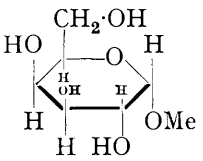
115. *The Properties of* 3 : 6-*Anhydrogalactose.*

By W. N. Haworth, J. Jackson, and F. Smith.

The syntheses of 3 : 6-anhydro-α- and -β-methylgalactopyranosides and their various methylated derivatives are described. 2 : 4-*Dimethyl* 3 : 6-*anhydro-α-methylgalactopyranoside* (IV), which is a liquid, can be directly transformed into crystalline 2 : 4-*dimethyl* 3 : 6-*anhydro-β-methylgalactopyranoside* (VIII) by small amounts of hydrogen chloride in air, hydrogen bromide in air, ethereal hydrogen chloride, ethyl-alcoholic hydrogen chloride and by methyl-alcoholic hydrogen chloride. This direct α ⟶ β isomerisation also takes place spontaneously when the α-form is kept for several months. None of these methods appears to involve the intermediate formation of a free reducing group. With excess of methyl-alcoholic hydrogen chloride both the α- and the β-form of 2 : 4-dimethyl 3 : 6-anhydromethylgalactopyranoside, which have strained structures, yield the relatively strainless 2 : 4-*dimethyl* 3 : 6-*anhydrogalactose dimethylacetal* (XVI). Treatment of the latter either with hydrogen chloride or with hydrogen bromide effects the removal of the elements of methyl alcohol and there is produced 2 : 4-dimethyl 3 : 6-anhydro-β-methylgalactopyranoside (VIII). It is suggested that the steric effect of the stable five-membered 3 : 6-anhydro-ring is responsible for some of the peculiar properties of 3 : 6-anhydrogalactose and its derivatives.

The transformation of an α-methylglycoside or a β-methyglycoside into an equilibrium mixture of the two forms may be effected by means of methyl-alcoholic hydrogen chloride and it is usually accepted that this transformation involves the intermediate formation of the free sugar. Haworth, Jackson, and Smith (*Nature*, 1938, **42**, 1075) have drawn attention to a glycoside, namely, 2 : 4-*dimethyl* 3 : 6-*anhydro-α-methylgalactopyranoside* (IV), which does not appear to conform to this explanation of the αβ isomerisation. This substance was prepared as follows. Treatment of α-methylgalactopyranoside (I) with *p*-toluenesulphonyl chloride in pyridine solution yields 6-tosyl α-methylgalactopyranoside (II), which is smoothly converted by the action of sodium hydroxide into crystalline

3 : 6-anhydro-α-methylgalactopyranoside (III). This compound has also been prepared by Valentin (*Coll. Czech. Chem. Comm.*, 1932, **4**, 364) and by Ohle and Thiel (*Ber.*, 1933, **66**, 528). Methylation of (III) with Purdie's reagents affords 2 : 4-dimethyl 3 : 6-anhydro-α-methylgalactopyranoside (IV) as a liquid.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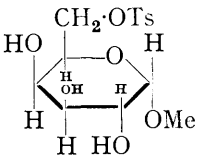
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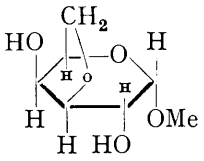
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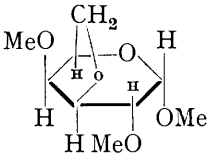
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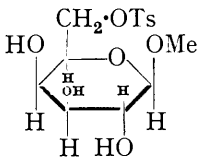
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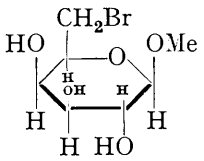
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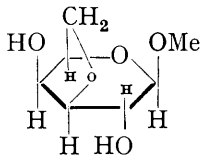
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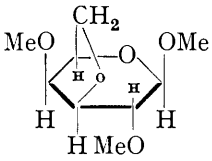
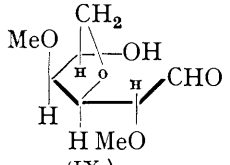

(VIII.)

(Ts = $SO_2 \cdot C_6H_4 \cdot CH_3$.)

This liquid 2 : 4-dimethyl 3 : 6-anhydro-α-methylgalactopyranoside (IV) is very sensitive to traces of acid; it is rapidly transformed into the corresponding crystalline β-*form* (VIII) by brief contact with (*a*) air containing hydrogen chloride or hydrogen bromide, (*b*) a drop of a solution of hydrogen chloride in ether or in ethyl alcohol. It has been observed that the α ⟶ β isomerisation takes place spontaneously when the α-glycoside is kept in a stoppered tube. The transformation can also be effected by a drop of methyl-alcoholic hydrogen chloride, but since the change occurs in the absence of methyl alcohol there can be no loss of a methyl residue and hence the mechanism of the reaction does not admit of the intermediate formation of the free sugar. Furthermore we have now discovered that 2 : 4-*dimethyl* 3 : 6-*anhydrogalactose dimethylacetal* (XVI), obtained from (IV) and from (VIII) (see below), is also quickly transformed by brief contact with hydrogen chloride or hydrogen bromide into 2 : 4-dimethyl 3 : 6-anhydro-β-methylgalactopyranoside (VIII). Both the α- and the β-form of 2 : 4-dimethyl 3 : 6-anhydromethylgalactopyranoside appear, by ebullioscopic methods, to be monomeric and this is confirmed for the β-form by *X*-ray examination.

The designation of the crystalline substance obtained from the liquid α-form as 2 : 4-dimethyl 3 : 6-anhydro-β-methylgalactopyranoside follows from the fact that it is obtained when either 6-*tosyl* β-*methylgalactopyranoside* (V) or β-methylgalactopyranoside 6-bromohydrin (VI) is treated with sodium hydroxide and the product, 3 : 6-*anhydro*-β-*methylgalactopyranoside* (VII), completely methylated with silver oxide and methyl iodide. The same conclusion was reached independently by Percival and Forbes (*Nature*, 1938, **142**, 1076). The enantiomorph of 2 : 4-dimethyl 3 : 6-anhydro-β-methylgalactopyranoside has been encountered by Hands and Peat (*ibid.*, p. 797) and by Forbes, Percival, and Somerville (*ibid.*, p. 797) during their investigations upon the structure of the polysaccharide agar-agar.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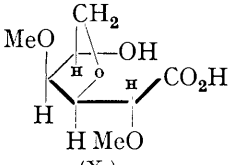
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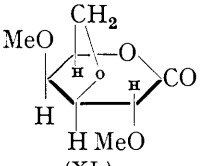
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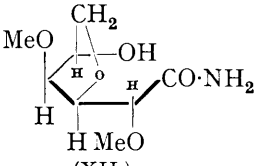
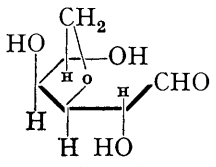

(XII.)

Both the α- and the β-form of 2 : 4-dimethyl 3 : 6-anhydromethylgalactoside are very labile towards dilute acids and behave like methylfuranosides inasmuch as each is hydrolysed with 0·1N-sulphuric acid, slowly at room temperature and rapidly on heating, with

the formation of 2 : 4-dimethyl 3 : 6-anhydrogalactose. From a comparison of the rates of hydrolysis it seems that the β-form is more stable than the α-form. The reducing methylated sugar, which can be characterised as a crystalline *anilide*, appears to have an aldehydic structure as shown in (IX), for it restores the colour to Schiff's reagent and immediately decolorises neutral potassium permanganate. Oxidation of (IX) with bromine affords crystalline 2 : 4-*dimethyl* 3 : 6-*anhydrogalactonic acid* (X) and this acid on treatment with diazomethane yields the corresponding crystalline methyl ester, which can be distilled unchanged. When the acid (X) is heated above its melting point for some time and then subjected to distillation, there is produced 2 : 4-*dimethyl* 3 : 6-*anhydrogalactonolactone* (XI); the latter and the above methyl ester can be characterised by their conversion into the corresponding crystalline *amide* (XII). Some indication of the stability of the 3 : 6-anhydro-ring is revealed by the observation that the acid (X) may be prepared by the oxidation of 2 : 4-dimethyl 3 : 6-anhydro-α-methylgalactoside (IV) with nitric acid.

Both forms of 3 : 6-anhydromethylgalactopyranoside undergo hydrolysis at room temperature when treated with 0·1N-sulphuric acid to give 3 : 6-anhydrogalactose, the properties of which indicate that it has an aldehydic structure as in (XIII). In agreement with the observation that dimethyl 3 : 6-anhydro-β-methylgalactopyranoside (VIII) is more stable than the α-form (IV) it is found that 3 : 6-anhydro-β-methylgalactopyranoside (VII) is hydrolysed more slowly than the α-form (III).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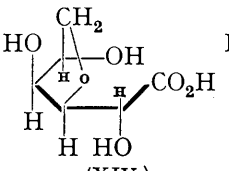
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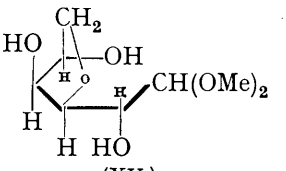
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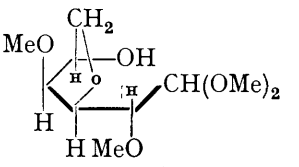
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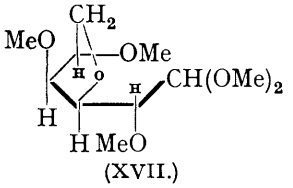
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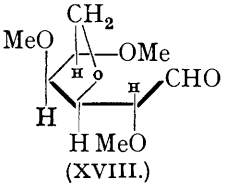
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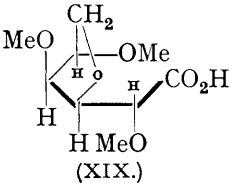
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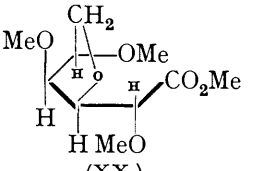
(XX.)

When either the α- or the β-form of 2 : 4-dimethyl 3 : 6-anhydromethylgalactopyranoside is treated at room temperature with an excess of 0·5% methyl-alcoholic hydrogen chloride, there is produced 2 : 4-dimethyl 3 : 6-anhydrogalactose dimethylacetal (XVI). Similarly, when the α- and the β-form of 3 : 6-anhydromethylgalactopyranoside are treated with excess of methyl-alcoholic hydrogen chloride, the pyranose ring opens and in each case there is produced 3 : 6-*anhydrogalactose dimethylacetal* (XV). The assignment of an open-chain aldehydic structure to (XVI) and (XV) is based upon the following experimental facts. The 2 : 4-dimethyl 3 : 6-anhydrogalactose dimethylacetal (XVI) yields a *mono*-p-*nitrobenzoate* and the 3 : 6-anhydrogalactose dimethylacetal (XV) gives a *tri*-p-*nitrobenzoate*; the acetal methyl groups attached to position 1 are easily eliminated from (XVI) and from (XV) by acid hydrolysis with the formation of 2 : 4-dimethyl 3 : 6-anhydrogalactose (IX) and aldehydo 3 : 6-anhydrogalactose (XIII) respectively. It is particularly interesting to note that the 2 : 4-dimethyl 3 : 6-anhydrogalactose dimethylacetal (XVI) is directly transformed into 2 : 4-dimethyl 3 : 6-anhydro-β-methylgalactopyranoside (VIII) by the agency of hydrogen chloride or hydrogen bromide in air and in the process one methyl group is eliminated. Moreover both (XVI) and (XV) give on methylation with Purdie's reagents, 2 : 4 : 5-*trimethyl* 3 : 6-*anhydrogalactose dimethylacetal* (XVII). Two of the methyl groups of the latter, those attached to position 1, are easily removed on hydrolysis with dilute sulphuric acid to give 2 : 4 : 5-*trimethyl aldehydo* 3 : 6-*anhydrogalactose* (XVIII), which quickly restores the colour to Schiff's reagent and immediately decolorises potassium permanganate. Oxidation of (XVIII) with bromine yields 2 : 4 : 5-

trimethyl 3 : 6-*anhydrogalactonic acid* (XIX), which with ethereal diazomethane gives the corresponding *methyl* ester (XX). The latter is also produced by complete methylation of the 3 : 6-*anhydrogalactonic acid* (XIV) obtained from aldehydo 3 : 6-anhydrogalactose (XIII) by bromine oxidation.

Inspection of the above experimental facts demonstrates that the properties of the 3 : 6-anhydrogalactose and its derivatives are unusual in several ways. For instance, the α- and the β-form of 3 : 6-anhydromethylgalactopyranoside and the two forms of its 2 : 4-dimethyl derivative are transformed by excess of acid methyl alcohol into the corresponding dimethylacetals (XV and XVI respectively); and also worthy of note is the great ease with which the anhydromethylgalactopyranosides undergo acid hydrolysis to give the reducing methylated sugars, which appear to exist in the aldehydic forms (XIII) and (IX). These facts point to instability of the dicyclic system present in the 3 : 6-anhydromethylgalactosides. An examination of models furnishes an explanation of these remarkable properties; a molecule containing a 1 : 5-pyranose ring and a 3 : 6-anhydro-ring is in a state of considerable strain and furthermore this strain can be eliminated by the opening of either of the ring systems. Under the conditions employed in this work the etheric 3 : 6-anhydro-ring is more stable than the 1 : 5-pyranose ring and the molecule relieves itself of strain by the opening of the 1 : 5-ring; hence the formation of the aldehydo-sugars and the dimethylacetals. Elimination of strain due to the presence of the two ring systems is apparently not achieved by the rupture of the 3 : 6-anhydro-ring, the steric effect of which is so pronounced that it appears to govern the form of the molecule in which it exists. It is clear that the formation of the dicyclic structure in the anhydromethylgalactopyranoside is facilitated by the 1 : 5-pyranose ring being stabilised (as methylgalactopyranoside) before closure of the 3 : 6-anhydro-ring takes place.

The direct transformation of 2 : 4-dimethyl 3 : 6-anhydro-α-methylgalactopyranoside (IV) into the corresponding β-isomeride (VIII) appears to be a new phenomenon in the sugar series; the mechanism of the reaction involved in this isomerisation and also that involved in the transformation of 2 : 4-dimethyl 3 : 6-anhydrogalactose dimethylacetal (XVI) into the 2 : 4-dimethyl 3 : 6-anhydro-β-methylgalactopyranoside are not yet clear. With regard to the conversion of the anhydro-α-methylgalactoside (IV) into the β-form (VIII) it is noteworthy that treatment of 2 : 4-dimethyl 3 : 6-anhydro-α-methylgalactoside with an excess of a solution of hydrogen chloride in methyl alcohol affords an equilibrium mixture consisting of the dimethylacetal (XVI) and the anhydro-β-methylgalactoside (VIII) while little or no anhydro-α-methylgalactoside remains unchanged and hence it would appear that the dicyclic β-form (VIII) is more stable than the α-form (IV). On the other hand it is abundantly clear that the conversion of the dimethylacetal (XVI), which has only one ring, into the 2 : 4-dimethyl 3 : 6-anhydro-β-methylgalactoside (VIII), which possesses a two-ring system, cannot be explained on the basis of a change from an unstable configuration to a more stable one, because the acetal (XVI) has a more stable structure than the anhydro-β-methylgalactoside (VIII). Although the 2 : 4-dimethyl 3 : 6-anhydrogalactose dimethylacetal (XVI) can be crystallised (m. p. 36°), it is usually obtained as a liquid and it seems significant that both 2 : 4-dimethyl 3 : 6-anhydro-α-methylgalactoside (IV) and the acetal (XVI) are liquid while the 2 : 4-dimethyl 3 : 6-anhydro-β-methylgalactoside (VIII) obtained from both of these liquids is a crystalline compound (m. p. 83°); furthermore the conversion of (IV) and (XVI) into (VIII) proceeds more nearly to completion with gaseous hydrogen chloride than with an excess of a solution of hydrogen chloride in an organic solvent which dissolves all the reaction products. These facts suggest that both the transformation from the liquid α-form (IV) and from the liquid dimethylacetal (XVI) to the solid β-form (VIII) is a question of an equilibrium in which the β-form crystallises as it is produced, with the result that more of (IV) and of (XVI) will pass into the crystalline 2 : 4-dimethyl 3 : 6-anhydro-β-methylgalactoside.

Experimental.

6-*Tosyl* α-*Methylgalactopyranoside* (II).—A solution of syrupy anhydrous α-methylgalactopyranoside [prepared from the crystalline monohydrate (100 g.) by heating under reduced

pressure at 100—110°] in dry pyridine (150 c.c.) was treated with *p*-toluenesulphonyl chloride (1·5 mols.) for 12 hours at room temperature and for 2 days at 30°. The viscous product was poured into water with stirring and the insoluble syrupy precipitate was triturated many times with water to remove as much of the pyridine as possible. The crude material was triturated with methyl alcohol or acetone, and the crystalline 6-tosyl α-methylgalactoside filtered off, washed with acetone, and dried. Yield, 40 g.; m. p. 178° (decomp.). After recrystallisation from pyridine–light petroleum it had m. p. 188°, $[\alpha]_D^{17°}$ + 118° in pyridine (*c*, 1·4) (Ohle and Thiel, *loc. cit.*, record m. p. 170°, $[\alpha]_D^{18°}$ + 103·5°) (Found: C, 48·1; H, 5·8; OMe, 8·8; S, 9·4. Calc. for $C_{14}H_{20}O_8S$: C, 48·3; H, 5·8; OMe, 8·9; S, 9·2%).

Removal of the solvent under diminished pressure from the mother-liquors gave a syrupy product, which was dissolved in chloroform. The solution was extracted several times with dilute sulphuric acid to remove pyridine, with a solution of sodium bicarbonate, and finally with water, dried over anhydrous magnesium sulphate, filtered, and concentrated to a syrup, which was dissolved in ethyl alcohol and allowed to crystallise. Recrystallisation from ethyl alcohol gave a *ditosyl α-methylgalactopyranoside*, m. p. 148°, $[\alpha]_D^{16°}$ + 68° in pyridine (*c*, 2·0) (Found: C, 49·9; H, 5·1; OMe, 6·1. $C_{21}H_{26}O_{10}S_2$ requires C, 50·2; H, 5·2; OMe, 6·2%). The disposition of the two tosyl groups in this compound is now under investigation.

3 : 6-*Anhydro-α-methylgalactopyranoside* (III).—A solution of 6-tosyl α-methylgalactoside (5 g.) in ethyl alcohol (200 c.c.), after addition of N-sodium hydroxide (16 c.c.), was heated for 1 hour at 60°, neutralised with carbon dioxide, and evaporated to dryness under reduced pressure. Extraction of the solid residue with acetone gave 3 : 6-anhydro-α-methylgalactopyranoside in almost quantitative yield, m. p. 140°, $[\alpha]_D^{18°}$ + 80° in water (*c*, 1·0), after recrystallisation from ethyl acetate (Found: C, 48·0; H, 6·6; OMe, 17·7. Calc. for $C_7H_{12}O_5$: C, 47·7; H, 6·8; OMe, 17·6%).

2 : 4-*Dimethyl* 3 : 6-*Anhydro-α-methylgalactopyranoside* (IV).—3 : 6-Anhydro-α-methylgalactopyranoside (4 g.) was subjected to methylation with methyl iodide and silver oxide in the presence of sufficient acetone to dissolve the crystalline material. The partly methylated product, isolated by means of acetone, was given two further treatments with Purdie's reagents (without the addition of acetone) and then distilled, giving 2 : 4-*dimethyl* 3 : 6-*anhydro-α-methylgalactopyranoside* as a colourless mobile liquid (4·3 g.), b. p. (bath temp.) 90°/0·01 mm., $n_D^{17°}$ 1·4640, $[\alpha]_D^{17°}$ + 73° in water (*c*, 1·2), $[\alpha]_D^{15°}$ + 99° in ether (*c*, 0·6) (Found: OMe, 45·3; *M*, 208 by elevation of b. p. of chloroform. $C_9H_{16}O_5$ requires OMe, 45·6%; *M*, 204).

After being kept for 4 months in a tube closed with a rubber stopper, the liquid α-form had changed into a solid crystalline β-form. After recrystallisation from ether–light petroleum or, better, from a small volume of water 2 : 4-*dimethyl* 3 : 6-*anhydro-β-methylgalactopyranoside* had m. p. 83°, $[\alpha]_D^{18°}$ − 77° in water (*c*, 0·7), $[\alpha]_D^{12°}$ − 81° in methyl alcohol (*c*, 0·7), $[\alpha]_D^{18°}$ − 87° in chloroform (*c*, 0·8) (Found: C, 53·1; H, 8·0; OMe, 45·5; *M*, 202, by elevation of b. p. of chloroform. $C_9H_{16}O_5$ requires C, 52·9; H, 7·8; OMe, 45·6%; *M*, 204). The syrup obtained from the mother-liquors had a positive rotation ($[\alpha]_D$ + 21°), showing that complete transformation into the β-form had not taken place.

2 : 4-*Dimethyl* 3 : 6-*Anhydrogalactose* (IX).—(a) *Hydrolysis of* 2 : 4-*dimethyl* 3 : 6-*anhydro-β-methylgalactoside*. A solution of 2 : 4-dimethyl 3 : 6-anhydro-β-methylgalactoside (0·1 g.) in 0·1N-sulphuric acid (20 c.c.), which showed $[\alpha]_D$ − 70°, was heated for 2½ hours on the boiling water-bath. The hydrolysis was then complete and the rotation was constant ($[\alpha]_D$ + 21°); the solution was neutralised with 0·1N-sodium hydroxide (20 c.c.) and evaporated to dryness. Extraction of the residue with acetone gave 2 : 4-dimethyl 3 : 6-anhydrogalactose, m. p. 112° (after recrystallisation from ethyl alcohol–ether). This crystalline material changed to a syrup after a few days and it has not been found possible to repeat the preparation of the crystalline material. Several subsequent preparations have furnished a syrupy product.

A solution of 2 : 4-dimethyl 3 : 6-anhydro-β-methylgalactoside (0·0397 g.) in 0·1N-sulphuric acid showed $[\alpha]_D$ − 76° (initial value), − 68° (after 16 hours), − 55° (64 hours), − 42° (88 hours), − 21° (144 hours), − 2·5° (240 hours), + 23° (44 days). The solution ($[\alpha]_D$ + 23°) quickly restored the colour to Schiff's reagent.

A solution in N-sulphuric acid showed $[\alpha]_D$ − 70·5° (after 2¼ hours), − 65° (4 hours), − 54·5° (6 hours), − 46·5° (9 hours), − 9·5° (23 hours), + 20° (47 hours), + 23° (59 hours), + 25° (71 hours), + 26·5° (95 hours) (constant for 20 hours). The product isolated from this experiment was a colourless syrup which failed to crystallise. It restored the colour to Schiff's reagent and reduced hot Fehling's solution.

(b) *Hydrolysis of* 2 : 4-*dimethyl* 3 : 6-*anhydro-α-methylgalactopyranoside* (IV).—A solution of 2 : 4-dimethyl 3 : 6-anhydro-α-methylgalactoside (1·7 g.) in 0·1N-sulphuric acid (50 c.c.)

was heated on the boiling water-bath for 1 hour. The solution, which now had $[\alpha]_D$ + 22°, was neutralised with barium carbonate, filtered, and evaporated to a syrup, which was distilled, giving a colourless liquid, b. p. (bath temp.) 150°/0·03 mm., $n_D^{17°}$ 1·4830, $[\alpha]_D^{16°}$ + 24° in water (*c*, 1·4). This material, *aldehydo* 2 : 4-*dimethyl* 3 : 6-*anhydrogalactose*, restored the colour to Schiff's reagent; it decolorised an aqueous solution of potassium permanganate and reduced hot Fehling's solution actively (Found : OMe, 33·0. $C_8H_{14}O_5$ requires OMe, 32·6%).

A solution of 2 : 4-dimethyl 3 : 6-anydro-α-methylgalactopyranoside (0·3 g.) in 0·1N-sulphuric acid had $[\alpha]_D$ + 53° (initial value), + 47·5° (after 2½ hours), + 28·7° (19½ hours), + 26·5° (26 hours), + 26° (39 hours) (constant for 6 days). The solution was neutralised with barium carbonate, filtered, and evaporated under reduced pressure to a syrup, which was distilled, giving 2 : 4-dimethyl 3 : 6-anhydrogalactose, b. p. (bath temp.) 145°/0·05 mm., $n_D^{18°}$ 1·4820 (Found : OMe, 33·3%). The distillate restored the colour to Schiff's reagent and readily reduced hot Fehling's solution.

When a solution of this syrupy 2 : 4-dimethyl 3 : 6-anhydrogalactose (50 mg.) (prepared from either the α- or the β-form of the corresponding galactoside) was treated with aniline (30 mg.) in boiling ethyl alcohol (2 c.c.) for 3 hours, the corresponding 2 : 4-*dimethyl* 3 : 6-*anhydrogalactose anilide* was produced. Removal of excess of the solvent furnished crystals, m. p. 123°, $[\alpha]_D^{18°}$ + 56° (equilibrium value) in ethyl alcohol (*c*, 0·8) (after recrystallisation from ethyl alcohol–ether) (Found : C, 63·5; H, 7·4; OMe, 23·0; N, 5·4. $C_{14}H_{19}O_4N$ requires C, 63·4; H, 7·2; OMe, 23·4; N, 5·3%).

2 : 4-*Dimethyl* 3 : 6-*Anhydrogalactonolactone* (XI).—A solution of 2 : 4-dimethyl 3 : 6-anhydrogalactose (0·5 g.) in water (10 c.c.) was treated with bromine (0·5 c.c.) and left at room temperature for 3 days. The solution was freed from excess of the bromine by aeration, neutralised with silver oxide, filtered before and after treatment with hydrogen sulphide, and evaporated to dryness under reduced pressure. The syrupy product was distilled, giving a mixture of 2 : 4-*dimethyl* 3 : 6-*anhydrogalactonolactone* and the free acid as a liquid, b. p. (bath temp.) 150°/0·01 mm., $n_D^{17°}$ 1·4690, $[\alpha]_D^{18°}$ + 36° (initial value) in water (*c*, 1·3). The distillate showed an acid reaction to Congo paper (Found : OMe, 32·8. $C_8H_{12}O_5$ requires OMe, 32·95%).

Treatment of this lactone with methyl-alcoholic ammonia for 2 days at − 5° gave the *amide* of 2 : 4-dimethyl 3 : 6-anhydrogalactonic acid, m. p. 151°, $[\alpha]_D^{17°}$ + 81° in water (*c*, 0·7) (after recrystallisation from ethyl alcohol). The yield was not good owing to the lactone being contaminated with some of the corresponding acid (Found : C, 46·9; H, 7·4; OMe, 30·1; N, 6·8. $C_8H_{15}O_5N$ requires C, 46·8; H, 7·3; OMe, 30·2; N, 6·8%).

2 : 4-*Dimethyl* 3 : 6-*Anhydrogalactonic Acid.*—When a solution of the lactone was slowly evaporated in air, crystals of 2 : 4-*dimethyl* 3 : 6-*anhydrogalactonic acid* (X) were obtained, m. p. 152°, $[\alpha]_D^{19°}$ − 66°, initial value in water (*c*, 1·0) (after recrystallisation from ethyl acetate) (Found : C, 46·4; H, 6·9; OMe, 29·1. $C_8H_{14}O_6$ requires C, 46·6; H, 6·9; OMe, 30·1%).

The following method proved to be better than the previous one for the preparation of 2 : 4-dimethyl 3 : 6-anhydrogalactonic acid. To a solution of 2 : 4-dimethyl galactose (0·5 g.) in water (15 c.c.), bromine (1 c.c.) and excess of basic lead carbonate were added. From time to time the mixture was shaken and after 12 hours the oxidation was complete. The solution was filtered, treated with hydrogen sulphide, filtered, and concentrated to half volume to remove hydrogen sulphide. The solution was neutralised with silver oxide to remove hydrobromic acid, filtered before and after treatment with hydrogen sulphide, and evaporated to dryness, giving crystalline 2 : 4-dimethyl 3 : 6-anhydrogalactonic acid, m. p. 152°, $[\alpha]_D^{15°}$ + 66° in water (*c*, 0·9) (after recrystallisation from ethyl acetate) (Found : OMe, 29·9%; equiv., 207). The stability of this acid is shown by the fact that it can be sublimed unchanged in a vacuum. If, however, the acid is heated for 4 hours above its m. p. and then distilled, some lactone is produced as a colourless liquid, b. p. (bath temp.) 140—150°/0·01 mm., $n_D^{11°}$ 1·4720; $[\alpha]_D^{14°}$ + 4°, initial value in water (*c*, 1·2), constant for 4 days; no change in rotation took place when the solution was boiled, but after about 3 minutes' heating with 1·5 equivalent proportions of N-sodium hydroxide the rotation was + 59°.

Methyl 2 : 4-*Dimethyl* 3 : 6-*Anhydrogalactonate.*—When a solution of 2 : 4-dimethyl 3 : 6-anhydrogalactonic acid (0·03 g.) in methyl alcohol (2 c.c.) was treated with a slight excess of ethereal diazomethane (*i.e.*, until the yellow colour due to excess of diazomethane persisted for several minutes), esterification proceeded rapidly; removal of the solvent gave methyl 2 : 4-dimethyl 3 : 6-anhydrogalactonate, m. p. 51°, $[\alpha]_D^{15°}$ + 67° in water (*c*, 3·3) (after recrystallisation from ether–light petroleum) (Found : C, 49·3; H, 7·3; OMe, 41·3. Calc. for $C_9H_{16}O_6$: C, 49·1; H, 7·35; OMe, 42·25%) (see Forbes and Percival, J., 1939, 1844). Treatment of this ester with methyl-alcoholic ammonia gave an almost quantitative yield of the corresponding

amide of 2 : 4-dimethyl 3 : 6-anhydrogalactonic acid, m. p. 151° (after recrystallisation from ethyl alcohol).

Oxidation of 2 : 4-*Dimethyl* 3 : 6-*Anhydro-α-methylgalactopyranoside with Nitric Acid.*—A solution of 2 : 4-dimethyl 3 : 6-anhydro-α-methylgalactoside (0·6 g.) in nitric acid (10 c.c., *d* 1·42) was heated for 1 hour at 50—60° and for 2 hours at 80°. Water was then added and the solution was evaporated to dryness under reduced pressure to remove nitric acid, water and finally methyl alcohol being added to facilitate the process. When quite free from nitric acid, the acidic product was distilled in the presence of a few mg. of barium carbonate, giving a colourless distillate (0·4 g.), b. p. 140°/0·02 mm., $n_D^{18°}$ 1·4610 (Found : OMe, 29%). The distillate reacted acid to Congo paper and when treated with methyl-alcoholic ammonia it yielded the amide of 2 : 4-dimethyl 3 : 6-anhydrogalactonic acid, m. p. and mixed m. p. 151°, $[\alpha]_D^{15°}$ + 79° in water (*c*, 1·2) (after recrystallisation from ethyl alcohol).

Transformation of 2 : 4-*Dimethyl* 3 : 6-*Anhydro-α-methylgalactopyranoside* (IV) *into* 2 : 4-*Dimethyl* 3 : 6-*Anhydro-β-methylgalactopyranoside* (VIII).—(a) *With hydrogen chloride.* 2 : 4-Dimethyl 3 : 6-anhydro-α-methylgalactoside (20 mg.), contained in a small ignition tube, was subjected to the action of dry hydrogen chloride, issuing from a narrow jet, for about 30 seconds. On scratching, the product solidified and after removal of the hydrogen chloride, either by evacuation over soda lime or, better, by dissolving the solid in ether and neutralising the ethereal solution with silver carbonate, followed by removal of the solvent, there was obtained 2 : 4-dimethyl 3 : 6-anhydro-β-methylgalactopyranoside, m. p. and mixed m. p. 83°, $[\alpha]_D^{18°}$ − 77° in water (*c*, 1·0) (after recrystallisation from water) (Found : OMe, 45·3%).

(b) *With hydrogen bromide.* By following the procedure used in (*a*), the α-form (20 mg.) gave the β-form in good yield, m. p. and mixed m. p. 83° (after recrystallisation from water).

(c) *With ethereal hydrogen chloride.* 2 : 4-Dimethyl 3 : 6-anhydro-α-methylgalactoside shows $[\alpha]_D$ + 99° in ethereal solution; when dissolved in ethereal hydrogen chloride (2·4N), the solution had $[\alpha]_D^{15°}$ − 22° (initial value). Treatment of the liquid α-form (50 mg.) with 1 drop of ethereal hydrogen chloride (2·4N) caused almost immediate crystallisation and, when dissolved in ether, the crude product showed $[\alpha]_D^{15°}$ − 60°. This second procedure therefore appears to be the better method for effecting the isomerisation. Removal of the hydrogen chloride, followed by crystallisation from water, gave the pure β-form, m. p. and mixed m. p. 83°.

(d) *With ethyl-alcoholic hydrogen chloride.* Treatment of the liquid α-form (20 mg.) with 1 drop of ethyl-alcoholic hydrogen chloride (2·6N) caused immediate crystallisation. Ether (1—2 c.c.) was added, and the hydrogen chloride immediately neutralised with silver carbonate; the solution was filtered and freed from solvent, and the product crystallised from ether–light petroleum, giving the pure β-form, m. p. and mixed m. p. 83°.

(e) *With methyl-alcoholic hydrogen chloride.* The α-form (30 mg.) was transformed into the β-form by treating it with 1 drop of methyl-alcoholic hydrogen chloride (2N). Isolated as under (d), the 2 : 4-dimethyl 3 : 6-anhydro-β-methylgalactoside had m. p. and mixed m. p. 83°, $[\alpha]_D^{18°}$ − 82° in methyl alcohol (*c*, 0·5).

Unsuccessful attempts were also made to effect the isomerisation with small amounts of chloroformic hydrogen chloride (0·4N), ethyl-alcoholic hydrogen chloride (0·5N), and with hydrochloric acid (0·1N). The 2 : 4-dimethyl 3 : 6-anhydro-α-methylgalactopyranoside is not affected by solutions of ammonia in ether or in methyl alcohol.

Preparation of 2 : 4-*Dimethyl* 3 : 6-*Anhydrogalactose Dimethylacetal* (XVI).—(a) *From* 2 : 4-*dimethyl* 3 : 6-*anhydro-α-methylgalactoside.* A solution of 2 : 4-dimethyl 3 : 6-anhydro-α-methylgalactoside (0·118 g.) in 0·5% methyl-alcoholic hydrogen chloride (9 c.c.) showed the following change in rotation when left at room temperature : $[\alpha]_D$ *ca.* + 54° (after 1 min.), + 48° (3 mins.), + 40° (40 mins.), + 33·7° (100 mins.), + 30° (170 mins.), + 28° (840 mins.). Neutralisation of the mineral acid, followed by removal of the solvent, gave 2 : 4-dimethyl 3 : 6-anhydrogalactose dimethylacetal, which distilled as a colourless mobile liquid, b. p. (bath temp.) 107°/0·03 mm., $n_D^{18°}$ 1·4525, $[\alpha]_D^{18°}$ + 20° in water (*c*, 2·0) (Found : OMe, 49·7. $C_{10}H_{20}O_6$ requires OMe, 52·6%). The low methoxyl value is due to the presence of some 2 : 4-dimethyl 3 : 6-anhydro-β-methylgalactoside. When the 2 : 4-dimethyl 3 : 6-anhydro-α-methylgalactoside is boiled with 1·5% methyl-alcoholic hydrogen chloride, the dimethylacetal is accompanied by more 2 : 4-dimethyl 3 : 6-anhydro-β-methylgalactoside than is the case when cold 0·5% methyl-alcoholic hydrogen chloride is employed. Thus from the product obtained with boiling acid methyl alcohol in this way there is produced a liquid, b. p. 110—120° (bath temp.)/0·03 mm., $n_D^{15°}$ 1·4564 (Found : OMe, 46·4%), which crystallised on nucleation with 2 : 4-dimethyl 3 : 6-anhydro-β-methylgalactoside. The crystals were isolated by tiling and had m. p. and mixed m. p. 82° (after recrystallisation from water).

(b) *From* 2 : 4-*dimethyl* 3 : 6-*anhydro*-β-*methylgalactoside.* A solution of 2 : 4-dimethyl 3 : 6-anhydro-β-methylgalactoside in 1% methyl alcohol at room temperature showed $[\alpha]_D$ *ca.* − 46° (after 2 mins.), − 20° (6 mins.), + 20° (23 mins.), + 40° (4 hours), + 30° (6 hours) (constant for several hours). The action of 0·5% methyl-alcoholic hydrogen chloride also effects the same rotational change and from 2 : 4-dimethyl 3 : 6-anhydro-β-methylgalactoside (0·4 g.) there was obtained 2 : 4-dimethyl 3 : 6-anhydrogalactose dimethylacetal (0·37 g.), b. p. (bath temp.) 110°/0·02 mm., $n_D^{20°}$ 1·4540, $[\alpha]_D$ + 23° in water (*c*, 0·8) (Found : OMe, 51·0%).

When specimens of 2 : 4-dimethyl 3 : 6-anhydrogalactose dimethylacetal (30 mg.) prepared as in (a) and (b) were subjected to the action of gaseous hydrogen chloride for about 30 seconds, the liquid acetal was almost immediately converted into the crystalline 2 : 4-dimethyl 3 : 6-anhydro-β-methylgalactoside. The crystalline product was dissolved in ether (2 c.c.); the solution was neutralised with silver carbonate, filtered, and freed from solvent, and 2 : 4-dimethyl 3 : 6-anhydro-β-methylgalactoside was obtained, m. p. and mixed m. p. 83°, (after recrystallisation from water) (Found : OMe, 45·3%).

A solution of the 2 : 4-dimethyl 3 : 6-anhydrogalactose dimethylacetal (0·2 g.) in pyridine (0·3 c.c.) was treated with *p*-nitrobenzoyl chloride (0·18 g.) for 3 days at room temperature. The syrupy crystalline mass was triturated with a saturated solution of potassium bicarbonate to react with the excess of the *p*-nitrobenzoyl chloride; the syrupy product was dissolved in chloroform (10 c.c.) and the chloroform solution was washed twice with 0·1N-sulphuric acid to remove pyridine, once with an aqueous solution of sodium bicarbonate, and then twice with water. After being dried over anhydrous magnesium sulphate, the chloroform solution was filtered and evaporated to a syrup, which was distilled, giving fraction (i) 2 : 4-dimethyl 3 : 6 anhydro-β-methylgalactoside (0·05 g.), b. p. (bath temp.) 90°/0·03 mm.; this material solidified immediately and had m. p. and mixed m. p. 83° (after recrystallisation from water); fraction (ii) 5-p-*nitrobenzoyl* 2 : 4-*dimethyl* 3 : 6-*anhydrogalactose dimethylacetal* (0·2 g.), b. p. (bath temp.) 215°/0·03 mm., $n_D^{20°}$ 1·4513 (Found : C, 52·8; H, 6·1; OMe, 32·0; N, 3·7. $C_{17}H_{23}O_9N$ requires C, 53·0; H, 6·0; OMe, 32·2; N, 3·6%).

In order to make certain that the pure 2 : 4-dimethyl 3 : 6-anhydrogalactose dimethylacetal can be transformed into the crystalline 2 : 4-dimethyl 3 : 6-anhydro-β-methylgalactoside the acetal was regenerated from the mono-*p*-nitrobenzoate and treated with hydrogen chloride as follows. To a solution of the mono-*p*-nitrobenzoate (0·5 g.) in dry methyl alcohol (15 c.c.), sodium (8 mg.) was added and the solution was left for 12 hours at room temperature. Removal of the solvent under reduced pressure gave a mixture of crystalline methyl *p*-nitrobenzoate and the syrupy acetal. The mixture was triturated with water and filtered to remove the methyl *p*-nitrobenzoate; evaporation of the filtrate gave the crude acetal, which was purified by extraction with a mixture of acetone (5 c.c.) and ether (15 c.c.). The 2 : 4-dimethyl 3 : 6-anhydrogalactose dimethylacetal was obtained as a colourless liquid (0·25 g.), b. p. (bath temp.) 95°/0·02 mm., $n_D^{17°}$ 1·4525, $[\alpha]_D^{18°}$ + 35° in water (*c*, 0·7) (Found : C, 50·7; H, 8·6; OMe, 51·9%). Redistillation of this liquid acetal gave a colourless distillate, which crystallised spontaneously on keeping, and after recrystallisation from light petroleum containing a little ether the 2 : 4-*dimethyl* 3 : 6-*anhydrogalactose dimethylacetal* had m. p. 36°; $[\alpha]_D^{18°}$ + 36° in water (*c*, 3·6) (Found : C, 50·9; H, 8·3; OMe, 52·3. $C_{10}H_{20}O_6$ requires C, 50·8; H, 8·6; OMe, 52·6%).

When the pure liquid acetal (20 mg.) was subjected to the action of gaseous hydrogen chloride for about 30 seconds at room temperature, it was quickly transformed into the crystalline dimethyl 3 : 6-anhydro-β-methylgalactoside. The hydrogen chloride was removed as in previous cases and there was obtained 2 : 4-dimethyl 3 : 6-anhydro-β-methylgalactopyranoside, m. p. 83°, $[\alpha]_D^{20°}$ − 78° in water (*c*, 0·6) (after recrystallisation from water) (Found : C, 52·8; H, 7·95; OMe, 45·65%). The same transformation can be effected by means of hydrogen bromide.

Hydrolysis of 2 : 4-*Dimethyl* 3 : 6-*Anhydrogalactose Dimethylacetal.*—A solution of the 2 : 4-dimethyl 3 : 6-anhydrogalactose dimethylacetal in 0·1N-sulphuric acid had $[\alpha]_D$ + 36° (initial value); + 33° (after 2 days); + 30° (3 days); + 28° (4 days); + 26° (7 days); + 25° (9 days); + 20·5° (14 days, constant value). The solution ($[\alpha]_D$ + 20·5°) quickly restored the colour to Schiff's reagent.

The dimethylacetal (0·2 g.), dissolved in 0·1N-sulphuric acid (5 c.c.), was hydrolysed by heating for 1½ hours on the boiling water-bath; after neutralisation of the sulphuric acid with barium carbonate the solution was filtered and evaporated to dryness under reduced pressure to give syrupy 2 : 4-dimethyl aldehydo 3 : 6-anhydrogalactose, b. p. (bath temp.)

140°/0·03 mm., n_D 1·4825, $[\alpha]_D$ + 20° in water (*c*, 1·0) (Found : OMe, 33·6%). The distillate readily reduced Fehling's solution and restored the colour to Schiff's reagent. When it was treated with ethyl-alcoholic aniline (see above), the characteristic anilide of 2 : 4-dimethyl 3 : 6-anhydrogalactose was obtained, m. p. and mixed m. p. 122° (after recrystallisation from ethyl alcohol–ether).

2 : 4 : 5-*Trimethyl* 3 : 6-*Anhydrogalactose Dimethylacetal* (XVII).—2 : 4-Dimethyl 3 : 6-anhydrogalactose dimethylacetal (2·5 g.; OMe, 51·0%) which probably contained a little 2 : 4-dimethyl 3 : 6-anhydromethylgalactoside was methylated once with silver oxide and methyl iodide to give a liquid, b. p. (bath temp.) 120°/0·03 mm., $n_D^{21°}$ 1·4465, $[\alpha]_D$ + 28° in water (*c*, 0·9) (Found : OMe, 57·5%). This product was then treated with 0·5% methyl-alcoholic hydrogen chloride (50 c.c.) for 12 hours; neutralisation of the mineral acid with silver carbonate, followed by removal of the solvent, furnished a liquid, which was treated once with Purdie's reagents. The product obtained in this way was distilled, giving 2 : 4 : 5-*trimethyl* 3 : 6-*anhydrogalactose dimethylacetal* as a colourless mobile liquid (2·4 g.), b. p. (bath temp.) 120°/0·03 mm., $n_D^{18°}$ 1·4450, $[\alpha]_D^{12°}$ + 41·0° in water (*c*, 0·8) (Found : OMe, 61·1. $C_{11}H_{21}O_6$ requires OMe, 61·9%). A 1% solution of 2 : 4 : 5-trimethyl 3 : 6-anhydrogalactose dimethylacetal in 0·1N-sulphuric acid showed $[\alpha]_D^{13°}$ + 38°; on keeping for 20 hours, no change in rotation was observed and the solution neither reduced Fehling's solution nor restored the colour to Schiff's reagent.

2 : 4 : 5-*Trimethyl Aldehydo* 3 : 6-*Anhydrogalactose* (XVIII).—A solution of the 2 : 4 : 5-trimethyl 3 : 6-anhydrogalactose dimethylacetal (2·2 g.) in 0·01N-sulphuric acid (45 c.c.) was heated for 2 hours on the boiling water-bath; the rotation changed from $[\alpha]_D$ + 37° (initial value) to + 27° (equilibrium value). The solution at this stage reduced Fehling's solution actively and quickly restored the colour to Schiff's reagent. After neutralisation of the sulphuric acid with barium carbonate, and removal of the solvent under reduced pressure, there was obtained a liquid, which was purified by extraction with ether. This material was distilled, giving 2 : 4 : 5-*trimethyl aldehydo* 3 : 6-*anhydrogalactose* (0·9 g.), b. p. (bath temp.) 105°/0·02 mm., $n_D^{17°}$ 1·4510, $[\alpha]_D^{19°}$ + 41° in water (*c*, 0·5) (Found : OMe, 45·8. $C_9H_{16}O_5$ requires OMe, 45·6%). The low yield of the 2 : 4 : 5-trimethyl 3 : 6-anhydrogalactose may be partly due to loss which is inevitable during the concentration of an aqueous solution of such a volatile liquid and partly due to decomposition during distillation; support for the latter view is forthcoming from the observation that a second viscous fraction can be distilled, b. p. (bath temp.) 160°/0·02 mm., $n_D^{18°}$ 1·4710 (Found : OMe, 40·6%), which also reduces Fehling's solution and gives a positive Schiff's test.

The 2 : 4 : 5-trimethyl 3 : 6-anhydrogalactose appeared to react with aniline; heat was produced when equimolecular proportions were mixed but no crystalline product was isolated.

When a solution of the 2 : 4 : 5-trimethyl 3 : 6-anhydrogalactose (0·2 g.) in 1% methyl-alcoholic hydrogen chloride (10 c.c.) was kept at room temperature for 12 hours, the corresponding acetal was regenerated. The solution was neutralised with silver carbonate, filtered, and evaporated to dryness, giving 2 : 4 : 5-trimethyl galactose dimethylacetal (0·2 g.), b. p. (bath temp.) 115°/0·02 mm., $n_D^{14°}$ 1·4450, $[\alpha]_D^{15°}$ + 42° in water (*c*, 1·1) (Found : OMe, 61·1%).

2 : 4 : 5-*Trimethyl* 3 : 6-*Anhydrogalactonic Acid* (XIX).—A solution of 2 : 4 : 5-trimethyl 3 : 6-anhydrogalactose (0·45 g.) in water (6 c.c.) was treated with bromine (1 c.c.) for 2 days at room temperature. The solution, which no longer reduced Fehling's solution, was freed from excess of the bromine by aeration, neutralised with silver oxide, filtered before and after treatment with hydrogen sulphide, and evaporated to dryness under reduced pressure, giving a syrup, which was purified by extraction with ether. The 2 : 4 : 5-*trimethyl* 3 : 6-*anhydrogalactonic acid* (0·4 g.) was a mobile liquid which had $[\alpha]_D^{17°}$ + 64°. The substance reacted acid to Congo paper [Found : equiv., 215 (by direct titration with N/50-sodium hydroxide); OMe, 40·5. $C_9H_{16}O_6$ requires equiv., 220; OMe, 42·2%].

Methyl 2 : 4 : 5-*Trimethyl* 3 : 6-*Anhydrogalactonate* (XX).—When a solution of 2 : 4 : 5-trimethyl 3 : 6-anhydrogalactonic acid (0·35 g.) in methyl alcohol (2 c.c.) was treated with excess of an ethereal solution of diazomethane, esterification rapidly ensued, and on removal of the solvent there was obtained *methyl* 2 : 4 : 5-*trimethyl* 3 : 6-*anhydrogalactonate* as a colourless liquid, b. p. (bath temp.) 115°/0·03 mm., $n_D^{19°}$ 1·4480, $[\alpha]_D^{17°}$ + 67° in water (*c*, 1·1). Yield, 0·31 g. [Found : equiv., 230 (by heating with N/50-sodium hydroxide); OMe, 52·1. $C_{10}H_{18}O_6$ requires equiv., 234; OMe, 53·0%]. By heating with barium hydroxide one methoxyl group is eliminated with the formation of a barium salt (Found : OMe, 38·0. Calc. for loss of one methoxyl group : OMe, 39·8%) (see Haworth, Hirst, and Smith, J., 1934, 1556).

This ester failed to give either a crystalline amide or a methylamide. The *brucine* salt of

2 : 4 : 5-trimethyl galactonic acid was prepared from the ester as follows. A solution of methyl 2 : 4 : 5-trimethyl 3 : 6-anhydrogalactonate (0·11 g.) in 0·1N-sodium hydroxide (5·0 c.c.) was heated for 1 hour at 60°; 0·1N-sulphuric acid (5·0 c.c.) was then added, and the solution evaporated to dryness. Extraction of the residue with acetone gave 2 : 4 : 5-trimethyl 3 : 6-anhydrogalactonic acid (yield, almost quantitative). To a solution of this acid in acetone (2 c.c.) the calculated amount of brucine (1 mol.) was added. More acetone (2 c.c.) was then added, followed by ether and light petroleum until a faint turbidity was produced. On cooling, the brucine salt separated in needles, m. p. 114°, $[\alpha]_D$ *ca.* − 3° in water (*c*, 3·0), after recrystallisation from ethyl acetate (Found : OMe, 24·0; N, 4·7. $C_{32}H_{42}O_{10}N_2$ requires OMe, 25·2; N, 4·5%).

Synthesis of 3 : 6-*Anhydro*-β-*methylgalactopyranoside* (VII).—*Method A.* 6-Tosyl galactose, prepared according to the directions of Ohle and Thiel (*Ber.*, 1933, **66**, 528), had m. p. 128°, $[\alpha]_D^{18°}$ + 46° in pyridine (*c*, 2·0). To a solution of 6-tosyl galactose (14·5 g.) in pyridine (75 c.c.) cooled to − 10°, acetic anhydride (20 c.c.) was slowly added with stirring. The acetylation mixture was kept for 12 hours at 0° and then poured into water, giving a syrup; this was freed from pyridine, most of it by trituration with water and the last traces by washing a chloroform solution of the acetate several times with 3N-sulphuric acid. The chloroform solution was then washed with sodium bicarbonate solution and with water, dried over anhydrous magnesium sulphate, and filtered. Removal of the solvent under diminished pressure gave a syrup, which was dissolved in a small volume of methyl alcohol and left at room temperature for 12 hours, crystallisation then appearing to be complete. After a second recrystallisaton from methyl alcohol the 6-tosyl tetra-acetyl galactose had m. p. 107°, $[\alpha]_D$ + 42° in chloroform (*c*, 1·3); yield, 16·0 g. (Ohle and Thiel, *loc. cit.*, record m. p. 127°, $[\alpha]_D$ + 9·3° in chloroform for the β-form and m. p. 147°, $[\alpha]_D$ + 16·1° in chloroform for the α-form) (Found : C, 50·3; H, 5·3; S, 6·55. Calc. for $C_{21}H_{26}O_{12}S$: C, 50·2; H, 5·2; S, 6·4%).

6-Tosyl tetra-acetyl galactose (3 g.) was treated for 2½ hours at room temperature with a saturated solution of hydrogen bromide in glacial acetic acid (12 c.c., saturated at 0°). The tosyl acetate quickly dissolved, giving a pale yellow viscous liquid from which no crystalline material separated. The pale yellow liquid was diluted with ether (50 c.c.) and poured into ice-water with stirring, and the aqueous layer separated immediately. From the ethereal layer crystals separated; these were filtered off, washed with ether, and dried [yield, 1·3 g.; m. p. 149° (decomp.)]. Benzene (40 c.c.) was added to the ethereal mother-liquors and the solution was washed three times with water, dried over anhydrous magnesium sulphate, and filtered. Removal of the solvent from the filtrate yielded more of the acetobromo-compound, which, when crystallised from benzene–ether–light petroleum, had m. p. 148° (decomp.) (yield, 1·7 g.). After recrystallisation from ethyl alcohol the 6-tosyl α-acetobromogalactose had m. p. 149° (decomp.), $[\alpha]_D^{20°}$ + 165° in chloroform (*c*, 0·9) (Found : C, 43·8; H, 4·7; S, 6·0; Br, 14·3. Calc. for $C_{19}H_{23}O_{10}SBr$: C, 43·6; H, 4·2; S, 5·8; Br, 14·5%).

A solution of 6-tosyl α-acetobromogalactose (12·9 g.) in dry methyl alcohol (300 c.c.) was shaken with an excess of dry silver carbonate for 12 hours. The solution was filtered and evaporated under reduced pressure, giving 6-tosyl 2 : 3 : 4-triacetyl β-methylgalactoside, which did not crystallise. It had $[\alpha]_D^{18°}$ *ca.* 2·5° in chloroform (*c*, 1·0) (Found : OMe, 6·8. $C_{20}H_{26}O_{11}S$ requires OMe, 6·6%).

To a solution of the 6-tosyl 2 : 3 : 4-triacetyl β-methylgalactoside, obtained in the previous experiment, in dry methyl alcohol (200 c.c.) there was added a small amount of sodium (*ca.* 20 mg.) (see Zemplén and Pacsu, *Ber.*, 1929, **62**, 1613). Deacetylation proceeded smoothly and after 36 hours the solution was evaporated to dryness, giving crystalline 6-*tosyl* β-*methylgalactopyranoside*, m. p. 137°, $[\alpha]_D$ *ca.* − 3·5° in pyridine (*c*, 0·8) (after crystallisation from acetone–ether–light petroleum or from ethyl alcohol–light petroleum). Yield, 7 g. (Found : C, 48·6; H, 5·9; OMe, 8·8; S, 9·1. $C_{14}H_{19}O_8S$ requires C, 48·3; H, 5·25; OMe, 8·9; S, 9·2%).

A solution of 6-tosyl β-methylgalactoside (4·1 g.) in ethyl alcohol (50 c.c.) was heated under reflux for 2 hours with N-sodium hydroxide (13 c.c.; calc. for 1 equiv., 11·8 c.c.). The solution was neutralised with carbon dioxide and evaporated to dryness under reduced pressure. The residue was exhaustively extracted with acetone and on removal of the solvent there was obtained a quantitative yield of 3 : 6-*anhydro*-β-*methylgalactopyranoside*, m. p. 119°, $[\alpha]_D^{18°}$ − 115° in water (*c*, 1·0) (after crystallisation from ethyl acetate) (Found : C, 48·0; H, 6·85; OMe, 17·65. $C_7H_{12}O_5$ requires C, 47·7; H, 6·9; OMe, 17·6%).

Method B. A Carius tube containing well-powdered, dry α-penta-acetyl galactose (5 g.) was cooled in liquid air, and dry hydrogen bromide admitted. After about 15 c.c. of liquid hydrogen bromide had collected and solidified, the tube was sealed off and left at room

temperature for 8 hours. The reaction mixture was then cooled in liquid air and when the contents of the tube had solidified the tube was opened. On keeping at room temperature the hydrogen bromide melted and most of it volatilised, leaving a reddish syrupy residue which still contained hydrogen bromide. A solution of the syrup in chloroform (100 c.c.) was quickly washed with ice-cold water (twice) and with sodium bicarbonate solution (once) and then with water (once). After the chloroform solution had been dried over anhydrous magnesium sulphate, it was filtered, and evaporated under reduced pressure, giving 1 : 6-acetodibromogalactose (cf. Schlubach and Wagenitz, *Ber.*, 1932, **65**, 304). The product did not crystallise when kept for 2 hours and hence it was converted into 2 : 3 : 4-triacetyl β-methylgalactoside 6-bromohydrin as follows. A solution of the syrupy 1 : 6-acetodibromogalactose (11 g.) in dry methyl alcohol (200 c.c.) was shaken for 3 hours with an excess of silver carbonate. The solution was filtered and evaporated to dryness under diminished pressure, giving 2 : 3 : 4-triacetyl β-methylgalactopyranoside 6-bromohydrin (8·0 g.), m. p. 94° (after recrystallisation from ethyl alcohol or aqueous alcohol) (Found: OMe, 8·0. Calc. for $C_{13}H_{19}O_8Br$: OMe, 8·1%).

To a solution of 2 : 3 : 4-triacetyl β-methylgalactoside 6-bromohydrin (4 g.) in dry methyl alcohol (100 c.c.), sodium (15 mg.) was added. After keeping overnight, the deacetylation was complete and removal of the solvent under diminished pressure gave β-*methylgalactopyranoside* 6-*bromohydrin* (VI), m. p. 106° after sintering at 75° (after recrystallisation from dioxan). The substance appeared to contain dioxan of crystallisation and after drying under reduced pressure over phosphoric oxide it had $[\alpha]_D^{20°}$ + 11° in water (*c*, 1·3) (Found: C, 36·1; H, 6·0; OMe, 15·7; Br, 25·2. $C_7H_{13}O_5Br,\frac{1}{2}C_4H_8O_2$ requires C, 35·8; H, 5·7; OMe, 15·4; Br, 26·6. $C_7H_{13}O_5Br$ requires C, 32·7; H, 5·1; OMe, 12·05; Br, 31·1%).

A solution of β-methylgalactoside 6-bromohydrin (1·0 g.) in water (10 c.c.) was warmed for 1 hour at 80° with N-sodium hydroxide (10 c.c.). The solution was cooled, neutralised with carbon dioxide, and evaporated to dryness under reduced pressure. The 3 : 6-anhydro-β-methylgalactoside was extracted from the residue with a mixture of ethyl acetate and ethyl alcohol (1 : 1) and on removal of the solvent the product crystallised spontaneously (yield, almost quantitative). In order to remove a small amount of impurity which could not be eliminated by crystallisation the substance was distilled, b. p. (bath temp.) 190°/0·07 mm., m. p. 119° alone or in admixture with a specimen previously prepared from 6-tosyl β-methylgalactoside (see above). $[\alpha]_D^{20°}$ − 114° in water (*c*, 0·5) (after recrystallisation from ethyl acetate).

Complete methylation of 3 : 6-anhydro-β-methylgalactopyranoside prepared by each of the methods (A and B), by three treatments with Purdie's reagents, yielded 2 : 4-dimethyl 3 : 6-anhydro-β-methylgalactopyranoside (in the first Purdie methylation sufficient acetone was added to the methyl iodide to dissolve the 3 : 6-anhydro-β-methylgalactoside). The product had m. p. 83°, $[\alpha]_D^{18°}$ − 76° in water (*c*, 1·0). No depression of the m. p. was observed when it was mixed with 2 : 4-dimethyl 3 : 6-anhydro-β-methylgalactoside prepared from the dimethyl 3 : 6-anhydro-α-methylgalactoside or from the 2 : 4-dimethyl 3 : 6-anhydrogalactose dimethylacetal by the methods previously described.

Preparation of 3 : 6-*Anhydrogalactose Dimethylacetal* (XV).—(a) *From* 3 : 6-*anhydro-α-methylgalactoside.* To a solution of 3 : 6-anhydro-α-methylgalactoside (5·2 g.) in methyl alcohol (90 c.c.) which showed $[\alpha]_D$ + 90°, was added methyl alcohol (10 c.c.) containing hydrogen chloride (0·8 g.). The solution had $[\alpha]_D$ + 55·2° (after 2 mins.), + 60° (6 mins.), + 57° (40 mins.) (constant for 17½ hours). After neutralisation of the mineral acid with silver carbonate followed by removal of the solvent, 3 : 6-*anhydrogalactose dimethylacetal* was obtained as a liquid, $[\alpha]_D^{18°}$ + 36·5° in water (*c*, 0·9). The product did not reduce Fehling's solution even on prolonged boiling (Found: OMe, 29·0. $C_8H_{16}O_6$ requires OMe, 29·8%).

(b) *From* 3 : 6-*anhydro-β-methylgalactoside.* To a solution of 3 : 6-anhydro-β-methylgalactoside (0·333 g.) in methyl alcohol (8·5 c.c.) which showed $[\alpha]_D^{16°}$ − 114°, was added 5·4% methyl-alcoholic hydrogen chloride (1·5 c.c.); the solution showed $[\alpha]_D$ − 58° (after 3 mins.); − 39° (4 mins.), − 16° (6 mins.), − 6° (7 mins.), + 8° (9 mins.), + 14° (10 mins.), + 27° (13 mins.), + 33° (15 mins.), + 43° (20 mins.), + 50° (27 mins.), + 52° (30 mins.), + 54° (35 mins.), + 55° (40 mins.), + 57° (50 mins.), + 57·5° (120 mins.), + 58° (180 mins.) (constant for 12 hours). After neutralisation of the hydrogen chloride with silver carbonate, followed by removal of the solvent under reduced pressure, 3 : 6-anhydrogalactose dimethylacetal was obtained as a liquid, $[\alpha]_D^{18°}$ + 34° in water (*c*, 1·2) (Found: OMe, 28·5%).

A solution of the 3 : 6-anhydrogalactose dimethylacetal (0·6 g.) in 0·1N-sulphuric acid showed $[\alpha]_D^{16°}$ + 35·5°; no change in rotation took place when the solution was kept at room

temperature for 12 hours and the solution neither reduced boiling Fehling's solution nor restored the colour to Schiff's reagent. When the solution was heated on the boiling water-bath, hydrolysis was complete in 2½ hours and the solution had $[\alpha]_D$ + 22° (prolonged heating causes decomposition). The solution ($[\alpha]_D$ + 22°) reduced Fehling's solution and restored the colour to Schiff's reagent. After neutralisation of the sulphuric acid with barium carbonate the solution was evaporated to dryness under reduced pressure to give 3 : 6-anhydrogalactose as a glass (0·4 g.), $[\alpha]_D$ + 24° in water (*c*, 1·0). The anhydro-sugar readily reduced Fehling's solution and quickly restored the colour to Schiff's reagent (Found : OMe, nil).

When a solution of the 3 : 6-anhydrogalactose (0·2 g.) in 30% aqueous acetic acid (3·0 c.c.) was heated for 2 hours at 75—80° with phenylhydrazine (0·45 g.), 3 : 6-anhydrogalactose-phenylosazone was obtained as a pale yellow crystalline solid, which was filtered off, washed with dilute acetic acid, water, and methyl alcohol, and dried, m. p. and mixed m. p. 216°. The osazone showed no appreciable rotation in pyridine (*c*, 1·2) (Found : N, 16·8. Calc. for $C_{18}H_{20}O_3N_4$: N, 16·5%).

A solution of 3 : 6-anhydrogalactose dimethylacetal (0·1 g.) in pyridine (1·5 c.c.) was treated with *p*-nitrobenzoyl chloride (0·3 g.) for 3 days at room temperature; the pasty mass was triturated several times with a saturated solution of potassium bicarbonate and then with water and dried. The crude product was dissolved in ethyl acetate, and ethyl alcohol added, giving a small precipitate which was rejected; to the ethyl acetate–ethyl alcohol solution a little ether and also a little light petroleum were added, giving a further small precipitate which was also rejected. After addition of more light petroleum, the solution was left at room temperature; there then separated the crystalline 2 : 4 : 5-*tri*-p-*nitrobenzoyl* 3 : 6-*anhydrogalactose dimethylacetal*, m. p. 112° (after further recrystallisation from ether–acetone–light petroleum), insoluble in water and light petroleum, sparingly soluble in ethyl alcohol, and soluble in methyl alcohol, acetone, ethyl acetate, and benzene (Found : C, 53·2; H, 3·9; OMe, 9·2; N, 6·6. $C_{29}H_{25}O_{15}N$ requires C, 53·2; H, 3·9; OMe, 9·5; N, 6·4%).

Complete methylation of the 3 : 6-anhydrogalactose dimethylacetal with Purdie's reagents afforded 2 : 4 : 5-trimethyl 3 : 6-anhydrogalactose dimethylacetal, a colourless liquid, b. p. (bath temp.) 120°/0·02 mm., $n_D^{19°}$ 1·4430, $[\alpha]_D^{18°}$ + 37° in water (*c*, 1·0) (Found : OMe, 62·1%). When a solution of this product in 0·01N-sulphuric acid was heated on the boiling water-bath for 2 hours, hydrolysis took place and the rotation changed from $[\alpha]_D$ + 36° to + 27°. Neutralisation of the mineral acid, followed by the removal of the solvent, gave 2 : 4 : 5-trimethyl aldehydo 3 : 6-anhydrogalactose, a colourless liquid, b. p. (bath temp.) 105°/0·02 mm., $n_D^{17°}$ 1·4510, OMe, 45·2%. The product restored the colour to Schiff's reagent and reduced Fehling's solution actively.

Hydrolysis of the 3 : 6-*Anhydromethylgalactopyranosides with* 0·1N-*Sulphuric Acid.*—A solution of 3 : 6-anhydro-β-methylgalactopyranoside (0·031 g.) in 0·1N-sulphuric acid (3·0 c.c.) showed $[\alpha]_D$ − 109° (initial value), − 72° (after 18½ hours), − 65° (22½ hours), − 29° (42½ hours, ± 0° (66½ hours), + 15° (94 hours), + 23° (116 hours), + 26° (138 hours, constant value). This solution ($[\alpha]_D$ + 28°) readily reduced Fehling's solution and restored the colour to Schiff's reagent. To the remainder of the solution containing 3 : 6-anhydrogalactose, sodium acetate (0·2 g.), glacial acetic acid (1·5 c.c.), and phenylhydrazine (0·08 g.) were added; when the mixture was heated for 1½ hours at 85°, pale yellow needles of 3 : 6-anhydrogalactose-phenylosazone separated which, when purified as above, had m. p. and mixed m. p. 217°.

A solution of 3 : 6-anhydro-α-methylgalactopyranoside (0·05 g.) in 0·1N-sulphuric acid (2·5 c.c.) had $[\alpha]_D$ + 78° (initial value), + 60° (1 hour), + 46° (2½ hours), + 38° (3½ hours), + 32° (4½ hours), + 29° (5½ hours), + 26·5° (6½ hours), + 26° (7½ hours), + 24° (12 hours, constant value). The solution ($[\alpha]_D$ + 24·5°) readily reduced hot Fehling's solution and restored the colour to Schiff's reagent. The solution was then treated with sodium acetate (0·2 g.), acetic acid (1 c.c.), and phenylhydrazine (0·1 g.) at 75—80° for 2 hours and there separated 3 : 6-anhydrogalactosephenylosazone, m. p. 216° after being purified as described above (Found : C, 63·7; H, 5·9; N, 16·6. Calc. for $C_{18}H_{20}O_3N_4$: C, 63·5; H, 5·9; N, 16·5%).

3 : 6-*Anhydrogalactonic Acid* (XIV).—A solution of 3 : 6-anhydro-α-methylgalactopyranoside (2 g.) in 0·1N-sulphuric acid (25 c.c.) was kept for 2 days at room temperature, neutralised with barium carbonate, filtered, and evaporated to a glass (1·8 g.) under reduced pressure. A solution of 3 : 6-anhydrogalactose (1·5 g.) in water (20 c.c.) obtained in this way was treated with bromine (2 c.c.); an excess of lead carbonate was added and from time to time the reaction mixture was shaken. After 12 hours the oxidation was complete; the excess of bromine was removed by aeration, the lead bromide filtered off, and the filtrate treated with hydrogen sulphide. The filtrate was concentrated to half volume under reduced pressure to remove

hydrogen sulphide, neutralised with silver oxide, filtered before and after treatment with hydrogen sulphide, and then evaporated to dryness under reduced pressure to give 3 : 6-anhydrogalactonic acid, $[\alpha]_D^{20°}$ + 33° in water (*c*, 1·5). This anhydro-acid reacts acid to Congo paper. Treatment of a solution of this acid in acetone (20 c.c.) with an excess of an ethereal solution of diazomethane furnished the *methyl* ester, which was obtained as a syrup on removal of the solvent. The product was distilled, b. p. (bath temp.) 160—170°/0·03 mm., $n_D^{18°}$ 1·4840, $[\alpha]_D$ + 38° in water (*c*, 1·6) (Found : OMe, 17·0. $C_7H_{12}O_7$ requires OMe, 16·2%).

Complete methylation of the methyl ester of 3 : 6-anhydrogalactonic acid by three treatments with Purdie's reagents afforded methyl 2 : 4 : 5-trimethyl 3 : 6-anhydrogalactonate, b. p. 130°/0·08 mm., $n_D^{17°}$ 1·4490, $[\alpha]_D^{20°}$ + 68° in water (*c*, 1·1) (Found : OMe, 52·3%). This ester was converted, as described previously, into the brucine salt, which had m. p. 114°, $[\alpha]_D^{17°}$ *ca.* − 2·5° in water (*c*, 2·5) (Found : N, 4·7%).

Crystallographic Data for 2 : 4-*Dimethyl* 3 : 6-*Anhydro*-β-*methylgalactoside*.—This substance forms monoclinic crystals, elongated parallel to the *b* axis, and flattened on (001). The dimensions of the unit cell, which contains two molecules, are approximately $a = 9·1$, $b = 6·6$, $c = 8·1$ A.; $\beta = 81°$. These results show that the substance is unimolecular (density observed 1·33 g./c.c., whence $M = 195$; calc., 204).

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