1-dm. tube). This is taken as the specific rotation of pure α-methyl *l*-arabinoside.

The melting point of pure α-methyl *l*-arabinoside is 131°. A preparation showing $[\alpha]_D^{20} = +20$ melted at 130°, one showing $[\alpha]_D^{20} = +49$ at 123°. Fractions giving $[\alpha]_D^{20}$ higher than + 60 did not melt sharply. Purdie and Rose reported 115–117° as the melting point of their preparation. Proof that their product having $[\alpha]_D^{20} = +73$ was in all probability a mixture is given by the fact that on successive recrystallizations of a fraction having approximately this rotation, the $[\alpha]_D^{20}$ values of the recrystallized products gave the series $+75 \longrightarrow +34 \longrightarrow +20 \longrightarrow +17.7 \longrightarrow +17.3$.

*Anal.* Subs. ($[\alpha]_D^{20} = +17.3$), 0.2728: $H_2O$, 0.1745; $CO_2$, 0.4420. Calcd.: C, 44.18; H, 7.15. Found: C, 43.88; H, 7.37.

Summarizing, the following values have been found for the specific rotations of the four pure substances in dilute aqueous solution: α-methyl *d*-xyloside, $[\alpha]_D^{20} = +153.9$, α-methyl *l*-arabinoside, $[\alpha]_D^{20} = +17.3$; β-methyl *d*-xyloside, $[\alpha]_D^{20} = -65.5$, β-methyl *l*-arabinoside, $[\alpha]_D^{20} = +245.5$.

My thanks are expressed to Dr. D. H. Brauns for the skilful assistance that he has rendered in the course of the experiments.

WASHINGTON, D. C.

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[CONTRIBUTION FROM THE POLARIMETRY SECTION OF THE BUREAU OF STANDARDS, UNITED STATES DEPARTMENT OF COMMERCE[1]]

# RELATIONS BETWEEN ROTATORY POWER AND STRUCTURE IN THE SUGAR GROUP. VII.[2] THE METHYL GLYCOSIDIC DERIVATIVES OF THE SUGARS

BY C. S. HUDSON

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The developments that have followed from the discovery of the methyl glycosides[3] in 1893 by Emil Fischer[4] are of much historical interest. His study of the composition and reactions of these crystalline compounds which result from the union of the reducing sugars with methyl alcohol led him to conclude that they are not of the acetal type of structure, which he had expected they would prove to be, but that the semi-acetal ring structure should be assigned to them. He then drew from the van't Hoff-LeBel theory of the asymmetric carbon atom the deduction that

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[1] Published by permission of the Director of the Bureau of Standards of the U. S. Department of Commerce.

[2] Part VI immediately precedes this article.

[3] Following the practice of several writers the word "glycoside" is here used as a convenient class name for the various aldosides (glucosides, galactosides, maltosides, etc.) and ketosides (fructosides, sorbosides, etc.).

[4] Fischer, *Ber.*, **26**, 2400 (1893).

Carbon 1 in such a ring must be asymmetric, and concluded therefore that two isomeric forms of the glycosides must be expected. He showed, likewise, that if the reducing sugars have this ring structure, a view which Tollens[5] had suggested from rather uncertain indications some years before, two such isomeric forms of them must be assumed. These conclusions have been fully verified. The numerous alpha and beta forms of the sugars and their derivatives that are now known represent the type of isomers that Fischer predicted. He adopted Tollens' suggestion that the union between the monosaccharides in the structures of the compound sugars is of the semi-acetal ring form and this idea of the "glycosidic union" has proved to be correct. The widespread occurrence of this linkage in the synthetic and natural glycosides and compound sugars causes it to be regarded today as one of the most important structural features of the carbohydrates. These far-reaching consequences have come from Fischer's discovery of the methyl glycosides, by which Tollens' formula received an experimental basis and a correlation with the theory of the asymmetric carbon atom.

When the writer showed in 1909[6] that van't Hoff's hypothesis of optical superposition applies fairly closely to the rotations of some typical substances of the sugar group the proof was based upon the comparison of the rotations of the alpha and beta forms of glucose, galactose, lactose, methyl and ethyl glucoside and galactoside and methyl xyloside—fourteen substances in all.[7] From the good agreement between theory and observation it appeared probable that the principle might apply to many other substances of the sugar group and be of use in the study of structure. Accordingly, the preparation in pure form of a large number of sugar derivatives was begun and in a series of researches extending through the subsequent 15 years it has been shown that the principle of optical superposition applies so generally in the sugar group that its use furnishes a valuable method for studying structural questions. From the data that were obtained in these investigations the principal coefficients that are now used in comparing rotations in the sugar group were derived. Reference may be made to the results that have come in this field from like researches by Bourquelot[8] in comparing the rotations of many glucosides and galactosides, by Irvine[9] in studying the alpha and beta forms of the methylated sugars and glucosamine, and by Levene[10] in classifying the al-

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[5] Tollens, *Ber.*, **16,** 921 (1883).

[6] Hudson, This Journal, **31,** 66 (1909).

[7] The inclusion of arabinose in the experimental data of the 1909 article was a mistake. The low-rotating alpha form of *l*-arabinose has never been crystallized.

[8] Bourquelot, (a) *Ann. chim.*, **4,** 310 (1915); (b) **7,** 218 (1917).

[9] Irvine and Scott, *J. Chem. Soc.*, **103,** 575 (1913). Irvine and Hogg, *ibid.*, **105,** 1386 (1914). Irvine and Earl, *ibid.*, **121,** 2370 (1922).

[10] Levene, "Hexosamines, Their Derivatives and Mucins and Mucoids," Monograph No. 18, The Rockefeller Institute for Medical Research, New York, 1922.

dosamines and many related substances. It seems reasonably certain from these various investigations that van't Hoff's hypothesis applies, in first approximation at least, to the sugars and many diverse types of their derivatives.

In applying the method of comparing rotations a number of exceptions have been found where theory and observation do not agree. The most striking of these disagreements was lately removed by the reinvestigation of the chloro- and bromo-acetyl derivatives of arabinose, as described in Part V. Experimental work in connection with another prominent disagreement, namely the exceptional rotation of α-methyl-*l*-arabinoside, was performed in 1917. Through unavoidable circumstances it has not been possible to publish the results until the present time. They are recorded in Part VI, immediately preceding this article. Meanwhile, Maltby[11] has called attention to the exceptional rotation of this arabinoside, a matter which had not previously received publication, although the writer had obviously known of it previous to 1917. In the present article the new data of Part VI will be discussed and occasion will also be taken to refer to the rotatory powers of nearly all the known methyl glycosides of the sugars.

## The Rotation of the Terminal Asymmetric Carbon Atom in the Methyl Glucosides, Galactosides, Xylosides and Arabinosides

It is now possible to revise the experimental test of the applicability of the principle of optical superposition to the rotations of the methyl glycosides that was originally published in 1909, by the use of the accurate measurements of Bourquelot[8b] for the two forms of methyl glucoside and

TABLE I

PROOF OF THE APPLICABILITY OF THE PRINCIPLE OF OPTICAL SUPERPOSITION TO THE METHYL GLUCOSIDES, GALACTOSIDES, XYLOSIDES AND ARABINOSIDES

| Substance | Mol. wt. | $[\alpha]_D$ in water | $[M]_D$ | Difference 2 $a_{Me}$ | Sum |
|---|---|---|---|---|---|
| α-Methyl *d*-glucoside | 194 | 157.9 | 30,630 | | |
| β-Methyl *d*-glucoside | 194 | −32.5 | −6300 | 36,930 | 24,330 |
| α-Methyl *d*-galactoside | 194 | 192.7 | 37,380 | | |
| β-Methyl *d*-galactoside | 194 | −0.4 | −80 | 37,460 | 37,300 |
| α-Methyl *d*-xyloside | 164 | 153.9 | 25,240 | | |
| β-Methyl *d*-xyloside | 164 | −65.5 | −10,740 | 35,980 | 14,500 |
| α-Methyl *l*-arabinoside | 164 | 17.3 | 2840 | | |
| β-Methyl *l*-arabinoside | 164 | 245.5 | 40,260 | −37,420[12] | 43,100 |
| | | | Av. | 36,950, hence $a_{Me}$ = 18,500 | |

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[11] Maltby, *J. Chem. Soc.*, **123**, 1404 (1923).

[12] For the explanation of the minus sign, which is a consequence of the system of nomenclature, see Part V.

galactoside and those of the preceding article for the methyl xylosides and arabinosides. It will be recalled that optical superposition requires that the difference of the molecular rotations for the four pairs of substances be a constant quantity.

The extreme values of the difference diverge by about 4% only and it may be concluded that the principle applies closely. Any test to determine the limit of applicability of the principle to these compounds will obviously require a consideration of the influences of temperature, concentration, wave length, solvent, etc., on the rotations. The exceptional rotations of the pair of methyl arabinosides to which Maltby has called attention are now replaced by new values that agree with the theory.

TABLE II

THE VALUES OF $a_{\text{Me}}-a_{\text{OH}}$ FOR VARIOUS SUGARS AND THEIR METHYL GLYCOSIDES

| Substance | Mol. wt. | $[\alpha]_D$ in water | $[M]_D$ | $a_{\text{Me}}-a_{\text{OH}}$ |
|---|---|---|---|---|
| α-Methyl *d*-glucoside | 194 | 157.9 | 30,630 | 10,290 |
| α-*d*-Glucose[13] | 180 | 113 | 20,340 | |
| β-Methyl *d*-glucoside | 194 | −32.5 | −6300 | −9700 |
| β-*d*-Glucose[13] | 180 | 19 | 3400 | |
| α-Methyl *d*-galactoside | 194 | 192.7 | 37,380 | 11,460 |
| α-*d*-Galactose[13] | 180 | 144 | 25,920 | |
| β-Methyl *d*-galactoside | 194 | −0.4 | −80 | −9440 |
| β-*d*-Galactose[13] | 180 | 52 | 9360 | |
| β-Methyl *d*-fructoside[14] | 194 | −172 | −33,400 | −9500 |
| β-*d*-Fructose[13] | 180 | −133 | −23,900 | |
| α-Methyl *d*-mannoside[15] | 194 | 79 | 15,330 | 9930 |
| α-*d*-Mannose[16] | 180 | 30 | 5400 | |
| α-Methyl *l*-rhamnoside[17] | 178 | −62.5 | −11,120 | −9860 |
| α-*l*-Rhamnose[13] | 164 | −7.7 | −1260 | |
| β-Methyl *d*-α-glucoheptoside[17] | 224 | −74.6 | −16,710 | −10,750 |
| β-*d*-α-Glucoheptose[13] | 210 | −28.4 | −5960 | |
| β-Methyl gentiobioside[18] | 356 | −36 | −12,820 | −9060 |
| β-Gentiobiose[19] | 342 | −11 | −3760 | |
| α-Methyl *d*-xyloside | 164 | 153.9 | 25,240 | 11,440 |
| α-*d*-Xylose[13] | 150 | 92 | 13,800 | |
| β-Methyl cellobioside[20] | 356 | −18.9 | −6700 | −12,170 |
| β-Cellobiose[13] | 342 | 16 | 5470 | |
| β-Methyl *l*-arabinoside | 164 | 245.5 | 40,260 | 14,010 |
| β-*l*-Arabinose[13] | 150 | 175 | 26,250 | |

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[13] Hudson and Yanovsky, THIS JOURNAL, **39**, 1035 (1917).

[14] Hudson and Brauns, *ibid.*, **38**, 1216 (1916).

[15] Van Ekenstein, *Rec. trav. chim.*, **15**, 223 (1896).

[16] Levene, *J. Biol. Chem.*, **57**, 329 (1923).

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

[18] Hudson and Johnson, THIS JOURNAL, **39**, 1272 (1917).

[19] Bourquelot and Hérissey, *J. pharm. chim.*, [6] **16**, 418 (1902). See THIS JOURNAL, **38**, 1569 (1916).

[20] Helferich, Loewa, Nippe and Riedel, *Z. physiol. Chem.*, **128**, 149 (1923).

## Comparison of the Rotations of Various Methyl Glycosides with Those of the Respective Sugars

Quite a number of methyl glycosides have been isolated in only one modification. Some idea of the applicability of the principle to their rotations can in many cases be obtained from a comparison of the molecular rotation of a given glycoside with that of its parent sugar. Since the rotation of an α-methyl glycoside of a sugar of the *d*-series is written $b + a_{Me}$ and that of the alpha form of the parent sugar $b + a_{OH}$ the difference is $a_{Me} - a_{OH}$, and the similar difference for the respective beta compounds is $-(a_{Me} - a_{OH})$. The signs of the differences are the reverse of these if the sugar is of the *l*-series. It is to be expected that these differences will have the same numerical value and the proper signs, throughout the sugar group. The question of the correctness of this conclusion from the theory may be judged by a consideration of the data of Table II.

In all cases the sign of the difference is correct. Eight of the twelve pairs show a fairly constant value for the difference. The explanation of the larger values for the remaining four pairs must be left to future investigation. The fact that a better purification of the respective forms of the four sugars must be expected to cause these larger differences to approach the normal average is suggestive, since there can be little doubt that some of the sugars have not yet been obtained in pure alpha and beta forms.

It is a very noteworthy fact that the normal value of the difference holds for mannose and rhamnose. These sugars and lyxose are closely related in configuration and it has been shown that the three exhibit a considerable and similar deviation from the principle of optical superposition when the rotations of their respective alpha and beta forms are compared.[13] On the basis of the present experimental results it is suggested that the known alpha forms of mannose ($[\alpha]_D = +30$) and methyl mannoside (+ 79), rhamnose (—7.7) and methyl rhamnoside (—62.5), and lyxose (+ 5.5) and benzyl lyxoside (+ 80.5) (see the next section of this article) possess ring structures common to the respective members of each pair (and possibly common also to the three pairs). Such an hypothesis accounts for the observed agreements of the rotations with the principle in these cases. At the same time it is suggested that the beta forms of these sugars, the rotations of which have been shown to differ from those of the respective alpha forms by a much smaller amount than is required by the principle, *possess rings that are different from those of the alpha forms.* This view will be more fully developed in a subsequent article through the further comparison of many rotatory measurements that strongly support it.

## Methyl *d*-Lyxoside

This crystalline substance was prepared by van Ekenstein and Blanksma[21] by the interaction of lyxose and acidified methyl alcohol.

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[21] Van Ekenstein and Blanksma, *Z. Ver. deut. Zucker-Ind.*, **58**, 114 (1908).

Its specific rotation is recorded as + 40.2. Since this value is more dextrorotatory than that of α-*d*-lyxose (+ 5.5 changing to —14 final)[13] the glycoside is to be classed as an alpha form. The specific rotation of methyl *d*-lyxoside can be calculated in three independent ways, (1) from the rotation of α-*d*-lyxose, (2) from that of α-methyl *d*-xyloside and (3) from that of benzyl lyxoside.

**Calculation by the First Method.**—The molecular rotation of α-*d*-lyxose (mol. wt., 150) is $b_{lyxose} + a_{OH} = 5.5(150) = 825$ and hence $b_{lyxose} = —7{,}675$, since $a_{OH}$ has the value 8,500 (see Part III, p. 488). The specific rotation of α-methyl *d*-lyxoside (mol. wt., 164) then becomes $(b_{lyxose} + a_{Me}) \div$ mol. wt. $= (—7675 + 18{,}500) \div 164 = + 66$.

**Calculation by the Second Method.**—Since the alpha forms of methyl *d*-lyxoside and methyl *d*-xyloside are epimers they differ in structure like the alpha forms of methyl *d*-mannoside and methyl *d*-glucoside and the differences between the molecular rotations of the members of each epimeric pair should be the same. Hence the specific rotation of α-methyl *d*-lyxoside is $(25{,}240 + 15{,}330 - 30{,}630) \div 164 = + 61$.

**Calculation by the Third Method.**—Van Ekenstein and Blanksma[21] prepared crystalline benzyl *d*-lyxoside (mol. wt., 240) from the sugar and acidified benzyl alcohol and found its specific rotation to be + 80.5 in water. The high dextrorotation indicates that the glycoside is an alpha form and its molecular rotation is accordingly $b_{lyxose} + a_{Bz} = 80.5\ (240) = 19{,}300$. The molecular rotation of β-benzyl *d*-glucoside ($[\alpha]_D = —55.7$ in water,[22] mol. wt., 270) is $b_{glucose} - a_{Bz} = —55.7\ (270) = —15{,}040$, and since $b_{glucose} = 11{,}880$, $a_{Bz} = 26{,}900$ and $b_{lyxose} = —7620$, a value which agrees closely with that found previously from the rotation of α-methyl *d*-xylose. Using the value from the benzyl lyxoside, which has just been shown to agree with the principle of optical superposition, the specific rotation of α-methyl *d*-lyxoside is calculated to be $(—7620 + 18{,}500) \div 164 = + 66$. The agreement of the three calculated values makes it appear very likely that van Ekenstein and Blanksma's methyl lyxoside was not a pure alpha form but contained some other substance, probably the beta isomer. The matter is of considerable importance because it relates to the difference of the rotations of epimers in the sugar group.

## Beta-Methyl *d*-Isorhamnoside

This crystalline substance was prepared by Fischer and Zach[23] by the saponification of its triacetate, which was made by the reduction of 6-bromo-2,3,5-acetyl β-methyl glucoside, which in turn was made from dibromo-acetyl glucose (Structure XVI of Part I; see also Part V) by Koenigs and Knorr's synthesis. Fischer and Zach have designated it a β-gly-

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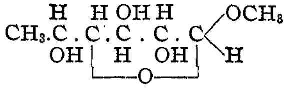
[22] Fischer and Helferich, *Ann.*, **383,** 68 (1911).

[23] Fischer and Zach, *Ber.*, **45,** 3767 (1912).

coside because they found that emulsin hydrolyzes it; it will be seen from the following considerations of rotatory data that this designation is correct. The configuration of β-methyl *d*-isorhamnoside is



$$\begin{array}{l} \quad\ H \quad H\ OH\ H \qquad\ /OCH_3 \\ CH_3.C\,.\,C\,.\,C\,.\,C\,.\,C\!\!< \\ \quad OH \,|\; H \quad OH \,| \quad \backslash H \\ \qquad\ \ \lfloor\!\!-\!-O\!-\!-\!\!\rfloor \end{array}$$

(I)

If the rotation of the beta form of isorhamnose were known the value of $(A'_{Me} - A'_{OH})$ could be found, but the beta form has not been crystallized. There is another way, however, through which the applicability of the principle of optical superposition to this glycoside of isorhamnose can be tested, and the result shows that the principle applies. It is seen from the structural Formula I of the glycoside that *d*-isorhamnose itself is a reduced *d*-glucose. Likewise it is known that *d*-rhamnose (that is, the antipode of natural *l*-rhamnose) is to be considered a reduced *d*-mannose.[24,23] If the change in structure from a methyl mannoside to the corresponding methyl rhamnoside causes a change in rotation of Y it is to be expected that the same change will be found in the case of the rotations of methyl glucoside and methyl isorhamnoside, if *like changes in structure cause like changes in rotation*, a rule which may be deduced from the principle of optical superposition, as was shown in Part IV. The comparisons are recorded in Table III for the respective pairs of methyl glycosides. The rotation of methyl *d*-rhamnoside is written as equal to that observed for methyl *l*-rhamnoside but of reverse sign.

TABLE III

THE RELATED ROTATIONS OF CORRESPONDING METHYL GLYCOSIDES OF *d*-GLUCOSE, *d*-ISORHAMNOSE, *d*-MANNOSE AND *d*-RHAMNOSE

| Substance | Mol. wt. | $[\alpha]_D$ in water | $[M]_D$ | Difference |
|---|---|---|---|---|
| β-Methyl *d*-glucoside | 194 | −32.5 | −6,300 | +3,500 |
| β-Methyl *d*-isorhamnoside | 178 | −55.2 | −9,800 | |
| α-Methyl *d*-mannoside | 194 | 79 | 15,300 | +4,200 |
| α-Methyl *d*-rhamnoside | 178 | 62.5 | 11,100 | |

The differences for the two pairs of glycosides are nearly alike, the variation of 700 corresponding to only about four degrees in specific rotation. The agreement with theory proves that the known methyl *d*-isorhamnoside is a beta form, confirming Fischer and Zach's classification.[25] In Part V it was shown that 6-bromo-1,2,3,5-acetyl glucose is a β-acetate and its

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[24] Hudson, THIS JOURNAL, **31**, 338 (1910).

[25] It would be interesting to compare the rotations of the acetates of these four methyl glycosides, all of which have been prepared in pure form, but unfortunately they have not been measured in the same solvent, chloroform having been used for two of them, alcohol for the third and acetylene tetrachloride for the fourth. This example again emphasizes the importance of measuring the rotations of new substances in chloroform or water whenever possible (see Parts I and V).

production by the interaction of dibromo-acetyl glucose and silver acetate follows the rule that Koenigs and Knorr's reaction yields beta derivatives. It is now shown that the similar glycoside synthesis from dibromo-acetyl glucose yields the beta derivative. Since these two syntheses thus follow the usual course of Koenigs and Knorr's reaction it seems very probable that the Walden inversion that was shown in Part I to accompany this reaction likewise occurs here, that dibromo-acetyl glucose is an alpha form and that its rotation, which has not yet been measured, will be found to be near the value that has been calculated in Parts I and V on this supposition, + 196 in chloroform.

## Calculation of the Rotations of the Forms of *d*-Isorhamnose

From the molecular rotation of β-methyl *d*-isorhamnoside, $[M]_D = b_{\text{isorhamnose}} - a_{Me} = -9800$, and the value of $a_{Me}$ from Table I the rotation of the basal chain of the methyl pentose is *$b_{isorhamnose}$ = 8700 in water.* The molecular and specific rotations of the alpha and beta forms of the sugar (mol. wt., 164) are calculated from this value and the rotation ($a_{OH}$) of the end asymmetric carbon atom (8500, see Part III, p. 488) to be α-*d*-Isorhamnose, $[M]_D = 8700 + 8500 = 17{,}200$, $[\alpha]_D = +105$; β-*d*-isorhamnose, $[M]_D = 8700 - 8500 = 200$, $[\alpha]_D = +1$.

Fischer and Zach crystallized *d*-isorhamnose and recorded one measurement of the course of its mutarotation, $[\alpha]_D$ five minutes after solution in water being 73 and the final value being 29.7. The readings that were made at intermediate times do not show a constant coefficient for a unimolecular reaction, from which it seems probable that the temperature varied during the mutarotation. By extrapolation the writer obtains an initial value of about 83, which is at best only a minimum value and will doubtless be increased considerably when more careful observations and a better purification of the sugar are obtained. Such has indeed been the usual result when even such well-known sugars as glucose and lactose were carefully studied with the object of obtaining pure alpha and beta forms. It is probable, therefore, that the calculated value for crystalline α-*d*-isorhamnose is more reliable than that measured by Fischer and Zach. Their value of the final rotation lies between those calculated for the two forms, as would be expected.

## Methyl Fucoside

Tadokoro and Nakamura[26] have recently described the preparation of a crystalline methyl *l*-fucoside by the action of acidified methyl alcohol on *l*-fucose and record its $[\alpha]_D = -122$ in water. The final rotation of *l*-fucose is —75; hence the fucoside is to be named an alpha form because its rotation is more levorotatory than that of the parent sugar of the levo

[26] Tadokoro and Nakamura, *J. Biochem. (Japan)*, **2,** 461 (1923).

series. It has been shown by Clark[27] that the configuration of *l*-fucose is that of a reduced *l*-galactose, the group $CH_2OH$ of the hexose becoming $CH_3$ in the methyl pentose. There are two independent ways by which the rotation of this fucoside can be calculated: first, from the rotation of $\alpha$-methyl *d*-galactoside; and second, from the rotation of $\alpha$-*l*-fucose.

**Calculation by the First Method.**—The configuration of Carbon 5 is the same for *d*-glucose, *d*-mannose and *d*-galactose if the butylene ring structure (or the amylene) is assumed for the three sugars. The reduction of the primary alcohol group attached to the symmetric Carbon 6 of *d*-glucose and *d*-mannose causes an increased molecular levorotation of about 4000 (see Table III), and it may be assumed on good grounds that this change is mainly referable to the adjacent Carbon 5. Therefore $\alpha$-methyl *d*-fucoside may be expected to rotate more levo by 4000 than $\alpha$-methyl *d*-galactoside, that is, $[M]_D = 37{,}380 - 4000 = 33{,}380$—and the molecular rotation of its antipode, $\alpha$-methyl *l*-fucoside, is then —33,380 and its $[\alpha]_D = —33{,}380 \div 178 = —188$.

**Calculation by the Second Method.**—Tollens and Rorive[28] have recorded the rotation of $\alpha$-*l*-fucose in water ten minutes after dissolving as —124.1, which changed gradually to become constant at —75.6. From the mutarotation curve they obtained by graphical extrapolation the value —150 for the initial rotation, but this method is not reliable in the case of an extensive extrapolation. By using the equation for a unimolecular reaction the extrapolated value is —144, which seems more reliable. The molecular rotation of $\alpha$-*l*-fucose is $(b_{l\text{-fucose}} - a_{OH}) = —(144)(164) = —23{,}600$ and hence $b_{l\text{-fucose}} = —15{,}100$. For $\alpha$-methyl *l*-fucoside $[\alpha]_D = (b_{l\text{-fucose}} - a_{Me}) \div \text{mol. wt.} = (—15{,}100 - 18{,}500) \div 178 = —190$, which agrees well with the previously calculated value. It seems probable that Tadokoro and Nakamura's methyl fucoside preparation was a mixture of the alpha and beta isomers.

### Methyl Maltoside and its Hepta-acetate

Hudson and Sayre[29] have calculated the specific rotation of $\beta$-methyl maltoside hepta-acetate to be $(B_{\text{maltose}} - A_{Me}) \div \text{mol. wt.} = (62{,}700 - 26{,}900) \div 650 = +55$, which agrees almost exactly with the value which they observed for the pure substance in chloroform, + 54. By the saponification of this acetate Fischer and Armstrong[30] obtained $\beta$-methyl maltoside in amorphous form but were unable to crystallize it. The calculated specific rotation of the substance is derived as follows. The molecular rotation of $\beta$-maltose is $(b_{\text{maltose}} - a_{OH}) = (118)(342) = 40{,}400$, hence $b_{\text{maltose}} = 48{,}900$, and the specific rotation of $\beta$-methyl maltoside is

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[27] Clark, *J. Biol. Chem.*, **54,** 65 (1922).

[28] Tollens and Rorive, *Z. Ver. deut. Zucker-Ind.*, **59,** 579 (1909).

[29] Hudson and Sayre, THIS JOURNAL, **38,** 1867 (1916).

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

$(b_{maltose} - a_{Me}) \div$ mol. wt. = (48,900 − 18,500) ÷ 356 = + 85 in water. The value observed by Fischer and Armstrong was + 70 but the material was amorphous and it seems probable that if the pure crystalline substance could be obtained it would give a higher value. Indeed, they do not accept their observed value as being the correct rotation of the pure isomer.

## Ethyl Maltoside, Ethyl Glucoside and the Value of $a_{Et}$

Although the present article does not deal with the ethyl glycosides, reference may here be made to β-ethyl maltoside because from its rotation, which has been accurately measured recently by H. Fischer and Koegl,[31] that of β-methyl maltoside can be calculated by an independent way. By the saponification of hepta-acetyl ethyl maltoside, which was prepared from amorphous bromo-acetyl maltose ($[\alpha]_D$ = + 71 in chloroform) by Koenigs and Knorr's method, they obtained crystalline ethyl maltoside ($[\alpha]_D$ = + 79.22 in water, mol. wt. 370; hence $[M]_D$ = 29,310). It is probable from the method of synthesis that it is a β-glycoside and this allocation is confirmed by the following calculation. To derive its rotation it is necessary to know the value of $a_{Et}$, the rotation of the end asymmetric carbon atom of the ethyl glycosides. This can be found from the accurately known rotation of α-ethyl glucoside (mol. wt., 208) which Fischer[32] found to be 150.6 and Bourquelot[8b] on revision 150.9. Its molecular rotation is $(b_{glucose} + a_{Et})$ = (150.9) 208 = 31,390 and since $b_{glucose}$ = 11,880, *$a_{Et}$ = 19,510 in water.* The specific rotation of β-ethyl maltoside is then calculated to be $(b_{maltose} - a_{Et}) \div 370$ = (48,900 − 19,510) ÷ 370 = + 79.4, in good agreement with the observed value. The specific rotation of β-methyl maltoside is likewise calculated from these data to be $(b_{maltose} - a_{Et}) + (a_{Et} - a_{Me}) \div 356$ = (29,310 + 19,510 − 18,500) ÷ 356 = + 85, which agrees completely with the value calculated in the preceding section.

## Methyl Lactoside and its Hepta-acetate

The specific rotation of the beta form of hepta-acetyl methyl lactoside (mol. wt., 650) is $B_{lactose} - A_{Me}$ = (16,900 − 26,900) ÷ 650 = —15 in chloroform, from the data of Part I. Ditmar[33] prepared this substance by Koenigs and Knorr's synthesis, and the crystalline material which resulted from the action of methyl alcohol on chloro-acetyl lactose showed $[\alpha]_D$ = + 6, while from bromo-acetyl lactose a derivative of $[\alpha]_D$ = —6 was obtained. Judging from rotatory data, both preparations were probably impure β-hepta-acetyl methyl lactoside.

By the saponification of the acetate Ditmar prepared the methyl lac-

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[31] H. Fischer and Koegl, *Ann.*, **436**, 219 (1924).

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

[33] Ditmar, *Ber.*, **35**, 1951 (1902).

toside and describes it as a crystalline substance, m. p. 170–171°, but no record of its rotation is mentioned. The substance is doubtless the beta form, the specific rotation of which is calculated as follows. The molecular rotation of β-lactose is $b_{\text{lactose}} - a_{\text{OH}} = 35(342) = 11{,}970$; hence $b_{\text{lactose}} = 11{,}970 + 8500 = 20{,}470$, and the specific rotation of β-methyl lactoside becomes $(b_{\text{lactose}} - a_{\text{Me}}) \div \text{mol. wt.} = (20{,}470 - 18{,}500) \div 356 = +6$ in water.

### Methyl *l*-Sorboside

This substance (mol. wt., 194) was prepared by Fischer[32] who records $[\alpha]_D = -88.7$ in water, and the molecular rotation is accordingly —17,200. It has been shown[14] that this high negative rotation indicates that the substance is an alpha form because sorbose, a sugar of the levo series, rotates only —43. Sorbose does not show mutarotation. The specific rotation of α-*l*-sorbose is calculated from that of the sorboside in the usual manner to be $[(b_{\text{sorbose}} - a_{\text{Me}}) + (a_{\text{Me}} - a_{\text{OH}})] \div \text{mol. wt.} = (-17{,}200 + 18{,}500 - 8500) \div 180 = -40$, a value quite near the observed rotation of sorbose. This result apparently indicates that the rotation —43 is the true rotation of α-*l*-sorbose and is not an equilibrium rotation such as is the value 52 for glucose or —92 for fructose, because the final rotations of the many mutarotating sugars are in all cases widely different from the rotations of their alpha and beta forms. Such a conclusion deserves a careful consideration but it should be regarded as an indication only, not a proof, until it can be tested in some independent way, because it would be very surprising if sorbose does not establish an equilibrium between its alpha and beta forms in the way that the related ketoses, fructose and perseulose are known to do. It is remarked, however, that fructose and perseulose are the only crystalline ketoses which have been observed to mutarotate. On the other hand, fructose tetra-acetate, which would be expected to exhibit mutarotation because glucose tetra-acetate does, shows a constant rotatory power.[34] Mutarotation has not been detected so far for tagatose, mannoketoheptose or sorbose. Sedoheptose crystallizes as a non-reducing anhydro-sedoheptose which would not be expected on structural grounds to show mutarotation. The writer has supposed in the past that the mutarotation of tagatose, mannoketoheptose and sorbose was so rapid that it had escaped detection, and this view receives support from the fact that fructose mutarotates very rapidly indeed. *The rotatory relations that have just been disclosed suggest, however, a different explanation, namely, that sorbose does not isomerize in solution like fructose and the aldoses.*[35] Obviously the subject requires further experimental

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[34] Hudson and Brauns, This Journal, **37**, 2742 (1915).

[35] Levene [*J. biol. Chem.*, **59**, 135 (1924)] has recently made the novel suggestion that the apparent absence of mutarotation in the case of 2,5-anhydro-glucose and the certain absence of lactone formation in the cases of, 2,5-anhydro-gluconic and 2,5-

study. It seems practically certain that the recorded rotations of both sorbose and methyl sorboside are substantially correct because the rotation of the sugar has been measured by several observers with agreeing results, and the antipodal forms (*d*-sorbose and methyl *d*-sorboside) have been found to rotate + 43 and + 88.5.[36] There is another hypothesis, however, which offers an explanation of the present anomaly without excluding the possibility that sorbose may show very rapid mutarotation. *The methyl sorboside may possess a ring structure different from that of sorbose.* It would not be surprising if this explanation should prove correct, because the researches of the day are rapidly disclosing many examples of new ring structures among the substances of the sugar group. It seems premature to say more than that the comparison of rotations has disclosed in the case of sorbose and the other ketoses an interesting problem.

Nearly all the known methyl glycosides of the sugars proper have now been considered. For the sake of completeness it is mentioned that the omitted ones are methyl riboside, which is known only as an impure sirup, the methyl glycosides of the so-called gamma forms of some of the sugars, the recently discovered isomers of methyl rhamnoside and methyl mannoside, the two forms of methyl glucodesoside, and the methyl glycosides of 6-bromo-, 6-amino- and 3,6-anhydro-glucose, and of glucosamine and epiglucosamine. The rotations of some of these will be discussed at a later time; the consideration of them requires in some cases the obtaining of new experimental data and in others the presentation first of a further development of the method (Part IV) of classifying structurally similar derivatives of different sugars.

## Summary

From Bourquelot's measurements of the rotations of the methyl glucosides and galactosides and those of the methyl xylosides and arabinosides recorded in the preceding article (Part VI) it is found that van't Hoff's principle of optical superposition holds closely for these substances the maximum deviation being about 4% (Table I). The results confirm the writer's conclusion, in 1909, that the principle applies, as a first approximation at least, to the rotations of the methyl glycosides. The rotations of the methyl arabinosides, which in the past have been considered exceptional, are now shown to conform to the principle.

By comparing the rotation of a methyl glycoside with that of its parent sugar (Table II) it is shown that the principle likewise applies closely to $\beta$-methyl fructoside, $\alpha$-methyl mannoside, $\alpha$-methyl rhamnoside and $\beta$-

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anhydro-mannonic acids is due to a spatial interference of the 2,5 ring structure with the formation of the 1,4 ring that is assumed for the alpha and beta forms of glucose and for the lactones of gluconic and mannonic acids.

[36] Lobry de Bruyn and Van Ekenstein, *Rec. trav. chim.*, **16,** 262 (1897); **19,** 1 (1900). Van Ekenstein and Blanksma, *ibid.*, **27,** 1 (1908).

methyl gentiobioside. The known form of methyl α-glucoheptoside is classified in the beta series from rotatory data.

The specific rotation of α-methyl *d*-lyxoside is calculated by three independent ways to be + 66, + 61 and + 66; these values agree well with one another but deviate greatly from the value of + 40 measured by van Ekenstein and Blanksma. Benzyl *d*-lyxoside ($[\alpha]_D$ = + 80.5) is classified as an alpha form; its rotation agrees with the theory.

Fischer and Zach's classification of methyl *d*-isorhamnoside as a beta form from the fact that emulsin hydrolyzes it, is confirmed through rotatory data (Table III), which likewise prove that the principle applies to its rotation. The rotations of the alpha and beta forms of *d*-isorhamnose are calculated and the results compared with Fischer and Zach's measurements.

It is shown that Tollens and Rorive's curve for the mutarotation of fucose indicates —144 rather than their extrapolated value —150 as the initial specific rotation of α-*l*-fucose. The rotation of α-methyl *l*-fucoside is calculated in two independent ways to be —188 and —190. These agreeing values indicate that the rotation recently found by Tadokoro and Nakamura, —122, may refer to a mixture of the alpha and beta isomers.

The rotation of β-methyl maltoside is calculated by two independent ways to be + 85. The value + 70 has been recorded by Fischer and Armstrong for an amorphous and probably impure preparation of the substance. The calculated rotation of β-ethyl maltoside (+ 79.4) agrees closely with that recently observed by H. Fischer and Koegl (+ 79.2) who prepared the substance in pure crystalline form. In this calculation the new coefficient $a_{Et}$, the rotation of the end asymmetric carbon atom of the ethyl glycosides, has been found to have the value + 19,440 in water, from Fischer's measurement of the rotation of α-ethyl glucoside, which was confirmed by Bourquelot.

The rotations of β-methyl lactoside and its hepta-acetate, substances which were crystallized by Ditmar but not accurately purified, are calculated to be + 6 and —15, respectively.

The relation of the rotation of methyl sorboside to that of sorbose is shown to indicate either (1) that sorbose, a ketose for which mutarotation has not been detected so far, persists in solution as its alpha form, or (2) that sorbose and methyl sorboside possess different ring structures.

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