XLVIII.—*A New Form of Methylgalactoside and its Conversion into Octamethyldigalactose and into a Methyldigalactoside.*

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THE isolation of a new form of methylglucoside by Fischer (*Ber.*, 1914, **47**, 1980), and the detailed study of its derivatives by Irvine, Fyfe, and Hogg (*T.*, 1915, **107**, 524), naturally suggests the possibility that members of the dulcitol series of hexoses may also exhibit the same structural isomerism. Observations have, in fact, already been recorded indicating that galactose can react in a form other than the α - and β -modifications, and recently all doubt on this point has been removed by the preparation of four galactose pentaacetates by Hudson and his co-workers (*J. Amer. Chem. Soc.*, 1916, **38**, 1223). The first mention of this unexpected isomerism occurs, however, in Fischer's original description of the methylhexosides (*Ber.*, 1895, **28**, 1174). By concentrating an acid methyl-alcoholic solution of the crystalline α - and β -methylgalactosides, an amorphous product was obtained which Fischer regarded as a third form of methylgalactoside. The absence of analytical data

rendered complete identification of this substance impossible, and some years later Irvine and Cameron (T., 1905, **86**, 907) suggested that a methylated galactoside prepared by them and found to possess abnormal properties might be a derivative of the third isomeride referred to by Fischer. In this research, Irvine and Cameron isolated a syrupy form of methylgalactoside, which from its low specific rotation was at first regarded as consisting mainly of the β -modification. This particular methylhexoside is now shown to be a true methylgalactoside of the γ -series resembling γ -methylglucoside in its properties, but it is not identical with Fischer's amorphous product, which, as shown by analysis and a molecular weight determination, is a *methyl digalactoside*. The new form of methylgalactoside gives on methylation, followed by hydrolysis, tetramethyl γ -galactose, identical with the compound previously prepared by Irvine and Cameron (*loc. cit.*), and this sugar has now been found to possess the unique property of undergoing auto-condensation to give octamethyl γ -digalactose. The reaction in question proceeds spontaneously at the ordinary temperature and in the absence of any recognisable catalyst. This is, of course, a most unusual result, and, taken in conjunction with the formation, in somewhat similar circumstances, of a substituted disaccharide derivative from γ -methylglucoside (Irvine, Fyfe, and Hogg, *loc. cit.*), it serves to emphasise the extraordinarily reactive character of ethylene-oxide sugars. Moreover, it has been shown that the reaction which gives rise to methyl digalactoside also involves the presence—probably only transitory—of a variety of galactose conforming to this particular type of sugar. This conclusion seems warranted by the fact that the digalactoside, as shown by a study of its behaviour on hydrolysis, consists of the stable forms of methylgalactoside (α - and β -) united to the unstable form of the sugar. The union involves the reducing group of the latter, and accordingly the structure of the complex is represented by the formula

A significant observation is that no structural modification of the digalactoside can be obtained by varying the form of methylgalactoside employed in its preparation. Thus, whether the starting point is an acid, methyl-alcoholic solution of pure α -, pure γ -, or an equilibrium mixture of α - and β -methylgalactosides, a compound having the same constants and properties and giving the same results on hydrolysis is formed in each case. The most prob-

able explanation of this rather surprising result seems to be that under the influence of acid methyl alcohol, any one form of methylgalactoside passes to an equilibrium mixture of the three isomerides α -, β -, γ -, and of these the unstable γ -variety is subsequently hydrolysed on concentration to give the reactive type of the sugar. This immediately combines with the stable hexosides to give a non-reducing complex, regeneration of γ -methylgalactoside being impossible owing to the removal of the alcohol. The course of the reaction would be represented by the following scheme:

These suggestions are, moreover, in accord with the results previously obtained by Irvine and Cameron (T., 1905, **86**, 907), who found that fully methylated hexosides of stable form could be heated at 110° to 150° without any hydrolysis occurring, the only change observed being an interconversion to an equilibrium mixture of the α - and β -isomerides. In these experiments, the formation of the γ -variety was impossible owing to the presence of the methoxyl groups, so that the complicated reactions described above could not take place.

EXPERIMENTAL.

γ -Methylgalactoside.—Galactose was heated at 100° with methyl alcohol containing 0.25 per cent. of hydrogen chloride in essentially the way described by Fischer for the preparation of α - and β -methylgalactosides, except that the acid was neutralised before removing the solvent. The neutralised solution deposited crystals of α -methylgalactoside on slight concentration, and from the filtrate a viscid syrup was obtained on further heating. On the addition of ether, this syrup formed a semi-solid mass consisting for the

most part of α - and β -methylgalactosides, but on triturating the mass with small quantities of absolute alcohol, some of the adhering syrup passed into solution and was removed by filtration. In this manner, a nearly colourless syrup of a non-reducing character was prepared which, in order to remove impurities, was dissolved in methyl alcohol and the solution fractionally precipitated by successive additions of ethyl acetate. The yield was 30 per cent. of the sugar used. For analysis, the syrup was dried to constant weight at $60^{\circ}/20$ mm. This method of preparation, it will be observed, differs considerably from that described by Fischer (*loc. cit.*) for the isolation of γ -methylglucoside, and it seems to point to the interesting conclusion that in the ordinary process of hexoside synthesis, the three modifications, α -, β -, and γ -, are produced together.

Found: C=42.94; H=7.3; OMe=15.7.

$C_7H_{14}O_6$ requires C=43.27; H=7.27; OMe=15.98 per cent.

The new compound thus isolated as a mixture of stereoisomerides showed the characteristic reactions of derivatives of the γ -series and gave $[\alpha]_D +12.95^{\circ}$ in methyl alcohol and $+25.9^{\circ}$ in water. It should be mentioned that attempts to prepare acetone derivatives similar to γ -methylglucosidemonoacetone were entirely unsuccessful.

Hydrolysis of γ -Methylgalactoside.— γ -Methylgalactoside is somewhat more stable towards dilute acids than the corresponding glucoside, as it is necessary to carry out the hydrolysis with $N/100$ -hydrochloric acid at 100° . The changes in optical activity observed are shown in Fig. 1, and it will be seen that the specific rotation increases without any irregularities until the value for galactose is reached, at the end of four and a-half hours. The continuity of the curve might at first suggest that only one of the two possible modifications of the ethylene-oxide type was present, but subsequent methylation showed the existence of the two varieties. The form of the curve does, however, prove that Fischer's amorphous product cannot be one of these γ -isomerides. This compound is more dextrorotatory than galactose itself, and if it were present, the curve would show a point above the specific rotation of galactose before the constant value was reached.

Tetramethyl γ -Methylgalactoside.— γ -Methylgalactoside was methylated by the silver oxide method under the usual conditions, and the alkylation proceeded normally. After three methylations, the product was extracted with ether, and on distilling at 142 – $145^{\circ}/12$ mm., a colourless, mobile liquid was obtained having $[\alpha]_D +3.98^{\circ}$ in alcohol. The value given by Irvine and Cameron for their abnormal form of tetramethyl methylgalactoside was

+4.06°, so that the two compounds are identical. Fractionation separated the distillate into two portions; the one boiling at 135°/12 mm. gave $[\alpha]_D -4.3^\circ$, and the other, boiling at 150°/12 mm., showed $[\alpha]_D +8.8^\circ$, but the analytical composition of each fraction was identical.

Hydrolysis of Tetramethyl γ -Methylgalactoside, Tetramethyl γ -Galactose, and Octamethyl γ -Digalactose.—The methylated galactoside is only completely converted into the corresponding

FIG. 1.

Hydrolysis of γ -methylgalactoside.

sugar by heating at 100° with *N*/100-hydrochloric acid for eight hours, and consequently hydrolysis experiments were carried out with *N*/10-acid at 100°. As shown on the accompanying curve (Fig. 2), the specific rotation falls initially and then rises, the constant value +25.9° being reached at the end of five hours. The specific rotation given by Irvine and Cameron (*loc. cit.*) for the methylated sugar was 26.1°, so that there was no doubt that tetramethyl γ -galactose was present, but as new and unexpected cases

of auto-condensation had recently been observed, the sugar, isolated as usual, was left to remain for some time before distillation with the idea that a disaccharide derivative might possibly be formed. After an interval of seven days, the syrup was distilled at the low pressure of the Gaede pump. The distillate (b. p. 114—117°/0.03 mm.), which was a colourless syrup, had now lost the properties of a reducing sugar and acquired those of a glucoside. More-

FIG. 2.

Hydrolysis of tetramethyl γ -methylgalactoside.

over, the specific rotation had increased greatly, the values for $[\alpha]_D$ in alcohol and water being +54.4° and +75° respectively. As was to be expected, the new compound reduced potassium permanganate solution instantaneously.

Found: C=52.2, 52.4; H=8.5, 8.7; OMe=57.1, 57.3.

$C_{20}H_{38}O_{11}$ requires C=52.86; H=8.4; OMe=54.6 per cent.

The analytical figures indicate that the compound is octamethyl-digalactose; but it is obviously not quite pure.

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Hydrolysis of Octamethyl γ -Digalactose.—On heating a solution of the methylated disaccharide in $N/10$ -hydrochloric acid at 100° , the specific rotation decreased, and at the end of eight and a-half hours reached the constant value $+25.6^\circ$, which agrees with the figure previously found for tetramethyl γ -galactose, and establishes the compound as essentially a disaccharide derivative.

Methyldigalactoside (1) from α - and β -Methylgalactosides.—A solution of 10 grams of an equilibrium mixture of α - and β -methylgalactosides in 50 c.c. of methyl alcohol was concentrated to a viscid syrup, which was dissolved in methyl alcohol and the solution filtered. Addition of absolute alcohol to the filtrate gave a white, amorphous product of an extremely deliquescent nature which, after remaining for some time in a vacuum, was dried to constant weight at $70^\circ/20$ mm. The compound behaved as a glucoside to Fehling's solution, and gave $[\alpha]_D$ in methyl alcohol $+85.6^\circ$ and in water $+101.1^\circ$.

Found: C=43.88; H=6.9; OMe=9.05.

$C_{13}H_{24}O_{11}$ requires C=43.8; H=6.8; OMe=8.7 per cent.

A molecular weight determination by the cryoscopic method gave M.W.=341; $C_{13}H_{24}O_{11}$ requires M.W.=356.

An estimation by the ebullioscopic method could not be carried out, owing to the sparing solubility of the compound in any suitable solvent.

Hydrolysis of Methyldigalactoside.—The digalactoside showed the marked instability towards neutral potassium permanganate solution characteristic of ethylene-oxide compounds, so that it evidently contained one or more unstable linkings, and as these are ruptured by heating at 100° with $N/100$ -hydrochloric acid, their number and position in the molecule of the digalactoside could be ascertained by following the course of the hydrolysis with the polarimeter. The specific rotation was found to increase and reached a constant value at the end of three hours, whilst the solution acquired reducing properties. This reduction was entirely due to the formation of galactose, as indicated by the fact that treatment with phenylhydrazine yielded galactosephenylosazone alone. At the same time, a methoxyl estimation carried out on the products isolated at this first stage of the hydrolysis showed that a hexoside was present. Hence the increase in specific rotation is not due to the formation of a disaccharide, but is occasioned by the liberation of α -methylgalactoside, $[\alpha]_D +180^\circ$. The molecule of the digalactoside therefore contains only one unstable linking, which is situated in one of the sugar residues, and the stability of the glucosidic methyl group shows that this portion of the molecule

retains the normal butylene-oxide structure. These observations are summarised in the constitutional formula given on p. 597. The maximum value for the optical activity is, however, less than that required for an equimolecular mixture of α -methylgalactoside, $[\alpha]_D +180^\circ$, and galactoside, $[\alpha]_D +81^\circ$. This deficiency is most likely due to the presence of the practically inactive β -methylgalactoside, and the form of the rotation curve when the hydrolysis is carried out with *N*/10-hydrochloric acid supports this contention. The changes in specific rotation are shown in Fig. 3, and it will be

FIG. 3.
Hydrolysis of methyl digalactoside.

observed that the rapid rise to the maximum value in the first twenty minutes is succeeded by a constant period of forty minutes, during which the decline in activity due to the hydrolysis of the α -isomeride is balanced by the increase in activity occasioned by the more quickly hydrolysed β -form, whilst the marked fall in the next ten minutes indicates that this masking effect has now disappeared. The specific rotation then decreases regularly until the value for galactose is reached after four hours. This preparation of the digalactoside therefore undoubtedly consists of α - and β -methylgalactosides in union with γ -galactose.

Methyldigalactoside (2) from γ -*Methylgalactoside*.— γ -Methylgalactoside was treated in the same way as the mixture of α - and β -methylgalactosides. The compound isolated gave the same values for the specific rotation as the previous preparation, $+85.6^\circ$ in methyl alcohol and 101.1° in water. On hydrolysis with $N/100$ -hydrochloric acid at 100° , the specific rotation increased to the constant value $+109.6^\circ$ at the end of three hours, and after the acid concentration had been raised to $N/10$, the same characteristic points were observed as before. The specific rotation remained constant for forty minutes, and then fell sharply to 104.5° in the next twenty minutes, after which it decreased steadily until the hydrolysis was complete.

Methyldigalactoside (3) from α -*Methylgalactoside*.—In this experiment, a specimen of α -methylgalactoside was used which had been several times recrystallised until entirely free from traces of either the β - or the γ -isomeride. The specific rotation of the digalactoside obtained was $+100.9^\circ$ in water, and this increased on heating with $N/100$ -hydrochloric acid at 100° to the maximum value 110.3° at the end of three hours. Thereafter the concentration of acid was changed as before, when the variations in activity previously described were again observed. The preparations of the digalactosides are therefore indistinguishable from each other.

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