or $(+52 - 5)\ 678 \div 2 = 15{,}900$.[50] The specific rotation of α-bromo-acetyl gentiobiose may be written $(B_{gentiobiose} + A_{Br}) \div$ mol. wt. $= (15{,}900 + 59{,}300) \div 699 = +108$ in chloroform.

In concluding I express the hope that others may assist as occasion presents itself in revising to higher accuracy the large amount of data that are considered in this article. For the extension of this method of treatment of constitutional questions in the sugar group it is desirable that the rotations of new substances be measured in water or in chloroform solution.

WASHINGTON, D. C.

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

RELATIONS BETWEEN ROTATORY POWER AND STRUCTURE IN THE SUGAR GROUP. II.[2] THE HALOGEN-ACETYL DERIVATIVES OF A KETOSE SUGAR (*d*-FRUCTOSE)

BY C. S. HUDSON

RECEIVED NOVEMBER 14, 1923

In Part I it was shown that Van't Hoff's hypothesis of additive optical superposition holds for many diverse types of acyl derivatives of the various aldose sugars. In seeking to determine the applicability of this principle to similar compounds of the ketose sugars one meets the difficulty that only a few such derivatives have ever been prepared. The number of known crystalline ketoses is itself rather small, fructose, sorbose, tagatose, perseulose, manno-keto heptose and sedoheptose making up the list, and for only one of them, namely fructose, have acyl derivatives been described in sufficient number to permit a test of the principle. D. H. Brauns has prepared fructose tetra-acetate,[3] two chloro-acetyl fructoses,[4] and quite recently he has described fluoro-acetyl and bromo-acetyl fructose.[5] Hudson and Brauns[6] have described a methyl fructoside and its tetra-acetate, and two penta-acetates of fructose, and Hudson and Yanovsky[7] have prepared β-fructose in pure condition. From a comparison of the structures and rotations of these substances a substantial beginning can be made in applying the principle of optical superposition to the ketoses and

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

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

[2] Part I immediately precedes this article.

[3] Brauns, *Verslag. Akad. Wetenschappen Amsterdam*, **1908**, p. 577. See also THIS JOURNAL, **37**, 2736 (1915).

[4] Brauns, THIS JOURNAL, **42**, 1846 (1920).

[5] Brauns, *ibid.*, **45**, 2381 (1923).

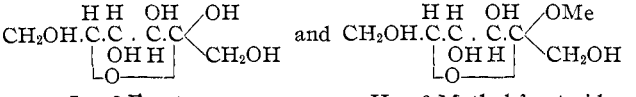
[6] Hudson and Brauns, *ibid.*, **38**, 1216 (1916); **37**, 1283, 2736 (1915).

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

their acyl derivatives. The method of comparison is that which has been used in Part I.

The Rotations of Beta-Fructose and Beta-Methyl Fructoside

Pure crystalline β-fructose, so designated[8] because it exhibits mutarotation in the dextro direction, shows $[\alpha]_D^{20} = -133$ in aqueous solution. By acetylating this crystalline substance at low temperature with acetic anhydride and zinc chloride Brauns prepared crystalline tetra-acetyl fructose in good yield; $[\alpha]_D^{20}$ was −91.6 in chloroform solution.[9] The methylation of this tetra-acetate by Purdie and Irvine's method (with methyl iodide and silver oxide) yielded crystalline tetra-acetyl methyl fructoside of $[\alpha]_D^{20} = -125$ in chloroform solution, and the removal of the acetyl groups from the latter compound by alkali yielded crystalline methyl fructoside, of $[\alpha]_D^{20} = -172$ in water. The last substance was known to be a fructoside because it did not reduce Fehling's solution. As its rotation is more levo than that of β-fructose it was designated β-methyl fructoside, and its tetra-acetate and the fructose tetra-acetate which was used in the methylation were accordingly also allocated to the beta series. These synthetical relations appear to give a series of beta compounds starting with β-fructose and ending with its β-methyl fructoside, and it is almost certain that the four members of the series have the same ring structure. While the position of the ring is not known, it will be written for the sake of definiteness as a butylene linkage with the understanding that the present argument really does not involve any assumption of the location of this ring and would apply without change in case the ring is in some other than the butylene position. The structures of β-fructose and β-methyl fructoside are written



I. β-Fructose and II. β-Methyl fructoside

and the molecular rotation of I is $(b'_{fructose} - a'_{OH})$, where a'_{OH} represents the rotation of Carbon 2, the asymmetric carbon at the right hand end of the ring, and $b'_{fructose}$ designates the rotation of the remainder of the structure, comprising asymmetric carbon atoms 3, 4 and 5. In similar manner the molecular rotation of II is $(b'_{fructose} - a'_{Me})$, and the difference of the molecular rotations of I and II is then $(b'_{fructose} - a'_{OH}) - (b'_{fructose} - a'_{Me}) = a'_{Me} - a'_{OH}$. Compare the similar difference for β-glucose and its β-methyl glucoside; their molecular rotations may be written $(B'_{glucose} - A'_{OH})$ and $(B'_{glucose} - A'_{Me})$ respectively, and the difference is $(A'_{Me} - A'_{OH})$.

[8] Hudson, THIS JOURNAL, **31**, 77 (1909).

[9] Private communication from Dr. Brauns.

TABLE I

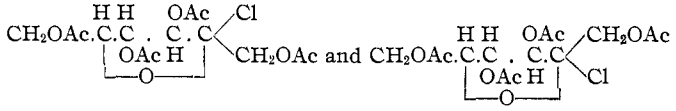
COMPARISON OF THE MOLECULAR ROTATIONS OF β-GLUCOSE, β-FRUCTOSE AND THEIR β-METHYL GLUCOSIDIC DERIVATIVES

Substance	Mol. wt.	$[\alpha]_D^{20}$ in water	$[M]_D^{20}$	Difference
β-*d*-Glucose	180	+ 19	+ 3,400	$+9600 = (A'_{Me} - A'_{OH})$
β-*d*-Methyl glucoside	194	− 32	− 6,200	
β-*d*-Fructose	180	−133	−23,900	$+9500 = (a'_{Me} - a'_{OH})'$
β-*d*-Methyl fructoside	194	−172	−33,400	

The difference is the same in both magnitude and sign for the ketose and the aldose. From independent evidence which will be presented in the next section it is probable that $A'_{Me} = a'_{Me}$ and $A'_{OH} = a'_{OH}$. If such is the case the substitution of —CH_2OH for —H on asymmetric carbon atom 2 does not change the rotation. On the other hand, the equality that is proved by the values in Table I would still hold provided the indicated substitution caused the same change of rotation in both β-fructose and its methyl fructoside.

The Rotations of the Two Chloro-Acetyl Fructoses

Brauns has prepared from tetra-acetyl fructose two isomeric chloro-acetyl fructoses which he has provisionally designated as α and β forms of the same ring structure. As it will appear from what follows that Brauns' allocations should be reversed, it seems desirable to designate provisionally the one having $[\alpha]_D^{20} = -161$ in chloroform as the first chloro-acetyl fructose, and the one having $[\alpha]_D^{20} = +45$ in chloroform as the second chloro-acetyl fructose. The first chloro-acetyl fructose was made from fructose tetra-acetate by the action of acetic anhydride with phosphorus pentachloride and aluminum chloride, while the second one resulted when the aluminum chloride was omitted. In agreement with Brauns it is here assumed that the isomers constitute an α,β pair and their structures are written with the same ring that was assumed for the parent tetra-acetate, thus,



III. First chloro-acetyl fructose IV. Second chloro-acetyl fructose

Their molecular rotations are written ($a_{fructose} - a_{Cl}$) and ($a_{fructose} + a_{Cl}$), the meaning of the symbols being apparent from what precedes. One-half the difference of these molecular rotations is a_{Cl}, which gives the value of a_{Cl} for an acetylated ketose and permits a comparison with the value of the similar A_{Cl} for the aldoses, which was found in Part I to be about +37,800.

The value of a_{Cl} for the ketose is the same in both magnitude and sign as that of A_{Cl} for the aldoses. This is good evidence that the substitution

of —CH_2OAc for —H does not change the rotation of carbon atom 2. Since the second chloro-acetyl fructose is more dextrorotatory than the first one it should be designated the α form and the first one the β form, thus reversing the naming which Brauns provisionally proposed.

TABLE II

COMPARISON OF a_{Cl} FOR A KETOSE (*d*-FRUCTOSE) WITH A_{Cl} FOR THE ALDOSES

Substance	Mol. wt.	$[\alpha]_D^{20}$ in $CHCl_3$	$[M]_D^{20}$	A_{Cl}	A_{Cl} for the aldoses	$A_{fructose}$[a]
Second chloro-acetyl fructose (α form).....	366	+ 45	+16,500	+37,700	+37,800	—21,200
First chloro-acetyl fructose (β form).....	366	—161	—58,900	....	....	....

[a] The rotation under this heading is one-half the sum of the molecular rotations of column four, and is here appended for later reference.

The Rotations of Fluoro-Acetyl and Bromo-Acetyl Fructose

In considering the rotations of these compounds the calculations are made slightly differently, following a method that was used frequently in Part I. Brauns prepared the substances from β-fructose penta-acetate (see below) which is a derivative in its turn of the fructose tetra-acetate previously mentioned. They probably have the same structure as the first (or β) chloro-acetyl fructose, III with the Cl atom replaced by F or by Br; the proof of this allocation will appear in the calculations. The rotation of the acetylated basal chain of fructose is one-half the sum of the molecular rotations of the first and second chloro-acetyl fructoses, $a_{fructose} = [(a_{fructose} + a_{Cl}) + (a_{fructose} - a_{Cl})] \div 2 = -21{,}200$ (see Table II). Since the molecular rotation of fluoro-acetyl fructose is more negative than $a_{fructose}$ (see Table III) the substance should be designated a β form and its rotation written $(a_{fructose} - a_F)$, and similarly the rotation of bromo-acetyl fructose becomes $(a_{fructose} - a_{Br})$. From the values of these rotations the coefficients a_F and a_{Br} are obtained, and in Table III they are recorded in comparison with the similar values for the aldose derivatives.

TABLE III

COMPARISON OF THE VALUES OF a_F AND a_{Br} FOR A KETOSE (*d*-FRUCTOSE) WITH THE SIMILAR VALUES FOR THE ALDOSES

Substance	Mol. wt.	$[\alpha]_D^{20}$ in $CHCl_3$	$[M]_D^{20}$	$a_{fructose} - [M]_D^{20}$	Aldose coefficients
Fluoro-acetyl fructose.....	350	— 90	—31,500	+10,500 (a_F)	+ 9,800 (A_F)
Bromo-acetyl fructose.....	411	—189	—77,700	+56,500 (a_{Br})	+59,300 (A_{Br})

Here again the derivatives of the ketose show the same coefficients as do those of the aldoses. In further support of the conclusion that the fluoro-acetyl and bromo-acetyl fructoses and the first chloro-acetyl fructose are beta compounds it is observed that the rotation of the end asymmetric

carbon atom increases in the levo direction with increasing weight of the halogen, the three values being $-a_F = -9800$, $-a_{Cl} = -37{,}700$, and $-a_{Br} = -56{,}500$, whereas the similar progression for the halogen-acetyl glucoses, which belong to the alpha series (see Part I), is a change in the dextro direction. This independent method of deciding the assignment of compounds to the alpha or beta series is here emphasized, as it will be used in later articles in some cases where other methods cannot be applied.

The Rotation of β-Tetra-Acetyl Methyl Fructoside

The $[\alpha]_D^{20}$ of this compound, which has been mentioned previously, is —125 in chloroform and its molecular weight is 362. Its structure is that of II with the four hydroxyl groups replaced by acetate groups, and accordingly its molecular rotation is written $(a_{fructose} - a_{Me}) = (-125)\ 362 = -45{,}200$. Subtracting $a_{fructose}$ (—21,200) gives $a_{Me} = 24{,}000$, which is in fair agreement with the value of $A_{Me} = 26{,}900$, obtained in Part I for the aldose series.

The Rotations of the Two Isomeric Penta-Acetates of Fructose

By analogy with the halogen-acetyl compounds of fructose it is to be expected that two fructose penta-acetates can exist, having the structures of III and IV with the chlorine atom replaced by acetate group. The rotations of these compounds will now be calculated and the results compared with the rotations of the two fructose penta-acetates that Hudson and Brauns have described. Since the values of a_F, a_{Cl} and a_{Br} in the fructose group have been found to be equal to the corresponding values for the aldose group it seems safe to assume that $a_{ac} = A_{ac} = +19{,}100$ from Part I. The molecular rotation of α-fructose penta-acetate (mol. wt., 399) then becomes $a_{fructose} + a_{ac} = -21{,}200 + 19{,}100 = -2100$; that of β-fructose penta-acetate $-21{,}200 - 19{,}100 = -40{,}300$ and the $[\alpha]_D^{20}$ values for the two substances become $-2100 \div 399 = -5$ and $-40{,}300 \div 399 = -103$, respectively, in chloroform. The two known penta-acetates of fructose show $[\alpha]_D^{20} = +34.7$ and —121 in chloroform, respectively. It seems very unlikely that the dextrorotatory penta-acetate can be the expected α-form; possibly it has a ring structure different from that of the compounds hitherto considered. The other known penta-acetate, of $[\alpha]_D^{20} = -121$, may be the expected β form, though the difference of 18° in specific rotation makes such a conclusion uncertain. The fact that the fluoro-acetyl and bromo-acetyl fructoses, the rotations of which fit in normally in the calculations, were prepared by Brauns from this penta-acetate seems good evidence that it is the expected β form. Further study of these penta-acetates and the conversion of the halogen-acetyl fructoses into penta-acetates will doubtless clear up the present uncertainty.

Discussion of the Conclusions

While the derivatives of fructose have been shown to yield the same coefficients for the rotations of carbon atom 2 as do the aldose derivatives for their similarly constituted carbon atom 1, in another respect they differ markedly from aldose compounds, and this difference will doubtless be found to be a general characteristic of ketose derivatives. Reference is made to the exhibition of mutarotation. Fructose itself mutarotates, as do the aldoses. But fructose tetra-acetate does not exhibit this change, though glucose tetra-acetate does, and likewise it has not been possible to change either penta-acetate of fructose to an isomeric form by heating in acetic anhydride containing zinc chloride, a reaction which proceeds readily with the similar aldose acetates. This difference makes the synthesis of acyl compounds of fructose quite a different problem from that of the aldose derivatives. Thus the known levorotatory penta-acetate of fructose, which has been allocated to the β-series, cannot be transformed by this reaction to its expected α isomer. The other known penta-acetate, of dextrorotation, was made from fructose tetra-acetate by the action of acetic anhydride and sulfuric acid, a method of preparation that gives little evidence regarding the structure of the substance.

It has been shown in Part I that in the aldose series the known halogen-acetyl derivatives are alpha compounds, with the one exception of the second chloro-acetyl galactose, which is a beta form. In the ketose series, as represented by fructose, the known fluoro-acetyl and bromo-acetyl fructoses are beta compounds, while for chloro-acetyl fructose both the alpha and beta forms have been prepared. Brauns has remarked on the great difference in stability between α-chloro-acetyl fructose and its β isomer, the chlorine in the α form being much more firmly held. He has also emphasized that bromo-acetyl fructose, which has now been shown to be a beta derivative, is a very unstable substance. By analogy one may expect that α-bromo-acetyl fructose will be more stable than its known isomer, and it seems possible that α-iodo-acetyl fructose might be of sufficient stability to permit its preparation, whereas Brauns' experience with β-bromo-acetyl fructose makes it doubtful whether β-iodo-acetyl fructose could be prepared, since the iodo-acetyl sugars are in general less stable than the bromo compounds.

This greater stability of the α-forms has a bearing on the question of the structure of the chloro-acetyl maltose that Freudenberg has described as a chloro-octa-acetyl maltose. In Part I it was suggested that this substance may be the expected β-chloro-hepta-acetyl maltose, since its rotation approaches the calculated value and the analytical data make a distinction between the hepta- and octa-acetate rather uncertain. Freudenberg emphasized that the substance is very reactive, exchanging its chlorine atom much more easily than the known chloro-acetyl maltose.

On comparing this behavior with that of β-chloro-acetyl fructose it does not appear anomalous and is indeed what would be expected of β-chloro-acetyl maltose.

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

RELATIONS BETWEEN ROTATORY POWER AND STRUCTURE IN THE SUGAR GROUP. III.[2] THE BIOSE OF AMYGDALIN (GENTIOBIOSE) AND ITS CONFIGURATION

BY C. S. HUDSON

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Haworth and Leitch[3] have recently applied Irvine's method of methylation and subsequent hydrolysis to the old problem of the determination of the structure of the biose of amygdalin, the glucoside of bitter almonds. It has long been known that the amygdalin molecule is composed of two molecules of *d*-glucose and one of *l*-mandelonitrile,

$$\underset{\text{(amygdalin)}}{C_{20}H_{27}O_{11}N} + 2\ H_2O = 2\ \underset{\text{(}d\text{-glucose)}}{C_6H_{12}O_6} + \underset{\text{(}l\text{-mandelonitrile)}}{C_6H_5.CHOH.CN}$$

By methylating amygdalin with dimethyl sulfate and sodium hydroxide solution it was transformed to the methyl ester of heptamethyl amygdalinic acid and this crystalline substance yielded on acid hydrolysis (1) *d,l*-mandelic acid, (2) 2,3,5,6-tetramethyl glucose and (3) a trimethyl glucose which was shown to have the methyl groups on Carbons 2, 3 and 5. The occurrence of racemic mandelic acid is explained by the racemizing and subsequent saponifying action of alkali on the *l*-mandelonitrile grouping in amygdalin. The tri- and tetramethyl glucoses that were found were the same substances that Haworth and Leitch[4] had previously isolated through the hydrolysis of fully methylated maltose, a fact which led them to express the conclusion:

"The disaccharide of amygdalin has therefore the structure of maltose and quite definitely cannot be cellobiose. For the stereochemical formulation of this maltose structure we are dependent on the researches of other workers on the selective action of enzymes, and here the results, if not conflicting, are certainly anomalous. Their results favor the view that the amygdalin biose is a glucose α-glucoside.....and therefore, on this reasoning, the biose itself must be maltose and amygdalin is mandelonitrile α-maltoside.....Should it ultimately be the case that the stereochemical representation of the biose is found to be that of a glucose β-glucoside, this cannot, of course, affect the structural formula we have herein ascribed to the sugar, but it may point to the identity of the amygdalin biose with isomaltose or gentiobiose."

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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 II immediately precedes this article.

[3] Haworth and Leitch, *J. Chem. Soc.*, **121**, 1921 (1922).

[4] Haworth and Leitch, *ibid.*, **115**, 809 (1919).