethyl glucose and tetramethyl galactose, when similarly treated, give a mixture of the  $\alpha$ - and  $\beta$ -modifications of the condensation products, the  $\alpha$ -form being produced, however, in large excess in the latter case.

The behaviour of tetramethylmannose as regards the alkylating effect of a mixture of silver oxide and methyl iodide is in accordance with the idea that the sugar is capable of assuming the tautomeric  $\alpha$ - and  $\beta$ -forms. A liquid product was obtained which, from its composition and reactions, was shown to be likewise tetramethyl methylmannoside. In aqueous solution it was, however, laevorotatory ( $[\alpha]_D^{20} - 34\cdot1^\circ$ ), and when hydrolysed by means of aqueous hydrochloric acid, the characteristic rise and fall in rotatory power was observed which has been shown in previous work to be significant of the presence of both the  $\alpha$ - and  $\beta$ -varieties of an alkylated glucoside. The liquid in question was, moreover, partially hydrolysed by emulsin, and this confirms the idea that it contains the  $\beta$ -isomeride. It was, however, found impossible to separate the constituents of the mixture by fractionation, and no data could therefore be obtained as to the exact specific rotation of the  $\beta$ -form.

As mannose, like its tetramethyl ether, when condensed with methyl alcohol by means of hydrogen chloride yields only the  $\alpha$ -mannoside, the foregoing result therefore offers a unique example of the application of the silver oxide method of alkylation in the preparation of a type of glucoside which is not produced in the ordinary condensation process.

#### EXPERIMENTAL.

##### *Preparation of Tetramethyl $\alpha$ -Methylmannoside.*

The  $\alpha$ -methylmannoside used in our experiments was prepared by Fischer's method (*Ber.*, 1896, 29, 2927), in which dry mannose is heated at 100° for 45 hours with excess of methyl alcohol containing 0.25 per cent. hydrochloric acid. We found that the amount of solvent alcohol used could be conveniently reduced to eight times the weight of sugar taken, and this effects a considerable economy when the preparation is carried out in sealed tubes. The yield of crude product was almost quantitative, and, after recrystallisation from methyl alcohol, the compound melted at 190–191°. The mother liquors collected during the recrystallisation were examined with the view of ascertaining if any of the isomeric  $\beta$ -methylmannoside had been produced, but only a small quantity of an uncrystallisable syrup was obtained.

The alkylation of the methylmannoside was carried out exactly as already described for methylglucoside and methylgalactoside (*Trans.*, 1904, 85, 1058, 1074), and the proportions of alkylating material were the same. Owing, however, to the sparing solubility of the compound in methyl alcohol, a larger quantity of solvent is required, and the process is more tedious. Three successive alkylations were necessary, two in methyl-alcoholic solution and one in methyl iodide, and the final product was isolated as usual and purified by distillation in a vacuum. The pure substance was thus obtained boiling at 148–150° under 15 mm. pressure. On standing, the distillate solidified completely to a mass of complicated prisms, which were freed from adherent oil by draining on a tile. The less volatile fractions crystallised only partially, and were therefore again alkylated together with the oil recovered from the tiles, and thus a total yield of crystalline product amounting to 74 per cent. of the mannoside taken was obtained. The compound proved to be exceedingly soluble in water and organic solvents generally, but was recrystallised with some difficulty from a concentrated solution in methyl alcohol. After drying in a vacuum, the crystals melted at 37–38°. The analysis was conducted on a sample of the compound dried at 100° in a vacuum.

0.1771 gave 0.3416 CO<sub>2</sub> and 0.1439 H<sub>2</sub>O. C = 52.61; H = 9.02.

0.1325 „ 0.6214 AgI. CH<sub>3</sub>O = 61.90.

C<sub>11</sub>H<sub>22</sub>O<sub>6</sub> requires C = 52.80; H = 8.80 per cent.

C<sub>6</sub>H<sub>7</sub>O(OCH<sub>3</sub>)<sub>5</sub> „ CH<sub>3</sub>O = 62.0 per cent.

The compound is neutral in reaction, and is devoid of any action on Fehling's solution. It is readily hydrolysed on warming with dilute hydrochloric acid to give tetramethyl mannose, but resists the hydrolytic action of emulsin entirely, from which we conclude that the compound is the pure  $\alpha$ -form. The molecular weight was determined by the cryoscopic method in benzene solution, and gave the value 249, the calculated number being 250.

The following observations were made on the optical activity of the substance:

Solvent.	c.	l.	$\alpha_{20^\circ}$ .	$[\alpha]_D^{20^\circ}$ .
Water ...	9.9963	2	+8.57°	+42.9°
Methyl alcohol ...	9.9890	2	14.05	70.5
Ethyl alcohol ...	7.9520	1	6.01	75.5

The numbers quoted above show that the rotatory power is much greater in the dextrorotatory sense in alcoholic than in aqueous solutions, and in this respect the compound resembles tetramethyl  $\alpha$ -methylglucoside, but differs from the corresponding galactoside.

### *Tetramethyl Mannose.*

This compound is readily prepared by the hydrolysis of tetramethyl  $\alpha$ -methylmannoside. An aqueous solution containing 8 per cent. of the alkylated mannoside and 8 per cent. of hydrochloric acid was heated in boiling water until the rotation became constant. After about two hours' heating, the specific rotation, calculated on the weight of mannoside taken, diminished from +42.5° to the constant value +2.6°. The product was then isolated in the manner already described for tetramethyl glucose (*loc. cit.*), and purified by fractional distillation in a vacuum. The pure substance distilled at 187–189° under 19 mm. pressure, and as it could not be obtained in a crystalline state it was examined in the form of a viscid, colourless, highly refractive syrup.

0.2103 gave 0.3923 CO<sub>2</sub> and 0.1634 H<sub>2</sub>O. C = 50.87; H = 8.63.

0.1930 „ 0.7709 AgI. CH<sub>3</sub>O = 52.72.

C<sub>10</sub>H<sub>20</sub>O<sub>6</sub> requires C = 50.85; H = 8.47 per cent.

C<sub>6</sub>H<sub>8</sub>O<sub>2</sub>(OCH<sub>3</sub>)<sub>4</sub> „ CH<sub>3</sub>O = 52.54 per cent.

The molecular weight was determined in aqueous solution by the cryoscopic method and gave 219, the calculated value being 236.

Like the other alkylated sugars hitherto examined, tetramethyl mannose is soluble not only in water but in all the ordinary organic solvents, and retains the characteristic properties of a reducing sugar. The aqueous solution reduces Fehling's solution readily on warming, turns brown when boiled with caustic soda, gives a silver mirror with ammoniacal silver nitrate, and also gives positive results with the Schiff and the Molisch reactions. The compound likewise reacts with phenylhydrazine dissolved in acetic acid to give an oil which is devoid of any action on Fehling's solution until after it has been hydrolysed, and which is doubtless a hydrazone.

On account of the syrupy nature of the compound, our experiments on multirotation were necessarily restricted. Previous experience with tetramethyl glucose and tetramethyl galactose has, however, shown that by distillation or by heating these compounds to a temperature of 120—130°, the proportion of the  $\beta$ -form of the sugar is increased above that contained in the equilibrium mixture, and consequently after such treatment the product exhibits multirotation. We find that tetramethyl mannose gives a similar result. A quantity of the sugar was heated for two hours at 120°, and the specific rotations were then determined without delay in water and in methyl alcohol. A 5 per cent. aqueous solution proved to be lævorotatory ( $[\alpha]_D^{20} - 1.7^\circ$ ), but, on standing, this gradually became dextrorotatory. After fifteen hours, the constant value of  $[\alpha]_D^{20} + 1.2^\circ$  was attained, and this remained unaltered on the addition of a trace of alkali. A similar solution in methyl alcohol gave the initial specific rotation  $[\alpha]_D^{20} + 14.6^\circ$ , which gradually increased to the constant value of  $+17.2^\circ$ . It will thus be seen that tetramethyl mannose, like the alkylated mannoside from which it is derived, exhibits a much higher rotation in the dextrorotatory sense in alcohol than in water. In this respect also the series of compounds described differs sharply from the corresponding galactose derivatives, which display the maximum dextrorotation in aqueous solution.

#### *Condensation of Tetramethyl Mannose with Methyl Alcohol.*

Tetramethyl mannose, like the parent sugar, condenses with methyl alcohol to give only the  $\alpha$ -form of the corresponding mannoside. The reaction was carried out by heating a 5 per cent. solution of the sugar in methyl alcohol containing 0.25 per cent. of hydrochloric acid to 100° for twelve hours. The specific rotation of the solution increased during the change from  $+17^\circ$  to  $+69^\circ$ , so that the conversion into tetramethyl  $\alpha$ -methylmannoside was almost complete. The hydrochloric acid was removed by shaking with silver carbonate, and, after evaporating off the solvent alcohol, the product was distilled in a

vacuum. The distillate, on nucleation with tetramethyl  $\alpha$ -methylmannoside, crystallised completely, and after recrystallisation from methyl alcohol the crystals melted at 37—38°. The identity of the substance with the crystalline methylated mannoside obtained from  $\alpha$ -methylmannoside was further confirmed by a determination of the specific rotation in methyl alcohol. The yield was almost quantitative.

*Methylation of Tetramethyl Mannose by the Silver Oxide Reaction.*

In the case of tetramethyl mannose, this reaction possesses considerable interest, as it affords a means of preparing a fully methylated derivative of the unknown  $\beta$ -methylmannoside. The alkylation was carried out as usual by adding silver oxide (5 mols.) to a solution of the sugar (1 mol.) in methyl iodide (10 mols.), and warming on a water-bath for eight hours. The product was extracted with ether, and, after drying over sodium sulphate and removal of the solvent, was distilled in a vacuum. The main fraction boiled at 151—152° under 18 mm. pressure, and presented the appearance of a colourless, highly refractive, mobile liquid which behaved like a glucoside towards Fehling's solution. Despite the fact that the liquid could not be made to crystallise, analysis nevertheless showed that the substance also possessed the composition of a fully methylated methylmannoside.

0.1646 gave 0.3183 CO<sub>2</sub> and 0.1341 H<sub>2</sub>O. C = 52.74; H = 9.05.

0.1896 „ 0.9160 AgI. CH<sub>3</sub>O = 63.7.

C<sub>11</sub>H<sub>22</sub>O<sub>6</sub> requires C = 52.80; H = 8.80 per cent.

C<sub>8</sub>H<sub>7</sub>O(OCH<sub>3</sub>)<sub>5</sub> „ CH<sub>3</sub>O = 62.0 per cent.

Determinations of the specific rotatory powers of the substance gave the following results:

Solvent.	<i>c.</i>	<i>l.</i>	$\alpha_{20^\circ}$ .	$[\alpha]_D^{20}$ .
Methyl alcohol ...	7.8810	2	-4.20°	-26.6°
Water.....	6.6065	2	-4.51	-34.1

From the liquid nature of the compound and the laevorotatory powers of its solutions, the substance is evidently either tetramethyl  $\beta$ -methylmannoside or a mixture of this compound with the  $\alpha$ -isomeride. In order to establish this point the substance was hydrolysed. A 5 per cent. solution of the supposed mixture was made in 8 per cent. aqueous hydrochloric acid and heated to 80°, the progress of the hydrolysis being followed by means of polarimetric observations at intervals of ten minutes. The laevorotation rapidly diminished, and after fifty minutes the solution was dextrorotatory. In order to hasten the change, the temperature of the solution was

then raised to  $100^{\circ}$ , and this was attended with a further increase of dextrorotatory power until the maximum value of  $[\alpha]_D + 6.5^{\circ}$  was reached, after which the specific rotation, calculated on the weight of mannoside taken, diminished to the constant value of  $+2.5^{\circ}$ . This rise with an ultimate fall in rotatory power to approximately the value required for tetramethyl mannose shows that the liquid under examination consists of a mixture of tetramethyl  $\alpha$ -methylmannoside with a more easily hydrolysable levorotatory isomeride of similar structure, which we conclude is the corresponding  $\beta$ -isomeride.

In the following table, the changes in optical activity shown on hydrolysis by the crystalline methylated  $\alpha$ -mannoside are contrasted with those of the liquid mixture referred to above, the values in each case being calculated on the weight of mannoside taken :

<i>Pure <math>\alpha</math>-form.</i>		<i>Mixture of <math>\alpha</math>- and <math>\beta</math>-forms.</i>	
Time of heating.	$[\alpha]_D$ .	Time of heating.	$[\alpha]_D$ .
0 .....	$+42.5^{\circ}$	0 .....	$-34.7^{\circ}$
30 min. at $100^{\circ}$ .....	$+12.0$	30 min. at $80^{\circ}$ .....	$-7.8$
80 „ „ „ .....	$+3.6$	50 „ „ „ .....	$+0.7$
110 „ „ „ .....	$+2.6$	10 min. at $100^{\circ}$ ...	$+6.5$
		40 „ „ „ ...	$+2.5$

It will thus be seen that the levorotatory isomeride is hydrolysed more readily than the pure  $\alpha$  form, and in previous work on alkylated sugars we have shown this to be a feature of alkylated  $\beta$ -glucosides.

The action of emulsin on the liquid mixture of mannosides was carried out by adding the finely-powdered enzyme to a 5 per cent. aqueous solution of the material and preserving the mixture at  $38^{\circ}$  for several hours. The levorotation gradually diminished, and the solution now reacted decidedly with Fehling's solution, thus indicating that partial hydrolysis had occurred.

In conclusion, we take this opportunity of expressing our thanks to Professor Purdie, in whose laboratory the research was carried out, for his valuable advice, and also to the Executive Committee of the Carnegie Trust for defraying the expenses of the investigation.

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