[CONTRIBUTION FROM THE HYGIENIC LABORATORY, UNITED STATES PUBLIC HEALTH SERVICE]

RELATIONS BETWEEN ROTATORY POWER AND STRUCTURE IN THE SUGAR GROUP. XXV. THE RING STRUCTURES OF VARIOUS MONOSACCHARIDES[1]

BY C. S. HUDSON

RECEIVED JANUARY 8, 1930 PUBLISHED APRIL 7, 1930

1. Four years ago the writer[2] published a critical examination of the rotations of many substances in the mannose and rhamnose series which had previously been considered as exceptions to the rules of optical superposition and isorotation.[3] It was shown that while many pairs of these substances exhibit comparative rotations that are abnormal, many other pairs show close conformity with the rules. To account for this significant fact, there was proposed the hypothesis *that among the known derivatives of mannose and rhamnose there occur substances of various ring types (which accounts for the observed exceptional comparative rotations) and that substances belonging to the same ring type show normal comparative rotations (which accounts for the normal values).* As a consequence of this view the substances in these series were allocated to three types, the rings of which were designated 1,A, 1,B and 1,C. The question of the assignment of positions A, B and C to particular carbon atoms was left open in so far as the use of arguments based upon rotatory relations is concerned.

2. In an accompanying article[4] it was then sought to determine the positions of A and B by the use of results that had been obtained shortly before from methylation studies by several workers, who had shown that normal methyl xyloside,[5] galactoside[6] and arabinoside[7] must possess a 1,5-ring provided the assumption that rings do not shift during methylation is correct. This assumption had never been questioned and no evidence was known against it, though on the other hand its validity had never been

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[1] Publication authorized by the Surgeon General, U. S. Public Health Service. Presented at the Organic Symposium of the American Chemical Society, Princeton, New Jersey, January 1, 1930. No. XXIV of this series was published in THIS JOURNAL, **52**, 1270 (1930).

[2] Hudson, *ibid.*, **48**, 1424 (1926).

[3] Hudson, *ibid.*, **31**, 66 (1909); Scientific Papers of the Bureau of Standards, No. 533 (1926). In the latter paper (pages 245–249) the distinction between optical superposition and isorotation is discussed; the paper is obtainable from the Superintendent of Documents, Government Printing Office, Washington, D. C., price, 35 cents.

[4] Hudson, THIS JOURNAL, **48**, 1434 (1926).

[5] Hirst and Purves, *J. Chem. Soc.*, 1352 (1923).

[6] Pryde, *ibid.*, 1808 (1923).

[7] Hirst and Robertson, *ibid.*, 358 (1925).

definitely established in the case of any glycoside.[8] Using these 1,5-ring allocations for the xyloside, galactoside and arabinoside, the writer showed that the rotatory powers of the alpha and beta forms of methyl glucoside of the same 1,5-ring structure can be deduced through the rules of isorotation; the values so calculated were widely different from the rotations of the known normal methylglucosides and it was concluded that the 1,5-ring does not occur in the latter. Since other methylation data, to which reference was there made, limited the ring to the 1,4- and 1,5-positions, it was inferred that the normal methylglucosides possess the 1,4-ring. The same result followed from the similar consideration of the rotations of the fully acetylated derivatives of the glycosides mentioned.

3. This ring assignment for the glucosides conflicted with the results which Charlton, Haworth and Peat[9] had published shortly before; their studies indicated that normal tetramethylglucose possesses the 1,5- rather than the 1,4-ring and that the like structure pertains to the normal methylglucosides on the assumption that methylation does not cause ring-shifting. If the writer's argument for the 1,4-ring structure of these glucosides had been limited to the data that have been summarized in paragraph 2, it is probable that publication would not have been made in view of the conflict with the results of Charlton, Haworth and Peat, because this disagreement could be accounted for by questioning the applicability of the isorotation rules to the case in hand, particularly the assumption that r_4, the rotation of Carbon 4, has the same value in the pentoside and hexoside structures. This assumption, while not derivable from the rule of optical superposition, appeared probable to the writer from the large number of cases where the rules of isorotation, by which the assumption could be supported, had been found to hold fairly closely. It was emphasized in the article that objection might be made to the assumption but *it was shown that it led to the prediction of values for the rotations of unknown substances the correctness of which could be supported by independent evidence.* Thus it was found that the calculated rotations of the unknown methylglucosides fit accurately, along with the rotations of the known forms, in the system of ring structures that had just been developed for the mannose and rhamnose series, as epimers of the methylmannosides of the 1,A and 1,B ring structures, respectively. The rotations of the acetates of these various glycosides showed the same correlation. Because of the support which these independent results gave to the assumption that r_4 has the same rotation in the pentosides and hexosides, the writer decided to publish the calculations, which indicated that the 1,A ring is 1,5, the 1,B ring is 1,4 and that the

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[8] The word glycoside is used in the generic sense to include glucoside-like derivatives of any of the aldoses or ketoses; the term glucoside is limited to the glycosides of the particular sugar glucose.

[9] Charlton, Haworth and Peat, *J. Chem. Soc.*, 89 (1926).

normal methylglucosides have the 1,4-ring, and to leave to the future the discernment of the reason for the disagreement with the results of Charlton, Haworth and Peat concerning the ring position in the glucosides.[10]

4. The existence of this disagreement prompted the writer to seek new experimental evidence which might disclose its cause. It was early recognized that the value of the epimeric difference of rotation sharply distinguishes the viewpoints of the rival classifications of rings and that decision between the two systems might be obtainable from measurements of the rotations of a pair of substances having configurations that could be epimeric but in which only one of the two rings 1,4 and 1,5 could be assumed to exist. Such a pair of substances would be represented, for instance, by cellobiose and 4-glucosido-mannose because Zemplén[11] had proved by evidence which did not involve methylation that cellobiose is 4-glucosido-glucose and Bergmann and Schotte[12] had synthesized the epimeric 4-glucosido-mannose from cellobiose by reactions which did not sever the disaccharide union. In these sugars the 1,4-ring for the reducing hexose molecule is excluded and only the 1,5-ring is probable; their rotations should in consequence give the correct value for the epimeric difference of rotation. Another pair of sugars to which the same argument applies is lactose[13] and 4-galactosido-mannose.[14] One is not restricted to the sugars themselves but can also employ suitable acetylated derivatives, as is evident from the writer's table[4] in which the values of the molecular epimeric difference for the sugars ($2r_2 = 6700$) and for their acetylated derivatives ($2R_2 = 11{,}300$) were shown. Plans were accordingly made for obtaining the necessary substances in pure form. By a fortunate circumstance, however, the appropriate data became available within a few months after the appearance of the writer's article through a publication by D. H. Brauns[15] of the carefully measured rotations of four pure acetohalogeno

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[10] Drew and Haworth [*J. Chem. Soc.*, 2303 (1926)] later sought to explain the disagreement by questioning the validity of the assumption regarding r_4, without mentioning, however, that the writer had raised the same question and had considered that he had answered it by adducing the independent evidence referred to above. This evidence, which they have passed over, seems of far more significance than the purely speculative discussion of the twisting of ring structures and carbon valences by which they have sought to show that r_4 should have different values in the pentoside and hexoside structures. However, it will be shown presently (paragraph 5) that the cause of the disagreement is a matter that is quite apart from the question of the constancy of the value of r_4, and (paragraph 16) that the assumption of constancy can be supported by further independent evidence. In regard to a second matter that Drew and Haworth presented, concerning some supposed evidence on the ring structures in the galactose and glucose series, see paragraph 22.

[11] Zemplén, *Ber.*, **59**, 1254 (1926).

[12] Bergmann and Schotte, *ibid.*, **54**, 1564 (1921).

[13] Zemplén, *ibid.*, **60**, 1309 (1927).

[14] Bergmann, *Ann.*, **434**, 79 (1923).

[15] Brauns, This Journal, **48**, 2776 (1926).

derivatives of 4-glucosido-mannose. The epimeric difference is obtainable from these measurements in conjunction with Brauns' other measurements[16] of the rotations of the analogous derivatives of cellobiose. The comparisons are shown in Table I. The good agreement of the values in the last column is evidence that the isorotation rules apply closely among these pairs; the greatest deviation from the mean represents only two or three degrees in specific rotation. The average value of $2R_2$ (11,800) agrees closely with the writer's original determination[4] from the rotations of acetylated substances of the glucose and mannose series (11,300); on the other hand, the ring assignments of Haworth lead to a far different value for $2R_2$ (29,500), obtained from the molecular rotations of the tetraacetates of normal α-methylglucoside[4] (47,300) and normal α-methylmannoside[4] (17,800).

TABLE I

THE EPIMERIC DIFFERENCE OF MOLECULAR ROTATION FOR ACETYLATED DERIVATIVES OF THE CELLOBIOSE AND 4-GLUCOSIDO-MANNOSE SERIES (D. H. BRAUNS' DATA)

Substance	$[\alpha]^{20}_{D}$ in $CHCl_3$	$[M]^{20}_{D}$	Epimeric difference ($2R_2$)
α-Acetofluorocellobiose	30.6	19,520	10,840
α-Acetofluoro-4-glucosido-mannose (mol. wt. 638)	13.6	8680	
α-Acetochlorocellobiose	71.7	46,960	13,420
α-Acetochloro-4-glucosido-mannose (mol. wt. 655)	51.2	33,540	
α-Acetobromocellobiose	95.8	66,970	12,520
α-Acetobromo-4-glucosido-mannose (mol. wt. 699)	77.9	54,450	
α-Aceto-iodocellobiose	125.7	93,770	10,590
α-Aceto-iodo-4-glucosido-mannose (mol. wt. 746)	111.5	83,180	
	Average	$2R_2$	11,800

5. This crucial test convinced the writer at the time when Brauns' article appeared (1926) that Haworth's assignment of the same ring to the normal methylglucoside and mannoside must be invalid. In consequence a choice between the following alternative views appeared necessary: either (1) the chemical studies on the tetramethyl derivatives of glucose and mannose by Haworth and his collaborators contain some faulty identification which invalidates his conclusion or (2) the experimental work being accepted as correct, the tetramethyl derivatives possess the ring which he has assigned (1,5) but there has occurred a ring-shifting during the methylation of at least one of the glycosides. Decision between these alternatives became possible two years later when Wolfrom and Lewis[17] showed that the normal tetramethyl derivatives of glucose and mannose are interconvertible in alkaline solution and that they must consequently possess the same ring. This result left no escape from the conclusion that

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[16] D. H. Brauns, THIS JOURNAL, **45**, 833 (1923).

[17] M. L. Wolfrom and W. Lee Lewis, *ibid.*, **50**, 837 (1928).

the cause of the divergence between the views of H worth and the writer on ring structures lies in the invalidity of Haworth's assumption that ring-shifts do not occur during the methylation of glycosides.

6. It now became necessary to discard the methylation data that had been used in allocating positions for the rings 1,A and 1,B of the mannose and rhamnose series and to seek the solution of this problem in other ways. It was evident that the ring of the normal methylglucosides, by virtue of the decision that had been reached concerning the true value of the epimeric difference, is 1,B, as was found in the writer's article,[4] but the necessity of discarding methylation data because of the proved ring-shifting left both the 1,4- and 1,5-positions as possibilities for 1,B. How can this question be determined without the use of methylation data? Experimental studies with this object in view have been conducted during the past three to four years by the writer with the assistance of W. C. Austin, J. K. Dale, H. S. Isbell, Edna Montgomery, F. P. Phelps and Clifford B. Purves, to whom grateful acknowledgment of their valuable help is expressed. Their experimental results are published in separate papers. The bearing of these results upon the problem of the ring structures of the sugars will now be discussed.

7. **Evidence from the Study of Thiophenol Glycosides.**—Purves[18] has confirmed the observation of Fischer and Delbrück[19] that the acid hydrolysis of β-thiophenol lactoside yields galactose and a β-thiophenol glucoside which is identical with normal β-thiophenol glucoside made from acetobromoglucose by the same Koenigs–Knorr synthesis that produces normal β-methylglucoside. He has established the production of the same glucoside from β-thiophenol cellobioside and maltoside by acid hydrolysis. Since the glucose constituent which carries the thiophenyl radical in these disaccharide glycosides is substituted at its Carbon 4 by a second hexose molecule, as shown by Zemplén[20] from data that do not involve methylation, the 1,4-ring for it is excluded and the 1,5-ring is to be chosen for normal thiophenol glucoside and likewise in all probability for the normal methylglucosides. This indicates that the 1,B ring of the rotatory classifications is 1,5. In consequence 1,A is 1,4. One now perceives that since the methylation of normal methylglucoside (1,B = 1,5) yields normal tetramethylglucose (1,5 by Haworth's results), the 1,5 ring in the glucoside does not shift during methylation. It is in the mannose series that the shift occurs, where normal α-methylmannoside (1,A = 1,4) yields normal tetramethylmannose (1,5 by Haworth's results). (See also par. 25.)

8. **Evidence from the Study of Ketoses.**—The writer[21] inferred some

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[18] Clifford B. Purves, This Journal, **51**, 3619, 3627, 3631 (1929).

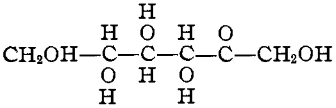
[19] Fischer and Delbrück, *Ber.*, **42**, 1476 (1909).

[20] Zemplén, Refs. 11 and 13 and, for the structure of maltose, *ibid.*, **60**, 1555 (1927).

[21] Hudson, This Journal, **47**, 278 (1925).

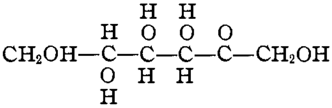
years ago from the value of the difference between the rotation of *l*-sorbose, which does not exhibit mutarotation, and that of α-methyl-*l*-sorboside, that the ketose may persist in solution as its α-form; in such case the absence of mutarotation is to be ascribed to this stability. This view was new and it opened a novel line of inquiry. It has been found subsequently that the development of this idea furnishes a new method of wide applicability for correlating ring structures by comparisons of rotations, as will now be described.

9. Fischer's formulas for the two ketoses that are now named, according to Rosanoff's[22] suggestion, *d*-sorbose and *d*-tagatose are (I) and (II). If these are written with rings of the furan type, for example, (III) represents an α-*d*-sorbose and (IV) an α-*d*-tagatose. It is seen that (III) and (IV) are modifications of the structure for an α-*d*-xylose (V) and an α-*d*-lyxose (VI), respectively, of the same ring type, by the substitution of CH_2OH for H. Since the writer[23] has shown that the rules of isorotation apply for β-fructose, β-methylfructoside and the two acetochlorofructoses with the same coefficients that are shown for the aldoses, there is at least considerable probability for the validity of an assumption that *the rotation of Carbon 3* (r'_3) *in the ketoses is the same as that of Carbon 2* (r_2) *in the aldoses.* These are corresponding carbons because they have like positions with respect to the ring. If this assumption is correct, the value of $2r'_3$ for an appropriate pair of ketoses should be the epimeric difference ($2r_2 = 6700$) of the aldose sugars. The $[\alpha]_D$ value of an α-*d*-tagatose (m. w. 180) may be calculated from that of the known α-*d*-sorbose[24] (43) by this relation to be (43 −



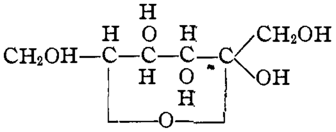
$$\begin{array}{rccccccccl} & & & \mathrm{H} & & & & & & \\ & \mathrm{H} & & \mathrm{O} & & \mathrm{H} & & \mathrm{O} & & \\ \mathrm{CH_2OH}\text{—} & \mathrm{C} & \text{—} & \mathrm{C} & \text{—} & \mathrm{C} & \text{—} & \mathrm{C} & \text{—} & \mathrm{CH_2OH} \\ & \mathrm{O} & & \mathrm{H} & & \mathrm{O} & & & & \\ & \mathrm{H} & & & & \mathrm{H} & & & & \end{array}$$

(I) *d*-Sorbose

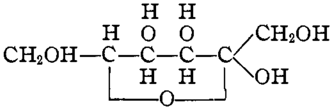


$$\begin{array}{rccccccccl} & & & \mathrm{H} & & \mathrm{H} & & & & \\ & \mathrm{H} & & \mathrm{O} & & \mathrm{O} & & \mathrm{O} & & \\ \mathrm{CH_2OH}\text{—} & \mathrm{C} & \text{—} & \mathrm{C} & \text{—} & \mathrm{C} & \text{—} & \mathrm{C} & \text{—} & \mathrm{CH_2OH} \\ & \mathrm{O} & & \mathrm{H} & & \mathrm{H} & & & & \\ & \mathrm{H} & & & & & & & & \end{array}$$

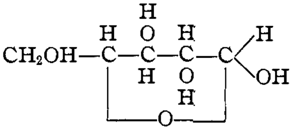
(II) *d*-Tagatose



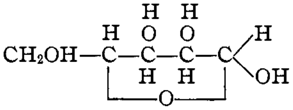
(III) α-*d*-Sorbose (2,5)



(IV) α-*d*-Tagatose (2,5)



(V) α-*d*-Xylose (1,4)



(VI) α-*d*-Lyxose (1,4)

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[22] Rosanoff, This Journal, **28**, 114 (1906).

[23] Hudson, *ibid.*, **46**, 477 (1924).

[24] In order to make the designation of isomers unmistakable, the $[\alpha]_D$ value will be appended to the names of many substances in this article.

6700/180) = +6°. Tagatose does not exhibit mutarotation[25] and its $[\alpha]_D$ value is +1, which is close enough to the calculated value to warrant the designation of the sugar as *α-d*-tagatose,[26] of the same ring type as *α-d*-sorbose (43), though the position of the common ring is not disclosed because the use of the furan ring in the formulas was arbitrary. Since the assumption regarding Carbon 3 of the ketoses appears justified by the result, one may go a step farther with some confidence and assume that *Carbons 4 and 5 of the ketoses have the rotations of the corresponding Carbons 3 and 4 of the aldoses.* If this assumption is correct, the molecular rotation of *α-d*-tagatose (1 × 180 = 180) should be the same as that of an *α-d*-lyxose of the same ring type and the $[\alpha]_D$ value of the latter substance can thus be calculated as (1)(180)/150 = 1.2. The rotation of the well-known crystalline lyxose, which is indeed an *α*-form,[27] is +5.5. The agreement is again sufficiently close to warrant the conclusion that *α-d-sorbose (+43), α-d-tagatose (+1) and α-d-lyxose (+5.5) possess a common ring.* The allocation of this ring to a definite position will be taken up later in paragraph 16.

10. If the foregoing results (paragraph 9) stood alone, one might be warranted in regarding the theoretical background as speculative and uncertain and the objection might be raised that the rotation of the known form of xylose, *α-d*-xylose (+92), is far removed from that of its structural relative *α-d*-sorbose (+43) and that the rotations of *β*-fructose (−133) and *β-d*-arabinose (−175) also do not show correspondence. But let the argument continue and it will be found that much additional evidence supports the theory. The calculated rotation of that hypothetical *α-d*-xylose which would have the same ring structure as the known *α-d*-sorbose is $[\alpha]_D$ = 43(180)/150 = +52. This value in comparison with that of the known *α-d*-lyxose (5.5) gives a molecular difference (52 − 5.5)150 = 6975 which is quite near the known epimeric difference for sugars (6700), the divergence being less than 2° in specific rotation;[27] the result is clear evidence that the unknown xylose form is the true epimer of the known *α-d*-lyxose (5.5). It also follows that the known form of *α-d*-xylose must possess a different ring from that of *α-d*-lyxose, *α-d*-sorbose and *α-d*-tagatose. One can surmise that these rings are 1,4 and 1,5, but for the present let the question remain open; it will be considered further in paragraph 16. A similar view in the case of the divergence between the rotations of fructose and arabinose is natural; it will be considered in paragraph 19.

11. In the case of *d*-mannoketoheptose,[28] another ketose which does

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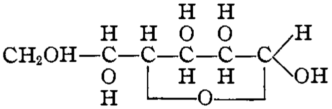
[25] Lobry de Bruyn and van Ekenstein, *Rec. trav. chim.*, **16**, 241 (1897).

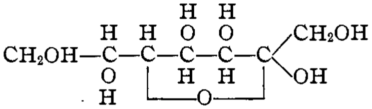
[26] Independent evidence on the question whether crystalline tagatose is an alpha or beta form of the sugar would be obtainable from the preparation of a pure methyltagatoside, as is obvious from the discussion of the similar sorbose example (Ref. 21).

[27] Compare the similar indications made by Phelps and Hudson, THIS JOURNAL, **50**, 2050 (1928).

[28] F. B. LaForge, *J. Biol. Chem.*, **28**, 511 (1917).

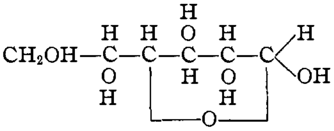
not show mutarotation, its $[\alpha]_D$ value (+29) gives good support to the theory and its ring structure can be definitely allocated. Its configuration (VIII) is like that of *d*-mannose (VII) and its molecular rotation ((29)(210) = 6090) is so near that of the known *α-d*-mannose[29] ((30)(180) = 5400), which has been shown to possess the 1,A = 1,4 ring (paragraph 7), that one can confidently assign the same ring to this ketose and further designate it as being an alpha form, *α-d*-mannoketoheptose (2,5).

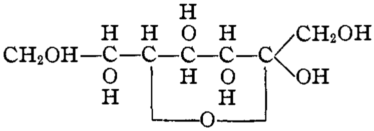

(VII) *α-d*-Mannose (30)


(VIII) *α-d*-Mannoketoheptose (29)

12. The numerical agreements that have been shown in paragraphs 9, 10 and 11 led the writer to believe that the theoretical views which account for them are sound as a first approximation, but it was considered prudent to submit them to a further experimental test before possible publication. The additional evidence which was obtained will now be described.

13. The ketose which would be epimeric with *α-d*-mannoketoheptose (VIII) would have the structure (X) and would be designated *α-d*-glucoheptulose by recognized custom.[30] Its structure is like that of *α-d*-glucose (1,A = 1,4) (IX), an unknown form of *d*-glucose whose rotation was calculated by the writer,[4] through the addition of the epimeric difference to the rotation of *α-d*-mannose (30), to be $[\alpha]_D$ +67. Having regard to the molecular weights of the two sugars, the $[\alpha]_D$ value of *α-d*-glucoheptulose (2,5) is calculated to be (67)(180)/210 = +57. The rotation can also be calculated from that of the known *α-d*-mannoketoheptose (29), by adding the epimeric difference, as (29 + 6700/210) = +61. Bertrand and Nitzberg[31] have obtained a new crystalline ketoheptose through the oxidation of *α*-glucoheptitol by the sorbose bacterium and have expressed the view, for which they have adduced considerable experimental evidence, that it is either the *d*- or the *l*- form of glucoheptulose. Its $[\alpha]_D$ value is


(IX) *α-d*-Glucose (1,A = 1,4)


(X) *α-d*-Glucoheptulose (2,5)

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[29] P. A. Levene, *J. Biol. Chem.*, **57**, 329 (1923); **59**, 129, 141 (1924).

[30] It seems to the writer that it would be of distinct advantage to adopt for *d*-mannoketoheptose the new name *d-mannoheptulose* in conformity with the practice of using the ending -ulose (taken from levulose) for ketoses (Bertrand, Wohl and Freudenberg).

[31] Bertrand and Nitzberg, *Compt. rend.*, **186**, 925 (1928).

−67.5 and mutarotation is not exhibited. If this ketose is truly an α-form of *l*-glucoheptulose, its existence supports the theory, because the rotation of α-*d*-glucoheptulose must then be +67.5, which is near the values given by the two independent calculations. On the contrary, if it is *d*-glucoheptulose or is a β-form, no support is given the theory. It appeared necessary, therefore, to synthesize *d*-glucoheptulose by chemical means in order to decide these questions and the task was undertaken by W. C. Austin. He has synthesized the pure crystalline ketose, found its $[\alpha]_D = +67.5$ in water, without mutarotation, and has prepared a pure crystalline methyl-*d*-glucoheptuloside from it, the rotation of which ($[\alpha]_D$ +108.5) proves that the sugar is an α-form; the results thus support the theory excellently. The method of synthesis was the Lobry de Bruyn rearrangement of *d*-α-glucoheptose in alkaline solution, and Austin's work was much aided through earlier studies by Edna Montgomery, who had synthesized by this rearrangement a new ketose, named lactulose, from lactose and had determined the optimum conditions for the rearrangement and for separating the resulting ketose from its accompanying aldoses. This separation was accomplished by oxidizing the aldoses with bromine water in the presence of barium or calcium benzoate as a buffer. The latter development came in turn from the work of H. S. Isbell.[32]

14. The evidence which has been presented in paragraphs 9–13 correlates the rotations of so many ketoses and aldoses that the essential correctness and usefulness of the theory which has accomplished this result appear established. The next step in logical order would be the allocation of definite ring positions to the forms of lyxose, sorbose, tagatose and xylose that were correlated in paragraphs 9 and 10, but this will be deferred to paragraph 16 in order that Dale's evidence regarding a third form of mannose may be shown in its relationship to the problem of ring structure.

15. Evidence from the Existence of a Third Form of Mannose.— J. K. Dale[33] has isolated a crystalline compound of *d*-mannose and calcium chloride possessing the composition $C_6H_{12}O_6 \cdot CaCl_2 \cdot 4H_2O$. Its initial rotation corresponds to the value $[\alpha]_D$ −60 for its mannose component. This

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[32] Hudson and Isbell, THIS JOURNAL, **51**, 2225 (1929). The synthesis of lactulose was described by Montgomery and Hudson in an address before the National Academy of Sciences at its meeting in Washington in April, 1929, and the paper will be published in the near future. The new ketose was named lactoketose [*Science*, **69**, 556 (1929)] but the authors have subsequently decided to name it lactulose. The synthesis of *d*-glucoheptulose by Austin was announced on the program of the meeting of the American Chemical Society in Minneapolis, Sept. 9–13, 1929, and the paper will be published soon by him. His synthesis of α-methyl-*d*-glucoheptuloside, which has been accomplished since his return to his own laboratory, will likewise be published soon. The writer is indebted to Dr. Austin for the kind permission to refer in the present article to his measurement of the rotation of the latter substance and to the resulting proof that the ketose and its methylglycoside are alpha forms.

[33] J. K. Dale, THIS JOURNAL, **51**, 2788 (1929).

is closely the rotation which the writer predicted[2] (−65) for *β-d*-mannose of the 1,A ring structure. The discovery of this substance is another link in that long chain of experimental evidence which shows that the two forms of mannose which were previously known, of rotations +30 and −17, possess unlike rings. The rotation of Dale's third form shows that it possesses the ring of *α-d*-mannose (30) and consequently that the *β-d*-mannose of −17 rotation must be of another ring type because the existence in solution of three forms of the same ring structure cannot be reconciled with the firmly established Le Bel–van't Hoff theory of the asymmetric carbon atom. Since Haworth and Hirst[34] deny the validity of the writer's conclusion from rotatory considerations that the two older forms of mannose do not possess the same ring, the writer replies by referring to Dale's third form of mannose and the significance attached to the magnitude and sign of its rotation.

16. Referring back to paragraphs 9 and 10 there will now be considered the problem of assigning definite ring positions to the known alpha forms of xylose, lyxose, tagatose and sorbose. Xylose is similar to glucose in the configurations of its carbon atoms and lyxose is similar to mannose. It has long been known[2] that lyxose shows certain peculiarities that pertain likewise to mannose and rhamnose. Recently Levene and Wolfrom[35] have synthesized an acetylated methyllyxoside which closely resembles in its peculiar behavior on alkaline de-acetylation those similar derivatives of mannose and rhamnose to which the writer assigned the 1,C = 1,3 ring structure.[2] Both mannose and lyxose are exceptions to the general rule that a monosaccharide aldose yields a mixture of its alpha and beta methylglycosides when heated with acidified methyl alcohol; with these sugars the reaction proceeds nearly quantitatively to *α*-methylmannoside[36] (79) or lyxoside[37] (59) without the production of a beta isomer, in so far as has been determined. It is natural to surmise from these similarities that *α*-methyllyxoside (59), and therefore *α-d*-lyxose[2] (5.5), possesses the 1,A = 1,4 ring of *α*-methylmannoside (79); on this view the other ring 1,B = 1,5 should be assigned to *α-d*-xylose (92) and its methylxylosides (see paragraph 10). This result would show that crystalline xylose and glucose have the same ring, which seems probable from the fact that their configurations are similar. On the contrary, if the lyxoside is 1,5 the xyloside is 1,4 and the behavior of the pentoses becomes dissimilar to that of the analogous hexoses, which seems improbable. However, this argument is founded only on probabilities concerning chemical behavior and it needs a definite quantitative basis. Data from which the ring assignment can be made

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[34] Haworth and Hirst, *J. Chem. Soc.*, 1221 (1928).

[35] Levene and Wolfrom, *J. Biol. Chem.*, **78**, 525 (1928).

[36] Van Ekenstein, *Rec. trav. chim.*, **15**, 223 (1896); Fischer and Beensch, *Ber.*, **29**, 2927 (1896).

[37] Phelps and Hudson, THIS JOURNAL, **48**, 503 (1926).

with assurance have just recently been published by H. S. Isbell,[38] who has prepared α-methyl-*d*-guloside ($[\alpha]_D$ +106 in water) and its beta isomer (−83 in water). Since the difference between the molecular rotations (194 (106 − 83) = 36,700) is quite near the usual value for an α,β pair of glycosides (approximately 36,950),[39] there is no doubt that these gulosides possess the same ring, whatever its position may be. Let it be assumed that the ring is 1,B = 1,5. Then we may write the molecular rotations of these *d*-gulosides as follows, where a_{me}, r_2, r_3, r_4 and r_5 represent the molecular rotations of Carbons 1 to 5 and the signs correspond with the configurations established by Fischer

$$\alpha\text{-Methyl-}d\text{-guloside,}\quad a_{me} + r_2 + r_3 - r_4 + r_5 = 20{,}600 \tag{1}$$
$$\beta\text{-Methyl-}d\text{-guloside,}\quad -a_{me} + r_2 + r_3 - r_4 + r_5 = -16{,}100 \tag{2}$$

Applying the rule of optical superposition, we have for the methyl-*d*-glucosides[40] of the same 1,B = 1,5 ring type

$$\alpha\text{-Methyl-}d\text{-glucoside,}\quad a_{me} + r_2 - r_3 + r_4 + r_5 = 30{,}830 \tag{3}$$
$$\beta\text{-Methyl-}d\text{-glucoside,}\quad -a_{me} + r_2 - r_3 + r_4 + r_5 = -6{,}630 \tag{4}$$

The pairs of equations (1), (2) and (3), (4) yield (5) and (6), respectively,

$$r_2 + r_3 - r_4 + r_5 = 2{,}250 \tag{5}$$
$$r_2 - r_3 + r_4 + r_5 = 12{,}100 \tag{6}$$

The value of the epimeric difference, $2r_2$ = 6700, gives

$$r_2 = 3{,}350 \tag{7}$$

Equations (5), (6) and (7) can be transposed to

$$r_2 - r_3 + r_4 = 8{,}275 \tag{8}$$

If it is assumed that the rules of isorotation hold for the pentoside and hexoside series, Equation 8 represents the molecular rotation of the chain of that pair of methyl-*d*-xylosides which possesses the 1,B = 1,5 ring structure and the molecular rotations of the alpha and beta members of this pair can be obtained by adding a_{me} and $-a_{me}$, respectively, to Equation (8). The value of a_{me} is taken from the rotations of the known pair of methyl-*d*-

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[38] Isbell, *Bur. of Standards J. of Research*, December, 1929. Dr. Isbell and the writer collaborated in the large-scale laboratory production of gulonic lactone and it was planned to proceed in the work to the study of derivatives of gulose and the higher carbon aldoses and ketoses obtainable from it. Subsequent to the writer's transfer from the Bureau of Standards to the Hygienic Laboratory in November, 1928, Dr. Isbell continued the project alone. The importance of the experimental results which he has now published is obvious, but the theoretical part of his article appears unsound to the writer because the invalid ring assignments of Haworth have been postulated. An obvious algebraic misstatement in the paper requires correction at once because it concerns the important question whether β-*l*-arabinose (175) possesses the same ring as β-methyl-*l*-arabinoside (245). The required correction is explained in the subsequent paragraph 20 that deals with the arabinose structures.

[39] Hudson, THIS JOURNAL, **47**, 270 (1925).

[40] The values for the glucosides are taken from the measurements of C. N. Riiber, *Ber.*, **57**, 1797 (1924).

xylosides as 17,990,[39] giving for the 1,B = 1,5 methyl-*d*-xylosides the calculated values

$$\alpha\text{-Form,}\quad a_{\text{me}} + r_2 - r_3 + r_4 = 26{,}265,\ [\alpha]_{\text{D}}\ 160 \qquad (9)$$
$$\beta\text{-Form,}\quad -a_{\text{me}} + r_2 - r_3 + r_4 = -9{,}715,\ [\alpha]_{\text{D}}\ -59 \qquad (10)$$

These values are near the rotations of the known methylxylosides (154 and −65, respectively) but are far removed from those that may be calculated from the application of the epimeric difference to the rotation of α-methyl-*d*-lyxoside (59), namely, 100 and −119.[41] This result is supported by a similar calculation in which one assumes that the gulosides possess a 1,4-ring; in this case Equations 1, 2, 5 and 7 remain unchanged but the rotations in 3 and 4 become 22,030 and −15,430, respectively, since these are the values for the methyl-*d*-glucosides of the 1,A = 1,4 ring form.[4] The solution now yields for the α-form of methyl-*d*-xyloside (1,4) the $[\alpha]_{\text{D}}$ value 133 and for the β-form −86; these calculated values are so widely divergent from those of the known methylxylosides (154 and −65) and also from those of the other expected forms mentioned above (100 and −119) that the original assumption of a 1,4-ring for the methylgulosides must be discarded. These two calculations thus show that the known methylxylosides and gulosides possess the 1,5-ring of the glucosides. Combining this result with the conclusions of paragraphs 9 and 10, it is seen that the 1,A = 1,4 ring pertains to α-*d*-lyxose (5.5), α-*d*-sorbose (43) and α-*d*-tagatose (1), and it is interesting to observe that this ring has now been allocated to the known forms of the four non-mutarotating ketoses (sorbose, tagatose, mannoketoheptose and glucoheptulose) and that all these sugars are alpha forms. Lastly, it is mentioned that the correlations which are shown in this paragraph are based upon the assumption that the isorotation rules hold between the pentoside and hexoside series; this is the further independent evidence that was mentioned in paragraph 3, footnote 10, as forthcoming in support of the writer's assumption[4] that r_4 has the same value in the pentoside and hexoside series.

17. The ring structure of the known form of *d*-α-glucoheptose[42]

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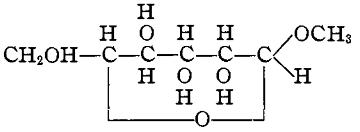
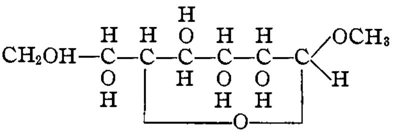
[41] Ref. 27. The value for the levorotary form is obtained by subtracting the difference in specific rotation of the known methylxylosides (219) from the calculated rotation (100) of the dextrorotary form. It is evident from consideration of paragraph 10 that the xylosides of rotations 100 and −119 belong to the unknown form of xylose that has the same ring structure as α-methyl-*d*-lyxoside (59).

[42] Fischer's designation of the two *d*-glucoheptoses, which are distinct sugars, by the symbols α and β was expressly stated by him to be provisional in the lack of a better plan [*Ann.*, **270**, 64 (1892)]. The subsequent use of these letters to designate a pair of forms of a sugar or its glycosides, such as α- and β-glucose, α- and β-methylglucoside, etc., has become universal. In consequence there is considerable chance for confusion today when we must refer to the known form of α-glucoheptose (a beta modification) as β-*d*-α-glucoheptose. The writer is strongly in favor of adopting some new system for naming the higher carbon sugars in order that the terms α and β may be restricted

can be found from the allocation that has been made for the 1,5-ring in the methylgulosides. Referring to the structures (XI) and (XII), it is seen that



(XI) β-Methyl-*d*-guloside (−83).



(XII) β-Methyl-*d*-α-glucoheptoside[43] (−75)

the observed molecular rotations [(−83)(194) = −16,100 and (−75)(224) = −16,700] are so closely alike that one may ascribe the same ring to the two substances, provided the rotation of Carbon 6 in the heptoside is negligible. That this is the case is indicated by the results that were found some years ago in comparing several substances from the galactose and mannoheptose series.[44] In paragraph 16 it was shown that the ring of the guloside is 1,B = 1,5, hence this is the structure of the glucoheptoside and of the known beta[39] form of *d*-α-glucoheptose (−28). The data indicate that the determination of ring structures in the heptose series through comparison with the allocations in the hexose series will be a comparatively simple matter and it may be surmised that this remark will apply also to the octoses and higher monosaccharides.

18. It will next be shown that the rotation of a new form of lyxose recently discovered by Haworth and Hirst,[34] which they have designated β-*d*-lyxose ($[\alpha]_D$ −70), fits accurately in the writer's system of ring classifications. It has been indicated[27] that the $[\alpha]_D$ value for an unknown α-*d*-lyxose epimeric with the known α-*d*-xylose (92) may be calculated to be (92 − 6700/150) = 47. The ring of this epimeric pair is 1,B = 1,5 (paragraph 16). The rotation of the corresponding β-*d*-lyxose (1,B) may be obtained from the last value by subtracting the difference between the rotations of an α- and β-form of a sugar[45] ($2a_{OH}$ = 16,900 for glucose, corresponding to 16,900/150 = 113 in the $[\alpha]_D$ value of a pentose) and it is $[\alpha]_D$ 47 − 113 = −66, which shows that the new form of lyxose (−70) is β-*d*-lyxose (1,B = 1,5). Since Haworth and Hirst have regarded their discovery of this sugar as an experimental proof that the writer's ring classifications are incorrect, reply is here made by calling attention to this excellent agreement of its rotation with his views.

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in the sugar group to the names of different forms of single sugars, their glycosides, etc. In order that any new system of nomenclature for these higher sugars may receive the general support of research workers in the carbohydrate field, it is believed best to have the subject discussed first by correspondence. The writer plans therefore to send out a circular letter on this subject soon to many workers and it is courteously requested that the possible publication of proposals by individuals be not made while the effort to obtain general agreement is in progress.

[43] Fischer, *Ber.*, **28**, 1145 (1895).

[44] Hudson and Monroe, This Journal, **46**, 979 (1924).

[45] Hudson and Yanovsky, *ibid.*, **39**, 1013 (1917).

19. Substances of the arabinose, galactose and fructose series will now be considered. These sugars are related structurally in the same way as the members of the trio xylose, glucose and sorbose or lyxose, mannose and tagatose, and the following comparisons (Table II) apply according to the rules of isorotation. It is seen that the first, fourth and fifth pairs give agreeing rotations for Carbon 4, but that pairs two and three yield very different values. The occurrence of the three agreements leads the writer to believe that substances of like ring structure are represented in pairs one, four and five and this view is supported by the occurrence of the greatly divergent values for pairs two and three. These comparisons thus indicate that the known methyl-*l*-arabinosides (17.3 and 245.5) have the 1,B = 1,5 ring, but that the 1,A = 1,4 ring is possessed by the known methyl-*d*-galactosides (192.7 and 0.4) and β-methyl-*d*-fructoside (−172.1). Since the known α- and β-forms of *d*-galactose (144 and 52) possess the same ring as these galactosides, and β-fructose (−133) the same ring as this fructoside,[21] the 1,A = 1,4 ring pertains to the known forms of these sugars. The rotation of the only known form of *l*-arabinose (175) differs from that of β-methyl-*l*-arabinoside (245) by a value that has been shown[21] to be abnormal, and in consequence the writer leaves the question of its ring form undecided and awaits the production of new experimental evidence regarding this point. It is interesting to observe from pairs one, four and five of the table that *the rotation of Carbon 4 has concordant values for the 1,4- and 1,5-ring structures.* This new result appears to offer explanation for the fact that while the original comparisons[4] of the writer, which led to the

TABLE II

RING INDICATIONS FOR THE ARABINOSE, GALACTOSE AND FRUCTOSE SERIES

Substance	$[M]_D$	Rotation of Carbon 4 (Difference /2)
β-Methyl-*l*-arabinoside	40,300	7,550
α-Methyl-*d*-xyloside (1,5)	25,200	
β-Methyl-*l*-arabinoside	40,300	11,930
α-Methyl-*d*-xyloside (1,4)	16,440[46]	
α-Methyl-*d*-galactoside	37,380	3,275
α-Methyl-*d*-glucoside (1,5)	30,830	
α-Methyl-*d*-galactoside	37,380	7,675
α-Methyl-*d*-glucoside (1,4)	22,030[47]	
β-Methyl-*l*-fructoside	33,400	8,100[a]
α-Methyl-*d*-sorboside (1,4)	17,200	

[a] This value applies to Carbon 5 of the ketosides, which is the analog of Carbon 4 of the aldosides (paragraph 9).

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[46] This value is calculated from that of the known α-methyl-*d*-lyxoside (59.4) by use of the epimeric difference (6700).

[47] This value is calculated from that of the known α-methyl-*d*-mannoside (79) by use of the epimeric difference.

conclusion that an unknown form of α-methyl-*d*-glucoside of $[\alpha]_D$ 115 may be expected, were based upon the evidence from methylation data that the known methylxylosides, arabinosides and galactosides are 1,5-forms and this evidence is now apparently invalid in the case of the galactosides, the comparison gave a correct result even though its theoretical background is now seen to have been formally defective. It yielded a correct result because essentially the same value for the rotation of Carbon 4 pertains to the 1,4- and the 1,5-ring structures.

20. The writer's original comparisons[4] of the rotations of the methyl glucosides, galactosides, xylosides and arabinosides, discussed in the preceding paragraph, will now be modified in Table III through the use of the new ring assignments of the present article, so that they may obtain a proper theoretical basis. The symbols are the ones originally used.

Table III

Derivation of the Rotations of α-Methyl-*d*-galactoside (1,5) and β-Methyl-*l*-arabinoside (1,4)

Substance	Molecular rotation	
β-Methyl-*l*-arabinoside (1,5)	$r_4 + p = 40{,}300$	(11)
α-Methyl-*d*-xyloside (1,5)	$-r_4 + p = 25{,}200$	(12)
α-Methyl-*d*-galactoside (1,5)	$r_4 + p' = X$	(13)
α-Methyl-*d*-glucoside (1,5)	$-r_4 + p' = 30{,}830$	(14)
β-Methyl-*l*-arabinoside (1,4)	$r_4' + p'' = Y$	(15)
α-Methyl-*d*-xyloside (1,4)	$-r_4' + p'' = 16{,}440$[46]	(16)
α-Methyl-*d*-galactoside (1,4)	$r_4' + p''' = 37{,}380$	(17)
α-Methyl-*d*-glucoside (1,4)	$-r_4' + p''' = 22{,}030$[47]	(18)

Solving Equations 11 to 14 gives the $[\alpha]_D$ value 237 for the unknown α-methyl-*d*-galactoside (1,5) and Equations 15 to 18 lead to 193 as the $[\alpha]_D$ value of the unknown β-methyl-*l*-arabinoside (1,4). It is thus to be expected that the unknown 1,5-methylgalactosides will be more dextrorotatory than the known 1,4-forms and the same conclusion follows for the corresponding forms of galactose of the 1,5-ring type; an α-*d*-galactose (1,5), of greater dextrorotation than the known 1,4 α-form (144) is thus predicted. In the arabinose series the unknown β-*l*-arabinose (1,4) would be expected to have the $[\alpha]_D$ value[48] $[(193)(164) - (a_{\text{me}} - a_{\text{OH}})]/150 = 144$, approximately. The question whether these predictions are correct is a subject for future experimental study, but it will be shown in the following paragraph that there is at least some evidence now known which supports them.

21. In 1917 Dr. E. Yanovsky and the writer made several precise measurements of the mutarotation curves for α-*d*-galactose and β-*l*-arabinose in water at 20°, seeking especially to follow the change in its early stages. The first readings were made one minute after solution of the

[48] Ref. 21. The value of $a_{\text{me}} - a_{\text{OH}}$ was there shown to be about 10,000.

sugar. In the case of both sugars these curves gave coefficients from the unimolecular formula which progressively decreased during the mutarotation. The value for galactose in the early stages was 0.014, expressed in minutes and decimal logarithms, and decreased to 0.0087, a relatively large change; the similar values for arabinose were 0.042 in the early stages and 0.034 toward the end. The initial $[\alpha]_D$ value for arabinose, obtained by extrapolation through the first minute, was +186, which is considerably higher than the value usually accepted for this sugar, 175. Due to interruptions caused by war the subject was not studied further and the results were never published. It is now seen that they throw much light on the possible existence of new forms of galactose and arabinose, and it is planned to publish them soon, together with measurements of the mutarotation of two tetra-acetates of galactose which were performed in the same period. The indication that the initial rotation of β-*l*-arabinose may be considerably higher than 175 throws much light on the question[21] of the supposed anomalous difference between this rotation and that of β-methyl-*l*-arabinoside (245), as it was shown that $a_{\text{me}} - a_{\text{OH}}$ has an unusually large value for this pair if the rotation of 175 is assigned to arabinose. The experiments indicate that this value may be much too low. The calculations of Isbell[38] by which he has sought to explain the exceptional value (175) of the rotation of arabinose constitute reasoning in a circle. He has set up a series of simultaneous equations just sufficient in number to allow the determination of the unknown variables, has assumed, of course, that the unknowns have constant values in the set and has solved the equations to obtain these values. Then he has used the values so obtained and found that the difference of two of them ($a_{\text{me}} - a_{\text{OH}}$) is a constant throughout the set of equations. His conclusion that he has explained the writer's observation regarding the unusual rotation of arabinose is clearly invalid because all that he has done is to check the computations that he made in solving the equations.

22. Similar Sugars.—The writer has long had in mind the idea that it may be possible in time to correlate the physical and chemical properties of sugars with their configurations. The first step toward this goal was the correlation of α- and β-forms in the group. It was then seen[2] that the occurrence in the mannose, rhamnose and lyxose series of forms with various types of ring structure presented a second problem which it is necessary to solve before a comprehensive comparison can be made. The writer believes that the problem of ring structures has now been solved for the greater number of the monosaccharides and that the extension of the solution along the present lines to the remaining simple sugars should offer no obstacles, though the obtaining of the necessary experimental measurements of rotations may require much time. The present results do comprise, however, a sufficiently large number of ring structure determinations to permit the logical comparison of the physical and chemical properties of substances of known configuration and ring structure. These comparisons will be presented in a forthcoming article but it may be mentioned here that the configurations for Carbons 1, 2, 3, 4 and 5 are the principal factors that determine the physical and chemical properties of a monosaccharide. Each of these configurations greatly influences the properties. In the heptoses and higher-carbon monosaccharides the configurations of Carbons 6, 7, etc., have a very minor influence. The writer cannot agree with Drew and Haworth[10] that their comparisons of the rotations of various hexoses and higher carbon monosaccharides constitute evidence for the occurrence of 1,5-rings in the normal forms of all these sugars; his objection arises from the fact that Drew and Haworth have compared the properties of only a few *types* of sugars, although the number of sugars which they have included is large. If other types are considered, their conclusion becomes invalid, as will be shown in detail in the forthcoming article.[49]

23. Haworth and Hirst[34] have criticized the writer's view that the two forms of mannose (30 and −17) differ from each other in ring structure while the alpha and beta forms of glucose (113 and 19) do not, by a statement to the effect that if the historical order of events had been different and the forms of mannose had been discovered before those of glucose, the writer would now be assuming that the mannose forms possess a like ring and the glucose modifications different ones. The writer requests to be excused from the task of considering an altered historical order for the origin of ideas in science; the subject is too complex for portrayal or even for precise definition. Instead, he will put the question raised by Haworth and Hirst in a form that is suitable for scientific discussion and then make his reply. *Does conclusive evidence exist today that the forms of glucose (113 and 19), rather than those of mannose (30 and −17), give the true difference of rotation for alpha and beta structures of the same ring type?* The answer is in the affirmative. Zemplén's proof[13] that lactose is 4-galactosidoglucose excludes the 1,4-ring for the glucose constituent of this disaccharide and limits the alpha and beta forms of lactose to one type (1,5) of ring structure. The writer showed[3] in 1909 that the difference of their molecu-

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[49] In H. S. Isbell's recent article (Ref. 38) he states that the synthesis of many substances in the hexose group is planned in order to obtain further data for studying the question of ring structures. Since this appears to be notice of the reservation of a part of the experimental field of study in which the writer has been working for twenty years it becomes necessary to record that he was not consulted by Dr. Isbell before this broad statement was made. It is true that Dr. Isbell made an arrangement with the writer for undertaking the pertinent studies in the idose series but the agreement did not include the whole hexose group. While the writer will be much pleased to have other workers undertake the preparation of substances that are needed for the extension of these ring classifications and will gladly make proper arrangements upon request, he obviously must object to Dr. Isbell's unwarranted assumption of the right to reserve a portion of this field against him.

lar rotations has essentially the same value as is found for the forms of glucose; it is thus established that the correct value for the rotation difference is found in the glucose rather than in the mannose series. Corroboration of this evidence can be obtained through similar reasoning by combining (1) the observation that the alpha and beta acetates of glucose, lactose, cellobiose and maltose show a uniform difference of molecular rotation,[50] with (2) Zemplén's proof[20] that each of these disaccharides is a 4-hexosido-glucose.

24. The ring structures that have been disclosed in this article cannot be reconciled with an idea that has become current from various publications by Haworth, who maintains that glycosides which possess the furan ring are very readily hydrolyzed. The furan-ringed methylglycosides, such as α-methylmannoside (79), α-methyllyxoside (59) and β-methylfructoside (-172) are quite comparable with the normal methylglycosides of the 1,5-ring in resistance to acid hydrolysis. In the writer's opinion the very easily hydrolyzed glycosides, of the type of Fischer's third methylglucoside, possess neither the 1,4- nor the 1,5-ring but rather the 1,C = 1,3 ring that has been assigned[2] to those peculiar acetylated methylglycosides of the rhamnose, mannose and lyxose[35] series which hold one acetyl group so firmly bound that it is not removable by alkali. Haworth's experimental results from the study of the methylation of the readily hydrolyzable so-called gamma glycosides, which have led him to regard the methylated products as possessing the furan ring, can be accounted for on the view that the original 1,3-ring has shifted during the methylation. *From this viewpoint the property of being readily hydrolyzed is a strong indication of the presence of a propylene oxide ring and on these grounds the writer would assign this ring to the fructose constituent of sucrose.* It is obvious that the whole system of butylene oxide structures that Haworth has proposed for sugars and glycosides of the so-called gamma type must be revised and reconstructed from evidence that avoids the invalid assumption of ring stability during methylation. This assumption is likewise present in all of Haworth's ring allocations among the compound sugars and this subject must likewise be reopened. In the following article the writer will endeavor to show that ring allocations for the compound sugars can be made through the use of the rules of isorotation and that the results indicate that ring shifting during the methylation of several of the compound sugars has occurred in Haworth's experimentation.

25. **Postscript of January 13, 1930.**—After this article was sent in for publication, the writer noticed the observation of Fischer and Armstrong,[51] made 29 years ago, that normal β-methylglucoside is produced from β-methylmaltoside by the hydrolytic action of the enzymes present in yeast.

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[50] Hudson and Dale, This Journal, **40**, 993 (1918).

[51] Fischer and Armstrong, *Ber.*, **34**, 2885 (1901).

It will be seen on reference to paragraph 7, that this observation proves that β-methylglucoside cannot possess the 1,4-ring, and must therefore be assigned the 1,5-ring. The old observation falls quite in line with the views which have come from the study of the thiophenol glycosides of lactose, cellobiose and maltose and Zemplén's proof that the disaccharide linkages are at Carbon 4 in these sugars. Referring to paragraph 16, it will be observed that it is possible to calculate the rotations of the unknown methyl-*d*-gulosides of the 1,A = 1,4 ring from the molecular rotations of the methyl-*d*-glucosides (1,A = 1,4), the methyl-*d*-xylosides (1,A = 1,4) and the epimeric difference ($2r_2 = 6700$). The appropriate equations are similar to those already recorded and the details may be omitted; the solution yields for α-methyl-*d*-guloside (1,A = 1,4) the $[\alpha]_D$ value +164 and for the β-form −29. These gulosides are now unknown. It is obvious that the rotations of a very large number of other glycosides and sugars, both aldoses and ketoses, of the pentose, hexose and heptose series and of the 1,4- and 1,5-ring structures may now be calculated from existing data by the rules of optical superposition and isorotation. The rotations of the individual asymmetric carbon atoms in these substances can likewise now be obtained; the values are of course quite different from the erroneous ones that Isbell[38] has recently published for the pentose and hexose series. He has fallen into the error of Haworth and has neglected to examine the fundamental assumption regarding ring stability during methylation, with the result that he has assigned incorrect rings to many substances. The writer would prefer to postpone the publication of the very obvious calculations of the rotations of the individual carbon atoms until the question of the ring structures in the galactose, arabinose and fructose series becomes definitely settled and he hopes that others will not burden the literature with such calculations while the subject still involves some possible uncertainties.

26. **Postscript of January 16, 1930. The Ethyl Glucosides of the 1,A = 1,4 Ring Type Recently Isolated by Haworth and Porter.**—It is stated by the authors[52] in their December, 1929, article, which has just come to hand, that the observed rotations of these compounds ($[\alpha]_D$ 98 for the α-form and −86 for the β) disprove the writer's views on ring structure and the "epimeric difference of rotation" as expressed in his 1926 articles. The writer disputes this conclusion and maintains on the contrary that the isolation of these substances of the observed rotations is a striking experimental confirmation of his prediction of the rotations in the glucose (1,A) series from the epimeric difference as applied to the substances of the mannose (1,A) series. The reading of the present article, in which it is shown (paragraphs 4–7) that the writer's acceptance of methylation data in his 1926 work led to the erroneous assignment of the 1,5-ring to the 1,A substances whereas the discarding of such data now leads to the assignment

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[52] Haworth and Porter, *J. Chem. Soc.*, 2796 (1929).

of the 1,4-ring to these compounds, clears up in full the objections which Haworth and Porter have made and shows that their latest results confirm the writer's ring system and do not agree, as regards the mannose series, with their own assignments of ring structure nor with Haworth's assumption that ring shifts never occur during the methylation of glycosides. It will now be shown that the rotations of the new ethylglucosides correspond with the values that the writer calculated in 1926 for the analogous methylglucosides of the 1,A ring, which is shown in the present article to be the 1,4-ring. Since the value of $a_{\text{et}} - a_{\text{me}}$ is approximately 1000,[21] the specific rotations of the ethyl-*d*-glucosides (1,A = 1,4) (mol. wt. 208) may be obtained from the rotations of the methyl-*d*-glucosides (1,A = 1,4) (mol. wt. 194) that were calculated in the 1926 articles ($[\alpha]_D$ 114 for the α-form and -77 for the β) as follows

α-Ethyl-*d*-glucoside (1,A = 1,4), $[\alpha]_D = [(114)(194) + 1000]/208 = 111$

β-Ethyl-*d*-glucoside (1,A = 1,4), $[\alpha]_D = [(-77)(194) - 1000]/208 = -77$

These calculated values indicate quite clearly that the new substances of Haworth and Porter may well be the ethylglucosides of the 1,4-ring, as they contend; the rotations fall in with the writer's system of ring structures but they prove at the same time, through the epimeric difference, that α-methyl-*d*-mannoside (79) possesses the 1,4-ring likewise, as contended by the writer, and not the 1,5-ring that has been assigned by Haworth to the latter substance. The difference of 9-13 between the calculated and observed values for the new ethylglucosides is not large enough to show conflict with the writer's views; such moderate differences are readily accounted for when it is remembered that the isorotation rules are in reality only first approximations, though it is known that they hold for sugars and alkylglycosides far within the limits by which substances of different ring structure vary in rotation. In connection with the new ethylglucosides it should be mentioned that Haworth and Porter find them to be very easily hydrolyzed by acids; if this is a fact and if they are really the expected 1,4-glucosides, the writer regards the observation as evidence that the ease of hydrolysis of glycosides is not conditioned solely by the type of ring that is present but that other structural elements are also of influence. It may be necessary to accumulate much additional experimental evidence on this question before definite correlations between structure and relative ease of hydrolysis can be made on a sound basis, and some of the reasoning of paragraph 24 may be affected by such new data. It is possible also that the same view may apply regarding the ease of oxidation of sugars of different ring structures by permanganate; who can say that because glucose of the 1,4-ring may be more easily oxidized than glucose of the 1,5-ring that the same correlation applies to a sugar of another configuration, for example galactose, mannose or fructose? Such questions as these, regarding which very definite assumptions applying throughout the sugar group have been made by Haworth, can be decided by experiment alone and the necessary data do not now exist.

27. Summary

It is shown that the measurements of Brauns on the aceto-halogeno derivatives of cellobiose and 4-glucosidomannose, taken in conjunction with the proof by Wolfrom and Lewis that normal tetramethylglucose and normal tetramethylmannose are true epimers, disprove Haworth's assumption that rings never shift during the methylation of glycosides. In consequence the whole system of ring structures which Haworth has built up for the simple and compound sugars, which is based upon this assumption, loses its foundation and the questions must be restudied through the use of evidence which avoids this invalid assumption. Such evidence is presented and the ring structures of many of the monosaccharides are disclosed through the application of the rules of optical superposition and isorotation.

WASHINGTON, D. C.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

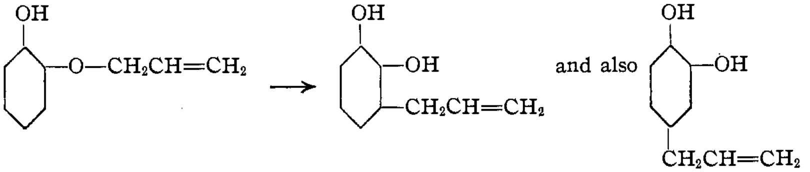
THE BEHAVIOR OF ALLYL DERIVATIVES OF CATECHOL AND RESORCINOL TOWARD HEAT

BY CHARLES D. HURD, HARRY GREENGARD AND FORREST D. PILGRIM

RECEIVED JANUARY 10, 1930 PUBLISHED APRIL 7, 1930

Except in a few instances, study of the pyrolytic rearrangement of allyl aryl ethers[1] has been confined to derivatives of monohydric phenols. In many such cases it has been observed that the allyl group wanders to an ortho carbon of the aromatic nucleus, thereby forming an *o*-allyl-phenol, unless both ortho positions are previously substituted, in which case the rearrangement proceeds normally to the para position.

Similar experiments with dihydric phenols have been little studied. In fact, when these experiments were undertaken in 1926 no work whatsoever had been published in this field. Two articles[2] have since appeared dealing with the mono- and diallyl ethers of catechol. The former has been shown to rearrange into both 3-allylcatechol and 4-allylcatechol, the former predominating.



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[1] For a survey of this topic, see Hurd, "The Pyrolysis of Carbon Compounds," The Chemical Catalog Co., New York, **1929**, pp. 214–228.

[2] Kawai, *Sci. Papers Inst. Phys. Chem. Res.*, **3**, 263 (1926); Perkin, Jr., and Trikojus, *J. Chem. Soc.*, 1663 (1927).