

**358.** *The Crystalline Structure of the Sugars. Part II. Methylated Sugars and the Conformation of the Pyranose Ring.*

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It was pointed out in Part I (this vol., p. 979) that, chiefly owing to extensive dipole association of hydroxyl groups, it is not usually possible to obtain any simple correlation between the unit cell dimensions of crystalline sugars and the molecular dimensions. In the case of methylated sugars, however, dipole interactions are probably of much less importance, and we have therefore made a preliminary study of a number of such compounds in the expectation that the desired correlation would thereby be more readily attained. A comparative examination of the present results in conjunction with others previously published has, in fact, led to definite conclusions regarding the conformation of the C<sub>5</sub>O ring in simple pyranose sugars. Apart from earlier X-ray studies, very little experimental evidence has previously been brought to bear on this problem, the principal interest of which lies in the fact that a small change in the shape of the ring may be accompanied by a considerable alteration in the extra-cyclic valency directions, so that, *e.g.*, the molecular form of a pyranose polysaccharide is very largely determined by the conformation of the rings in the monose residues of which it is composed.

Although a partially flat structure has been suggested, it has been generally supposed that the pyranose ring, like the hexamethylene ring, possesses one of the numerous "strained" Sachse forms. This view involves various assumptions, chief of which are that the different radius and (possibly) different valency angle of the oxygen atom can be ignored, and that the carbon valencies are strained unless they are directed to the corners of a regular tetrahedron. The latter assumption clearly requires modification for all but the

simplest organic molecules, and is almost certainly not justifiable for complex asymmetric compounds such as the sugars. Results obtained from simpler substances suggest that departures of several degrees from the tetrahedral angle are to be expected; *e.g.*, *X*-ray measurements by Piper (J., 1929, 234) suggest that in certain salts of long-chain fatty acids the carbon valency angle is at least  $111\frac{1}{2}^\circ$ , and recently Penney (*Trans. Faraday Soc.*, 1935, 31, 734) has concluded on theoretical grounds that in a molecule such as propane divergences of  $1^\circ$  or  $2^\circ$  are probable. If it is admitted that variations of a few degrees about the exact tetrahedral angle are permissible, and allowance is made for the different oxygen radius, then it becomes possible for a pyranose ring which is considerably different from any of the classical Sachse-Mohr forms to be strainless in the true sense. A decision between the numerous rings permitted by this modified tetrahedral theory can only be effected by means of direct experimental evidence such as is provided, *e.g.*, by the *X*-ray method.

It has been shown (Cox, J., 1932, 138) that the *X*-ray data for  $\beta$ -methylxyloside can be accounted for in a satisfactory manner if it is assumed that the five carbon atoms of the pyranose ring are nearly co-planar, the oxygen atom being displaced out of their plane by  $\frac{1}{2}$ —1 Å. A study of the much more extensive data now available substantiates this assumption, and leads to the conclusion that this form of ring probably exists without serious modification in most simple aldoses and their methyl derivatives. For convenience in the following discussion, this ring will be referred to as a "flat" ring, but it should be clearly understood that the evidence does not establish that the carbon atoms are *exactly* co-planar, while the oxygen atom is almost certainly not in the same plane as the others.

It is found that the crystallographic data for the methylated derivatives are usually much more readily interpreted in terms of the approximate shape and orientation of the molecules than is the case with the parent sugars. The crystals are acicular, the cell-dimension parallel to the direction of elongation is very short, and the birefringence is fairly high, the minimum refractive index being parallel to the needle axis. These facts suggest a relatively simple parallel arrangement of more or less flat, extended molecules whose "thickness" is represented by the short axis. This axis is indeed too short (about  $4\frac{1}{2}$  Å.) to correspond to any dimension of a sugar molecule containing a  $C_5O$  or  $C_4O$  ring other than that approximately normal to the ring, irrespective of the precise form of the latter. The values of these molecular "thicknesses" at present available are shown in Table I; this includes only actual cell dimensions of about  $4\frac{1}{2}$  Å. as determined by single-crystal measurements, and not substances for which the cell dimension is a multiple of this figure, since the interpretation in the latter cases would be open to criticism. (It should be noted that a molecular dimension may be measured in various ways; when deduced from a cell dimension, it is definitely the distance apart of corresponding atoms in identically

TABLE I.

Substance.	Shortest axis (Å.).	Ref.	Substance.	Shortest axis (Å.).	Ref.
(a) <i>Pyranose sugars and glycosides.</i>			(b) <i>Methylated pyranoses.</i>		
$\beta$ -Arabinose *	4.85	C	Trimethyl $\beta$ -methylarabinoside *	4.87	CGW
$\alpha$ -Glucose *	4.99	HM	Trimethyl $\alpha$ -methylarabinoside	4.85	CGW
$\beta$ -Cellobiose	5.00	HM	2 : 3 : 6-Trimethyl $\alpha$ -glucose *	4.79	CGW
$\alpha$ -Lactose *	4.69	U	Tetramethyl $\alpha$ -glucose *	4.74	CGW
4 : 6-Benzylidene $\beta$ -methylglucoside	4.64	U	2 : 3 : 4-Trimethyl $\beta$ -methylglucoside	4.45	CGW
4 : 6-Benzylidene $\alpha$ -methylglucoside *	4.90	U	2 : 4 : 6-Trimethyl $\beta$ -methylglucoside	4.41	CGW
4- $\beta$ -Glucosido- $\alpha$ -mannose	4.99	U	2 : 3 : 6-Trimethyl $\beta$ -methylglucoside	4.41	CGW
$\alpha$ -Methylarabinoside	4.68	CG(a)	Tetramethyl $\alpha$ -galactose *	4.79	CGW
(c) <i>Furanoid compounds.</i>			Tetramethyl $\beta$ -methylgalactoside *	4.74	CGW
$\alpha$ -Methylmannoside	4.64	CG(b)	Trimethyl $\delta$ -xylonolactone	4.60	CGW
$\gamma$ -Mannonolactone	4.73	YS	2 : 3-Dimethyl 4 : 6-benzylidene $\alpha$ -methylglucoside *	4.84	U
Tetramethyl $\gamma$ -mannonolactone	4.50	YS			
Trimethyl $\gamma$ -rhamnonolactone	4.65	YS			
Trimethyl $\gamma$ -lyxonolactone	4.42	CGW			
Trimethyl $\gamma$ -arabonolactone	4.50	CGW			
Hexamethyl lyxosido-lyxoside	4.20	U			

\* See p. 1498.

situated molecules, whereas if it is derived from a spacing or sub-multiple of a cell dimension, its meaning is uncertain, since it involves molecules whose distance apart and relative orientation are both in general unknown.) The references above are as follows: CGW, present paper; YS, Young and Spiers, *Z. Krist.*, 1931, **78**, 101; HM, Hengstenberg and Mark, *ibid.*, 1929, **72**, 301; CG(a), Cox and Goodwin, *ibid.*, 1933, **85**, 462; CG(b), *idem*, J., 1932, 1844; C, Cox, J., 1931, 2313; U, unpublished work in this laboratory.

It will be observed that, on the whole, the more highly methylated substances have shorter axes; this indicates, as Young and Spiers (*loc. cit.*) had pointed out in the case of the lactones studied by them, that the methyl groups are situated in approximately the same plane as the sugar (or lactone) ring. It is not necessarily to be inferred, however, that the molecule of a methylated sugar is "thinner" than that of a free sugar; the axes in the table give an *upper limit* to the molecular thickness, the latter in general being ap-

FIG. 1.

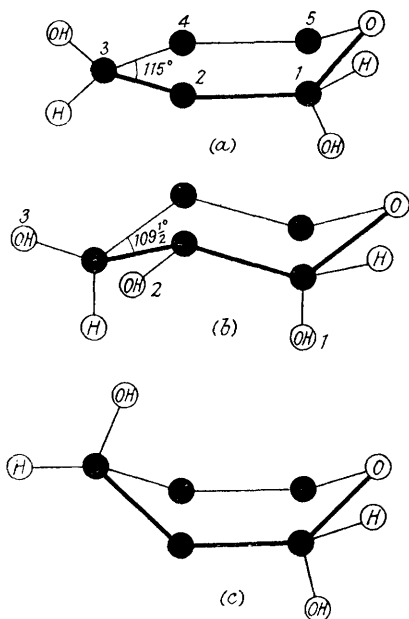


FIG. 2.

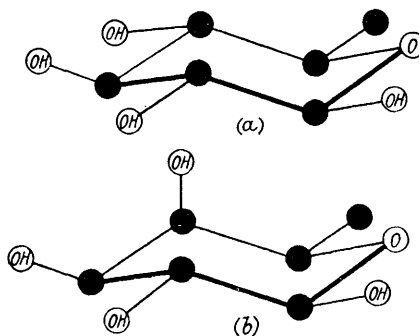
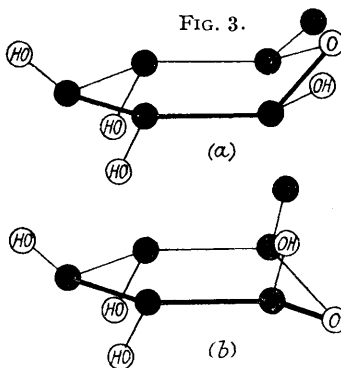


FIG. 3.



proximately  $c \sin \alpha$ , where  $c$  is the measured axis and  $\alpha$  the inclination of the axis to the plane of the molecules. The more disc-like methylated sugar molecules tend to pack together in parallel layers, so that the cell dimension (which in most of the cases considered is an axis of symmetry) is necessarily more nearly perpendicular to the plane of the molecule, and therefore approaches more closely to the actual "thickness" of the latter.

Table I shows that there is no great difference between the figures for the pyranose and furanose compounds, and that in the pyranose substances, configuration does not appear to influence the results very much. These facts are in agreement with a "flat" pyranose ring, but appear to be incompatible with any form of Sachse ring. In the "flat" ring [Fig. 1 (a)] the extracyclic valencies of carbon atoms 2, 3, and 4 are symmetrical about the plane of the ring, a feature which is exhibited also by the undoubtedly flat furanose or  $\gamma$ -lactone ring. The extracyclic valencies of carbon atoms 1 and 5, however, will be rotated from the symmetrical position by an amount depending upon the position of the ring oxygen atom; according as the addenda to  $C_1$  and  $C_5$  are *trans* or *cis* to the ring oxygen atom, they will project respectively more or less than similar addenda on the other carbon

atoms. A rough calculation may be made of the effect of the special positions of the  $C_1$  and  $C_5$  valencies. In the case of those valencies which are symmetrical about the plane of the ring, an attached oxygen atom (the C-O bond being supposed to be 1.46 Å.) will be situated at a distance of approximately  $1.46 \sin (\frac{1}{2} \times 109\frac{1}{2}^\circ)$ , *i.e.*, 1.18 Å. from the ring. In the extreme position of the *trans*  $C_5$  extracyclic valency (perpendicular to the line  $C_1C_5$ ) the attached  $C_6$  carbon atom will be at a distance of  $1.54 \sin 109\frac{1}{2}^\circ$ , *i.e.*, 1.44 Å. from the ring. The difference, 0.26 Å., between these values may be taken as the upper limit of the variation in molecular thickness which can be expected from variations in configuration of sugars based on a "flat" pyranose ring. The atoms of a Sachse ring [Fig. 1 (b) and (c)] lie in two parallel planes (0.5 Å. apart in a *trans*-ring and 0.8 Å. in a *cis*-ring), and the extracyclic valencies are either nearly parallel or nearly perpendicular to these planes. Hence, the oxygen atoms attached to a Sachse pyranose ring may be either practically in the mean plane of the ring, or about  $1\frac{1}{2}$  Å. out of it, according to the conformation of the ring and the configuration of the particular sugar concerned. It would thus be expected that the thickness of the molecules determined by X-ray measurements would show considerable variations as these factors were changed. All pyranoses can, in fact, be divided into two classes according as it is possible for them to possess "thin" conformations or not.  $\beta$ -Glucose [Fig. 2 (a)] is an example of the first class in which all the carbon and oxygen atoms can lie in two planes 0.5 Å. apart; with galactose [Fig. 2 (b)], on the other hand, this is not possible, and at least one oxygen atom must project about  $1\frac{1}{2}$  Å., no matter which form of the Sachse ring is assumed. It would thus be anticipated that the "thickness" of a molecule belonging to the second class (substances marked with an asterisk in Table I) would be greater by something of the order of 1 Å. than that of a molecule in the first class. The observed difference between the minimum values for the two classes is 0.28 Å.; this is suggestively close to the value deduced above for the variation in "flat" pyranose rings, and on the other hand, it is sufficiently remote from the value of 1 Å. expected for Sachse rings to suggest very strongly that the latter do not occur in sugars.

This conclusion is supported by a comparison of the furanose and pyranose results. It is evident, from the considerations advanced above, that the molecules of the first class of Sachse pyranoses (thickness about 4 Å.) should be thinner than furanose molecules, while those of the second class should be thicker (5 Å. or more). Now, three methyl derivatives of  $\beta$ -glucose (which according to the Sachse theory is the thinnest possible pyranose) have practically identical thicknesses (4.45, 4.41, and 4.41 Å.), from which it can be inferred that 4.41 Å. is the absolute minimum for the thickness of a methylated pyranose molecule. Reference to Table I shows, however, that one methylated furanolactone has the same thickness as the  $\beta$ -glucose derivatives, whilst the molecule of hexamethyl lyxofuranosido-lyxofuranoside is even thinner. These facts are inexplicable on the basis of a Sachse pyranose ring, but are to be expected if the pyranose ring is "flat." The exceptionally small value for hexamethyl lyxosido-lyxoside is probably due to the somewhat closer packing consequent upon the greater van der Waals forces between the much larger methylated disaccharide molecules. Support for this view is afforded by the result, 4.3 Å. (Trogus and Hess, *Ber.*, 1935, **68**, 1605), for  $\beta$ -octamethyl cellobiose, although this value should be accepted with caution, since the measurements were not made on single crystals, and other numerical data in the paper appear to be 2-4% low.

Comparison of the crystallographic data for the sugars with those for derivatives of cyclohexane also suggests that the Sachse ring is inadequate to account for the former. There is considerable evidence (see, *e.g.*, Hassel, *Trans. Faraday Soc.*, 1934, **30**, 874) that cyclohexane and its derivatives are based on a Sachse (usually *trans*) ring, so that if the ring form were the same for the sugars, it should be possible to find some parallelism (*e.g.*, in the "thickness" of the molecules) between the crystal structures of simple and methylated sugars on the one hand and the polyhydroxycyclohexanes and their methyl ethers on the other. This does not appear to be the case, however; of ten such substances which have been studied (Hassel, *loc. cit.*; Patterson and White, *Z. Krist.*, 1931, **78**, 76; **80**, 1; White, *ibid.*, p. 5), not one possesses a cell dimension less than  $5\frac{1}{2}$  Å.

Consideration of the X-ray data from various aspects thus leads to the same conclusion, *viz.*, that a pyranose ring of Sachse form is incompatible with the facts, and that a "flat"

ring affords a satisfactory alternative. Further and more detailed investigation is necessary to establish the exact form of the ring, and to determine what factors are responsible for the departure from the Sachse conformation. It seems that configuration and substitution are not the first of these factors, since the same influences would operate with, *e.g.*, cyclohexane derivatives, and moreover, the shape of the ring would be a much more obvious function of configuration than at present appears to be the case. Very few data for heterocyclic rings are available [Sutton and Brockway's experiments (*J. Amer. Chem. Soc.*, 1935, **57**, 473) upon 1:4-dioxan suggest that its ring approximates to the Sachse *trans*-form, but they were not sensitive enough to detect the small differences of angle or distance envisaged here]. It is probable, however, that the unusual form of the pyranose ring can be largely accounted for by its heterocyclic nature, the special function of the oxygen atom being borne in mind. Since the first carbon atom in a free sugar is potentially aldehydic, the ring oxygen atom to which it is attached cannot be regarded as of the normal ether type, so that the magnitude of its valency angle and the length of the O-C<sub>1</sub> bond should both be regarded as uncertain. The determination of these quantities in free sugars, glycosides, and  $\delta$ -lactones must be among the principal objects of further research.

The divergence of the carbon valency angles from  $109\frac{1}{2}^\circ$  in a flat pyranose ring cannot be determined exactly until the position of the oxygen atom relative to the remainder of the ring is known. If, however, the length of the O-C link is taken to be 1.46 Å., and the five carbon atoms are assumed to be co-planar, then calculation shows that their valency angles lie between  $113^\circ$  and  $116^\circ$ , the corresponding limits of the oxygen angle being  $90^\circ$  and  $106^\circ$ . If the C-O link is shorter, or the carbon atoms not quite co-planar, the carbon valency angle will be nearer  $109\frac{1}{2}^\circ$ . On account of the special nature of the oxygen atom, the above approximate calculation of its valency angle should not necessarily be regarded as giving support to Allen and Hibbert's view (*Ber.*, 1932, **65**, 1366; *J. Amer. Chem. Soc.*, 1934, **56**, 1398) that the "normal" valency angle of oxygen is  $90^\circ$ .

The above conclusions, being based upon crystallographic data, relate to the solid state; it is of interest to consider how far they may be applied to molecules in solution, and, in particular, to inquire whether the planar pyranose ring has any advantage over the Sachse form in the interpretation of chemical facts. Any model for a pyranose ring (other than a completely flat one) involves the possibility of the molecule of a given sugar (say  $\beta$ -*D*-glucose) existing in several modifications [in the case of the Sachse model, eight; with a "flat" ring, two, according as the glycosidic hydroxyl is *cis* or *trans* to the ring oxygen atom (Fig. 3)], and it is therefore necessary first to consider to what extent transformations between these forms can occur when the substance goes into solution.

In the case of the glycosides (in which ring opening is prevented) the molecule must undoubtedly be regarded as nearly rigid and unaffected by its state of aggregation; as Bernal (*Trans. Faraday Soc.*, 1934, **30**, 876) has pointed out for polyhydroxy-cyclohexane derivatives, transition from one form to another would require an exceedingly large activation energy, since it involves, not only a considerable bending of valencies in the ring, but also large relative movements of the polar addenda. The relative dispositions of hydroxyl groups with the different forms of Sachse ring are indeed so different that even in free sugars (in which theoretically the ring may open, and close again with a different conformation) the difference in stability of the various forms would be sufficiently great to ensure that practically only one (*i.e.*, that occurring in the solid state) existed in solution. Interchange between the two "flat" conformations (Fig. 3), however, probably can occur in solution through the intermediate aldehyde stage, since the difference between the two is small, involving only the addenda to C<sub>1</sub> and C<sub>5</sub>; the difference in energy in this case would probably be of the same order as that between  $\alpha$ - and  $\beta$ -forms. The attainment of equilibrium between these two forms may account for the complex mutarotation curves observed by various workers (*e.g.*, Smith and Lowry, *J.*, 1928, 666; Riiber, Minsaa, and Lyche, *J.*, 1929, 2173; Phelps, Isbell, and Pigman, *J. Amer. Chem. Soc.*, 1934, **56**, 747) and usually attributed to the presence of a third isomeride. Apart, however, from this effect in the case of the free sugars, it is reasonably certain that no change of ring conformation occurs during the process of solution. In this connexion, it is of interest to observe the close correspondence (Table II) between the molecular volume in the solid state

and the aqueous solution volume (the latter taken from Riiber and Minsaas, *Ber.*, 1927, **60**, 2407, and earlier papers); this appears to indicate, not only that the form of the molecule is constant, but also that in the hydrated molecule (in solution) the co-ordination of water molecules is of the same nature and extent as the co-ordination of the hydroxyls

TABLE II.

Substance.	Mol. vol. (Å. <sup>3</sup> per mol.).		Substance.	Mol. vol. (Å. <sup>3</sup> per mol.).	
	Solid.	Solution.		Solid.	Solution.
β-Arabinose .....	153·2	152·0	α-Methylglucoside .....	216·0	218·8
α-Methylarabinoside .....	184·5	187·3	α-Galactose .....	190·2	181·2
β-Methylarabinoside .....	184·4	187·5	β-Mannose .....	196·2	179·3
α-Glucose .....	193·2	183·5			

of neighbouring sugar molecules in the solid. The available data suggest further that the small changes which do occur on dissolution (as indicated by the difference between solid and solution volumes) can be related qualitatively to the heat of solution; *e.g.*, α-galactose and α-glucose, which show approximately 5% difference between solid and solution volumes, have fairly large heats of solution (21·4 and 14·5 cal./g.), whereas for α-methylglucoside (1% volume change) the heat of solution is only 3·1 cal./g. (Hendricks, Steinbach, Le Roy, and Moseley, *J. Amer. Chem. Soc.*, 1934, **56**, 99).

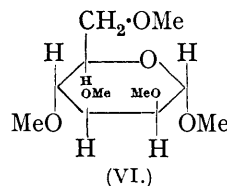
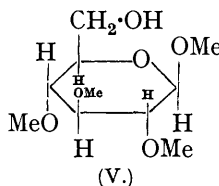
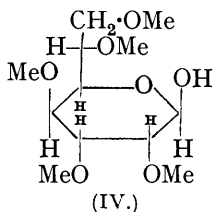
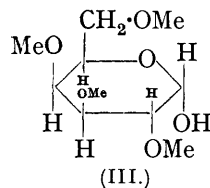
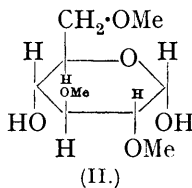
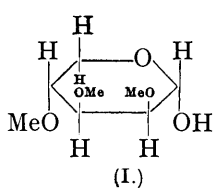
Consideration of various sugar derivatives from the point of view of the ring conformation shows that the "flat" ring is definitely more satisfactory than a Sachse ring. Various unusual derivatives do indeed exist (*e.g.*, certain anhydro-sugars) the structures of which require a "flat" molecule to be considerably strained, but in every case investigated it appears that a Sachse ring also must be strained (usually at least as much) to form the molecule concerned. On the other hand, many compounds which cannot be represented without strain by means of a Sachse ring can be formulated on the basis of a "flat" ring without any distortion.

Characteristic of the sugars is the ease with which *isopropylidene*, *benzylidene*, and similar derivatives involving a C<sub>3</sub>O<sub>2</sub> ring can be formed, usually without opening of the sugar ring; these condensations invariably occur with *cis*-hydroxyl groups. These facts suggest that the spatial arrangement necessary for the formation of the acetal ring (which when unstrained must be flat) already exists in the sugar molecule; *i.e.*, the two carbon atoms and their attached hydroxyl groups must be co-planar or nearly so. Now, while this condition is satisfied by a flat ring, it can be seen (Fig. 1) that, owing to the alternating form of the Sachse *trans* ring, two successive C–O bonds can never be co-planar, so that considerable strain is necessary for the formation of an *isopropylidene* or similar derivative; moreover, since one extracyclic valency on each carbon atom is parallel to the *bisector* of the external valency angles of its neighbours, the distance apart of *trans*-hydroxyl groups can be as small as that of *cis*-groups, so that, if it is supposed that strained acetal rings can be formed between *cis*-hydroxyls, then they should be possible with *trans*-groups also. [In Fig. 1 (*b*) the hydroxyl group 2 is equidistant from 3, to which it is *trans*, and from 1, to which it is *cis*.] The various forms of Sachse *cis*-rings enable two successive valencies to be parallel, but not two successive pairs of valencies, and are therefore inadequate to account, *e.g.*, for the various 1 : 2-3 : 4 fused ring derivatives which are known. Actually the behaviour of substances known to possess a Sachse configuration (*i.e.*, *cyclohexane* derivatives) is in marked contrast to that of the sugars. It has been shown (Karrer, *Helv. Chim. Acta*, 1926, **9**, 116; Micheel, Ruhkopf, and Suckfüll, *Ber.*, 1935, **68**, 1525) that even under very energetic conditions cyclic acetals of quercitol and inositol cannot be prepared; this is fully in accord with the geometrical properties of the Sachse ring, and confirms the view that the pyranose ring is not of this type. Finally, it may be noted that whereas, with a "flat" ring, *cis* C–OH links on C<sub>2</sub> and C<sub>3</sub> or C<sub>3</sub> and C<sub>4</sub> are exactly coplanar, yet there is in the case of C<sub>1</sub> and C<sub>2</sub> some divergence from parallelism (although not so much as with a Sachse ring). It is therefore to be expected that cyclic acetal formation will occur less readily in the 1 : 2-position than in others; this affords a possible explanation of the fact that in most cases the formation of 1 : 2-*isopropylidene* derivatives

is accompanied by change to the furanose form (in which, on account of the completely planar form of the ring, the  $C_1$ -OH and  $C_2$ -OH valencies are presumably exactly coplanar).

The relative configurations of the  $\alpha$ - and  $\beta$ -sugars are chiefly based on optical relationships (rules of Hudson and of Freudenberg and Kuhn), and it is important to obtain confirmation from X-ray data, particularly as other methods (conductivity in the presence of boric acid, velocity of hydrolysis, and refraction differences) do not appear to be entirely reliable (see *e.g.*, Sørensen and Trumphy, *Kong. Norske Vidensk. Selsk. Skr.*, 1934, No. 6). In Part I (this vol., p. 978) we pointed out that the close correspondence between the crystal structures of  $\beta$ -methylaraboside,  $\alpha$ -methylfucoside, and  $\alpha$ -methylgalactoside-6-bromohydrin leads to the conclusion that the three substances differ only in the addenda to the fifth carbon atom and that, in particular, they must possess the same configuration on the first carbon atom. This result is valuable in confirming that  $\beta$ -arabinose,  $\alpha$ -fucose, and  $\alpha$ -galactose possess the same configuration (and that the normal form of  $\alpha$ -methylfucoside is pyranose), but it affords no direct evidence as to the configuration of the reducing group relative to the remainder of the molecule in each case. The present results do, however, provide such evidence in the case of glucose. According to the accepted formulation, in derivatives of  $\beta$ -glucose the addenda to  $C_1$  and  $C_5$  are *cis*, while in derivatives of  $\alpha$ -glucose they are *trans*. Whatever the conformation of the pyranose ring, therefore, one of these two addenda must, in the case of  $\alpha$ -glucose derivatives, be *trans* to the ring oxygen atom and must in consequence project considerably from the plane of the ring. In  $\beta$ -glucose derivatives, on the other hand, the  $C_1$  and  $C_5$  addenda can both assume the *cis*-position (Fig. 3a), in which they project from the plane of the ring to a relatively small extent. As Table I shows, the derivatives of  $\alpha$ -glucose are actually "thicker" than those of  $\beta$ -glucose, while the low values for the latter show that they do indeed possess the *cis*-conformation; from this we conclude that the configurations of  $\alpha$ - and  $\beta$ -glucose are correctly assigned. By inference, on account of the close relation between glucose and xylose, this conclusion applies to the latter sugar also, and since the molecule of  $\beta$ -methylxyloside is "thinner" than those of  $\alpha$ -xylose and  $\alpha$ -methylxyloside (Cox, J., 1932, 138, 2535), it appears that in  $\beta$ -xylose, as in  $\beta$ -glucose, the glycosidic hydroxyl is *cis* to the ring oxygen atom. (It may be observed that, in contrast with the pyranoses, the "thickness" of a number of furanose derivatives now being studied appears to be quite independent of the configuration on the first carbon atom, as is to be expected from a flat  $C_4O$  ring.)

With few exceptions, methylated sugars do not crystallise well, so that in some cases we have carried out only a partial examination; full details of cell dimensions and space-groups have, however, been obtained for the following substances: 2:3:4-trimethyl  $\alpha$ -lyxose (I), 2:3:6-trimethyl  $\alpha$ -glucose (II), 2:3:4:6-tetramethyl  $\alpha$ -glucose, 2:3:4:6-tetramethyl  $\alpha$ -galactose (III), 2:3:4:6:7-pentamethyl  $\beta$ - $\alpha$ -glucoheptose (IV), 2:3:4-trimethyl  $\beta$ -methylglucoside (V), 2:3:4:6-tetramethyl  $\alpha$ -methylmannoside (VI), and



1:3:4-trimethyl fructose. The last substance is obtained by the degradation of the furanose polysaccharide trimethyl levan (Hibbert, Tipson, and Brauns, *Canadian J. Res.*, 1931,

4, 221; Challinor, Haworth, and Hirst, J., 1934, 676) but, as the latter authors have pointed out, the conditions of preparation do not exclude the possibility of a pyranose ring in the crystalline trimethyl fructose. A comparison (Table III) of its cell dimensions with those of 1 : 3 : 4 : 5-tetramethyl  $\beta$ -fructopyranose (Young and Spiers, *loc. cit.*), indeed, suggests that the two substances have related structures and therefore the same ring form, but the correspondence may be accidental, and further work is necessary.

TABLE III.

	Trimethyl fructose; Å.	Tetramethyl fructose; Å.
<i>a</i>	18.49	$\frac{1}{2} \times 18.44$
<i>b</i>	8.60	8.97
<i>c</i>	7.14	$2 \times 7.4$

As mentioned on p. 1496, the approximate orientation of the molecules in the unit cell of most of the methylated sugars can be determined without serious difficulty; the short axis of  $4\frac{1}{2}$  Å. must be approximately normal to the plane of the molecule, and in those substances which are not fully methylated it is reasonable to suppose that the molecular arrangement will be such as to permit the fullest degree of co-ordination between the remaining hydroxyl groups. The exact determination of the structures of these substances must, however, be deferred until more data have accumulated, and in the meanwhile the approximate structures as found by the application of the above principles are scarcely of sufficient precision to merit publication. It is nevertheless of interest to note that the optical properties of the methylated sugars are sufficiently characteristic to enable the approximate molecular orientation to be found in the absence of a short axis. The average birefringence of 27 sugars and glycosides is 0.021, and with one or two exceptions it is impossible at present to relate the optical properties to the structure; the mean birefringence of seven methylated compounds, on the other hand, is 0.075, and in each of the six cases in which an axis of  $4\frac{1}{2}$  Å. occurs, the minimum refractive index is parallel to this axis. In the remaining case of trimethyl  $\alpha$ -xylose, cell dimensions of 8.68 Å. (*a*) and 8.31 Å. (*b*) occur (Young and Spiers, *loc. cit.*); since the minimum index is parallel to the *b*-axis, we can assert that the molecules lie with their shortest dimension parallel to this axis, so their "thickness" is approximately  $\frac{1}{2}b$ , *i.e.*, 4.16 Å. For reasons discussed in connexion with Table I, this "thickness," not being a cell dimension, is not comparable with the figures upon which the arguments in the earlier part of this paper are based.

## EXPERIMENTAL.

Owing to the high solubilities of methylated sugars in practically all solvents, determinations of densities by flotation and of refractive indices by immersion are less accurate than the corresponding measurements for simple sugars. Density determinations are probably subject to an error of 4–5%, and refractive indices are correct to  $\pm 0.004$ .

A reference preceding a crystallographic description indicates the source of the specimen used for the present work.

2 : 3 : 4-Trimethyl  $\alpha$ -lyxose (I). This sugar (Hirst and Smith, J., 1928, 3147) crystallises from light petroleum in poorly developed orthorhombic needles, elongated along the *a*-axis and showing the forms  $q\{011\}$  and  $a\{100\}$  ( $q : q' = 84^\circ$ ). The cell dimensions are  $a = 12.75$ ,  $b = 9.29$ ,  $c = 8.19$  Å. The number (*n*) of asymmetric molecules in the unit cell is 4, whence  $d(\text{calc.}) = 1.31$  g./c.c. (obs. 1.26). The abnormal spacings are  $\{100\}$ ,  $\{010\}$  and  $\{001\}$  halved, so that the space-group is  $P2_12_12_1$  ( $Q^4$ ). The minimum refractive index is 1.48 and is perpendicular to the *a*-axis, but whether parallel to *b* or *c* could not be determined owing to the poorness and high solubility of the crystals.

2 : 3 : 6-Trimethyl  $\alpha$ -glucose (II). This substance crystallises from ether in acicular orthorhombic combinations of  $a\{100\}$  and  $b\{010\}$ , terminated by  $c\{001\}$ . The cell dimensions are  $a = 20.45$ ,  $b = 11.90$ ,  $c = 4.79$  Å.;  $n = 4$ ;  $d(\text{calc.}) = 1.28$  g./c.c. (obs. 1.26). The abnormal spacings are  $\{100\}$  and  $\{001\}$  halved, so the space-group is  $P2_12_12_1$  ( $Q^3$ ). The refractive indices are  $\alpha = 1.465$  (parallel to  $[c]$ ) and  $\gamma = 1.51$ . Trogus and Hess (*loc. cit.*) record cell dimensions (not from single-crystal photographs) for this substance differing by several % from those given above; the density (1.38) given by them is certainly much too high. Their reason for supposing that association to double molecules occurs in the crystal is entirely without foundation.

2 : 3 : 4 : 6-Tetramethyl  $\alpha$ -glucose. This compound forms elongated orthorhombic combin-



ations of  $a\{100\}$  and  $m\{110\}$ , terminated by  $c\{001\}$  ( $a : m = 51^\circ$ ). Cell dimensions:  $a = 18.29$ ,  $b = 14.85$ ,  $c = 4.74$  Å.,  $n = 4$ ;  $d$  (calc.) =  $1.22$  g./c.c.; space-group  $P2_12_12_1$ . The crystals are optically negative, the refractive indices being  $\alpha$  (parallel to  $[c]$ ) =  $1.475$  and  $\gamma$  (parallel to  $[a]$ )  $\geq 1.54$ .

**2 : 3 : 4 : 6-Tetramethyl  $\alpha$ -galactose (III).** The crystals of this substance are orthorhombic, elongated parallel to  $[c]$  and somewhat flattened on  $a\{100\}$ . Cell dimensions:  $a = 25.20$ ,  $b = 10.07$ ,  $c = 4.79$  Å.;  $n = 4$ ;  $d$  (calc.) =  $1.28$  g./c.c. (obs.  $1.24$ ); space-group  $P2_12_12_1$ . The plane of the optic axes is  $\{010\}$  and the minimum refractive index is parallel to  $[c]$ .

**2 : 3 : 4 : 6 : 7-Pentamethyl  $\beta$ - $\alpha$ -glucoheptose (IV).** This sugar (Haworth, Hirst, and Stacey, J., 1931, 2864) forms monoclinic crystals of approximately hexagonal outline, tabular on  $R\{10\bar{1}\}$ . Unit cell dimensions:  $a = 10.87$ ,  $b = 8.10$ ,  $c = 8.45$  Å.,  $\beta = 92^\circ 10'$ ;  $n = 2$ ;  $d$  (calc.) =  $1.25$  g./c.c. (obs.  $1.25$ ). The only abnormal spacings are  $\{010\}$  halved, so the space group is  $P2_1$  ( $C_2^2$ ). The plane of the optic axes is perpendicular to  $\{010\}$ , an acute bisectrix figure being visible through  $R\{10\bar{1}\}$ ;  $2E = 60^\circ$  approx.; birefringence moderate.

**2 : 3 : 4-Trimethyl  $\beta$ -methylglucoside (V).** This substance (Charlton, Haworth, and Hickinbottom, J., 1927, 1534) crystallises from light petroleum in orthorhombic needles, elongated parallel to  $[c]$ , and exhibiting the forms  $b\{010\}$ ,  $m\{110\}$  and  $c\{001\}$  ( $b : m = 42\frac{1}{2}^\circ$ ). Cell dimensions:  $a = 17.54$ ,  $b = 16.08$ ,  $c = 4.45$  Å.,  $n = 4$ ;  $d$  (calc.) =  $1.25$  g./c.c. (obs.  $1.25$ ); space-group  $P2_12_12$  ( $Q^3$ ); refractive indices,  $\alpha = 1.465$  (parallel to  $[c]$ ) and  $\gamma \geq 1.525$ .

**2 : 3 : 4 : 6-Tetramethyl  $\alpha$ -methylmannoside (VI).** The monoclinic crystals of this substance (Bott, Haworth, Hirst, and Tipson, J., 1930, 2658) were with one exception very poor. One crystal about 1 cm. across was obtained; this was tabular on  $c\{001\}$  and showed also the forms  $a\{100\}$ ,  $m\{110\}$ ,  $R\{10\bar{1}\}$  and  $p\{011\}$ , with perfect cleavage parallel to  $c\{001\}$ . Unit cell dimensions:  $a = 10.22$ ,  $b = 7.89$ ,  $c = 8.41$  Å.,  $\beta = 97^\circ 14'$  (calculated from  $[101] = 12.40$  Å.);  $n = 2$ ;  $d$  (calc.) =  $1.235$  g./c.c.; space-group  $P2_1$  ( $C_2^2$ ). Density or refractive-index measurements could not be made on account of the exceedingly high solubility of this substance.

**1 : 3 : 4-Trimethyl fructose.** The crystals of this substance (Challinor, Haworth, and Hirst, *loc. cit.*) were deliquescent. A simple micro-desiccator, transparent to X-rays, has been devised to preserve a deliquescent crystal over the period of hours or days necessary for a complete X-ray examination. This is formed by cementing together by their closed ends the smaller parts of two gelatin capsules such as are used for medicinal purposes (Parke Davis, No. 3). A hole is pierced through the surface of junction. One end fits closely over the small ebonite cylinder on the tapered end of which the crystal is mounted, while in the other end are placed small fragments of calcium chloride or other desiccating agent; this end is then closed by the larger part of a capsule. The two joints can be effectively sealed by means of vaselin, so that the air space around the crystal is kept perfectly dry for several days. The gelatin does not reduce the X-ray intensity by more than about 10%, and is sufficiently transparent and uniform to permit of the adjustment of the crystal on the goniometer head by the usual optical methods. By an obvious modification, the device has been used to preserve efflorescent crystals.

The crystals are orthorhombic prisms  $h\{210\}$  terminated by  $s\{201\}$  and sometimes by  $r\{101\}$  ( $s : s' = 75\frac{1}{2}^\circ$ ;  $h : h' = 86^\circ$ ); cell dimensions  $a = 18.49$ ,  $b = 8.60$ ,  $c = 7.14$  Å.;  $n = 4$ ;  $d$  (calc.) =  $1.29$  g./c.c. (obs.  $1.29$ ); space-group  $P2_12_12_1$ . The crystals exhibit imperfect cleavage parallel to  $\{010\}$ . They are optically negative, the plane of the optic axes being  $a(100)$ , and  $[b]$  the acute bisectrix. The optic axial angle is  $2E = 28^\circ$  approx., and the refractive indices are  $\alpha = 1.49$  and  $\gamma = 1.525$ .

Partial examinations have been made of various substances, either on account of the poorness of the crystals, or because their importance did not appear to merit a complete study. Such measurements as are recorded, however, have in all cases been made upon single crystals.

**2 : 3 : 6-Trimethyl  $\beta$ -methylglucoside** (Baird, Haworth, and Hirst, this vol., p. 1201). This substance forms very fine needles. The cell dimension parallel to the needle is  $c = 4.41$  Å.; refractive indices  $\alpha = 1.47$  (parallel to  $[c]$ ) and  $\gamma = 1.555$ .

**2 : 4 : 6-Trimethyl  $\beta$ -methylglucoside** (Haworth and Sedgwick, J., 1926, 2573). Very fine needles; cell dimension parallel to the needle is  $c = 4.41$  Å.; refractive indices  $\alpha = 1.465$  (parallel to  $[c]$ ) and  $\gamma \geq 1.535$ .

**2 : 3 : 4-Trimethyl  $\beta$ -methyl-d-arabinoside.** This substance ( $[\alpha]_D - 220^\circ$  in methyl alcohol,  $c = 2$ ), formerly known as the  $\alpha$ -form, crystallises in slightly deliquescent prisms, the length of the prism axis being  $c = 4.87$  Å.

**2 : 3 : 4-Trimethyl  $\alpha$ -methylarabinoside** (formerly known as  $\beta$ ). This compound forms fine needles, apparently orthorhombic, the length of the needle axis being  $c = 4.85$  Å.; refractive indices  $\alpha = 1.475$  (parallel to  $[c]$ ) and  $\gamma \geq 1.555$ .

2 : 3 : 4 : 6-Tetramethyl  $\beta$ -methylgalactoside. This substance crystallises in small flattened needles, the cell dimension parallel to the length of the needle being  $c = 4.74 \text{ \AA}$ . The birefringence is fairly high, with  $\alpha = 1.47$  (parallel to  $[c]$ ).

2 : 3 : 4-Trimethyl  $\delta$ -xyloolactone (Drew, Goodyear, and Haworth, J., 1927, 1237). This also crystallises in flattened needles, the length of the needle axis being  $c = 4.60 \text{ \AA}$ . The crystals are optically positive, with  $\alpha = 1.465$  (parallel to  $[c]$ ).

$\alpha$ -Ethylglucofuranoside (Haworth and Porter, J., 1929, 2796). This substance crystallises in small needles, the length of the needle axis being  $c = 5.69 \text{ \AA}$ . The minimum refractive index is not parallel to  $[c]$ .

2 : 3 : 5-Trimethyl  $\gamma$ -lyxonolactone (Bott, Hirst, and Smith, J., 1930, 658). This lactone forms long monoclinic prisms, the cell dimension parallel to the prism length being  $c = 4.42 \text{ \AA}$ . The birefringence is fairly high, with  $\alpha < 1.47$  (inclined at about  $20^\circ$  to  $[c]$ ). Full details of the structure of this substance will be published later.

2 : 3 : 5-Trimethyl  $\gamma$ -arabonolactone. This lactone (Drew, Goodyear, and Haworth, *loc. cit.*) forms needles (probably orthorhombic) which are difficult to handle on account of their low m. p. ( $33^\circ$ ). The needle axis is  $c = 4.50 \text{ \AA}$ . The crystals are optically positive,  $[c]$  being the obtuse bisectrix;  $2E = 80^\circ$  approx.; birefringence fairly high.

Hexamethyl lyxofuranosido-lyxofuranoside. This dipentose (Bott, Hirst, and Smith, *loc. cit.*) forms fine needles with  $c = 4.20 \text{ \AA}$ . Details of a more complete examination will be published later.

Optical measurements have been made on the following two substances, X-ray data for which have been recorded by Young and Spiers (*loc. cit.*).

1 : 3 : 4 : 5-Tetramethyl  $\beta$ -fructose. The crystals of this substance show very good cleavage parallel to  $\{001\}$ , which is the plane of the optic axes;  $2V = 90^\circ$  approx., the optic axes being nearly normal to  $\{110\}$ . The refractive indices are  $\alpha = 1.51$  and  $\gamma = 1.53$ .

2 : 3 : 4-Trimethyl  $\alpha$ -xylose. The monoclinic crystals of this sugar are frequently very unequally developed, being tabular on (110). The refractive indices are  $\alpha = 1.48$  (parallel to  $[b]$ ) and  $\gamma = 1.555$ . An optic axis is visible through (110).

We wish to correct a slight inaccuracy in Part I (this vol., p. 978). The sorbose prepared by the action of *B. xylinum* on sorbitol is the *l*-form, and not the *d*-form as implied in the experimental part of our paper; the earlier measurements were, however, carried out on *d*-sorbose.

#### SUMMARY.

X-Ray data for a number of crystalline methylated sugars are recorded. From a study of the results in conjunction with others previously published it is concluded that the carbon atoms in the  $C_5O$  ring of simple and methylated aldopyranoses are nearly co-planar, the oxygen atom being displaced out of their plane. Reasons are adduced for supposing that the ring form is not appreciably different in solution, and the conformation deduced from the X-ray data is shown to account satisfactorily for various chemical reactions (formation of acetone compounds). The X-ray data confirm the configurations assigned to  $\alpha$ - and  $\beta$ -glucose.

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