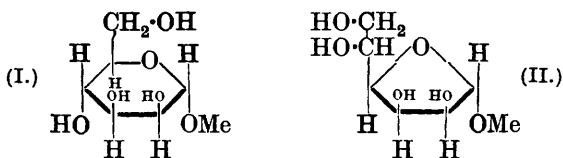


252. *X-Ray Evidence of the Structure of the Furanose and Pyranose Forms of α -Methylmannoside.*

By ERNEST GORDON COX and THOMAS HENRY GOODWIN.

α -METHYLMANNOSE exists in two stable forms differing considerably in their physical properties. The normal form (m. p. 193°), first described by Fischer and Beensch (*Ber.*, 1896, **29**, 2927), has been allotted the pyranose form (I) by Haworth (J., 1927, 3136), and the second isomeride (m. p. 118°), prepared by Haworth and Porter (J., 1930, 649) and by Haworth, Hirst, and Webb (*ibid.*, p. 651), is represented as a furanose form (II). The latter structure was

established by the conversion of the α -methylmannofuranoside into a tetramethyl- γ -mannonolactone, which had previously been shown to possess a five-atom ring structure.



The validity of the above formulæ was contested by Hudson (*J. Amer. Chem. Soc.*, 1930, **52**, 1680, 1707) on the grounds that the process of methylation is accompanied by changes of ring structure. It has been demonstrated very conclusively (J., 1930, 2636, 2644, 2653; 1931, 1349, 1354) that the pyranose and furanose formulæ were correctly assigned by Haworth in the first place; the present work was undertaken in the hope of obtaining some evidence of a physical nature to discriminate between the two ring forms. At this stage, it is not possible by means of X-ray investigation to determine precisely the position of every atom in an organic crystal of this kind, but we have been able to show fairly definitely that, in the crystalline state, the molecules of the two forms of α -methylmannoside have the above ring structures. At present no data for furanose sugars are available for comparison, but it is expected that considerably more evidence bearing on the present problem will result from examinations of various carbohydrates of this type which we intend to carry out in the near future.

α -Methylmannopyranoside.—Various crystallographic investigations of this substance are summarised by Groth ("Chemische Krystallographie," Vol. 3, p. 444). It forms very good orthorhombic bisphenoidal crystals, which do not exhibit any tendency to elongation or flattening in any particular direction and show weak positive double refraction (0.009). The axial ratios are variously given as $a : b : c = 0.9383 : 1 : 0.9275$ and $= 0.9336 : 1 : 0.9249$.

Good crystals were easily picked out from a pure sample of the substance available in the Birmingham laboratory; from X-ray rotation photographs the dimensions of the unit cell were found to be $a = 9.38$, $b = 9.99$, and $c = 9.23$ Å.U., with an accuracy of about 0.3%. The axial ratios are thus $a : b : c = 0.939 : 1 : 0.924$, in agreement with the goniometric results. From suitable series of oscillation photographs the {001}, {010}, and {100} planes were found to be halved, with no other halvings, so that the space-group is $Q^4(P2_12_12_1)$, which is characterised by three mutually perpendicular sets of two-fold screw axes. There are four asymmetric molecules in the unit cell, giving a calculated density of 1.481 g./c.c.,

whereas that found by flotation in α -bromonaphthalene was approximately 1.48.

In Table I the approximate intensities of the reflexions from some of the more important lattice planes are given. These intensities, with many others, were estimated visually, and are given in arbitrary units

TABLE I.

hkl	I	hkl	I	hkl	I	hkl	I
200	22	110	19	080	1	006	8
400	14	020	1½	220	26	008	0
600	0	040	20	002	8		
800	13	060	0	004	40		

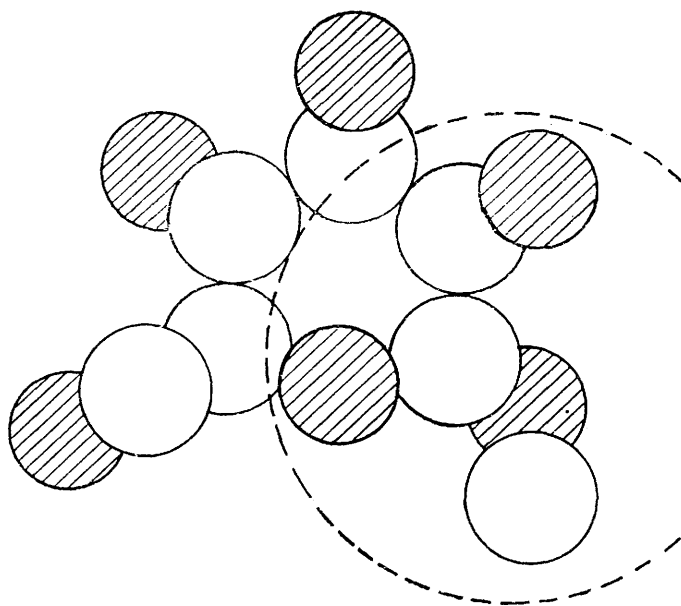
In attempting to fit molecules into the cell, we are faced with considerable difficulties on account of the numerous forms which a hexoside molecule of given stereochemical configuration may have. In the case of the molecule based on a six-atom ring, the ring itself may have one of several forms, and there is a certain amount of latitude for the position of the attached groups; in the furanose molecule, on the other hand, we may reasonably assume that the five-atom ring is planar, but there is a large range of possibilities for the position of the side-chain atoms. Thus we find in this case that the dimensions of the unit cell alone provide no certain criterion for distinguishing between the possibilities of a five- or a six-membered ring. Considerations of the intensities of reflexions, and of the general physical properties of the crystals, do, however, give valuable information on this point.

Previous work on the structure of the sugars has demonstrated the almost invariable occurrence of a dimension of about 4.5 Å.U. (This is illustrated very well by the presence in all X-ray powder photographs of sugars of a very strong line corresponding with this spacing.) This dimension has been identified with the thickness of the molecule normal to the plane of the ring. In the case of α -methylmannopyranoside we may assume provisionally that the rings are approximately parallel to (001), since $c = 2 \times 4.62$ Å.U. On comparing this with the value 4.55 Å.U. obtained in the case of β -mannose (Marwick, *Proc. Roy. Soc., A*, 1931, **131**, 621), it seems that the introduction of the CH_3 group does not increase the ring thickness appreciably, as was inferred also in the case of xylose (Cox, this vol., p. 138). Since the (004) reflexion is so strong, the four molecules are evidently arranged at approximate relative depths 0, $c/4$, $c/2$, and $3c/4$ in the direction of the c -axis; this would account also for the relative weakness of the (002) and (006) reflexions. The complete absence of a (008) reflexion might be due to the ring being puckered, or simply to the depths being slightly different from those suggested above. So far, the agreement with experiment

could be obtained equally well with either a five- or a six-membered ring, but this is not the case when the arrangement of the molecules in the other directions is considered.

The form of the six-atom-ring molecule which appears to be most satisfactory is shown in Fig. 1, the oxygen atoms being shaded and the hydrogens omitted. In Fig. 2 a plan of the unit cell on (001) is shown, with four such molecules arranged to comply with the symmetry conditions and also to give agreement with the principal reflexion intensities. The approximate depth of each molecule

FIG. 1.

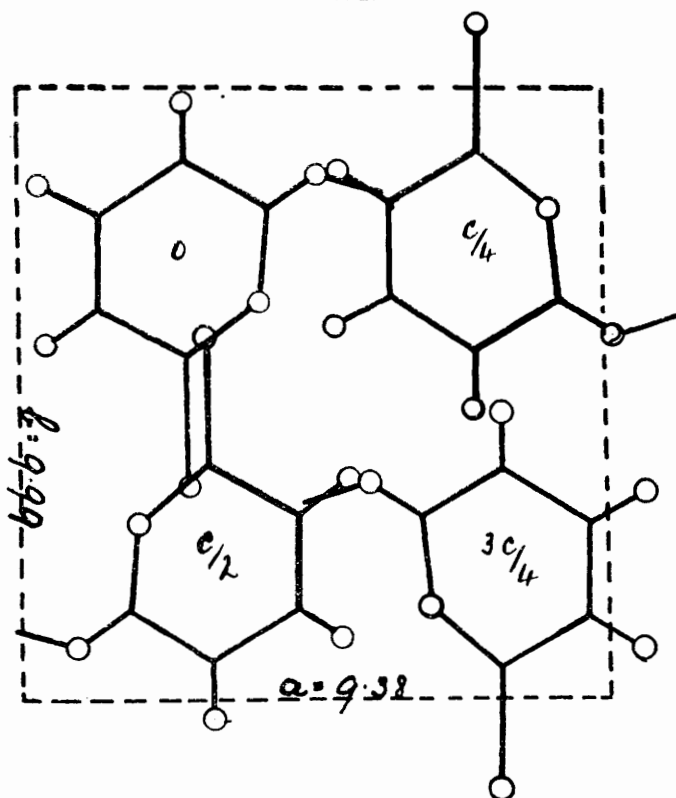


below the (001) plane is indicated. From Fig. 2 it can be seen qualitatively that (040) will give a much stronger reflexion than (020) owing to the concentration of atoms in layers at intervals of approximately $b/4$ parallel to (010); further, since each of these layers has a puckered form giving rise to two planes of atoms about 0.5 Å.U. apart, the (080) reflexion will be very weak. With regard to the various orders of (100), it appears that the proposed structure will cause the (200) reflexion to be fairly strong, (400) weaker, and (800) strong. This last reflexion is very strong indeed when allowance is made for its larger glancing angle; it suggests that possibly the ring is puckered, because in that case there would be a more pronounced concentration of scattering matter at intervals of $a/8$

Also, as mentioned above, the puckered ring would account very well for the absence of the (008) reflexion.

Since, finally, the structure proposed accounts for the (220) reflexion being somewhat stronger than the (110), it is seen that all the results of Table I can be accounted for qualitatively by the structure depicted in Fig. 2. It can be seen that this structure is almost equally strong in all directions and does not possess any

FIG. 2.



arrangement of molecules in well-defined rows or layers; this is in agreement with the facts that the crystals have low birefringence, do not show any tendency to elongation or flattening in any particular direction, and do not exhibit any marked cleavage.

The principal results of the X-ray examination and also the physical properties of this substance can thus be accounted for by supposing that the molecule has a pyranose form; we now show that a furanose molecule will not give such a good agreement.

As in the previous case, the thickness of the molecule would be identified with $\frac{1}{2}c$, and to explain the intensities of the various orders of (001), the depths of the four molecules would have to be approximately 0, $3c/16$, $c/2$, and $11c/16$ parallel to the c -axis. Next, if we arrange the side chain as shown in Fig. 3, the dimensions of the molecule in the directions aa and bb are about 9.4 Å.U. by 5.0 Å.U., *i.e.*, the molecules would fit quite well into the cell in the other two directions. It would be more difficult in this case, however, to arrange the molecules to make (040) so much stronger than (020) and (080), and moreover, it is found that a structure built up in this way gives (200) moderate, (400) strong, and (800) weak, in complete disagreement with the experimental results recorded in

FIG. 3.

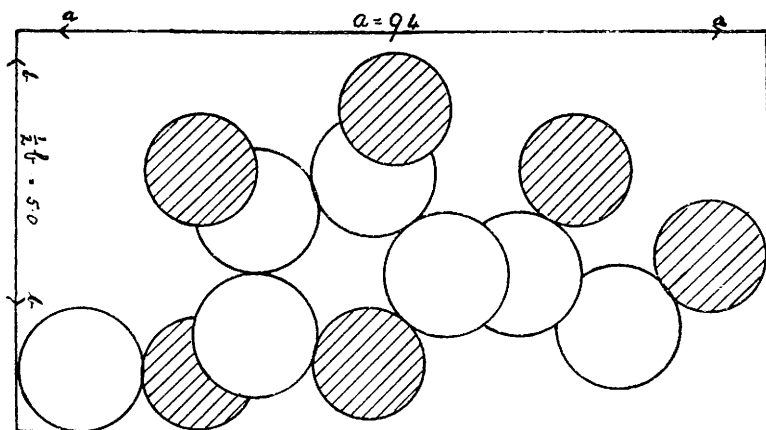


Table I. These conclusions, coupled with the very satisfactory agreement afforded by the pyranose model, make the possibility of the existence of a five-atom ring in this substance very remote.

Since the a and c axes only differ by about 1%, all that has been said so far regarding the fitting of the molecules into the cell-dimensions would apply equally well if a and c were interchanged, *i.e.*, if the plane of the rings were supposed parallel to (100). If this were so, then in order to get the right intensities for the orders of (100), the depths of the molecules would have to be approximately 0, 0, $a/2$, and $a/2$ in the direction of the a -axis. This would give a structure with rather pronounced layers which we should expect to result in moderately strong negative double refraction, some indications of cleavage parallel to (100), and probably a tendency to elongation parallel to the a -axis; quite different physical properties, in fact, from those actually observed. These remarks apply to

structures involving either five- or six-membered rings, but particularly to the former, since on the whole the furanose molecule is somewhat flatter. When the question of reflexion intensities is considered, the arguments brought forward previously regarding the orders of (010) would still be applicable; *i.e.*, the pyranose ring would give better agreement than the furanose form. In the case of the intensities of {001}, there would be difficulty in making either form fit very well.

The possibility that the molecules lie parallel to (010) need hardly be considered; apart from the fact that this would give a considerably higher value than any found so far for the ring thickness, it would lead to greater difficulties than the preceding supposition in explaining the experimental results. It may be remarked that, apart from other considerations, the outstandingly great intensity of the (004) reflexion would strongly suggest that the rings are parallel to (001), as suggested earlier.

The final conclusion is therefore that the crystalline structure of the ordinary form (m. p. 193°) of α -methylmannoside is approximately as indicated in Fig. 2, being built up of pyranose molecules arranged with their six-atom rings parallel to the *c*-plane, or nearly so. The possibility of a satisfactory structure based on furanose molecules is remote.

α -Methylmannofuranoside.—This substance had not previously been investigated crystallographically. The crystals used for this work were selected from part of the original preparation of Haworth, Hirst, and Webb (*loc. cit.*), which had been recrystallised several times. (The stability of the substance is shown by the fact that, although it had been kept in the laboratory without any special precautions for considerably over a year, there was no indication whatever of the presence of the pyranose form or, indeed, of anything other than the original material.) The compound crystallises in colourless needles, the largest being about $2 \times 0.3 \times 0.1$ mm.; only one pair of faces, perpendicular to the smallest dimension of the crystals, was distinguishable with certainty. Since the crystals showed straight extinction under the polarising microscope, it was assumed that they were orthorhombic, the direction of elongation being taken as the *c*-axis, with the *a*-axis perpendicular to the above-mentioned pair of faces, which thus have the indices (100).

Although the crystals were too poor to admit of goniometric measurements, refractive-index determinations were made by the immersion method. Owing to the flattening on (100), the crystals lie on the microscope slide with their *a*-axes parallel to the microscope axis, permitting accurate measurements of two of the indices to be made. Thus the indices for vibrations parallel to *b* and *c*

were found to be 1.549 and 1.518 respectively (both ± 0.002). The third was very difficult to measure, but by using a matted mass of crystals, some were observed edge-on, the refractive index being approximately 1.54. These results give $\alpha = 1.518$, $\beta = 1.54$, and $\gamma = 1.549$ for the D-line, α being parallel to c , and γ to b . The double refraction is therefore fairly strong and negative, (100) is the plane of optic axes, and c is the acute bisectrix. These conclusions are supported by the fact that the interference figure observed through (100) in convergent light appeared to be an optic normal figure.

An X-ray examination was carried out by the single-crystal rotation method; the fact that rotation photographs about the three axes already chosen showed row lines as well as layer lines confirmed the orthorhombic symmetry. Further confirmation was obtained from a Laue photograph taken with the X-ray beam parallel to the a -axis, which, although somewhat mis-set on account of the poorness of the crystal, showed two planes of symmetry. The dimensions of the unit cell were found to be $a = 15.87$, $b = 11.73$, and $c = 4.64$ Å.U. ($\pm 0.3\%$), from which, with four molecules to the cell, the density may be calculated to be 1.482 g./c.c., that determined directly by the flotation method being 1.48. From the results of the examination of a number of oscillation photographs, the space-group was found to be C^4 ($P2_12_12_1$) (the same as the pyranose form). From this it appears that the molecules are asymmetric, as would be expected; also that the crystals are definitely orthorhombic bisphenoidal, since no other space-group has the same halvings as $P2_12_12_1$.

In Table II the intensities of the reflexions from some of the more important lattice planes are given in arbitrary units; the relative values are not as accurate as those in Table I on account of the smallness of the crystals.

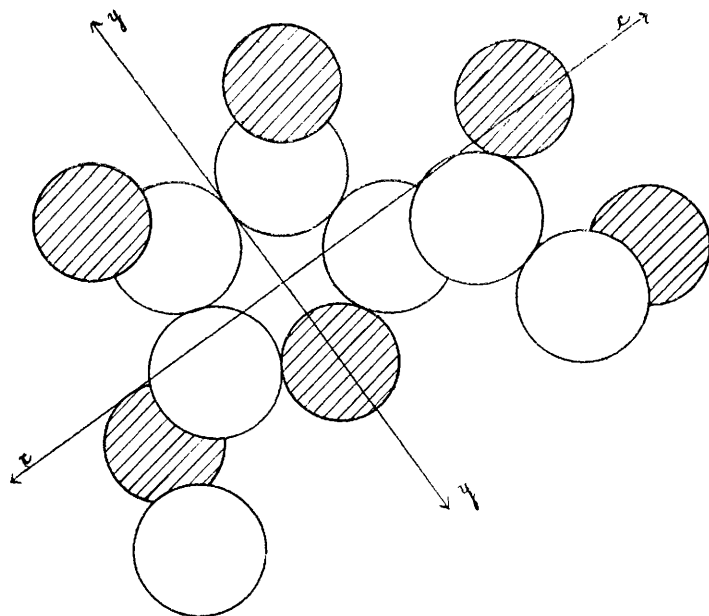
TABLE II.

hkl .	I .	hkl .	I .	hkl .	I .	hkl .	I .
200	24	020	16	002	24	011	32
400	2	040	0	004	2	021	0
600	24	060	6	110	4	101	23
800	$\frac{1}{2}$	080	2	220	12	201	30

When the possible arrangements of the molecules in the unit cell are considered, it appears fairly certain that they must lie parallel to (001), since the length of the c -axis (4.64 Å.U.) is too small to be any dimension of the molecule except that perpendicular to the plane of the ring. It being assumed provisionally that the molecules are of the furanose form, the value of c indicates that the side chain $-\text{CH}(\text{OH})\cdot\text{CH}_2\text{OH}$ lies approximately in the same plane as the ring.

This conclusion may be drawn also from the work of Young and Spiers (*Z. Krist.*, 1931, **78**, 101), who found the values 4.73 and 4.50 Å.U. for the lengths of the *c*-axes of γ -mannonolactone and 2:3:5:6-tetramethyl- γ -mannonolactone respectively. These two substances undoubtedly possess five-atom-ring structures, and their configuration, as regards the body of the molecule, is the same as that proposed for the substance now under discussion. A comparison

FIG. 4.



of the present results with those for the γ -mannonolactone is particularly interesting:

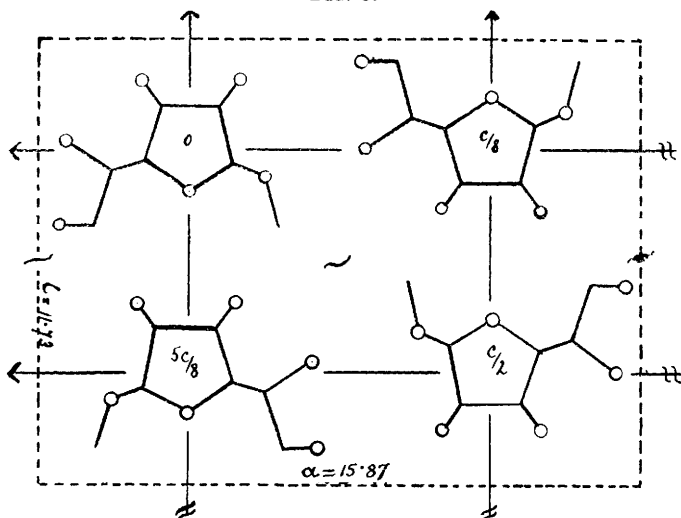
	Mannoside.	Lactone.
$a =$	15.87	14.0
$b =$	11.73	11.1
$c =$	4.64	4.73

The increases in a and b are just those to be expected from the replacement of the doubly-bound oxygen by H and OCH_3 . There is a very close resemblance to the case of β -methylxyloside (Cox, *loc. cit.*), where somewhat similar increases were found on replacing OH by OCH_3 . Another point of similarity is the slight *decrease* in the thickness of the ring on the introduction of the methyl group. Furthermore, this effect does not seem to be confined to the replacement of the reducing group only, since the value of c quoted above for the tetramethyl-lactone is less than that for either the lactone

or the glycoside. Evidently all the methyl groups lie in the same plane as the ring, while the flattening produced by their introduction may be due to a stretching of the C-O-C bonds in a direction radial to the ring. That this flattening is not absolutely general, however, is shown by the case of mannose and α -methylmannopyranoside, where the addition of the methyl group increases c slightly.

Proceeding now on the assumption that in the lattice of α -methylmannofuranoside the molecules lie with their rings parallel to (001), it is found that if the arrangement of the side chains is as shown in Fig. 4, then the dimensions in the directions xx and yy are about 7.2 and 5.3 Å.U., so that when allowance is made for the hydrogen

FIG. 5.



atoms, these dimensions will correspond with $\frac{1}{2}a$ and $\frac{1}{2}b$ respectively. (It will be observed that if the atoms are arranged in this way, they all lie, with the exception of the oxygen of the oxymethyl group, in two parallel planes about 1 Å.U. apart.) If four such molecules are disposed in the unit cell as in Fig. 5, which shows a projection on (001), the resulting structure leads to intensities of reflexions which are in good qualitative agreement with the results given in Table II; the relative depths of the molecules parallel to the c -axis, 0, $c/8$, $c/2$, and $5c/8$ (which are indicated in the figure) are chosen to give approximately the observed relative intensities for (002) and (004), and also for (011), (021), (101), and (201). It would hardly be feasible to obtain more than a qualitative agreement with experiment at this stage, on account of the very large number of para-

meters in the structure, and the limited accuracy of the intensity measurements.

The structure proposed is consistent also with the optical properties of the crystals; on the whole, there is a preponderance of strong bonds parallel to (001), which would be expected to give rise to a fairly considerable negative double refraction, with the two higher refractive indices in the (001) plane; this is actually the case. Further, the observed elongation of the crystals parallel to the *c*-axis might be anticipated from such a structure. Thus, the physical properties and the results of the X-ray examination of this substance are in very good accord with the supposition that its structure is built up of furanose molecules.

Turning to the possibility of a structure based on six-atom rings, the length of the *c*-axis, as in the previous case, would be identified with the thickness of the molecule. It is found that in order to fit the molecules into the cell in the other two directions, it is necessary to suppose that the methyl group, instead of having the position shown in Fig. 1, is situated much nearer to the second hydroxyl group. Four such molecules can then be arranged in the lattice so as to make the (200), (600), (020), and (002) reflexions strong, with the (040) and (004) weak, as required by Table II; however, (600) cannot be made as strong as (200) without making (400) too strong, while (220) is made weaker than (110) instead of stronger. The agreement in this case is therefore not good. A further objection is that the configuration of the half of the pyranose molecule to which the methyl group belongs (enclosed by the broken circle in Fig. 1) is exactly the same as that of the corresponding part of the β -methylxyloside molecule, so that we should expect the relative atomic positions in the two cases to be approximately the same. Now it appears (Cox, *loc. cit.*) that the methyl group in the xyloside is probably situated in the same position relative to the ring as shown for the mannopyranoside in Fig. 1, so that from this point of view it is unlikely that this molecule would have the form necessary for fitting into the furanoside cell. (Results for α -methylxyloside, to be published shortly, indicate that the methyl group has a similar position in this substance also.) There is finally the objection that the relations, mentioned above, between the cell-dimensions of the mannofuranoside and those of the γ -mannono-lactone, do not receive any rational explanation on the hypothesis of a six-atom-ring structure for the mannoside.

We conclude that the crystalline structure of the new form (m. p. 118°) of α -methylmannoside consists of molecules of a furanose type arranged approximately as shown in Fig. 5, and that the possibility of a satisfactory structure involving pyranose molecules is small.

These conclusions, taken in conjunction with those drawn from the examination of the mannopyranoside, indicate fairly definitely that, in the crystalline state, the molecules of the two forms of α -methylmannoside have the ring structures which were originally assigned to them respectively on purely chemical grounds by Haworth and his co-workers. Implied in this is the inference that changes of ring structure do not occur during the reactions whereby the configuration of the mannofuranoside was determined, and this receives support from the comparison of the cell-dimensions of the mannofuranoside with those of the corresponding lactone. Other conclusions to be drawn from this work are that the side chain in the furanose molecule lies in the same plane approximately as the ring, and that methyl groups, when present, also lie in this plane.

The authors wish to record their appreciation of the helpful interest taken in this work by Prof. W. N. Haworth, F.R.S.

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