21. *The Properties of* 3 : 6-*Anhydroglucose.*

By W. N. Haworth, L. N. Owen, and F. Smith.

This work shows that in 3 : 6-anhydroglucose and its derivatives the 3 : 6-anhydro ring acquires the character of the principal ring to which the pyranose and furanose ring is subsidiary. The 3 : 6-anhydro ring governs the structure of these substances and appears to be mainly responsible for their peculiar properties. For example, the α- and the β-form of 3 : 6-anhydromethylglucopyranoside can be directly converted into the more stable 3 : 6-anhydro-α- and -β-methylglucofuranoside respectively; this ring change from pyranoside to furanoside occurs without loss of the glycosidic methyl

residue. Direct transformation of 2 : 4-dimethyl 3 : 6-anhydro-α-methylglucopyranoside into the β-pyranoside has also been effected without loss of the glycosidic methyl group. This change is analogous to that which has been observed to take place in the corresponding compound of the galactose series. It is important to note that such remarkable changes do not occur in the case of pyranosides and furanosides which contain no anhydro ring.

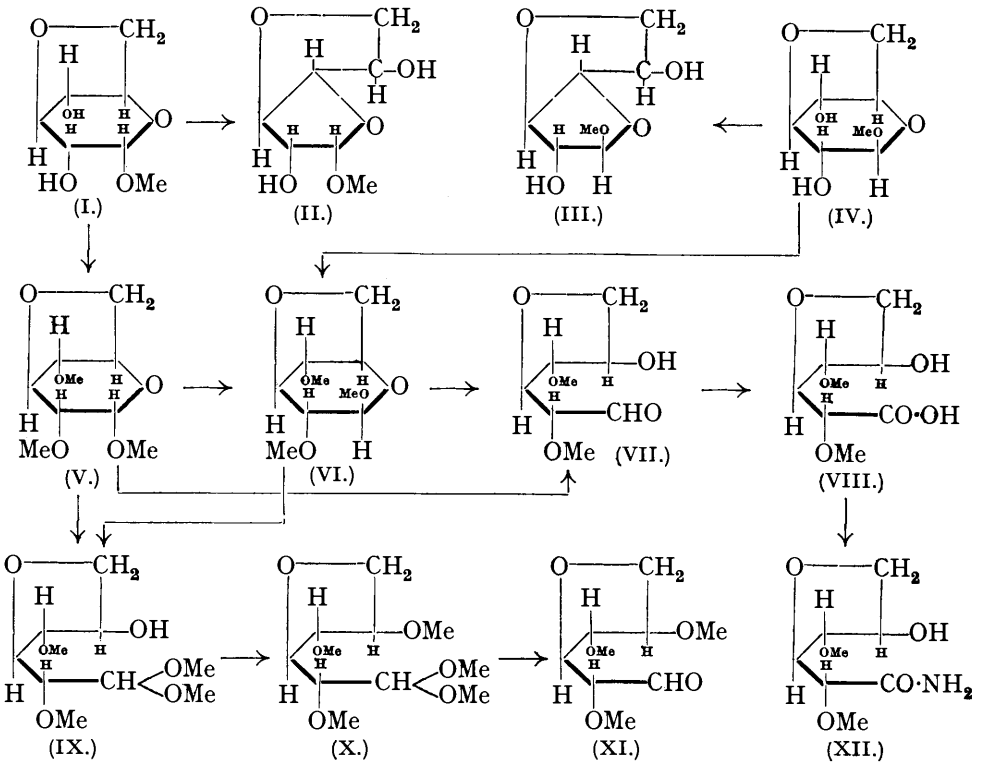
In a previous communication it was shown that the α-form of 2 : 4-dimethyl 3 : 6-anhydromethylgalactopyranoside could be directly converted into the β-form by methods which do not admit of the intermediate formation of the free sugar (Haworth, Jackson, and Smith, *Nature*, 1938, **142**, 1075; J., 1940, 620). It has now been observed that the same type of transformation can be effected with crystalline 2 : 4-*dimethyl* 3 : 6-*anhydro-α-methylglucopyranoside* (V); thus on treatment of the latter with hydrogen chloride in air or in ethereal solution it is rapidly converted into the β-*form* (VI) of 2 : 4-dimethyl 3 : 6-anhydromethylglucopyranoside.

Furthermore, this work has revealed the remarkable fact that the pyranoside forms of 3 : 6-anhydro-α-methylglucoside (I) and of 3 : 6-anhydro-β-methylglucoside (IV) can be directly transformed into the corresponding 3 : 6-anhydro-α- and -β-methylglucofuranosides (II) and (III) respectively. In this pyranoside ⟶ furanoside isomerisation, as in the α-pyranoside ⟶ β-pyranoside isomerisation observed with (V), the conditions do not allow of the intermediate formation of the free sugar. Moreover, this unexpected observation involves a change from a pyranoside sugar ring to a furanoside ring system without affecting the spatial arrangement of the groups (H and OMe) at C_1.

Direct conversion of crystalline 3 : 6-anhydro-α-methylglucopyranoside (I) and crystalline 3 : 6-anhydro-β-methylglucopyranoside (IV) into the corresponding crystalline furanosides, (II) and (III) respectively, can be effected by contact with a solution of hydrogen chloride in a mixture of ether and chloroform, or with methyl-alcoholic hydrogen chloride. In addition, it was observed that the α-methylpyranoside (I) is converted into the α-*methylfuranoside* (II) when a solution of the former in dilute sulphuric acid (0·1N) is kept at room temperature. This direct α-pyranoside ⟶ α-furanoside transformation in dilute sulphuric acid takes place much more slowly (approx. 4 hours) than the same conversion effected with hydrogen chloride in ether–chloroform or in methyl alcohol, which is almost instantaneous in both cases. Nevertheless, the fact emerges that despite the relatively slow rate of isomerisation in aqueous solution, the conversion is accompanied by only slight hydrolysis of the glycosidic methyl group. The reaction follows a different course when the β-methylpyranoside (IV) is treated with dilute sulphuric acid, for in this case hydrolysis occurs slowly with the formation of 3 : 6-anhydroglucose; no 3 : 6-anhydro-β-methylglucofuranoside appears to be formed.

The view expressed concerning the direct conversion of 2 : 4-dimethyl 3 : 6-anhydro-α-methylglucopyranoside (V) into the corresponding β-methylglucopyranoside (VI) is based upon the following experimental facts. Treatment of 6-tosyl α-methylglucopyranoside with a solution of sodium hydroxide results in the formation of 3 : 6-anhydro-α-methylglucopyranoside (I). By similar treatment with sodium hydroxide, β-methylglucopyranoside 6-bromohydrin, obtained from acetodibromoglucose (Fischer and Armstrong, *Ber.*, 1902, **35**, 833), affords 3 : 6-anhydro-β-methylglucopyranoside (IV) (cf. Fischer and Zach, *Ber.*, 1912, **45**, 456). Methylation of (I) with Purdie's reagents yields the crystalline 4-*methyl* 3 : 6-*anhydro-α-methylglucopyranoside* (XXV), which, on further methylation, gives rise to crystalline 2 : 4-*dimethyl* 3 : 6-*anhydro-α-methylglucopyranoside* (V). Similarly, methylation of (IV) with Purdie's reagents furnishes 2 : 4-*dimethyl* 3 : 6-*anhydro-β-methylglucopyranoside* (VI). The crystalline α-isomeride (V), even when kept in a sealed tube at room temperature, gradually changes into the liquid β-form (VI). The same change takes place more rapidly when (V) is exposed to the air, an effect which may be due to traces of acid, to which the compound is extremely sensitive. As previously stated, brief contact with hydrogen chloride in air or with a solution of hydrogen chloride in ether effects this α-pyranoside ⟶ β-pyranoside isomerisation almost instantaneously. Although both the α- and the β-form of 2 : 4-dimethyl 3 : 6-anhydroglucopyranoside undergo hydrolysis at room temperature with 0·1N-sulphuric acid, the β-form is more

slowly hydrolysed than the α-form. In each case there is produced 2 : 4-*dimethyl* 3 : 6-*anhydroglucose*, a liquid which reduces Fehling's solution, decolourises neutral potassium

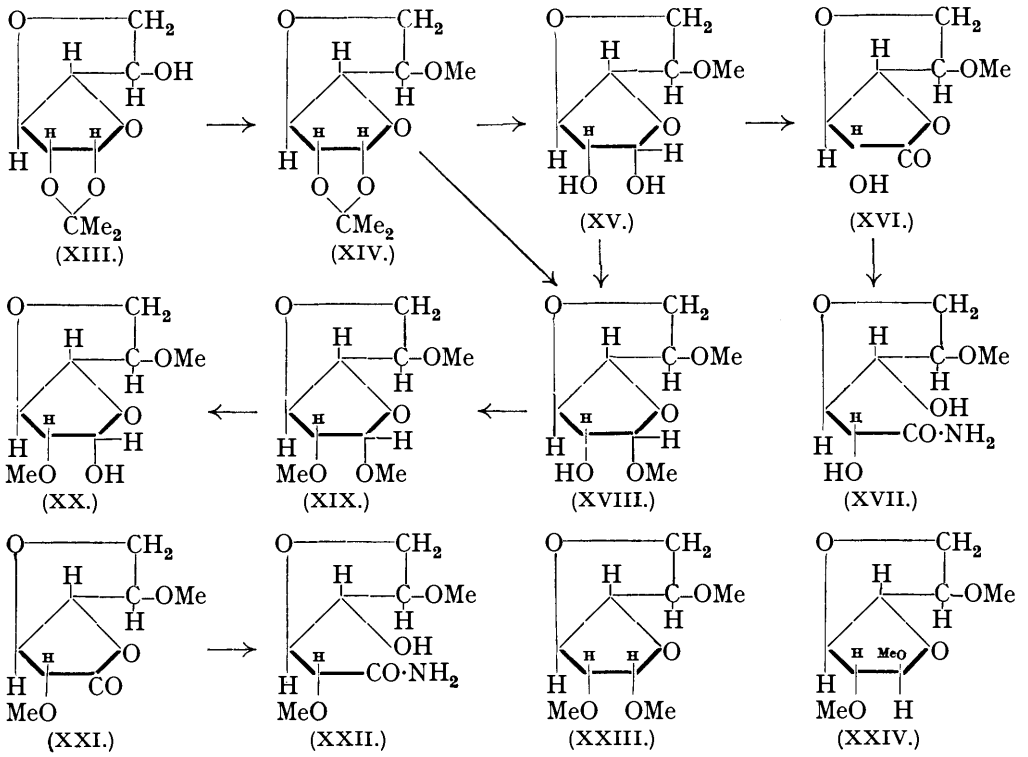


permanganate solution, and restores the colour to Schiff's reagent. Such properties suggest that the 2 : 4-dimethyl 3 : 6-anhydroglucose possesses the aldehydic structure shown in (VII). Oxidation of (VII) with bromine gives crystalline 2 : 4-*dimethyl* 3 : 6-*anhydrogluconic acid* (VIII); the latter is stable in aqueous solution, displays no mutarotation, sublimes unchanged in a vacuum, and shows no tendency to form a lactone. Esterification of (VIII) with diazomethane furnishes the *methyl* ester of 2 : 4-dimethyl 3 : 6-anhydrogluconic acid, which is readily identified by its conversion with methyl-alcoholic ammonia into the corresponding crystalline *amide* (XII).

When 2 : 4-dimethyl 3 : 6-anhydromethylglucopyranoside is treated with an excess of methyl-alcoholic hydrogen chloride at room temperature, it behaves in the same way as the α- and β-forms of 2 : 4-dimethyl 3 : 6-anhydromethylgalactopyranoside, *i.e.*, fission of the 1 : 5-pyranose ring occurs with the formation of 2 : 4-*dimethyl* 3 : 6-*anhydroglucose dimethylacetal* (IX). The only difference noted is that in the galactose series the transformation of the glycosides into the acetal proceeds further towards completion than in the glucose series. The open-chain character of (IX) is demonstrated by the fact that on further methylation with Purdie's reagents it yields 2 : 4 : 5-*trimethyl* 3 : 6-*anhydroglucose dimethylacetal* (X), from which the two methyl groups attached to position 1 can be removed by the agency of hot dilute sulphuric acid to give 2 : 4 : 5-*trimethyl* 3 : 6-*anhydro*aldehydo*glucose* (XI) (see Haworth, Jackson, and Smith, *loc. cit.*).

The furanoside structure of (II) and (III) was demonstrated by a comparison with methylated derivatives of 3 : 6-anhydroglucofuranose prepared for this purpose from 1 : 2-monoacetone 3 : 6-anhydroglucofuranose (XIII). This substance is known to have a furanose structure because it is derived from 1 : 2-monoacetone glucofuranose by a process which leaves the acetone residue intact (Ohle, von Vargha, and Erlbach, *Ber.*, 1928, **61**, 1214). Methylation of (XIII) with Purdie's reagents gives 1 : 2-*monoacetone*

5-*methyl* 3 : 6-*anhydroglucofuranose* (XIV) (isolated as a crystalline *hydrate*), from which the acetone residue is eliminated by heating with dilute sulphuric acid, yielding 5-*methyl*



3 : 6-*anhydroglucose* (XV). Oxidation of the latter with nitric acid furnishes 5-*methyl* 3 : 6-*anhydro-γ-gluconolactone* (XVI), which behaves as a typical γ-lactone in that it shows relatively slow mutarotation in aqueous solution; the lactone (XVI) is readily characterised by its conversion into the crystalline *amide* (XVII), in which the presence of a free hydroxyl group at C_2 is proved by the fact that it gives a positive Weerman test for α-hydroxy-amides. Treatment of 5-methyl 3 : 6-anhydroglucose (XV) or 5-methyl 1 : 2-monoacetone 3 : 6-anhydroglucofuranose (XIV) with acid methyl alcohol affords 5-*methyl* 3 : 6-*anhydro-methylglucoside*, which can only exist as the furanoside (XVIII) because the hydroxyl group in position 5 which would be involved in a pyranose structure is occupied by a methyl group. Further methylation of (XVIII) with Purdie's reagents gives 2 : 5-*dimethyl* 3 : 6-*anhydromethylglucofuranoside* (XIX), from which 2 : 5-*dimethyl* 3 : 6-*anhydroglucose* (XX) is prepared by hydrolysis with sulphuric acid. Although (XX) reduces Fehling's solution, it does not restore the colour to Schiff's reagent and in this respect it differs from the 2 : 4-dimethyl 3 : 6-anhydro*aldehydo*glucose (VII), previously mentioned, which reduces Fehling's solution and readily restores the colour to Schiff's reagent. The 2 : 5-dimethyl 3 : 6-anhydroglucose (XX) is easily recognised (*a*) by its conversion into a crystalline *anilide* and (*b*) by its oxidation with bromine to 2 : 5-*dimethyl* 3 : 6-*anhydro-γ-gluconolactone* (XXI) and conversion of the latter into the crystalline *amide* (XXII) of 2 : 5-dimethyl 3 : 6-anhydrogluconic acid. Like the 5-methyl 3 : 6-anhydro-γ-gluconolactone (XVI), the 2 : 5-dimethyl derivative (XXI) displays the typical slow mutarotation in aqueous solution characteristic of the γ-series of lactones.

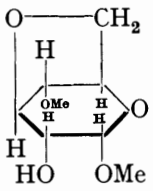
The structure of the 3 : 6-anhydromethylglucosides (II) and (III) was then determined as follows. Methylation of (II) and (III) with Purdie's reagents yields the corresponding *dimethyl* 3 : 6-*anhydromethylglucosides* (XXIII) and (XXIV), each of which undergoes hydrolysis on heating with 0·1N-sulphuric acid to give a dimethyl 3 : 6-anhydroglucose (XX). The anilide of the latter was identical with that of the authentic 2 : 5-di-

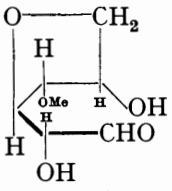
methyl 3 : 6-anhydroglucose prepared from monoacetone glucofuranose as previously described. The furanose structure of the methylglucosides (XXIII) and (XXIV), and therefore of (II) and (III), was further confirmed by converting the 2 : 5-dimethyl 3 : 6-anhydroglucose, obtained from (XXIII) and from (XXIV), successively into 2 : 5-dimethyl 3 : 6-anhydro-γ-gluconolactone (XXI) and the crystalline amide (XXII); these compounds were identical in every respect with the specimens obtained from 3 : 6-anhydroglucofuranose 1 : 2-monoacetone (XIII).

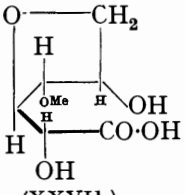
When 3 : 6-anhydro-α-methylglucopyranoside (I) is dissolved in 1% methyl-alcoholic hydrogen chloride, the extremely rapid formation of the anhydro-α-methylglucofuranoside (II) is accompanied by an instantaneous increase in the specific rotation from + 60° to + 145°; subsequently the rotation slowly falls to a constant value (+ 48°) simultaneously with the formation of an equilibrium mixture of the α- and the β-form of 3 : 6-anhydromethylglucofuranoside and no further change takes place when the solution is boiled. The same mixture of the α- and β-forms of anhydromethylglucofuranosides is produced when crystalline 3 : 6-anhydroglucose is treated with methyl-alcoholic hydrogen chloride either at room temperature or at the boiling point; both the α- and the β-form of 3 : 6-anhydromethylglucofuranosides (II) and (III) can be isolated from this equilibrium mixture by fractional crystallisation. Neither the α- nor the β-form of 3 : 6-anhydromethylglucopyranoside appears to be produced in this reaction, for complete methylation of the equilibrium mixture prepared either from 3 : 6-anhydro-α-methylglucopyranoside or from 3 : 6-anhydroglucose yields only 2 : 5-dimethyl 3 : 6-anhydro-αβ-methylglucofuranoside (XIX). The remarkable stability of the 3 : 6-anhydro ring in these substances is indicated by the fact that the direct oxidation of 5-methyl 3 : 6-anhydroglucose (XV) and 2 : 5-dimethyl 3 : 6-anhydroglucose (XX) with nitric acid affords an excellent method for the preparation of the corresponding lactones (XVI) and (XXI) respectively.

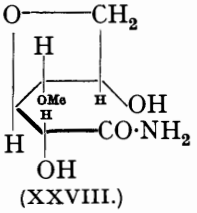
The facile conversion of the α- and β-forms of 3 : 6-anhydromethylglucopyranoside into the corresponding α- and β-methylfuranosides by the agency of a solution of mineral acid in organic solvents, referred to above, explains why the 2 : 5-dimethyl 3 : 6-anhydroglucose anilide and the 2 : 5-dimethyl 3 : 6-anhydrogluconamide (XXII) have been previously described as derivatives of 2 : 4-dimethyl 3 : 6-anhydroglucose (Peat and Wiggins, J., 1938, 1088).

The location of the methyl group in the monomethyl 3 : 6-anhydro-α-methylglucopyranoside (XXV), obtained as an intermediate product in the preparation of 2 : 4-dimethyl


(XXV.)


(XXVI.)


(XXVII.)

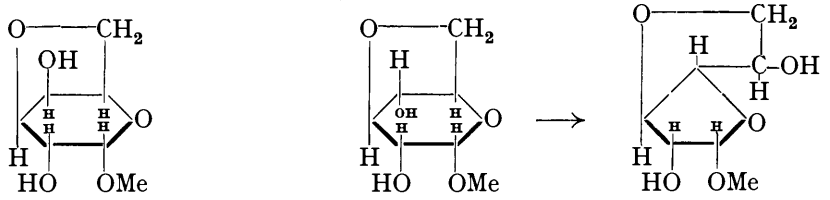

(XXVIII.)

3 : 6-anhydro-α-methylglucopyranoside (V), was ascertained as follows. Since complete methylation of (XXV) gives (V), the methyl group in (XXV) must occupy position 2 or 4. If the methyl group does not occupy position 4, then by analogy with 3 : 6-anhydro-α-methylglucopyranoside (I), it should be converted by means of dilute mineral acid into a monomethyl 3 : 6-anhydro-α-methylglucofuranoside. This monomethyl anhydro-α-methylglucoside (XXV), however, does not give a furanoside, but, like 2 : 4-dimethyl 3 : 6-anhydro-α-methylglucopyranoside (V), it undergoes hydrolysis when treated with 0·1N-sulphuric acid at room temperature to give a *monomethyl* 3 : 6-*anhydroglucose*, a substance which shows aldehydic properties and probably possesses the structure shown in (XXVI). Moreover, if a free hydroxy-group occupies position 4, then (XXV), upon treatment with methyl-alcoholic hydrogen chloride, would be expected to behave like 3 : 6-anhydro-α-methylglucopyranoside and undergo the pyranoside ⟶ furanoside change, a transformation which proceeds rapidly and one which is accompanied by a considerable change in rotation. A solution of (XXV) in 1% methyl-alcoholic hydrogen chloride, however,

exhibits no mutarotation. Such evidence suggests that the methyl group occupies position 4. Further evidence that the methyl group is in position 4 is forthcoming from the fact that (XXVI) can be converted by means of bromine into the *monomethyl* 3 : 6-*anhydrogluconic acid* (XXVII), which, when treated with ethereal diazomethane, affords the corresponding *methyl* ester, a substance which can be distilled without showing any tendency to form a lactone. Treatment of the methyl ester with methyl-alcoholic ammonia yields the *amide* (XXVIII) of the 3 : 6-anhydromonomethylgluconic acid which shows a positive test for α-hydroxy-amides; it is clear, therefore, that in (XXVIII) the hydroxyl group is present in position 2 and therefore the methyl group of (XXV) must occupy position 4.

Discussion.

An examination of the model of 3 : 6-anhydroglucose shows that the adjacent hydroxyl groups on C_4 and C_5 are so situated as to allow of the formation of either a furanose or a pyranose ring; the models also make it clear, however, that the dicyclic system composed of the 3 : 6-anhydro ring and the 1 : 5-pyranose ring is under considerable strain, whereas the system containing the 3 : 6-anhydro ring and the 1 : 4-furanose ring is much less strained. This suggests an explanation of the observations that the α- and β-methylglucopyranosides readily change into the corresponding α- and β-methylfuranosides, for in so doing the molecule passes from a strained into a much less strained structural form. Probably for similar stereochemical reasons, the 3 : 6-anhydroglucose gives, when treated with acid methyl alcohol, 3 : 6-anhydro-α- and -β-methylglucofuranosides and not the glucopyranosides. In the galactose series (compare J., 1940, 1620), neither the α-form nor the β-form of 3 : 6-anhydromethylgalactopyranoside can be transformed into a furanoside because of the pronounced strain which would be introduced into the molecule. The models of the 3 : 6-anhydro-α- and -β-methylgalactopyranoside show clearly that this is due to the fact that the hydroxyl group at C_4, which would be involved in a galactofuranose structure, is in the reverse position from that of the hydroxyl group at C_4 in the 3 : 6-anhydroglucose series in which the pyranoside furanoside transformation takes place so readily (see below).



Galactose Series. Glucose Series.

Noteworthy in this connection is the fact that 3 : 6-anhydrogluconolactone, which theoretically might possess either a 1 : 4- or a 1 : 5-lactone ring, was found to have the 1 : 4-γ-lactone structure; furthermore, both 2 : 5-dimethyl and 5-monomethyl 3 : 6-anhydro-γ-gluconolactone, which are comparatively strainless, are relatively quite stable in aqueous solution and behave as typical γ-lactones. The steric effect of the 3 : 6-anhydro ring, and the pronounced increase in strain which results from the introduction of the 1 : 5-pyranose ring, also explain the opening of the latter ring when 2 : 4-dimethyl 3 : 6-anhydromethylglucopyranoside is converted by means of an excess of methyl-alcoholic hydrogen chloride into the 2 : 4-dimethyl 3 : 6-anhydroglucose dimethylacetal. This steric effect of the 3 : 6-anhydro ring also explains the stability of the 2 : 4-dimethyl 3 : 6-anhydrogluconic acid and the failure to convert it into a lactone and, moreover, the reason for the existence of 2 : 4-dimethyl 3 : 6-anhydroglucose and 4-monomethyl 3 : 6-anhydroglucose as open-chain aldehydes is also apparent. It will be seen that in all these substances the final structure attained is the one which involves the least strain. Crystalline 3 : 6-anhydroglucose itself may exist in the dicyclic furanose form, but, even in this configuration, the presence of strain seems to be indicated by the fact that the open-chain aldehyde form of 3 : 6-anhydroglucose can be detected in aqueous solution by the positive test with Schiff's reagent (see Fischer and Zach, *loc. cit.*). The restoration of the

colour to Schiff's reagent is not effected as rapidly by 3 : 6-anhydroglucose as by 2 : 4-dimethyl 3 : 6-anhydro*aldehydo*glucose, and for this reason it is believed that in aqueous solution only a small portion of the 3 : 6-anhydroglucose exists in the open-chain aldehyde form. The formation of the dicyclic structure present in the 3 : 6-anhydro-α- and -β-methyl-glucopyranosides is apparently only possible because the 1 : 5-pyranose ring is stabilised (as methylpyranoside) before the anhydro ring is introduced. Of interest in this connection is an example in the galactose series in which the pyranose ring can be introduced after the 3 : 6-anhydro ring. The substance referred to is 2 : 4-dimethyl 3 : 6-anhydrogalactonic acid; this undergoes lactonisation on distillation, giving 2 : 4-dimethyl 3 : 6-anhydro-δ-galactonolactone, which contains the strained dicyclic system (Haworth, Jackson, and Smith, *loc. cit.*).

The exceptional properties of sugar derivatives possessing a 3 : 6-anhydro ring compel the conclusion that in these substances the anhydro ring takes on the character of the principal ring structure, to which the ordinary pyranose or furanose ring is only subsidiary. The remarkable changes outlined in this and the earlier paper (3 : 6-anhydrogalactose series) constitute a new aspect of the stability of pyranose and furanose forms; but it must be emphasised that these novel observations have no counterpart in the behaviour of the pyranosides and furanosides containing no anhydro ring. Indeed, in the latter we have sought in vain for similar analogies in properties.

Experimental.

1 : 2-*Monoacetone* 5-*Methyl* 3 : 6-*Anhydroglucofuranose* (XIV).—1 : 2-Monoacetone 3 : 6-anhydroglucofuranose (2·1 g.) prepared by the method of Ohle, von Vargha, and Erlbach (*Ber.*, 1928, **61**, 1214) was subjected to two methylations with Purdie's reagents; the mobile syrup isolated by means of acetone was distilled, giving 1 : 2-*monoacetone* 5-*methyl* 3 : 6-*anhydroglucofuranose* (2·2 g.), b. p. (bath temp.) 115°/0·03 mm., $n_D^{23°}$ 1·4595 (Found : OMe, 14·3. $C_{10}H_{16}O_5$ requires OMe, 14·35%). On exposure to the atmosphere the substance crystallised as a *hydrate* of 1 : 2-*monoacetone* 5-*methyl* 3 : 6-*anhydroglucofuranose*, m. p. 43—44°, $[\alpha]_D^{18°}$ + 82° in ethyl alcohol (*c*, 0·8) (after recrystallisation from water). The crystals were readily soluble in organic solvents, moderately soluble in water, and non-reducing to boiling Fehling's solution (Found : C, 53·0; H, 7·2; OMe, 14·0. $C_{10}H_{16}O_5,\frac{1}{2}H_2O$ requires C, 53·3; H, 7·6; OMe, 13·8%).

5-*Methyl* 3 : 6-*Anhydro-γ-gluconolactone* (XVI).—A solution of monoacetone 5-methyl anhydroglucose (2·0 g.) in ethyl alcohol (5 c.c.) and 0·1N-sulphuric acid (45 c.c.) was heated for 5 hours at 90°; the solution was neutralised with barium carbonate, filtered, and evaporated to a syrup under reduced pressure. This strongly reducing 5-methyl 3 : 6-anhydroglucose (1·55 g.) had $n_D^{20°}$ 1·4850.

A solution of 5-methyl 3 : 6-anhydroglucose (0·4 g.) in nitric acid (20 c.c., *d* 1·2) was heated for 20 hours at 50°. The solution was then diluted with water and freed from nitric acid by distillation under diminished pressure, water, and finally methyl alcohol, being added to facilitate the process; when quite free from solvent, the syrupy acid product was distilled, giving 5-*methyl* 3 : 6-*anhydro-γ-gluconolactone* as a colourless viscous syrup (0·3 g.), b. p. (bath temp.) 165—170°/0·02 mm.; $n_D^{20°}$ 1·4835; $[\alpha]_D^{18°}$ + 109° (initial value) in water (*c*, 1·1), + 107° (after 2 hours), + 99° (25 hours), + 85° (70 hours), + 78° (116 hours), + 74° (174 hours), + 71° (240 hours) (mutarotation still incomplete). The sodium salt showed $[\alpha]_D^{18°}$ + 28° in water (*c*, 0·6) (calculated as lactone) and after acidification with dilute sulphuric acid the solution had $[\alpha]_D^{18°}$ + 31° (initial value), + 40° (after 30 hours), + 47° (71 hours), + 58° (166 hours), + 60° (261 hours) [Found : OMe, 17·7; equiv., 171 (by titration). $C_7H_{10}O_5$ requires OMe, 17·8%; equiv., 174].

5-*Methyl* 3 : 6-*Anhydrogluconamide* (XVII).—Treatment of the syrupy 5-methyl 3 : 6-anhydrogluconolactone (0·1 g.) with methyl-alcoholic ammonia afforded a crystalline amide in almost quantitative yield. After recrystallisation from ethyl alcohol–acetone, the *amide* of 5-*methyl* 3 : 6-*anhydrogluconic acid* had m. p. 136—137°; $[\alpha]_D^{20°}$ + 68° in water (*c*, 0·6). A Weerman test upon this amide (20 mg.), carried out according to directions previously used, was positive (see Smith, J., 1939, 755; Bell, *ibid.*, p. 1871) (Found : C, 44·3; H, 6·9; OMe, 15·7; N, 7·6. $C_7H_{13}O_5N$ requires C, 44·0; H, 6·9; OMe, 16·2; N, 7·3%).

5-*Methyl* 3 : 6-*Anhydromethylglucofuranoside* (XVIII).—A solution of 5-methyl 3 : 6-anhydroglucose (1·1 g.) in 2% methyl-alcoholic hydrogen chloride (40 c.c.) was boiled for 8 hours, cooled, neutralised with silver carbonate, filtered, and concentrated under reduced pressure

to give syrupy 5-methyl 3 : 6-anhydromethylglucofuranoside. The latter was also obtained by boiling a solution of the 1 : 2-monoacetone 5-methyl 3 : 6-anhydroglucofuranose (1·8 g.) in 2% methyl-alcoholic hydrogen chloride (30 c.c.) for 6 hours. Simultaneous removal of the acetone residue and glycoside formation took place and after 6 hours the solution was cooled, neutralised with silver carbonate, filtered, and evaporated to give *5-methyl* 3 : 6-*anhydromethylglucofuranoside*, identical with that prepared by the first method, $n_D^{20°}$ 1·4730 (Found : OMe, 31·5. $C_8H_{14}O_5$ requires OMe, 32·6%).

2 : 5-*Dimethyl* 3 : 6-*Anhydromethylglucofuranoside* (XIX).—5-Methyl 3 : 6-anhydromethylglucofuranoside (1·6 g.) was subjected to two Purdie methylations, and the product distilled, giving 2 : 5-*dimethyl* 3 : 6-*anhydromethylglucofuranoside* as a colourless mobile liquid (1·6 g.), b. p. (bath temp.) 90—95°/0·03 mm.; $n_D^{23°}$ 1·4540 (Found : OMe, 45·5. $C_9H_{16}O_5$ requires OMe, 45·6%).

2 : 5-*Dimethyl* 3 : 6-*Anhydroglucose* (XX).—A solution of 2 : 5-dimethyl 3 : 6-anhydromethylglucofuranoside (0·6 g.) in 0·1N-sulphuric acid (22 c.c.) was heated on the boiling water-bath for 1·2 hours; the rotation then changed from $[\alpha]_D$ + 72° (initial value) to + 104° (constant value). After neutralisation of the mineral acid with barium carbonate, followed by filtration and the removal of the solvent under diminished pressure, there was obtained 2 : 5-*dimethyl* 3 : 6-*anhydroglucose* as a colourless viscous liquid (0·55 g.), b. p. (bath temp.) 120°/0·04 mm., $n_D^{18°}$ 1·4760; $[\alpha]_D^{18°}$ + 110° (initial value in water; *c*, 0·5), changing in 60 hours to + 120° (Found : OMe, 32·7. $C_8H_{14}O_5$ requires OMe, 32·6%).

2 : 5-*Dimethyl* 3 : 6-*Anhydroglucose Anilide*.—A solution of the 2 : 5-dimethyl 3 : 6-anhydroglucose (0·1 g.) and aniline (0·05 g.) in ethyl alcohol (2 c.c.) was boiled for 2 hours; removal of the solvent gave a syrup which solidified on cooling and, after recrystallisation from ethyl alcohol–ether the 2 : 5-*dimethyl* 3 : 6-*anhydroglucose anilide* had m. p. 96°; $[\alpha]_D^{18°}$ + 143° (equilibrium value in ethyl alcohol; *c*, 0·8) (Found : C, 63·3; H, 7·6; OMe, 23·2; N, 5·35. $C_{14}H_{19}O_4N$ requires C, 63·4; H, 7·2; OMe, 23·4; N, 5·3%).

2 : 5-*Dimethyl* 3 : 6-*Anhydro-γ-gluconolactone* (XXI).—A solution of 2 : 5-dimethyl 3 : 6-anhydroglucose (0·4 g.) in water (20 c.c.) was treated with bromine (2 c.c.) for 3 days at 40°. The solution was freed from the excess of bromine by aeration, neutralised with silver oxide, filtered before and after treatment with hydrogen sulphide, and evaporated under reduced pressure to give 2 : 5-*dimethyl* 3 : 6-*anhydro-γ-gluconolactone* as a liquid, b. p. (bath temp.) 130—135°/0·02 mm., $n_D^{15°}$ 1·4678; $[\alpha]_D^{18°}$ + 96° (initial value in water; *c*, 1·0), + 76° (after 96 hours), + 74° (144 hours), + 73° (200 hours, constant value) [Found : OMe, 32·2; equiv., 184 (by titration). $C_8H_{12}O_5$ requires OMe, 33·0%; equiv., 188].

Treatment of the 2 : 5-dimethyl 3 : 6-anhydro-γ-gluconolactone with methyl-alcoholic ammonia yielded the *amide* of 2 : 5-*dimethyl* 3 : 6-*anhydrogluconic acid* (XXII), m. p. 92°; $[\alpha]_D^{19°}$ + 41° in water (*c*, 0·7) (after recrystallisation from acetone–ether) (Found : C, 46·7; H, 7·4; OMe, 29·7; N, 6·8. $C_8H_{15}O_5N$ requires C, 46·8; H, 7·4; OMe, 30·2; N, 6·8%).

3 : 6-*Anhydroglucose*.—A solution of monoacetone 3 : 6-anhydroglucofuranose (32·2 g.) in 0·1N-sulphuric acid was heated for 1 hour on the boiling water-bath and was then neutralised with barium carbonate, filtered, and evaporated to dryness under reduced pressure to give a syrup which quickly crystallised. The crystals were dissolved in hot ethyl alcohol–ethyl acetate (1 : 1) and to the solution sufficient light petroleum was added to give a faint turbidity; on cooling, 3 : 6-anhydroglucose separated, m. p. 122° (yield, 21·4 g.). The anhydroglucose reduced boiling Fehling's solution and restored the colour to Schiff's reagent (5%) in a few minutes (see Fischer and Zach, *loc. cit.*).

3 : 6-*Anhydro-γ-gluconolactone*.—Oxidation of anhydroglucose (1·0 g.) in water (10 c.c.) with bromine (2 c.c.) at room temperature for 6 days afforded 3 : 6-anhydro-γ-gluconolactone. The solution was freed from the excess of bromine by aeration and from hydrobromic acid by neutralisation with silver oxide. The solution was then filtered, treated with hydrogen sulphide, and, after removal of the silver sulphide, evaporated under reduced pressure to give the crystalline lactone, m. p. 116° (after recrystallisation from ethyl alcohol–ether).

When this crystalline lactone was treated with methyl-alcoholic ammonia in the usual manner, the amide of 3 : 6-anhydrogluconic acid was obtained, m. p. 160°; $[\alpha]_D^{15°}$ + 109° in water (*c*, 1·0) (after recrystallisation from methyl alcohol) (Found : C, 40·8; H, 6·3; N, 7·9. Calc. for $C_6H_{11}O_5N$: C, 40·7; H, 6·3; N, 7·9%) {Fischer and Zach, *loc. cit.*, record m. p. *ca.* 149° (decomp.) and $[\alpha]_D^{20°}$ + 78° in water, for this amide}.

Complete methylation of the 3 : 6-anhydro-γ-gluconolactone (0·5 g.) was effected by two treatments with Purdie's reagents; the product, isolated by means of acetone, was a colourless mobile liquid (0·55 g.), b. p. (bath temp.) 130—140°/0·01 mm., $n_D^{18°}$ 1·4595 (Found : OMe, 37·5.

Calc. for 2 : 5-dimethyl 3 : 6-anhydrogluconolactone : OMe, 33·0%. Calc. for methyl 2 : 4 : 5-trimethyl 3 : 6-anhydrogluconate : OMe, 53·0%). The low refractive index and the high methoxyl content suggested that opening of the lactone ring had taken place to some extent. When this lactone was treated with methyl-alcoholic ammonia, there was obtained, in good yield, the crystalline amide of 2 : 5-dimethyl 3 : 6-anhydrogluconic acid, m. p. and mixed m. p. 92° (after crystallisation from acetone–ether). The original 3 : 6-anhydrogluconolactone must therefore be a γ-lactone.

The Action of Methyl-alcoholic Hydrogen Chloride upon 3 : 6-*Anhydroglucose.*—(a) *The structure of the* 3 : 6-*anhydromethylglucofuranoside.* A solution of 3 : 6-anhydroglucose (2·0 g.) in 1% methyl-alcoholic hydrogen chloride (110 c.c.) showed at room temperature $[\alpha]_D$ + 47° (initial value), changing in 1 hour to + 56° (constant value); no further change in rotation took place when the solution was boiled for 3 hours. Neutralisation of the hydrogen chloride with silver carbonate, followed by removal of the solvent, gave a syrupy mixture of the α- and the β-form of 3 : 6-anhydromethylglucofuranoside.

After three Purdie methylations the anhydro-αβ-methylglucoside yielded 2 : 5-dimethyl 3 : 6-anhydromethylglucofuranoside (2·17 g.), b. p. (bath temp.) 95°/0·03 mm., $n_D^{22°}$ 1·4545 (Found : OMe, 45·0%). Hydrolysis of this dimethyl anhydromethylglucoside was completed by heating for 1 hour at 20° with 5% hydrochloric acid; the specific rotation then changed from + 76° to + 95°. Neutralisation of the hydrochloric acid with silver carbonate, followed by removal of the solvent under diminished pressure, gave 2 : 5-dimethyl anhydroglucose, which was converted directly into the corresponding 2 : 5-dimethyl 3 : 6-anhydro-γ-lactone (see above), b. p. (bath temp.) 115—120°/0·02 mm., $n_D^{19°}$ 1·4668 (Found : OMe, 33·5%). When this lactone was treated with methyl-alcoholic ammonia, there was obtained in good yield the amide of 2 : 5-dimethyl 3 : 6-anhydrogluconic acid, m. p. and mixed m. p. 92° (after crystallisation from acetone–ether); neither the amide nor the ammonium salt of 2 : 4-dimethyl 3 : 6-anhydrogluconic acid could be detected (see below) and hence the mixture of glycosides prepared from the 3 : 6-anhydroglucose with acid methyl alcohol must be methylfuranosides.

(b) *The isolation of crystalline* 3 : 6-*anhydro-α- and -β-methylglucofuranoside.* A solution of 3 : 6-anhydroglucose (1·0 g.) in 1% methyl-alcoholic hydrogen chloride was kept for 1 hour at room temperature. Neutralisation of the solution with silver carbonate, followed by removal of the solvent, yielded a syrup, which was distilled, giving 3 : 6-anhydro-αβ-methylglucofuranoside, b. p. (bath temp.) 140—150°/0·04 mm., $n_D^{18°}$ 1·4912, $[\alpha]_D^{18°}$ + 38° in water (*c*, 1·0). The product, which did not reduce boiling Fehling's solution, crystallised spontaneously on keeping. A 1% solution of this 3 : 6-anhydro-αβ-methylglucofuranoside in 0·1N-sulphuric acid had at room temperature $[\alpha]_D^{18°}$ + 38° (initial value), + 41° (after 10 days), + 44° (22 days), + 52° (104 days) (hydrolysis still incomplete). A solution of the crystalline distillate in a little ethyl alcohol was diluted with ether and treated with light petroleum to give a slight turbidity. On standing at room temperature, needle-shaped crystals of 3 : 6-anhydro-α-methylglucofuranoside separated, followed by 3 : 6-anhydro-β-methylglucofuranoside in prisms. The two forms were separated mechanically and crystallised separately from ethyl alcohol–ether–light petroleum. The 3 : 6-*anhydro-α-methylglucofuranoside* (II) (0·25 g.) had m. p. 70°, $[\alpha]_D^{20°}$ + 164° in water (*c*, 0·9). A solution (0·6%) of the α-form in 0·1N-sulphuric acid at room temperature changed in 40 days from $[\alpha]_D$ + 164° (initial value) to + 126° (Found : C, 48·1; H, 7·0; OMe, 18·2. $C_7H_{12}O_5$ requires C, 47·7; H, 6·9; OMe, 17·6%). The 3 : 6-anhydro-β-methylglucofuranoside (III) (0·38 g.) had m. p. 98°, $[\alpha]_D^{20°}$ − 54° in water (*c*, 1·1) (Found : C, 48·1; H, 7·0; OMe, 17·9%). This β-form, which has also been obtained by Ohle and Wilcke (*Ber.*, 1938, **71**, 2324), showed $[\alpha]_D^{18°}$ − 54° (initial value) in 0·1N-sulphuric acid (*c*, 1·0), − 30° (after 11 days), − 4° (45 days).

Proof of the Structure of the 3 : 6-*Anhydro-α-methylglucofuranoside.*—The crystalline anhydro-α-methylglucoside (0·2 g.) was subjected to two Purdie methylations and there was obtained crystalline 2 : 5-*dimethyl* 3 : 6-*anhydro-α-methylglucofuranoside* (XXIII) (0·21 g.), m. p. 45°, $[\alpha]_D^{18°}$ + 208° in water (*c*, 1·0) (after recrystallisation from ether–light petroleum). The crystals were readily soluble in water, methyl and ethyl alcohols, chloroform, acetone, ether, and slightly soluble in light petroleum (Found : C, 53·0; H, 7·8; OMe, 44·6. $C_9H_{16}O_5$ requires C, 52·9; H, 7·9; OMe, 45·6%).

A solution of the 2 : 5-dimethyl 3 : 6-anhydro-α-methylglucofuranoside (0·11 g.) in 0·1N-sulphuric acid (6 c.c.) was heated on the boiling water-bath; the hydrolysis was followed polarimetrically : $[\alpha]_D$ + 207° (initial value), + 160° (after 1 hour), + 130° (2½ hours), + 117° (3½ hours), + 112° (4½ hours, constant value). Neutralisation of the sulphuric acid with barium carbonate, followed by the removal of the solvent under reduced pressure, gave 2 : 5-

dimethyl 3 : 6-anhydroglucofuranose as a liquid (0·08 g.), b. p. (bath temp.) 120—130°/0·03 mm., $n_D^{19°}$ 1·4750. On treatment with ethyl-alcoholic aniline the distillate readily afforded 2 : 5-dimethyl 3 : 6-anhydroglucose anilide, m. p. and mixed m. p. 95° (after recrystallisation from ethyl alcohol–ether).

Proof of the Structure of the 3 : 6-*Anhydro*-β-*methylglucofuranoside.*—Methylation of the anhydro-β-methylglucofuranoside (0·33 g.) with Purdie's reagents (two treatments) yielded a syrup, which was distilled, giving 2 : 5-*dimethyl* 3 : 6-*anhydro*-β-*methylglucofuranoside* (XXIV) as a colourless liquid (0·32 g.), b. p. (bath temp.) 100°/0·04 mm., $n_D^{19°}$ 1·4570, $n_D^{19°}$ 1·4550, $[\alpha]_D^{18°}$ + 15° in water (*c*, 2·0) (Found : OMe, 44·8%).

When a solution of the 2 : 5-dimethyl 3 : 6-anhydro-β-methylglucofuranoside (0·2 g.) in 0·1N-sulphuric acid (11 c.c.) was heated on the boiling water-bath, it showed $[\alpha]_D$ + 15° (initial value), + 59° (after 1 hour), + 83° (2 hours), + 97° (3¼ hours), + 103° (4½ hours), + 104° (5½ hours, constant value). The 2 : 5-dimethyl 3 : 6-anhydroglucose, isolated as previously described, was obtained as a colourless oil, b. p. (bath temp.) 120—130°/0·01 mm., $n_D^{19°}$ 1·4745 (Found : OMe, 32·8%). On treatment with ethyl-alcoholic aniline in the usual way it furnished, in good yield, the corresponding anilide of 2 : 5-dimethyl 3 : 6-anhydroglucose, m. p. and mixed m. p. 95° (after recrystallisation from ethyl alcohol–ether).

A solution (1%) of 2 : 5-dimethyl 3 : 6-anhydro-β-methylglucofuranoside in 0·1N-sulphuric acid showed at room temperature $[\alpha]_D$ + 16° (initial value); + 24° (after 14 days); + 36° (45 days, hydrolysis still incomplete).

Synthesis of 3 : 6-*Anhydro*-α-*methylglucopyranoside* (I).—A solution of α-methylglucopyranoside (53 g.), prepared by the method of Patterson and Robertson (J., 1929, 303), in dry pyridine (250 c.c.) was treated with trityl chloride (74 g.) for 16 hours at room temperature and for 2 hours at 40°. The solution was diluted with a little water and poured into ice-water. The pyridine was removed from the syrupy product, most of it by trituration with water and the rest by extraction of a chloroform solution of the product with dilute sulphuric acid; the chloroform solution was washed with sodium bicarbonate and then with water and finally dried over anhydrous magnesium sulphate. Removal of the solvent yielded 6-trityl α-methylglucopyranoside as a glass, which was acetylated by treatment with pyridine (300 c.c.) and acetic anhydride (180 c.c.) for 24 hours at room temperature. The solution was poured into ice-water and a solution of the product in chloroform was washed with water, dilute sulphuric acid, sodium bicarbonate solution, again with water, dried over anhydrous magnesium sulphate, filtered, and evaporated under reduced pressure to a syrup. The 6-trityl 2 : 3 : 4-triacetyl α-methylglucopyranoside crystallised on trituration with a little methyl alcohol and after recrystallisation from acetone–ether–light petroleum, it had m. p. 136° (yield, 90 g.).

Removal of the trityl residue from the 6-trityl triacetyl α-methylglucoside by means of hydrobromic acid in acetic acid solution (Helferich, Klein, and Schäfer, *Ber.*, 1926, **59**, 79) yielded 2 : 3 : 4-triacetyl α-methylglucoside, m. p. 110°, which gave, on treatment with *p*-toluenesulphonyl chloride, 6-tosyl 2 : 3 : 4-triacetyl α-methylglucopyranoside, m. p. 86°, $[\alpha]_D^{18°}$ + 126° in chloroform (*c*, 0·7) (see Helferich, Brederick, and Schneidmüller, *Annalen*, 1927, **458**, 113) (Found : C, 50·65; H, 5·3; OMe, 6·7; S, 6·5. Calc. for $C_{20}H_{26}O_{11}S$: C, 50·6; H, 5·5; OMe, 6·5; S, 6·7%).

To a solution of 6-tosyl triacetyl α-methylglucoside (21·8 g.) in dry methyl alcohol (500 c.c.), sodium (30 mg.) was added; this Zemplén deactylation proceeded smoothly when the solution was kept at room temperature for 12 hours; on removal of the solvent under diminished pressure there was obtained crystalline 6-tosyl α-methylglucopyranoside, m. p. 110—112°, which crystallised well from hot water as the hydrate, in plates, m. p. 56—58°; yield, 17 g. (cf. Helferich and Himmen, *Ber.*, 1928, **61**, 1825).

The 6-tosyl α-methylglucopyranoside (8 g.) in ethyl alcohol (50 c.c.) was treated with N-sodium hydroxide (25 c.c.) for 12 hours at room temperature and for 1 hour at 80°. The solution was neutralised with carbon dioxide and evaporated to dryness under diminished pressure. Extraction of the residue with boiling acetone gave a quantitative yield of 3 : 6-anhydro-α-methylglucopyranoside, m. p. 108°; $[\alpha]_D^{20°}$ + 56° in water (*c*, 1·0) after recrystallisation from ethyl acetate (Found : C, 47·85; H, 6·6; OMe, 17·6. Calc. for $C_7H_{12}O_5$: C, 47·7; H, 6·9; OMe, 17·6%). Helferich, Klein, and Schäfer (*loc. cit.*) record m. p. 89—95°, $[\alpha]_D$ + 40° in water.

Conversion of 3 : 6-*Anhydro*-α-*methylglucopyranoside* (I) *into* 3 : 6-*Anhydro*-α-*methylglucofuranoside* (II).—(a) *With* 0·1N-*sulphuric acid.* A solution of 3 : 6-anhydro-α-methylglucopyranoside (0·1 g.) in 0·1N-sulphuric acid (10 c.c.) had (at room temperature) $[\alpha]_{5461}$ + 74° (after 10 mins.), + 84° (15 mins.), + 115° (45 mins.), + 152° (105 mins.), + 160° (135 mins.),

+ 167° (240 mins.), + 169° and $[\alpha]_D$ + 145° (960 mins.). At this stage the solution ($[\alpha]_D$ + 145°) was neutralised with barium carbonate, filtered, and evaporated to dryness under reduced pressure to give a crystalline residue. Recrystallisation from ethyl alcohol–ether gave 3 : 6-anhydro-α-methylglucofuranoside (0·06 g.), m. p. and mixed m. p. 68°, $[\alpha]_D^{20°}$ + 164° in water (*c*, 1·5). The syrupy residue obtained from the mother-liquor was slightly reducing to boiling Fehling's solution.

(b) *With a solution of hydrogen chloride in a mixture of ether and chloroform.* A solution of the α-methylpyranoside (50 mg.) in chloroform (1 c.c.) was quickly mixed with ethereal hydrogen chloride (1 c.c. of 5N), immediately poured into a dish, and quickly evaporated under reduced pressure over soda lime in a desiccator. The crystalline residue thus obtained was triturated with ether and after recrystallisation from ethyl alcohol–ether the 3 : 6-anhydro-α-methylglucofuranoside was obtained in needles (35 mg.), m. p. and mixed m. p. 70°, $[\alpha]_D^{18°}$ + 164° in water (*c*, 0·6). The residues were slightly reducing to Fehling's solution.

(c) *With methyl-alcoholic hydrogen chloride.* A solution of the α-methylpyranoside (50 mg.) in dry methyl alcohol (1 c.c.) was treated with one drop of 4N-methyl-alcoholic hydrogen chloride, poured immediately into a dish, and evaporated under reduced pressure over soda lime in a desiccator. Trituration of the crystalline residue with ether, followed by recrystallisation from ethyl alcohol–ether, yielded 3 : 6-anhydro-α-methylglucofuranoside (25 mg.), m. p. and mixed m. p. 69°, $[\alpha]_D^{18°}$ + 166° in water (*c*, 1·0).

Prolonged Treatment of 3 : 6-*Anhydro-α-methylglucopyranoside with* 1% *Methyl-alcoholic Hydrogen Chloride.*—A solution of 3 : 6-anhydro-α-methylglucopyranoside (1 g.) in methyl alcohol (40 c.c.) had $[\alpha]_D^{17°}$ + 60°. 1·5N-Methyl-alcoholic hydrogen chloride (10 c.c.) was then added and the solution showed $[\alpha]_D^{19°}$ *ca.* + 144° (after 2 mins.); + 140° (11 mins.); + 137° (17 mins.); + 124° (47 mins.); + 98° (120 mins.); + 90° (150 mins.); + 79° (210 mins.); + 75° (240 mins.); + 62° (360 mins.); + 56° (480 mins.); + 52° (600 mins.); + 50° (720 mins.) (constant value). The solution showed little or no change when boiled for 2 hours and there was no change when it was kept for 12 hours at room temperature. Neutralisation of the solution with silver carbonate, followed by removal of the solvent, gave syrupy 3 : 6-anhydro-αβ-methylglucofuranoside, which was subjected to two Purdie methylations; in this way there was obtained 2 : 5-dimethyl 3 : 6-anhydro-αβ-methylglucofuranoside (XIX) (1·0 g.), b. p. (bath temp.) 95—100°/0·04 mm., $n_D^{21°}$ 1·4550, $[\alpha]_D^{18°}$ + 85° in water (*c*, 0·6) (Found : OMe, 44·8%).

When a solution of the 2 : 5-dimethyl 3 : 6-anhydro-αβ-methylglucofuranoside (0·7 g.) in 0·1N-sulphuric acid (30 c.c.) was heated on the boiling water-bath, it showed $[\alpha]_D$ + 81° (initial value); + 98° (1·3 hours); + 102° (2 hours); + 105° (3 hours); + 107° (4 hours); + 108° (6 hours) (constant value). The solution was neutralised with barium carbonate, filtered, and evaporated under diminished pressure to give 2 : 5-dimethyl 3 : 6-anhydroglucose (XX) as a liquid (0·5 g.), b. p. 120°/0·04 mm., $n_D^{19°}$ 1·4750; $[\alpha]_D^{18°}$ + 112° (initial value) in water (*c*, 0·5), changing in 60 hours to + 121° (Found : OMe, 32·4%). Treatment of this reducing methylated sugar with boiling ethyl-alcoholic aniline as previously described gave the corresponding anilide of 2 : 5-dimethyl 3 : 6-anhydroglucose, m. p. and mixed m. p. 96°; $[\alpha]_D^{17°}$ + 180° in ethyl alcohol (*c*, 0·8), changing to + 145° (40 mins., equilibrium value) (the initial rotation is recorded with reserve, since the ethyl alcohol was warmed to dissolve the anilide) (Found : C, 63·4; H, 7·4; OMe, 23·0; N, 5·3. Calc. for $C_{14}H_{19}O_4N$: C, 63·4; H, 7·2; OMe, 23·4; N, 5·3%).

A solution of 2 : 5-dimethyl 3 : 6-anhydroglucose (0·3 g.) in nitric acid (5 c.c., *d* 1·42) was heated for 1 hour at 70° and for 4 hours at 85° in an open flask; the residual liquid was diluted with water and freed from solvent by evaporation under reduced pressure; the last traces of nitric acid were eliminated by simultaneous addition and distillation of methyl alcohol. Distillation of the syrupy acidic residue in the presence of a few mg. of barium carbonate gave 2 : 5-dimethyl 3 : 6-anhydro-γ-gluconolactone (XXI) (0·23 g.), b. p. (bath temp.) 130—140°/0·03 mm., $n_D^{17°}$ 1·4670 (Found : OMe, 32·0%). The colourless distillate reacted acid to Congo-paper, and showed $[\alpha]_D^{18°}$ + 100° (initial value) in water (*c*, 0·9); + 93° (11 hours); + 79° (100 hours); + 77° (175 hours); + 75° (24 days). Treatment of the 2 : 5-dimethyl 3 : 6-anhydro-γ-gluconolactone with methyl-alcoholic ammonia afforded the corresponding amide (XXII) in good yield, m. p. and mixed m. p. 92°, $[\alpha]_D^{17°}$ + 46° in water (*c*, 1·7) (Found : C, 46·7; H, 7·4; OMe, 30·4; N, 6·8. Calc. for $C_8H_{15}O_5N$: C, 46·8; H, 7·4; OMe, 30·2; N, 6·8%).

Methylation of 3 : 6-*Anhydro-α-methylglucopyranoside.* 4-*Methyl* 3 : 6-*Anhydro-α-methylglucopyranoside* (XXV).—3 : 6-Anhydro-α-methylglucopyranoside (0·55 g.), dissolved in acetone (5 c.c.), was methylated once with Purdie's reagents. Isolation of the product by means of

acetone afforded a crystalline substance, which gave 4-*methyl* 3 : 6-*anhydro*-α-*methylglucopyranoside* (0·2 g.), m. p. 152°, $[\alpha]_D^{17°}$ + 24° in water (*c*, 1·1) (after recrystallisation from acetone–ether) (Found : C, 50·3; H, 7·3; OMe, 32·7. $C_8H_{14}O_5$ requires C, 50·5; H, 7·45; OMe, 32·6%).

A solution (1·3%) of the 4-methyl 3 : 6-anhydro-α-methylglucopyranoside in 1% methyl-alcoholic hydrogen chloride showed $[\alpha]_D^{18°}$ + 25° (constant for 16 hours). A solution of 4-methyl 3 : 6-anhydro-α-methylglucoside (0·2 g.) in 0·1N-sulphuric acid (10 c.c.) had $[\alpha]_D^{18°}$ + 18° (after 10 mins.); − 5° (60 mins.); − 14° (120 mins.); − 16° (180 mins.) (constant value). The solution at this stage reduced Fehling's solution and restored the colour to Schiff's reagent; it was neutralised with lead carbonate, filtered, and evaporated under reduced pressure to give 4-*methyl* 3 : 6-*anhydroglucose* (XXVI) as a syrup (0·17 g.), $[\alpha]_D^{18°}$ − 17° in water (*c*, 0·7). This syrup also reduced Fehling's solution and gave a positive Schiff's test (Found : OMe, 16·5. $C_7H_{12}O_5$ requires OMe, 17·6%).

A solution of the 4-methyl 3 : 6-anhydroglucose (0·16 g.) in water (10 c.c.) was treated with bromine (0·5 c.c.) for 12 hours at room temperature in the presence of a slight excess of lead carbonate. After 12 hours, when the oxidation was completed, the solution was freed from the excess of bromine by aeration, filtered, and treated with hydrogen sulphide. Removal of the lead sulphide gave a colourless filtrate, which 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 evaporated to a syrup under diminished pressure. The 4-*methyl* 3 : 6-*anhydrogluconic acid* (XXVII) obtained in this way reacted acid to litmus and Congo-paper. This acid was dissolved in methyl alcohol and treated with an excess of an ethereal solution of diazomethane for approximately 5 minutes. Removal of the solvent yielded *methyl* 4-*methyl* 3 : 6-*anhydrogluconate* as a colourless liquid (0·13 g.), b. p. 125°/0·03 mm., $n_D^{19°}$ 1·4660, $[\alpha]_D^{19°}$ *ca.* + 2° in water (*c*, 2·4) (Found : OMe, 29·8. $C_8H_{14}O_6$ requires OMe, 30·1%).

The b. p. given here and in subsequent paragraphs is the bath temperature at which the substance distils.

Treatment of the methyl ester of 4-methyl 3 : 6-anhydrogluconic acid with methyl-alcoholic ammonia afforded the corresponding *amide* (XXVIII), which, however, failed to crystallise; it had $[\alpha]_D^{20°}$ − 7·5° in water (*c*, 2·1) and gave a positive Weerman test (carried out on 20 mg.) (Found : N, 7·5. $C_7H_{13}O_5N$ requires N, 7·3%).

2 : 4-*Dimethyl* 3 : 6-*Anhydro*-α-*methylglucopyranoside* (V).—A further methylation of the syrupy product obtained from the mother-liquor of 4-methyl 3 : 6-anhydro-α-methylglucopyranoside (see above) with Purdie's reagents gave 2 : 4-*dimethyl* 3 : 6-*anhydro*-α-*methylglucopyranoside* (0·2 g.), m. p. 66°, $[\alpha]_D^{16°}$ + 50° in water (*c*, 1·0) (Found : C, 53·2; H, 7·9; OMe, 45·2. $C_9H_{16}O_5$ requires C, 52·9; H, 7·8; OMe, 45·6%).

One methylation of the 4-methyl 3 : 6-anhydro-α-methylglucopyranoside (20 mg.) with Purdie's reagents also afforded 2 : 4-dimethyl 3 : 6-anhydro-α-methylglucopyranoside (18 mg.), m. p. and mixed m. p. 66°, $[\alpha]_D^{18°}$ + 49·5° in water (*c*, 1·6) (Found : OMe, 45·5%).

Transformation of 2 : 4-*Dimethyl* 3 : 6-*Anhydro*-α-*methylglucopyranoside* (V) *into the Corresponding* β-*Methylglucopyranoside* (VI).—Although not hygroscopic, the crystalline 2 : 4-dimethyl 3 : 6-anhydro-α-methylglucopyranoside is extremely sensitive to traces of acid; on exposure to the atmosphere of the laboratory it gradually changes to a non-reducing syrup having a negative rotation. By brief contact with air containing a trace of dry hydrogen chloride the α-form was immediately converted into a non-reducing syrup which had a negative rotation. The crystalline α-form (50 mg.) was dissolved in 5N-ethereal hydrogen chloride (1 c.c.) and immediately evaporated over soda lime in a vacuum desiccator; the syrup thus obtained did not reduce Fehling's solution, showed $[\alpha]_D^{18°}$ − 55° in water (*c*, 1·1), and therefore contained a considerable proportion of the 2 : 4-dimethyl 3 : 6-anhydro-β-methylglucopyranoside (see below).

A few crystals of the crystalline α-form were dried over phosphoric oxide and sealed in a dry glass tube; after 4 months the crystals had completely changed to a non-reducing syrupy mixture of the α- and the β-form of 2 : 4-dimethyl 3 : 6-anhydromethylglucopyranoside. The ease with which the α-form is converted into the β-form is illustrated by the fact that in one experiment methylation of 3 : 6-anhydro-α-methylglucopyranoside (2·0 g.) by three treatments with Purdie's reagents gave a syrupy product (1·6 g.), b. p. 100—110°/0·02 mm., $n_D^{22°}$ 1·4640, $[\alpha]_D^{18°}$ − 63° in water (*c*, 2·0) (Found : OMe, 45·4%). Evidently at some stage during the preparation partial transformation to the 2 : 4-dimethyl 3 : 6-anhydro-β-methylglucopyranoside had taken place.

Hydrolysis of 2 : 4-*Dimethyl* 3 : 6-*Anhydro*-α-*methylglucopyranoside.*—When a solution of

2 : 4-dimethyl 3 : 6-anhydro-α-methylglucoside (0·2 g.) in 0·1N-sulphuric acid was kept at room temperature, it showed $[\alpha]_D$ + 43° (after 0·1 hour); + 38° (0·2 hour); + 34° (0·3 hour); − 2° (1½ hours); − 15° (3 hours); − 20° (8 hours) (constant for a further 5 hours). Neutralisation of the solution with barium carbonate, followed by filtration and by the removal of the solvent under reduced pressure, gave 2 : 4-*dimethyl* 3 : 6-*anhydroglucose* (VII), which distilled as a colourless liquid (0·15 g.), b. p. 120—125°/0·03 mm., $n_D^{18°}$ 1·4750, $[\alpha]_D^{19°}$ − 28° in water (*c*, 1·7). This substance reduced Fehling's solution and gave a positive Schiff's test. It failed to give a crystalline anilide (Found: OMe, 32·2. $C_8H_{14}O_5$ requires OMe, 32·6%).

2 : 4-*Dimethyl* 3 : 6-*Anhydrogluconic Acid* (VIII).—A solution of 2 : 4-dimethyl 3 : 6-anhydroglucose (0·2 g.) in water (5 c.c.) was treated with bromine (0·5 c.c.) for 3 days at 40—45°. The solution was freed from the excess of bromine, neutralised with silver oxide, filtered before and after treatment with hydrogen sulphide, and evaporated to dryness under reduced pressure; 2 : 4-*dimethyl* 3 : 6-*anhydrogluconic acid* was obtained in this way, m. p. 156°; $[\alpha]_D^{20°}$ + 52° in water (*c*, 1·0), remaining unchanged after 3 days (after recrystallisation from acetone–ether–light petroleum). The acid showed an acid reaction to Congo-paper and could be titrated directly with sodium hydroxide. At 140°/0·04 mm. the 2 : 4-dimethyl 3 : 6-anhydrogluconic acid sublimed unchanged (Found: C, 46·6; H, 6·7; OMe, 30·4; equiv., 200. $C_8H_{14}O_6$ requires C, 46·6; H, 6·9; OMe, 30·1%; equiv., 206).

2 : 4-*Dimethyl* 3 : 6-*Anhydrogluconamide* (XII).—The 2 : 4-dimethyl 3 : 6-anhydrogluconic acid (25 mg.), dissolved in acetone, was esterified by treatment with a slight excess of ethereal diazomethane for about 5 minutes; removal of the solvent under reduced pressure gave the methyl ester as a colourless liquid. Treatment of this ester with methyl-alcoholic ammonia for 36 hours at 5° gave the *amide* of 2 : 4-dimethyl 3 : 6-anhydrogluconic acid, m. p. 155°, $[\alpha]_D^{19°}$ + 63° in water (*c*, 0·8) (Found: OMe, 30·1; N, 7·0. $C_8H_{15}O_5N$ requires OMe, 30·2; N, 6·8%).

Synthesis of 3 : 6-*Anhydro*-β-*methylglucopyranoside* (IV).—Well-powdered penta-acetyl glucose (15 g.) in a Carius tube was covered with liquid hydrogen bromide (*ca.* 25 c.c.) by passing the gas into the tube surrounded by liquid air. While the reaction mixture was still solid, the tube was sealed and left for 9 days at room temperature. The tube was cooled in liquid air until the reaction mixture was solid; it was then opened, and kept at room temperature until as much as possible of the hydrogen bromide boiled away from the light brown syrup, leaving a crystalline residue. A solution of this residue in chloroform (150 c.c.) was washed with water and sodium bicarbonate solution and finally dried over anhydrous magnesium sulphate. Removal of the solvent from the filtered solution gave acetodibromoglucose (6·5 g.), m. p. 170° (after recrystallisation from acetone–light petroleum) (see Fischer and Armstrong, *loc. cit.*).

The acetodibromoglucose (6·5 g.) was converted into 2 : 3 : 4-triacetyl β-methylglucopyranoside 6-bromohydrin by shaking with dry methyl alcohol in the presence of silver carbonate. The product had m. p. 124° (yield, 4·5 g.).

To a solution of the 2 : 3 : 4-triacetyl β-methylglucopyranoside 6-bromohydrin (4·9 g.) in dry methyl alcohol (50 c.c.), sodium (20 mg.) was added. After keeping overnight, the solution, on evaporation, gave β-methylglucopyranoside 6-bromohydrin (3·3 g.), m. p. 154° (after crystallisation from ethyl acetate). This bromohydrin (3·2 g.) was heated for 2 hours at 85—90° with N-sodium hydroxide (15 c.c.). After neutralisation with carbon dioxide, the solution was evaporated to dryness, and the residue exhaustively extracted with boiling acetone. Removal of the solvent gave a syrup, which distilled as a colourless liquid (1·64 g.), b. p. (bath temp.) 160—170°/0·02 mm., $n_D^{21°}$ 1·4900, $[\alpha]_D^{20°}$ − 138° in water (*c*, 1·1) (Found: OMe, 17·8. Calc. for $C_7H_{12}O_5$: OMe, 17·6%). This syrupy 3 : 6-anhydro-β-methylglucopyranoside (IV) crystallised, but owing to its hygroscopic nature a successful crystallisation was not obtained; the m. p. of the crude material was *ca.* 50° (sealed tube) (cf. Fischer and Zach, *loc. cit.*).

Transformation of 3 : 6-*Anhydro*-β-*methylglucopyranoside* (IV) *into* 3 : 6-*Anhydro*-β-*methylglucofuranoside* (III).—(a) *With a chloroform–ether solution of hydrogen chloride.* A solution of 3 : 6-anhydro-β-methylglucopyranoside (50 mg.) in chloroform (1 c.c.) was mixed with ethereal hydrogen chloride (1 c.c., 5N), poured quickly into a dish, and immediately evaporated over soda lime in a vacuum desiccator. Trituration of the crystalline residue with ether, followed by recrystallisation from ethyl alcohol–ether, gave 3 : 6-anhydro-β-methylglucofuranoside (35 mg.), m. p. and mixed m. p. 97°, $[\alpha]_D^{17°}$ − 50° in water (*c*, 1·1).

(b) *With methyl-alcoholic hydrogen chloride.* A 6% solution of the 3 : 6-anhydro-β-methylglucopyranoside in 1% methyl-alcoholic hydrogen chloride showed $[\alpha]_D^{18°}$ − 12° (after 0·2 hour); + 12° (0·7 hour); + 14° (1 hour); + 23° (3 hours); + 35° (7 hours); + 39° (10½ hours);

+ 48° (22½ hours); after the solution had been boiled for 1 minute, it showed (when cooled to room temperature) $[\alpha]_D$ + 56°. This final value is identical with that shown by an equilibrium mixture of the α- and the β-form of 3 : 6-anhydromethylglucofuranoside, prepared from the 3 : 6-anhydro-α-methylglucopyranoside and from 3 : 6-anhydroglucose (see above). It was clear, therefore, that in order to isolate the β-methylfuranoside (which has $[\alpha]_D$ — 50° in water), the reaction with acid methyl alcohol must be arrested quickly.

Accordingly, a solution of the 3 : 6-anhydro-β-methylglucopyranoside (45 mg.) in 1% methyl-alcoholic hydrogen chloride (2 c.c.) was kept for 4 minutes and then neutralised with silver carbonate. Removal of the solvent from the filtered solution gave a syrup, which crystallised on nucleation with the 3 : 6-anhydro-β-methylfuranoside; recrystallisation from ethyl alcohol–ether gave 3 : 6-anhydro-β-methylglucofuranoside (15 mg.), m. p. and mixed m. p. 97°, $[\alpha]_D^{21°}$ — 51° in water (*c*, 1·5).

The Action of 0·1N-*Sulphuric Acid upon* 3 : 6-*Anhydro-β-methylglucopyranoside.*—The substance underwent slow hydrolysis; a solution of 3 : 6-anhydro-β-methylglucopyranoside (0·11 g.) in 0·1N-sulphuric acid (11 c.c.) at room temperature had $[\alpha]_D$ — 136° (after 0·1 hour); — 123° (0·8 hour); — 100° (2 hours); — 86° (3 hours); — 22° (15 hours); — 20° (16 hours); — 18° (17 hours). The solution at this stage reduced Fehling's solution; it was neutralised with barium carbonate, filtered, and evaporated to dryness. Extraction of the residue with acetone at room temperature gave a syrup, which crystallised on nucleation with 3 : 6-anhydroglucose. Recrystallisation from ethyl acetate gave 3 : 6-anhydroglucose, m. p. and mixed m. p. 121°. No 3 : 6-anhydro-β-methylglucofuranoside could be isolated.

2 : 4-*Dimethyl* 3 : 6-*Anhydro-β-methylglucopyranoside* (VI).—3 : 6-Anhydro-β-methylglucopyranoside (0·5 g.), dissolved in acetone, was methylated three times with Purdie's reagents. The product, 2 : 4-*dimethyl* 3 : 6-*anhydro-β-methylglucopyranoside*, isolated by means of acetone, distilled as a colourless liquid (0·45 g.), b. p. (bath temp.) 85—90°/0·01 mm., $n_D^{22°}$ 1·4620, $[\alpha]_D^{15°}$ — 96° in water (*c*, 2·0) (Found: OMe, 46·0. $C_9H_{16}O_5$ requires OMe, 45·6%).

A solution of 2 : 4-dimethyl 3 : 6-anhydro-β-methylglucopyranoside (0·2 g.) in 0·1N-sulphuric acid showed (at room temperature) $[\alpha]_D$ — 96° (initial value); — 86° (2 hours); — 65° (15 hours); — 40° (39 hours); — 30° (63 hours); — 25° (92 hours); — 23° (112 hours); — 19° (160 hours) (constant value). The rate of hydrolysis was thus considerably slower than that of the 2 : 4-dimethyl 3 : 6-anhydro-α-methylglucopyranoside (see above). Neutralisation of the solution ($[\alpha]_D$ — 19°) with barium carbonate, followed by filtration and evaporation under reduced pressure, yielded 2 : 4-dimethyl 3 : 6-anhydroglucose (VII), which distilled as a colourless liquid (0·14 g.), b. p. (bath temp.) 115—120°/0·02 mm., $n_D^{18°}$ 1·4720 (Found: OMe, 32·5. Calc.: OMe, 32·6%).

The 2 : 4-dimethyl 3 : 6-anhydroglucose (0·12 g.), oxidised with bromine as previously described, gave 2 : 4-dimethyl 3 : 6-anhydrogluconic acid, m. p. and mixed m. p. 155° (after recrystallisation from ethyl alcohol–ether).

2 : 4 : 5-*Trimethyl* 3 : 6-*Anhydroglucose Dimethylacetal* (X).—A solution of 2 : 4-dimethyl 3 : 6-anhydro-αβ-methylglucopyranoside (0·52 g.) in 0·5% methyl-alcoholic hydrogen chloride (20 c.c.), when left at room temperature, showed $[\alpha]_D$ —14° (initial value); — 6° (0·1 hour); — 3° (0·2 hour); + 4° (0·7 hour); + 6° (1·5 hours); + 8° (3·5 hours) (constant for 15 hours). Neutralisation of the mineral acid with silver carbonate, followed by removal of the solvent, gave a syrup, which was then methylated once with Purdie's reagents; the product, isolated by means of acetone, was again treated with 0·5% methyl-alcoholic hydrogen chloride. Both treatments were repeated and after a further methylation with Purdie's reagents the product was distilled, giving 2 : 4 : 5-*trimethyl* 3 : 6-*anhydroglucose dimethylacetal* as a colourless mobile liquid (0·25 g.), b. p. (bath temp.) 110—120°/0·01 mm., $n_D^{18°}$ 1·4480, $[\alpha]_D^{18°}$ — 6° in water (*c*, 2·0) (Found: OMe, 57·2. $C_{11}H_{22}O_6$ requires OMe, 61·9%). This acetal formation does not proceed as well in the glucose series as in the corresponding compound of the galactose series and the presence of unchanged 2 : 4-dimethyl 3 : 6-anhydromethylglucoside may explain the low methoxyl content recorded above.

A solution of 2 : 4 : 5-trimethyl 3 : 6-anhydroglucose dimethylacetal (0·2 g.) in 0·1N-sulphuric acid at room temperature had $[\alpha]_D$ — 6° (initial value); — 12° (after 2 hours); — 14° (14 hours) (constant value); no change in rotation was observed when the solution was heated for 1 hour on the boiling water-bath. The solution was neutralised with barium carbonate, filtered, and evaporated to dryness under diminished pressure. Extraction of the residue with acetone gave a syrup, which on distillation afforded 2 : 4 : 5-*trimethyl* 3 : 6-*anhydro*aldehydo-*glucose* (XI) as a colourless mobile liquid (0·1 g.), b. p. (bath temp.) 105—110°/0·01 mm., $n_D^{18°}$ 1·4510. The distillate was strongly reducing to Fehling's solution and restored the colour

to Schiff's reagent almost immediately; 2 : 4 : 5-trimethyl 3 : 6-anhydro*aldehydo*glucose did not give a crystalline anilide (Found : OMe, 45·9. $C_9H_{16}O_5$ requires OMe, 45·6%).

The authors are grateful to the Department of Scientific and Industrial Research for a grant in aid of this work.

THE A. E. HILLS LABORATORIES,
THE UNIVERSITY, EDGBASTON, BIRMINGHAM. [*Received, November 6th*, 1940.]