[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. VIII. SOME TERPENE ALCOHOL GLYCOSIDES OF GLUCOSE, GLUCURONIC ACID, MALTOSE AND LACTOSE

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RECEIVED NOVEMBER 4, 1924 PUBLISHED FEBRUARY 5, 1925

Most of the numerous glycosides that have been isolated from plants, such as amygdalin, salicin, arbutin, coniferin, quercitrin, etc., are combinations of reducing sugars (glycoses) with alcoholic or phenolic substances of the aromatic series, although a few aliphatic glycosides have been found, such as linamarin of the flax plant (acetone-cyanohydrin glucoside) and sinigrin of black mustard seed. While many glycosides of the commoner aliphatic alcohols have been synthesized, for example, the methyl, ethyl, propyl and glycol glucosides and galactosides, etc., such compounds have not yet been found in nature. Since the phenyl glycoside of glucuronic acid has been found to be a normal constituent of the urine of various animals, it seems probable that phenyl glucoside is a normal intermediate metabolic product which by oxidation yields phenyl-glucuronic acid (E. Fischer and Piloty).[2] Since the compound sugars are true glycosides, maltose being 1,6-α-glucosido glucose and lactose being 1,5-β-galactosido glucose, it is evident that both plants and animals synthesize glycosides of hydroxy aldehydes. Glycosidic compounds of the sugars obviously play important roles in biological processes and it must be expected that many new glycosides will in time be isolated from natural products as well as synthesized in the laboratory.

The writer has shown in several articles[3] that van't Hoff's principle of optical superposition applies to the rotations of the synthetic glycosides of the aliphatic alcohols and to the rotations of the compound sugars. Although it was indicated in the first of those articles (1909) that the principle probably applied to salicin, arbutin and coniferin, precise evidence relating to aromatic glycosides was lacking until it was shown by the recent comparison of the rotations of the glycosides of the amygdalin group in Part III[4] that the principle applies closely to the glycosides of mandelonitrile. In Part VII it has been shown that it applies likewise to two other aromatic glycosides, namely, benzyl glucoside and lyxoside.

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

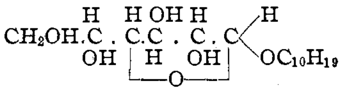
[2] E. Fischer and Piloty, *Ber.*, **24**, 521 (1891).

[3] Hudson, THIS JOURNAL, **31**, 66 (1909); **38**, 1566 (1916); **47**, 268 (1925). Bourquelot, *Ann. chim.*, **7**, 219 (1917). Maltby, *J. Chem. Soc.*, **123**, 1404 (1923).

[4] Hudson, THIS JOURNAL, **46**, 483 (1924).

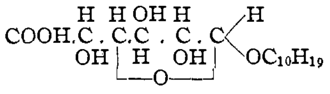
It seems desirable to extend the study to glycosides of diverse types because, if it should be found that the principle applies generally to them, the method of comparing rotations can be used in classifying the structures of the members of this large group of natural products.

The present article deals with the rotations of a group of glycosides of the related terpene alcohols, menthol and borneol. The *d*-glucosides of these alcohols have been synthesized in the past and although they have not as yet been isolated from plants or animals it seems quite probable that they may occur naturally. When menthol or borneol is fed to animals it is eliminated in the urine in the form of the corresponding glycoside of glucuronic acid; thus *l*-menthol yields *l*-menthyl-glucuronic acid. Bergmann and Wolff[5] have recently supplied conclusive proof that this substance is a β-glycoside. Starting with the alpha form of *l*-menthyl glucoside (Structure I) they oxidized it *in vitro* by means of bromine in alkaline solution and obtained an α-*l*-menthyl-glucuronic acid (Structure II) that is isomeric rather than identical with the older *l*-menthyl-glucuronic acid, which must accordingly be classed as the beta form. They mention that the strong dextrorotation of their alpha compound in contrast with the levorotation of the older form agrees with this classification. It is possible to develop this idea in a quantitative way and it will now be shown that Bergmann and Wolff's data prove that the principle of optical superposition applies, in first approximation at least, to the menthyl glucosides and the menthyl-glucuronic acids and indicate that it probably applies likewise to the bornyl glucosides described by E. Fischer and Raske and Hämäläinen.



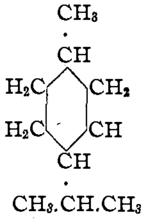
$$\mathrm{CH_2OH.\underset{OH}{\overset{H}{C}}\,.\,\underset{H}{\overset{H}{C}}.\underset{OH}{\overset{OH}{C}}\,.\,\overset{H}{C}\,.\,C{<}^{H}_{OC_{10}H_{19}}}$$

α-Menthyl *d*-glucoside (I)



$$\mathrm{COOH.\underset{OH}{\overset{H}{C}}\,.\,\underset{H}{\overset{H}{C}}.\underset{OH}{\overset{OH}{C}}\,.\,\overset{H}{C}\,.\,C{<}^{H}_{OC_{10}H_{19}}}$$

α-Menthyl *d*-glucuronic acid (II)



Menthyl radical ($C_{10}H_{19}$)

The Menthyl and Bornyl Glucosides and the Menthyl-glucuronic Acids

Consider the molecular rotation of *α-l-menthyl d-glucoside*, of Structure I. Let the rotation of the basal glucose chain be b_{glucose}, that of the terminal asymmetric carbon atom a_{menthyl}, and that of the menthyl radical, which is optically active due to the presence of three asymmetric carbon atoms, be $-c_{\text{menthyl}}$. Assuming that the principle of optical superposition holds, the rotation of the *β-l-menthyl d-glucoside* may be

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[5] Bergmann and Wolff, *Ber.*, **56B**, 1060 (1923).

referred to the same component rotations with the sign of a_{menthyl} reversed. For the alpha and beta forms of *l-menthyl-d-glucuronic acid* (see the Structure II of the alpha form) let the three components of the rotations be $b_{\text{glucuronic}}$, a_{menthyl} and $-c_{\text{menthyl}}$, similarly. In Table I the comparison of the rotations of the four substances in alcoholic solution is recorded, using the data of the literature.

TABLE I

COMPARISON OF THE MOLECULAR ROTATIONS OF THE MENTHYL AND BORNYL GLUCOSIDES AND MENTHYL-GLUCURONIC ACIDS IN ALCOHOL

Substance	$[\alpha]_D$	Molecular rotation	Diff./2	Sum/2
α-*l*-Menthyl glucoside[6]	64.2	$20{,}400 = b_{\text{glu}} + a_{\text{mth}} - c_{\text{mth}}$	25,100	−4700
β-*l*-Menthyl glucoside[6] (mol. wt., 318)	−93.7	$-29{,}800 = b_{\text{glu}} - a_{\text{mth}} - c_{\text{mth}}$	(a_{mth})	$(b_{\text{glu}} - c_{\text{mth}})$
α-*l*-Menthyl-glucuronic acid[5]	51.8	$17{,}200 = b_{\text{glr}} + a_{\text{mth}} - c_{\text{mth}}$	25,950	−8750
β-*l*-Menthyl-glucuronic acid[7] (mol. wt., 332)	−104.6	$-34{,}700 = b_{\text{glr}} - a_{\text{mth}} - c_{\text{mth}}$	(a_{mth})	$(b_{\text{glr}} - c_{\text{mth}})$
β-*d*-Bornyl glucoside[8]	−44.6	$-14{,}100 = b_{\text{glu}} - a_{\text{brn}} + c_{\text{brn}}$	2450	−16,550
β-*l*-Bornyl glucoside[9] (mol. wt., 316)	−60.1	$-19{,}000 = b_{\text{glu}} - a_{\text{brn}} - c_{\text{brn}}$	(c_{brn})	$(b_{\text{glu}} - a_{\text{brn}})$

(The subscripts glucose, glucuronic, menthyl and bornyl are abbreviated.)

It will be seen that the values of a_{menthyl} obtained independently, in one case from the glucosides and in the other from the glucuronic acids, agree closely (25,100 and 25,950), the difference of 850 corresponding to less than three degrees in specific rotation. The data refer to alcoholic solutions but the measurements were all made in the same solvent and it has been shown[10] that optical superposition holds for alcoholic solutions in the case of the acetyl derivatives of the methyl glucosides. The average value $a_{\text{menthyl}} = 25{,}500$ may therefore be accepted for alcoholic solution.

From the last column of Table I $b_{\text{glucose}} - c_{\text{menthyl}} = -4700$ in alcohol. The value of b_{glucose} in water is 11,880 (see Part VII) and the value in alcohol is doubtless nearly the same, since such is the case for 80% alcohol and for absolute methyl alcohol.[11] Subtracting this value leaves $c_{\text{menthyl}} = 16{,}600$ as a provisional value in alcoholic solution. It is possible from the knowledge of the values of these two coefficients to calculate approximately the rotations of the alpha and beta forms of a large

[6] E. Fischer and Bergmann, *Ber.*, **50**, 711 (1917). See also Ref. 8.

[7] H. Fischer, *Z. physiol. Chem.*, **70**, 262 (1911).

[8] E. Fischer and Raske, *Ber.*, **42**, 1465 (1909). Their value of the rotation of the monohydrate has been here increased to refer to the anhydride.

[9] Hämäläinen, *Biochem. Z.*, **50**, 209 (1913).

[10] Hudson and Dale, THIS JOURNAL, **37**, 1264 (1915).

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

number of menthyl glycosides of the reducing sugars for which the respective values of b in water are known, about 60 menthyl glycosides in all. The calculations are illustrated by examples in the next section of this article.

From bromo-acetyl glucose and *d*-borneol Fischer and Raske prepared *d*-bornyl glucoside and similarly from *l*-borneol Hämäläinen made *l*-bornyl glucoside. From the method of synthesis (Koenigs and Knorr's) and the fact that emulsin hydrolyzes both glucosides it is almost certain that they are beta compounds. From the formulation of their molecular rotations in Table I the value $b_{glucose} - a_{bornyl} = -16{,}550$ in alcohol is found and hence $a_{bornyl} = 28{,}400$ as a provisional value. This coefficient has about the same value as that found previously for $a_{menthyl}$ (25,100), a result which is to be expected because menthol and borneol have similar structures and nearly the same molecular weights. The agreement proves that the bornyl glucosides are beta compounds, as assumed.

It is obvious that these calculations can be extended to compounds such as fenchyl glucoside and fenchyl-glucuronic acid, the similar derivatives of phloroglucinol and many others.[12] At the present time, however, the rotations of such compounds are not known in a common solvent and accordingly the calculations must be deferred until the necessary experimental data are obtained.

Menthyl Maltoside and Menthyl Lactoside

These glycosides have been prepared by E. Fischer and H. Fischer through Koenigs and Knorr's synthesis, which makes it probable that they are beta forms. This conclusion is supported by the fact that menthyl lactoside is hydrolyzed by emulsin to yield menthol and lactose, according to H. Fischer. In Table II the calculated rotations of these glycosides are recorded in comparison with the observed values. The agreement shows that both glycosides are beta forms, since the calculated values have been obtained on that assumption. For comparison the calculated rotations of the corresponding alpha forms are shown; the results leave no doubt concerning the classifications. It should be mentioned that the observed rotations refer to aqueous solutions, whereas the calculated values are based upon the coefficients applying to alcoholic solutions, but it is improbable that this difference affects the conclusions.

The rotations of the two forms of *l*-menthyl gentiobioside and of *d*-menthyl gentiobioside, which have not yet been prepared, are calculated for the purpose of illustrating the method. The values of $b_{maltose}$ and $b_{lactose}$ are taken from Part VII, that of $b_{gentiobiose}$ from Part III.

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[12] For numerous references to the known derivatives of glucuronic acid see Abderhalden's "Biochemisches Handlexikon," Vols. 2, 8 and 10, under the title "glucuronic acid."

TABLE II

CALCULATED PROVISIONAL ROTATIONS OF THE MENTHYL MALTOSIDES, LACTOSIDES AND GENTIOBIOSIDES

Substance	Calculated molecular rotation	$[\alpha]_D$ Calcd.	Obs.
α-*l*-Menthyl maltoside	$b_{maltose} + a_{mth} - c_{mth} = 48{,}900 + 25{,}100 - 16{,}600$	+120	
β-*l*-Menthyl maltoside (mol. wt., 480)	$b_{maltose} - a_{mth} - c_{mth} = 48{,}900 - 25{,}100 - 16{,}600$	+15	+14[13]
α-*l*-Menthyl lactoside	$b_{lactose} + a_{mth} - c_{mth} = 20{,}470 + 25{,}100 - 16{,}600$	+60	
β-*l*-Menthyl lactoside	$b_{lactose} - a_{mth} - c_{mth} = 20{,}470 - 25{,}100 - 16{,}600$	−44	−38[7]
α-*l*-Menthyl gentiobioside	$b_{gnbiose} + a_{mth} - c_{mth} = 4{,}100 + 25{,}100 - 16{,}600$	+26	
β-*l*-Menthyl gentiobioside	$b_{gnbiose} - a_{mth} - c_{mth} = 4{,}100 - 25{,}100 - 16{,}600$	−78	
α-*d*-Menthyl gentiobioside	$b_{gnbiose} + a_{mth} + c_{mth} = 4{,}100 + 25{,}100 + 16{,}600$	+95	
β-*d*-Menthyl gentiobioside	$b_{gnbiose} - a_{mth} + c_{mth} = 4{,}100 - 25{,}100 + 16{,}600$	− 9	

6,x-Anhydro-*l*-Menthyl Glucoside

By the interaction of 1,6-dibromo-2,3,5-triacetyl glucose (dibromo-acetyl glucose, of Structure XVI, Part I[14]) and *l*-menthol, E. Fischer and Zach[15] prepared 6-bromo-2,3,5-triacetyl-menthyl glucoside, which is probably a beta form on account of its origin by Koenigs and Knorr's synthesis. By boiling it with alcoholic sodium hydroxide solution the acetyl groups were removed in the usual way but the bromine atom formed hydrobromic acid and there resulted an internal anhydride of menthyl glucoside, its Carbon 6 being united through an oxygen atom to some other carbon atom of the chain, the identity of which is at present not known. They suggest the rings 6,5 and 6,3 as probabilities. On account of the uncertainty this substance will be here referred to as 6,x-anhydro-menthyl glucoside. If the rotation of its basal chain be b_x its molecular rotation (mol. wt., 300; $[\alpha]_D = -96$ in alcohol; hence $[M]_D = -28{,}800$) may be written $b_x - a_{menthyl} - c_{menthyl} = b_x - 25{,}100 - 16{,}600 = -28{,}800$, and hence $b_x = 12{,}900$ in alcohol. Now, from dibromo-acetyl glucose and methyl alcohol E. Fischer and Armstrong[16] have prepared 6-bromo-2,3,5-triacetyl methyl glucoside, doubtless a beta compound, and by boiling this with an aqueous-alcoholic solution of barium hydroxide E. Fischer and Zach have made an anhydro methyl glucoside, which will be

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[13] E. Fischer and H. Fischer, *Ber.*, **43**, 2521 (1910).

[14] Hudson, THIS JOURNAL, **46**, 462 (1924).

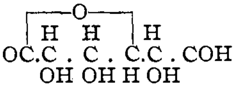
[15] E. Fischer and Zach, *Ber.*, **45**, 456 (1912).

[16] Fischer and Armstrong, *Ber.*, **35**, 833 (1902).

designated here as 6,y-anhydro-methyl glucoside. The question arises, is y the same as x, that is, does this anhydro-methyl glucoside possess the same anhydro ring as the anhydro-menthyl glucoside previously mentioned? If such is the case, it should be possible to calculate the rotation of the anhydro-methyl glucoside from the value of b_x that has just been found from the rotation of the anhydro-menthyl glucoside. If the substance is a β-glycoside, as seems probable, its specific rotation is calculated to be $(b_x - a_{\text{methyl}}) \div$ mol. wt. $= (12{,}900 - 18{,}500$[17]$) \div 176 = -32$, while if it is an alpha form $(b_x + a_{\text{methyl}}) \div$ mol. wt. $= +178$. Fischer and Zach purified their 6,y-anhydro-methyl glucoside by distillation in a high vacuum and the uncrystallizable sirup showed $[\alpha]_D = -137$. This value is so greatly different from those calculated that it appears probable that the assumption of the identity of x and y is incorrect and that on the contrary the two anhydro-glucosides should be regarded as derivatives of anhydro-glucoses of different structures. Possibly one is a 6,5- and the other a 6,3-anhydro-glucose.

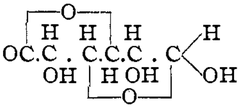
The Crystalline Lactone of *d*-Glucuronic Acid

The configuration of this lactone may be regarded as shown in III in case the aldehyde formula of glucose is assumed, or as in IV if the Tollens formula for glucose is accepted. Attention may be called to the asymmetry of Carbon 1 in Structure IV, the possible significance of which seems to have escaped notice in the past. It is obvious that if this structure applies, the occurrence of the lactone in alpha and beta forms similar to those of glucose becomes a possibility.



$$\begin{array}{l} \quad\ulcorner\!-\!\mathrm{O}\!-\!\urcorner \\ \quad\;\mathrm{H\;\;\;H\;\;\;\;H} \\ \mathrm{OC.C\;.\;C\;.\;C.C\;.\;COH} \\ \quad\mathrm{OH\;OH\;H\;OH} \end{array}$$

(III)



$$\begin{array}{l} \quad\ulcorner\!-\!\mathrm{O}\!-\!\urcorner \\ \quad\;\mathrm{H\;\;H\;\;H\;\;\;\;\;\;\;H} \\ \mathrm{OC.C\;.\;C.C.C\;.\;C}\!\!<\!\! \\ \quad\mathrm{OH\;\;H\;OH\;\;\;\;\;\;OH} \\ \qquad\;\llcorner\!-\!\mathrm{O}\!-\!\lrcorner \end{array}$$

(IV)

In like manner it is conceivable that the salts, amides and many other derivatives of glucuronic acid may occur in similar alpha and beta forms. Such isomers may be found to exhibit mutarotation.

Summary of Results

It has been shown from the data of the literature that van't Hoff's principle of optical superposition applies to the rotations of the menthyl glucosides, maltosides, lactoside and the menthyl-glucuronic acids and probably also to the bornyl glucosides. The calculations supplement those of Part III in illustrating how the method of comparing rotations can be applied to glycosides of optically active alcohols. The conclusion that the menthyl-glucuronic acids conform to the principle makes it probable that it applies in general to the numerous conjugated glucuronic acids that have been found to be eliminated in the urine under normal or experi-

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[17] This value of a_{methyl} in water is taken from Part VII.

mental conditions of feeding. On the basis of rotatory data it seems unlikely that 6,x-anhydro-menthyl glucoside and 6,y-anhydro-methyl glucoside are derivatives of the same anhydro-glucose. Lastly, it is pointed out on theoretical grounds that glucuronic lactone and the salts, amides, etc., of glucuronic acid may possibly occur in two isomeric forms corresponding to the alpha and beta forms of glucose and may exhibit mutarotation.

WASHINGTON, D. C.

PROPOSED INTERNATIONAL RULES FOR NUMBERING ORGANIC RING SYSTEMS

BY AUSTIN M. PATTERSON

RECEIVED NOVEMBER 7, 1924 PUBLISHED FEBRUARY 5, 1925

Preface

In 1921, the author reported to the Board of Editors of the JOURNAL OF THE AMERICAN CHEMICAL SOCIETY that data upon organic ring systems and their systematic numbering had been accumulated in connection with the indexing of *Chemical Abstracts*, and asked whether it would be advisable to publish a catalog of such systems, in the JOURNAL or elsewhere. The Board decided that it would be, but felt it extremely desirable to secure beforehand a wide agreement among chemists as to the numberings.

A joint committee of the American Chemical Society and the National Research Council, consisting of J. F. Norris, *chairman*, M. T. Bogert, J. W. Kinsman, W. A. Noyes and A. M. Patterson, was appointed to cooperate with the author. Rules for numbering ring systems were drawn up and submitted to this Committee and later to the Committee on Organic Nomenclature of the International Union of Pure and Applied Chemistry, consisting of A. F. Holleman (Netherlands), *chairman*, A. J. Greenaway (Great Britain), R. Marquis (France), E. Paternò (Italy), A. Pictet (Switzerland) and A. M. Patterson (United States). They were also shown unofficially to the late Prof. Jacobson and to Dr. Stelzner, of Germany. Several drafts were made and much improvement resulted from the criticisms.

In their present form the Rules have been approved by the International Committee for a provisional period of two years, during which they will be open for the criticism of chemists generally. At the end of that period, if no fundamental objections are found to the Rules, the expectation is that they will be finally adopted for use in the journals of the respective countries, with any further improvements or corrections that may have been suggested.

Considerable time has been given to devising a set of Rules that shall be applicable to all systems of simple or fused rings and yet be as simple and