XVII.—*A Revision of the Structural Formula of Glucose.*

By WILLIAM CHARLTON, WALTER NORMAN HAWORTH, and STANLEY PEAT.

THE discovery of the methylglucosides and the interpretation of the phenomena of mutarotation of sugars furnished the strongest reasons for the allocation of an oxide ring structure to the monosaccharides, and this formulation has been universally accepted. Tollens first ascribed to glucose a heterocyclic structure, and this conception was adopted by Fischer, who represented the normal methylglucosides by a five-membered or pentaphane ring, constituting the γ-oxide formula, which is the current and generally recognised basis for the formulation of sugars.

The methylglucosides were isolated in α- and β-stereochemical forms, and it was shown that corresponding to these there existed also α- and β-modifications of glucose. In 1914, Fischer (*Ber.*, **47**, 1980) prepared a new methylglucoside which differed profoundly in stability from the α- and β-modifications. This he described as "γ"-methylglucoside. The nomenclature he adopted seemed unfortunate inasmuch as in this case the Greek letter was not intended to have any stereochemical significance but merely represented a third or novel form. Fischer recognised that the new variety of methylglucoside was a structural isomeride, and thus the term γ-sugar introduced in this connexion had no essential relationship to the γ-lactones. Confusion has naturally arisen from the use of this terminology, and especially so since the term "γ-oxide form" was already applied to the normal sugars.

An experimental basis for the definite allocation to glucose of a γ-oxide (butylene oxide) constitution rather than that of any other oxide or heterocyclic structure was definitely lacking. Assuming, however, the spatial distribution of the oxygen valencies to be similar to those of carbon, and applying the considerations arising from the Baeyer strain theory, it was apprehended that a five-membered ring would involve the least strain in the sugar molecule, and this type of ring should, therefore, be capable of easy formation. It is tacitly assumed here that the conditions of strain in such a ring would be analogous to those in *cyclo*pentane, where the carbon atoms carry only hydrogen. These conditions seemed to be supported by the facility with which sugars give rise to lactones, and by the properties which the latter display suggesting their resemblance to γ-lactones. Kiliani and Kleemann (*Ber.*, 1884, **17**, 1300) attempted to obtain direct proof of the structure of gluconolactone, but it was left to Hudson to furnish, by his brilliant theoretical studies, the most convincing evidence of the γ-lactonic nature of the products of the oxidation of sugars.

In considering twenty-four lactones of the sugar series derived from the corresponding polyhydroxy-monobasic acids, Hudson (*J. Amer. Chem. Soc.*, 1910, **32**, 345) found that if it were postulated that ring formation occurred at the γ-carbon atom, a remarkable parallelism was exhibited between the position of the lactone ring and the sign of the rotation of the lactone, and that there were no cases of disagreement on the basis of this hypothesis. On the other hand, it was demonstrated that if this linking occurred at the α-, β-, or δ-carbon atom, the number of cases of disagreement with this " rule " were found to be 8, 10, and 12, respectively, out of the twenty-four lactones examined. He calculated that, on the theory of probability, the chances are 17 millions to one that the lactone will have the lactonic ring engaging the γ-carbon atom. This conclusion is supported by an abundance of other cases, and in the absence of direct synthetic evidence to the contrary, this view of the constitution of lactones derived from unsubstituted sugars must be adopted.

It has, however, been too readily assumed that an analogy should be drawn between this principle of lactone ring formation and the type of ring structure existing in the parent sugars. In instituting the inquiry of which details are given in this communication, the present authors have attempted to test the validity of the latter assumption.

It was considered that there should be recognisable differences in stability between lactones of the usual γ-type and those having a smaller or larger number of atoms than five constituting the ring, and that these differences would be reflected in a variation both in the rate and in the extent of hydrolysis to the open-chain acid. During the past 4 years the necessary synthetic materials and the data for this comparison have been accumulated, and in recent communications some of these results have been recorded by one of us without reference, however, to their essential bearing on the present problem.

The degree of accuracy attainable by direct titration of aqueous solutions of the lactones was insufficient for the purpose indicated. A more sensitive method of comparison was provided by studying the polarimetric changes accompanying ring scission from lactone to open-chain acid, using either aqueous or alcohol–water solutions.

Polarimetric data furnished by the completely methylated lactones derived from glucose, galactose, mannose, arabinose, and xylose led to a recognition of two types. Those lactones prepared from the normal forms of these sugars, by first methylating the aldoses and then submitting them to oxidation with bromine water, exhibited a rapid diminution or increase in specific rotation when dissolved in water or aqueous alcohol. Conversely, those lactones prepared from the labile or γ-sugars displayed a very slow and much less marked change in specific rotation.

Observed Changes in the Specific Rotation of the Lactones from the following Sugars (aqueous solutions).

	γ-Forms (Time, 20 days).	Normal forms (Time, 24 hrs.).	Nos. of Curves.
Tetramethyl glucose ...	+61·5° ⟶ 39·6°	+101·1° ⟶ 25·6°	i and ii
Tetramethyl galactose	−27·1° ⟶ 25·2°	+161·5° ⟶ 27·2°	iii and iv
Trimethyl arabinose ...	−42·2° ⟶ 25·1°	+145° ⟶ 22·4° *	v and vi
Trimethyl xylose	+74·1° ⟶ 61·4°	− 3·8° → +20·8°	vii and viii
		(Time, 7 days)	
Tetramethyl mannose.	+65·2° ⟶ 56·3°†	+105° ⟶ 45·6°	

* This value was determined by Pryde, Hirst, and Humphreys (J., 1925, **127**, 348).

† This figure is explained in the text, since it was obtained by Levene and Meyer from methylated mannonolactone. The time intervals are not recorded.

The curves given in Fig. 1 are those of the lactones related to glucose, galactose, and arabinose. Inspection of these curves suggests that the lactones represented by i, iii, and v are of the same type, and that those shown by ii, iv, and vi belong to a second and distinct type.

This second series illustrates the polarimetric data given by the lactones prepared from the normal forms of tetramethyl glucose, tetramethyl galactose and trimethyl arabinose, which exhibit a marked decline in specific rotation when dissolved in water. The equilibrium between the cyclic compound and open-chain acid is speedily reached and hydrolysis is also more nearly complete as revealed by direct titration at this stage.

On the other hand, the first series (Nos. i, iii, and v) represents lactones prepared from the labile or γ-sugars, and it is seen that the initial rotations are lower and that a much less profound change in the optical values occurs. Moreover, equilibrium between lactone and hydroxy-acid is only attained after several weeks, and at this stage hydrolysis is not nearly so complete as in the case of the former series.

The curves shown in Fig. 2 differ in a similar sense, but not in the same degree; the steeper of the two represents the lactone from normal trimethyl xylose, whilst the remaining curve, which is almost linear, is given by the lactone from trimethyl γ-xylose.

Fortunately, it is possible to correlate these data with constitutional formulæ which have been already determined for several of these sugars and their derived lactones, but for reasons which will be outlined later the constitution of the two glucoses and their gluconolactones had not yet admitted of any proof.

The method which is adopted in this communication shows that the data now recorded render it possible to reach a reasonable conclusion as to the structure of glucose and its γ-derivatives by observing the analogy which is found to subsist between their lactones and those of the other sugars of known constitution.

Of the four sugars examined (five, including mannose), two have been subjected to close constitutional study by direct methods

FIG. 1.

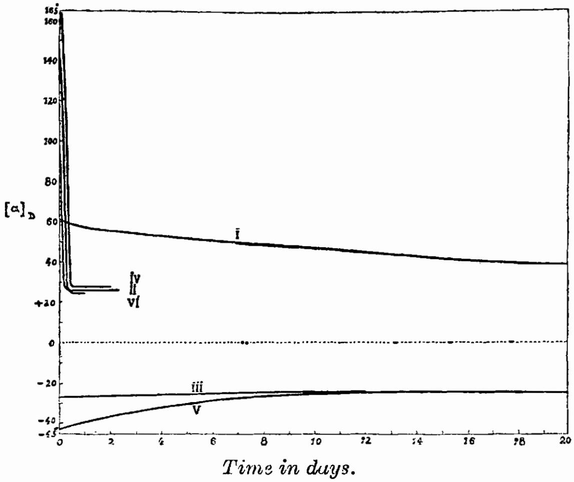
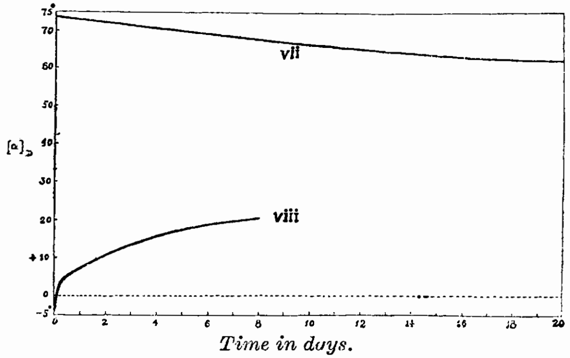
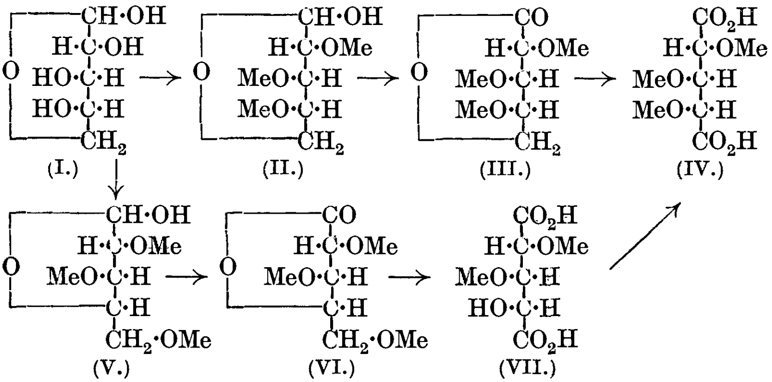


FIG. 2.

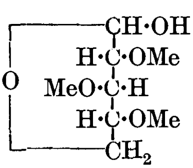


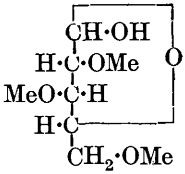
of oxidation. Thus Hirst and Robertson (J., 1925, **127**, 358) have demonstrated that the normal form of trimethyl *l*-arabinose must have the constitution (II), since it gives the dibasic acid (IV), namely, arabo-trimethoxyglutaric acid; and, since the properties of the trimethyl arabinose are in every respect similar to those of natural arabinose, the latter is given the constitution (I).

Another form of trimethyl arabinose was prepared by Baker and Haworth (J., 1925, **127**, 365), and this may be described as the "γ"-sugar. The formula (V) was allocated to this compound, since it gave rise to the lævorotatory lactone (VI) and, on further oxidation, to the dibasic acid (VII) which contained only two methoxyl residues. This latter, on complete methylation, was identical with Hirst and Robertson's acid (IV).



(VIII.)



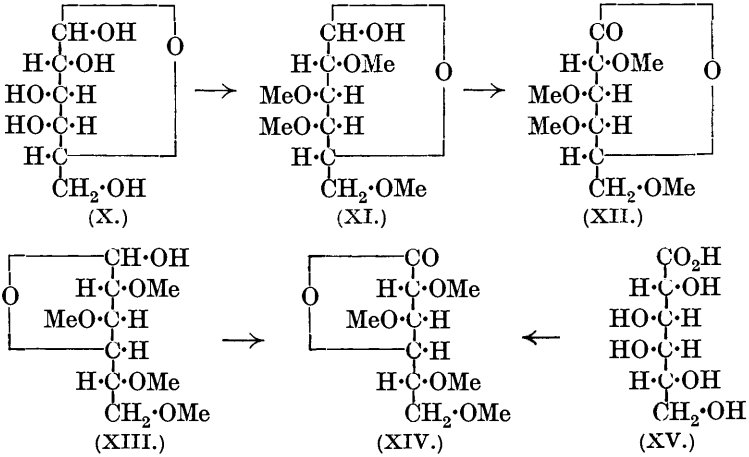


(IX.)

The same constitutional relationships have been established also for normal trimethyl xylose (VIII) (Hirst and Purves, J., 1923, **123**, 1352), which is found to give on oxidation the xylo-trimethoxyglutaric acid, stereoisomeric with the acid of formula (IV); and in a forthcoming paper by Haworth and Westgarth the preparation will be described of trimethyl γ-xylose, to which is allocated the structural formula (IX) analogous to that ascribed above (V) to trimethyl γ-arabinose.

Taking the two examples of the pentoses, xylose and arabinose, it is clear that the normal sugars are amylene-oxidic in structure, and that the labile or γ-forms are butylene oxides. The related lactones are therefore δ-lactones for the normal sugars and γ-lactones for the labile or γ-sugars.

Coming now to the case of galactose, it must be stated that the evidence as to structure depends here on Hudson's rule. Pryde (J., 1923, **123**, 1808) has shown that normal tetramethyl galactose (XI) changes to tetramethyl-δ-galactonolactone (XII) on oxidation, and therefore normal or naturally occurring galactose is given the constitution (X). The corresponding labile or γ-sugar (XIII) was prepared by Haworth, Ruell, and Westgarth (J., 1924, **125**, 2468) and this on oxidation gave rise to the γ-lactone (XIV), which is also obtained on passing from ordinary or normal galactose or from galactonic acid (XV) to its lactone. The rotations of the compounds resulting from all these transformations are completely in accord with Hudson's rule, which, it may be emphasised, requires that galactonolactone must be a γ-lactone (see p. 90).



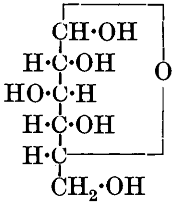
(X.) (XI.) (XII.)

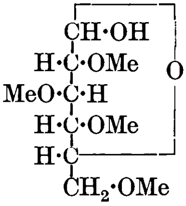
(XIII.) (XIV.) (XV.)

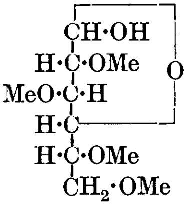
Similarly, mannose has been shown to conform to the above structural scheme. Levene and Meyer (*J. Biol. Chem.*, 1924, **60**, 167) found that normal tetramethyl mannose gave a lactone, $[\alpha]_D + 105° \longrightarrow 45{\cdot}6°$, whilst methylation of the lactone from mannonic acid led to the isolation of a different and crystalline tetramethyl mannonolactone having $[\alpha]_D + 65{\cdot}2° \longrightarrow 56{\cdot}3°$. These optical values will be found to be closely similar to those quoted later for δ- and γ-lactones, respectively, but as the authors did not record the intermediate rotation values at short period intervals the curves could not be included in Figs. 1 and 2.

It only remains, therefore, to apply this analogy to the lactone from normal tetramethyl glucose, which is indicated by the remaining curve (ii) in this series. This conforms definitely to the same type as the other three (Nos. iv, vi, and viii), and we therefore regard it as a δ-lactone, and the normal tetramethyl glucose is therefore considered to be amylene-oxidic and consequently we assign to it the structural formula (XVII), whence glucose has the formula (XVI).

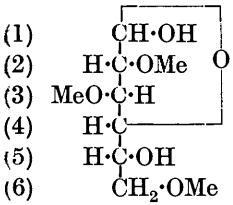
The other curves in Figs. 1 and 2, Nos. i, iii, v, and vii, clearly belong to a different category from those already discussed. All these represent the lactones prepared from the methylated "γ"-sugars. We have demonstrated that, since three of the four substances are γ-lactones, the sugars from which they are prepared are butylene-oxidic in structure, and by analogy the curve No. i is considered to be that of tetramethyl γ-gluconolactone, whence it follows that tetramethyl γ-glucose should be given the constitution (XVIII).


(XVI.)

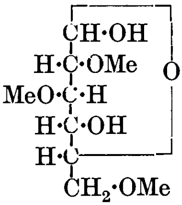

(XVII.)

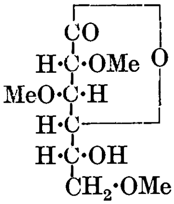

(XVIII.)

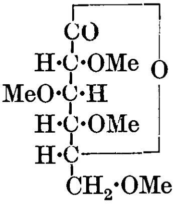
A second line of argument as to the constitution of glucose is provided by evidence drawn from the study of 2 : 3 : 6-trimethyl glucose. This sugar has been repeatedly examined and the relative positions of its three methyl groups are definitely determined (Denham and Woodhouse, J., 1914, **105**, 2361; Haworth and Leitch, J., 1918, **113**, 191; Haworth and Hirst, J., 1921, **119**, 193; Irvine and Hirst, J., 1922, **121**, 1213). We are concerned only with the ring structure of this compound, which, if the argument already presented in this paper be accepted, should now be revised from that indicated by formula (XIX) to the new formula (XX).



(XIX.)


(XX.)


(XXI.)


(XXII.)

Now it is known (Haworth and Hirst, *loc. cit.*) that the sugar is converted on further methylation into normal tetramethyl glucose and earlier in this paper the structural formula (XVII) has been ascribed to the latter on the ground that the derived lactone is a δ-lactone (XXII).

Inspection of the two alternative formulæ (XIX and XX) suggests, however, a possible application of this sugar as a means of testing the validity of this reasoning and of the conclusions already drawn. Thus this sugar on oxidation to the monobasic acid offers a choice of two free hydroxyl positions for the attachment of the lactone ring, namely, those on carbon atoms (4) and (5) (formula XXI), and this applies no matter which of the two sugar formulæ is the correct one.

Adopting Hudson's rule, this choice must be restricted to that of the γ-lactone (XXI). If now this trimethyl γ-gluconolactone should, on complete methylation, be shown to be identical with that tetramethyl gluconolactone derived from normal tetramethyl glucose, then the latter sugar (and therefore glucose also) would be butylene-oxidic in structure and the formula hitherto generally accepted for glucose would continue to hold.

In the actual event this was found not to be the case; it was observed that 2 : 3 : 6-trimethyl glucose gave a gluconolactone (XXI) which on methylation was identical with the tetramethyl γ-gluconolactone derived from the labile or γ-form of tetramethyl glucose (XVIII), and therefore the constitutional formula for the latter is substantiated, and fresh support is provided for the argument outlined in the former part of this communication.

Moreover, the crystalline phenylhydrazides of the tetramethyl gluconolactones from the three sources were prepared and analysed, and the following are the data for the melting points :

Phenylhydrazides of tetramethyl gluconolactones.

	M. p.	Mixed m. p. with (*c*).
(*a*) From normal tetramethyl glucose	109—112°	102—118°
(*b*) From tetramethyl γ-glucose	131—134	130—133
(*c*) From 2 : 3 : 6-trimethyl glucose	130—133	

Thus we again reach the conclusion that ordinary glucose should be given the formula (XVI). This assumes that ordinary free glucose is identical in structure with normal tetramethyl glucose, but this is shown to be the case because α- and β-methylglucosides give crystalline tetramethyl glucose on methylation followed by hydrolysis, as do those natural di-, tri-, and poly-saccharides which contain the glucose residue, and moreover, E. F. Armstrong has shown that α- and β-glucose are stereochemically parallel to α- and β-methylglucosides.

All the commonly occurring aldoses are therefore shown to exist normally as amylene- or 1 : 5-oxide forms, or, reverting to the older nomenclature which we prefer, they may now be described as δ-oxides. So far this has been shown to apply to glucose, galactose, mannose, arabinose, and xylose. By a curious coincidence the so-called "γ"-sugars of the aldose type, which have now been shown to give rise to γ-lactones, may be more accurately described as γ-oxides, since they exist as butylene- or 1 : 4-oxide forms.

There remain to be mentioned the ketoses, and the constitutional study here has been confined to fructose, which occurs naturally as a γ-form in sucrose, raffinose, and inulin. The results of oxidation experiments conducted on tetramethyl γ-fructose derived from sucrose indicate that, in this sugar, an amylene- or δ-oxide ring is present (Haworth and Linnell, Haworth and Mitchell, J., 1923, **123**, 294, 301). On the other hand, Irvine and Patterson (J., 1922, **121**, 2696) have examined the constitution of the normal form of tetramethyl fructose, which is crystalline, and which has not yet been isolated from a naturally occurring carbohydrate. This sugar they found to have the structure of a butylene- or γ-oxide. Thus, in the series of the ketoses, the position as compared with the aldoses would seem to be reversed, in that the labile sugar is the δ-oxide form, and the normal sugar the γ-oxide. It would therefore appear that, in nature, both aldoses and ketoses occur as amylene- or δ-oxides, a result which is in keeping with the simplest view of the synthesis of sucrose in the plant.

If this revision of the structural formula of glucose be accepted and applied to other carbohydrates, many fundamental readjustments are rendered necessary. Thus the constitutional formulæ allocated to natural di- and tri-saccharides by one of the present authors are directly implicated, as are also those suggested for starch and cellulose by other workers. These compounds will now require to be formulated as possessing δ-oxide rings in each hexose residue. In the case of lactose and cellobiose this change also involves a displacement of the point of attachment of the hexose chains from a position associated with the fifth carbon atom to that of the fourth.*

Leaving out of account the stereochemical relationships, it is now possible to represent the principal disaccharides by three formulæ :

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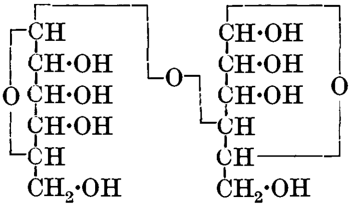
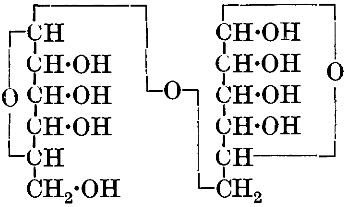
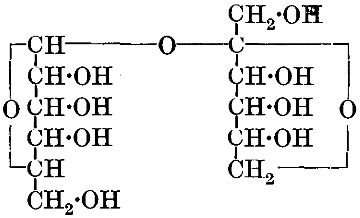
* It is, however, possible to regard one glucose residue in each of these disaccharides as existing as a γ-oxide or γ-sugar, in which case the earlier constitution will continue to hold with respect to the position of the biose linking, but this is an unlikely contingency. That 2 : 3 : 6-trimethyl glucose can pass into a γ-oxide form is extremely probable, and indeed we have some evidence of this. It is important to notice, however, that the sugar 2 : 3 : 5-trimethyl glucose must now be regarded as 2 : 3 : 4-trimethyl glucose, and that normal crystalline tetramethyl glucose is now 2:3:4:6-tetramethyl glucose.



Lactose and cellobiose.



Maltose, gentiobiose (amygdalin-biose) and melibiose.



Sucrose.

EXPERIMENTAL.

Tetramethyl δ-Gluconolactone.—This lactone was prepared by oxidising normal crystalline tetramethyl glucose with bromine water under the usual conditions (Purdie and Irvine, J., 1903, **83**, 1021). It was then dissolved in a slight deficiency of $N/10$-sodium hydroxide, and the aqueous solution evaporated at 35—40° under diminished pressure. The residue of sodium tetramethyl gluconate was triturated thrice with dry chloroform to remove traces of unoxidised sugar and other impurities and the remaining solid was filtered, washed with chloroform, dried, and weighed. An aqueous solution of the salt was then decomposed by adding the equivalent of dilute hydrochloric acid from a burette. Isolation of the purified lactone was effected by evaporation under diminished pressure, followed by extraction from the semi-solid residue with dry ether. The tetramethyl δ-gluconolactone distilled completely at about 100°/0·05 mm. and showed n_D 1·4532. *Titration.* 0·1355 g. required 6·05 c.c of 0·0965N-NaOH (Calc., 6·02 c.c.).

A titration was also conducted after keeping an aqueous solution of the lactone for 24 hours; it then appeared that more than 90% had been converted into the open-chain acid.

Determinations of the rotation of the lactone were recorded as follows:

In ethyl alcohol ($c = 3{\cdot}65$), $[\alpha]_D + 101{\cdot}1°$.

In aqueous alcohol (38% EtOH) ($c = 1{\cdot}39$):

Time in hours .	0·25	2	5	21	25	66	
$[\alpha]_D$	+90·3°	84·0°	68·0°	40·7°	38·4°	38·4°	constant

In water ($c = 1{\cdot}37$) :

Time in hours .	0·1	3	5	6·5	8·25	26·25	
$[\alpha]_D$	+88·5°	43·2°	31·4°	25·6°	25·6°	25·6°	constant

Phenylhydrazide Derivative.—This was obtained by heating for 3 hours at 100° phenylhydrazine (1 mol.) with the above lactone (1 mol.). The crystals which appeared on cooling were recrystallised from ether and light petroleum and melted at 109—112°. On admixture with the phenylhydrazide of the γ-lactone as prepared below under (A) and (B), (m. p. 130—133°) the melting point for the mixture was depressed to 102—118° (Found : C, 56·1 ; H, 7·6 ; N, 8·0. $C_{16}H_{26}O_6N_2$ requires C, 56·1 ; H, 7·6 ; N, 8·2%).

Tetramethyl γ-Gluconolactone.—(A) In one experiment, 4·3 g. of 2 : 3 : 6-trimethyl glucose were oxidised with bromine water and the corresponding lactone was isolated in the usual way. This product was purified by extraction with light petroleum, which dissolved the lactone, leaving as residue traces of unchanged sugar. *Titration.* 0·0943 g. required 4·24 c.c. of *N*/10-NaOH (Calc., 4·48 c.c.) (Found : OMe, 40·9. Calc., OMe, 42·2%).

The tetramethyl gluconolactone was obtained by twice methylating the above product with Purdie's reagents and was thereafter distilled. It showed n_D 1·4470 (Found : C, 51·6 ; H, 7·8 ; OMe, 53·5. Calc., C, 51·3 ; H, 7·7 ; OMe, 53·0%). *Titration.* 0·0945 g. required 3·86 c.c. of *N*/10-NaOH (Calc., 4·03 c.c.).

In a second experiment, using a highly purified specimen of 2 : 3 : 6-trimethyl glucose, the tetramethyl γ-gluconolactone distilled at 92—96°/0·02 mm. and the colourless liquid was dissolved in a slight excess of aqueous barium hydroxide, left over-night, and then heated at 70° for 1 hour. Thereafter the excess of barium hydroxide was precipitated by admitting carbon dioxide, the filtrate evaporated under diminished pressure, and the residue extracted with ether to remove impurities. Solution of the barium salt in water containing the requisite equivalent of hydrochloric acid led to the isolation of the purified γ-lactone, which showed $[\alpha]_D = +49{\cdot}7°$ in ethyl alcohol ($c = 2$), and on dilution with water (44%) this value changed in 3 hours to + 48·9°, and thereafter showed little change during 2 days. A titration showed that at this stage about 30% of the lactone had been converted into the acid.

The phenylhydrazide was prepared by adopting the same procedure as that described below. The product was washed with petroleum, and recrystallised from ether. M. p. 130—133° (Found : C, 56·05 ; H, 7·8 ; N, 8·2. Calc. for $C_{16}H_{26}O_6N_2$, C, 56·1 ; H, 7·6 ; N, 8·2%).

(B) The above lactone was also prepared from tetramethyl γ-glucose (Irvine, Fyfe, and Hogg, J., 1915, **107**, 529), the precaution being taken to separate any traces of the normal sugar by the method of hydrolysing the methylglucoside with $N/15$-hydrochloric acid, since acid of this concentration has little effect on the normal glucosides but effects the complete hydrolysis of the γ-form. The γ-sugar was oxidised with bromine water in the usual way, and the above lactone distilled as a colourless liquid, b. p. 97°/0·05 mm., n_D 1·4467. In ethyl alcohol ($c = 2{\cdot}07$) the specific rotation was $+ 53{\cdot}7°$, and on dilution with water (44%) the reading was $[\alpha]_D = + 49{\cdot}8°$, falling to 48·9° in 4 hours, at which value it remained constant for 2 days.

The polarimetric data were recorded for an aqueous solution of the lactone.

Time in hours ...	0·16	1·33	5·06	19·33	43·83
$[\alpha]_D$	+61·5°	60·7°	57·2°	56·2°	55·6°
Time in days	6	7	12	15	20
$[\alpha]_D$	+48°	47·4°	44·0°	39·6°	39·6°

Phenylhydrazide.—The lactone was heated during 3 hours at 100° with an equivalent proportion of phenylhydrazine. The product had crystallised during this period, and the crystals were purified from light petroleum and dry ether. M. p. 131—134°. In admixture with the specimen of the phenylhydrazide prepared as described above (A) there was no depression of the melting point (Found: C, 56·2; H, 7·8; N, 8·2%).

Tetramethyl δ-Galactonolactone.—The specimen prepared by Haworth, Ruell, and Westgarth (*loc. cit.*) was purified and used in the following determinations of specific rotations in water ($c = 0{\cdot}95$):

Time in mins. ...	19	40	70	100	165	220	280	340
$[\alpha]_D$	+161·1°	146·3°	122·1°	98·9°	62·1°	46·3°	36·8°	32·6°

Time in hours ...	7	8	10	22	46
$[\alpha]_D$	28·4°	28·2°	27·4°	27·2°	27·2°

Trimethyl γ-Arabonolactone.—The crystalline specimen used was that prepared by Baker and Haworth (*loc. cit.*). The solvent was water.

Time in days	0	4	10	20
$[\alpha]_D$	−42·0°	33·8°	26·0°	25·1°

Other optical data employed in constructing the curves given in the introduction will be found by consulting the references quoted.

The authors express their indebtedness to the Department of Scientific and Industrial Research for maintenance grants and to the Armstrong College Research Endowment Fund for financial assistance.

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[*Received, November 24th,* 1925.]