RELATIONS BETWEEN ROTATORY POWER AND STRUCTURE IN THE SUGAR GROUP. I. THE HALOGEN-ACYL AND NITRO-ACYL DERIVATIVES OF THE ALDOSE SUGARS

BY C. S. HUDSON

The extensive use of bromo-acetyl glucose in the accomplishment of syntheses in the sugar group makes the knowledge of its structure a matter of prime importance. At the present time it is considered to be a derivative of the beta form of the sugar and is designated β-bromo-acetyl glucose. In accordance with this view it is to be supposed that an isomeric α-bromo-acetyl glucose can exist, derivable from the α form of the hexose. Fischer and Armstrong[2] reported a description of two such forms of bromo acetyl, likewise of chloro-acetyl glucose, but Fischer's later work[3] in which he was unable to reproduce the preparation of the alpha forms of these compounds shows either that some detail of vital importance was not definitely recognized in the earlier research, or that the supposed alpha isomers were only impure crystals of the common beta forms.[4] The discovery of these so-called alpha forms, isomeric with the common β-halogen-acetyl glucoses, will unquestionably open a rich field of synthetic exploration in the sugar group. Since any evidence which relates to the constitution and properties of these compounds may be useful in aiding the attainment of their synthesis, the following comparison of the rotatory powers of various halogen-acyl sugars is presented. Anticipating some of the conclusions it may be stated that Van't Hoff's hypothesis of additive optical superposition holds, as a first approximation at least, among the halogen-acyl aldoses and that there is clear proof, based upon the application of this principle, that the common bromo-acetyl and chloro-acetyl glucoses are not beta compounds, as now accepted, but are alpha derivatives.

Consider the rotatory powers of the constituent asymmetric carbon atoms of the alpha and beta forms of glucose penta-acetate, the structural formulas of which are generally believed to be

$$CH_2OAc.C \overset{H}{\underset{OAc}{.}} C \overset{H}{\underset{|}{.}} C \overset{OAc}{\underset{H}{.}} C \overset{H}{\underset{OAc}{.}} C \overset{H}{\diagdown_{OAc}}$$, and $$CH_2OAc.C \overset{H}{\underset{OAc}{.}} C \overset{H}{\underset{|}{.}} C \overset{OAc}{\underset{H}{.}} C \overset{H}{\underset{OAc}{.}} C \overset{OAc}{\diagdown_{H}}$$

(Ac = CH_3—CO)

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

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

[3] Fischer, Ber., **44**, 1898 (1911).

[4] Kurt Hoesch, "Emil Fischer, sein Leben und sein Werk," Verlag Chemie, **1921**, p. 353. Emil Fischer, "Aus meinen Leben," J. Springer, Berlin, **1923**, p. 197.

Let the rotation of the terminal asymmetric carbon atom be written $+A_{Ac}$ for the alpha form and $-A_{Ac}$ for the beta modification and let the rotation of the remainder of the molecule, the acetylated basal chain that is common to both forms, be written $B_{glucose}$. The molecular rotation of the alpha form is then $(B_{glucose} + A_{Ac})$, that of the beta form is $(B_{glucose} - A_{Ac})$ and the value of $B_{glucose}$ is one-half the sum of the molecular rotations, that is, $[(B_{glucose} + A_{Ac}) + (B_{glucose} - A_{Ac})] \div 2 = B_{glucose}$.[5]

Bromo-acetyl glucose, which has been isolated with certainty in only one form, probably can exist in two modifications having structures similar to those of the glucose penta-acetates, namely,

$$\underset{OAc\ |\quad H\quad OAc\ |\quad \ ^{\backslash}Br}{\overset{H\quad H\quad OAc\ H\qquad ^{/}H}{CH_2OAc.C\ .\ C\ .\ C\ .\ C\ .\ C\!\!<}} \quad \text{and} \quad \underset{OAc\ |\quad H\quad OAc\ |\quad \ ^{\backslash}H}{\overset{H\quad H\quad OAc\ H\qquad ^{/}Br}{CH_2OAc.C\ .\ C\ .\ C\ .\ C\ .\ C\!\!<}}$$

the molecular rotations of which may be written $(B_{glucose} + A_{Br})$ and $(B_{glucose} - A_{Br})$, respectively. Subtracting $B_{glucose}$ from these leaves in the one case A_{Br} and in the other $-A_{Br}$, which shows that the numerical value of A_{Br} can be obtained from the rotations of the two glucose penta-acetates and the one known form of bromo-acetyl glucose without a knowledge of whether the bromo compound is an alpha or a beta derivative. Similar calculations may be applied to the rotations of chloro-acetyl glucose, iodo-acetyl glucose, nitro-acetyl glucose and the recently discovered fluoro-acetyl glucose,[6] as these compounds have the structure of bromo-acetyl glucose with the bromine atom replaced by chlorine, iodine, nitrate radical, or fluorine, respectively; and last, the calculations may be applied to the similar derivatives of other aldose sugars. We are thus in position to learn the values of the rotation of the terminal asymmetric carbon atom in the bromo-acetyl (A_{Br}), chloro-acetyl (A_{Cl}), iodo-acetyl (A_I), nitro-acetyl (A_{NO_3}), and fluoro-acetyl (A_F) aldose sugars. An example will indicate how these values are calculated from the data recorded in the accompanying two tables. Fluoro-acetyl xylose, for instance, shows a molecular rotation $[M]_D = (B_{xylose} + A_F) = + 18,600$ (Table II) and the rotation of the acetylated basal chain of xylose is $B_{xylose} = + 10,200$ (Table I), hence $A_F = ([M]_D - B_{xylose}) = + 8400$.

From the data recorded in the last two columns of Table II it may be concluded that *the rotation of the end asymmetric carbon atom of a halogen-acetyl or nitro-acetyl aldose is approximately a constant quantity for the various aldoses. The nitro group and each halogen give rise to the respective values:* $A_{NO_3} = 37,100$, $A_F = 9,800$, $A_{Cl} = 37,800$, $A_{Br} = 59,300$ and $A_I = 85,400$.

The rotations of certain of the substances mentioned in the tables require discussion. The value of the acetylated basal chain of *l*-rhamnose,

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[5] Hudson, THIS JOURNAL, **31**, 66 (1909).

[6] Brauns, *ibid.*, **45**, 833 (1923).

$B_{l\text{-rhamnose}} = -1,100$ (Table I), is obtained as half the sum of the molecular rotations of the alpha and beta forms of tri-acetyl-methyl-l-

TABLE I
THE VALUES OF THE QUANTITY B, THE ROTATION OF THE ACETYLATED BASAL CHAIN, FOR VARIOUS FULLY ACETYLATED ALDOSE SUGARS

Substance	$[\alpha]_D$ in chloroform	Molecular rotation	B = half the sum of the molecular rotations
α-d-glucose penta-acetate[7]	+102	+39,800	+20,700 (B$_{glucose}$)
β-d-glucose penta-acetate (mol. wt. 390)	+ 4	+ 1,600	
α-d-mannose penta-acetate	+ 55	+21,400	+ 5,800 (B$_{mannose}$)
β-d-mannose penta-acetate (mol. wt. 390)	− 25	− 9,800	
α-d-galactose penta-acetate	+107	+41,700	+25,400 (B$_{galactose}$)
β-d-galactose penta-acetate (mol. wt. 390)	+ 23	+ 9,000	
α-d-xylose tetra-acetate	+ 89	+28,300	+10,200 (B$_{xylose}$)
β-d-xylose tetra-acetate (mol. wt. 318)	− 25	− 7,900	
α-d-maltose octa-acetate	+122	+82,700	+62,700 (B$_{maltose}$)
β-d-maltose octa-acetate (mol. wt. 678)	+ 63	+42,700	
α-d-lactose octa-acetate	+ 54	+36,600	+16,900 (B$_{lactose}$)
β-d-lactose octa-acetate (mol. wt. 678)	− 4	− 2,700	
α-d-cellobiose octa-acetate	+ 41	+27,800	+ 8,800 (B$_{cellobiose}$)
β-d-cellobiose octa-acetate (mol. wt. 678)	− 15	−10,200	

To these are appended for later reference

Substance	$[\alpha]_D$ in chloroform	Molecular rotation	B = half the sum of the molecular rotations
4th galactose penta-acetate	+ 61	+23,800	+ 3,700 (B'$_{galactose}$)
3rd galactose penta-acetate (mol. wt. 390)	− 42	−16,400	
α-methyl l-rhamnoside triacetate[8]	− 53	−16,100	− 1,100 (B$_{l\text{-rhamnose}}$)
β-methyl l-rhamnoside triacetate[8] (mol. wt. 304)	+ 46	+14,000	

TABLE II
THE VALUES OF THE QUANTITY A, THE ROTATION OF THE END ASYMMETRIC CARBON ATOM, FOR THE HALOGEN-ACETYL AND NITRO-ACETYL ALDOSE SUGARS

Substance	Mol. wt.	$[\alpha]_D$ in CHCl$_3$	Molecular rotation $[M]_D$	Rotation of end carbon[a] A = $[M]_D$ − B	Av. A
Fluoro-acetyl xylose[7]	278	+ 67	+ 18,600	+ 8,400	⎫
Fluoro-acetyl glucose[7]	350	+ 90	+ 31,500	+10,800	⎬ + 9,800
Fluoro-acetyl cellobiose[7]	638	+ 30	+ 19,100	+10,300	⎭ (A$_F$)

[7] The references for the fully acetylated sugars are   (a) Hudson and Johnson, THIS JOURNAL, **37**, 1270 (1915), (lactose); (b) **37**, 1276 (1915), (cellobiose and maltose); (c) **37**, 2748 (1915), (xylose); (d) **38**, 1224 (1916), (galactose).   (e) Hudson and Dale, *ibid.*, **37**, 1264 (1915), (glucose); (f) **37**, 1280 (1915), (mannose).

[8] (a) Fischer, Bergmann and Rabe, *Ber.*, **53**, 2362 (1920).   (b) The rotations were measured in acetylene tetrachloride, CHCl$_2$.CHCl$_2$, but their values in chloroform, CHCl$_3$, are probably nearly the same.   See note b of Table II.

Chloro-acetyl xylose[9].........	294	+165	+ 48,500	+38,300	} +37,800
Chloro-acetyl glucose[10]........	366	+166	+ 60,800	+40,100	(A$_{Cl}$)
Chloro-acetyl mannose[11]	366	+ 90	+ 32,900	+27,100	(Excluding the
Chloro-acetyl lactose[12]........	654	+ 72	+ 47,100	+30,200	value for
Chloro-acetyl maltose[13]........	654	+159	+104,000	+41,300	chloro - acetyl[1]
Chloro-acetyl cellobiose[14].......	654	+ 73	+ 47,700	+38,900	} mannose)
Bromo-acetyl xylose[15].........	339	+212	+ 71,900	+61,700	
Bromo-acetyl glucose[16]........	411	+198	+ 81,400	+60,700	} +59,300
Bromo-acetyl cellobiose[17].......	699	+ 96	+ 67,100	+58,300	(A$_{Br}$)
Bromo-acetyl lactose[18]........	699	+105	+ 73,400	+56,500	}
Iodo-acetyl glucose[18,b]........	458	+232	+106,300	+85,600	} +85,400
Iodo-acetyl cellobiose[17]........	746	+126	+ 94,000	+85,200	} (A$_I$)
Nitro-acetyl glucose[19]..........	393	+149	+ 58,600	+37,900	
Nitro-acetyl galactose[20]........	393	+153	+ 60,100	+34,700	} +37,100
Nitro-acetyl maltose[21]..........	681	+149	+101,500	+38,800	} (A$_{NO_3}$)

To these are appended for special discussion later

Bromo-acetyl l-rhamnose[22]......	353	− 169	−59,700	− 58,600
First chloro-acetyl galactose[23]...	366	+212	+77,600	+52,200
Second chloro-acetyl galactose[24].	366	− 78	−28,500	−32,200

[a] The values of B are taken from Table I, each sugar having its own value. For galactose there are two values of B, derived respectively from the two pairs of penta-acetates; in the later discussion the grounds for choosing between these in particular cases are indicated.

[b] The rotation of iodo-acetyl glucose was measured in acetylene tetrachloride but the rotation in chloroform is probably about the same since iodo-acetyl cellobiose rotates 126 and 123 in these solvents and bromo-acetyl lactose rotates 105 in both of them.

rhamnoside recently described by Fischer, Bergmann and Rabe,[8a] which probably have the structures
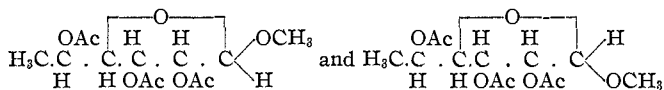
[9] Ref. 7c, p. 2751.

[10] von Arlt, *Monatsh.*, **22**, 147 (1901).

[11] Brauns, THIS JOURNAL, **44**, 401 (1922).

[12] Bodart, *Monatsh.*, **23**, 5 (1902).

[13] Schliephacke, *Ann.*, **377**, 186 (1910).   Foerg, *Monatsh.*, **23**, 44 (1902).

[14] Schliemann, *Ann.*, **378**, 374 (1911).   Skraup and Geinsperger [*Monatsh.*, **26**, 1470 (1905)] found +74.9 in chloroform.

[15] Dale, THIS JOURNAL, **37**, 2746 (1915).

[16] Koenigs and Knorr, *Ber.*, **34**, 962 (1901).

[17] Fischer and Zemplén, *Ber.*, **43**, 2536 (1910).

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

[19] Ref. 16, p. 976.

[20] Ref. 16, p. 978.

[21] Ref. 16, p. 4343.

[22] Ref. 8a.   The rotation was measured in acetylene tetrachloride. See Note *b*.

[23] Skraup and Kremann, *Monatsh.*, **22**, 380 (1901).

[24] Ref. 7d, p. 1226.

The negative sign for A_{Br} for bromo-acetyl rhamnose should not be considered exceptional; it is explained by the fact that rhamnose is a levo sugar having the configuration of a reduced l-mannose. Since the other compounds of Table II belong to the d-series, a systematic comparison should refer to derivatives of the dextro rather than the levo form of rhamnose and as the rotations of these compounds must be equal in magnitude and opposite in sign to the recorded rotations of the l-rhamnose derivatives the value of A_{Br} that will be obtained from them must be $+$ 58,600, which agrees not only in magnitude but also in sign with the values of A_{Br} shown by the other sugars.

The value of A_{Cl} for the first chloro-acetyl galactose and that of A_{NO_3} for nitro-acetyl galactose are based upon $B_{galactose} = +$ 25,400, from Table I, because these substances and the β-galactose penta-acetate from which they may be prepared presumably have a butylene oxide ring in common. While the value for A_{NO_3} is normal, that of A_{Cl} is exceptionally high and the reason is not apparent. The value of A_{Cl} for chloro-acetyl mannose is exceptionally low, and it has been omitted in taking the average value of A_{Cl}. The value of A_{Cl} for chloro-acetyl lactose is somewhat low and should be re-examined.

Mention may here be made that the chloro-acetyl and bromo-acetyl derivatives of l-arabinose, a sugar closely related in configuration to d-galactose, likewise show exceptional rotations, $[\alpha]_D = -225$ and -283, respectively, in chloroform solution.[25] The α and β tetra-acetates of l-arabinose[26] show $[\alpha]_D = +42$ and $+147$, respectively, in chloroform; hence, $B_{l\text{-arabinose}}$ is $(42 + 147)318 \div 2 = 30,100$, and the specific rotations of the alpha and beta forms of chloro-acetyl-l-arabinose are calculated, using the value of $A_{Cl} = 37,800$ from Table II, to be $(30,100-37,800) \div 294 = -26$, and $(30,100 + 37,800) \div 294 = 231$, respectively, and those of the two forms of bromo-acetyl-l-arabinose to be -86 and $+ 264$. While the magnitudes of the rotations that are recorded by Chavanne agree fairly well with those calculated (-225 instead of $+231$ and -283 instead of $+264$), the signs are just opposite; this complete disagreement obviously requires further experimental study.

The measurement of the rotation of bromo-acetyl galactose ($[\alpha]_D = +236$) by Fischer and Armstrong[27] has not been included in the table because benzene was used as the solvent and such solutions frequently rotate quite at variance from those made with chloroform; however, the value is approximately what would be expected.

Iodo-tetra-acetyl galactose has been prepared by Unna[28] in crystalline

[25] Chavanne, *Compt. rend.*, **134**, 661 (1902).

[26] Hudson and Dale, This Journal, **40**, 992 (1918).

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

[28] Unna, *Dissertation*, "Synthese einiger neuer Galactoside," Berlin, **1911**, p. 20.

form, but its rotation is not recorded. The substance melted at 88° and was quite unstable, decomposing in a short time, even in a vacuum desiccator.

Classification of the Halogen-Acetyl and Nitro-Acetyl Derivatives of the Aldose Sugars as Alpha or Beta Forms on the Basis of Their Rotatory Powers

The second chloro-acetyl galactose (Table II) is a derivative of the third galactose penta-acetate and doubtless the two substances possess the same internal oxygen ring. Since the butylene ring has been assigned to the first and second penta-acetates and the first chloro-acetate of galactose some other ring must be assumed for the structure of the second chloro-acetyl galactose and its parent penta-acetate. Whatever ring this may be[29] it doubtless also occurs in the fourth galactose penta-acetate since the third and fourth penta-acetates establish an equilibrium in acetic anhydride solution containing zinc chloride. On the basis of their rotations the third and fourth penta-acetates are beta and alpha forms, respectively, and the value of the rotation of the acetylated basal chain common to them is (Table I) $B'_{galactose} = +3,700$. The value of A_{Cl} for the second chloro-acetyl galactose is then (Table II) ($[M]_D - B'_{galactose}$) $= -28,500 - 3,700 = -32,200$, which agrees in magnitude with the average value of A_{Cl} from Table II (37,800), but differs in sign. Since galactose belongs to the dextro series, this negative sign is not a result of the convention used in naming the sugar derivatives, as was the case with the derivatives of l-rhamnose that have already been discussed. It may be explained, however, on the hypothesis that the molecular rotation of the second chloro-acetyl galactose is not ($B'_{galactose} + A_{Cl}$) but rather ($B'_{galactose} - A_{Cl}$), which means that the second chloro-acetyl galactose is a representative of an opposite type (alpha or beta) from the first chloro-acetyl galactose that gives a positive value for A_{Cl}. By this it is not assumed that the two chloro-acetyl galactoses are an α,β pair with a common ring, but rather that one is an alpha form of a certain ring type and the other a beta form of a second ring structure. If we follow the system of nomenclature which the writer suggested[30] in 1909, now in general use, and name the more dextrorotatory form of an α,β pair in the d-series the alpha form, the second chloro-acetyl galactose must be designated a beta compound since A_{Cl} for it has a negative value. Likewise, the first chloro-acetyl galactose and all the other halogen-acetyl and nitro-

[29] E. F. Armstrong ["The Simple Carbohydrates and Glucosides," Longmans, Green and Co., 3rd edition, 1919, p. 26] has assigned provisionally an ethylene oxide ring to these compounds. I regard this structure as representing only one of the possible rings and am of the opinion that the question is still an open one, awaiting the production of new experimental evidence.

[30] Ref. 5, p. 72.

acetyl aldose sugars that are listed in Table II must be classed as alpha derivatives, bromo-acetyl rhamnose being thus α-bromo-acetyl-l-rhamnose. The evidence upon which these compounds have been classed as beta derivatives in the past consists solely in the fact that they yield beta glucosides or beta acetates when the halogen or nitro group is replaced (synthesis of Koenigs and Knorr).[16] This evidence is, however, worthless because of the frequent occurrence of a Walden inversion during such replacements. In 1911 Emil Fischer[31] called attention to this possibility with the remark that "In the past the configuration which has been assigned to the halogen-acetyl glucoses is that of the (beta) glucosides that may be prepared from them. I would remark that the latest observations on the frequency of the occurrence of a change in configuration during a substitution on the asymmetric carbon atom[32] render this conclusion very unsafe. Possibly in this connection it should not be overlooked that the halogen-acetyl glucoses rotate strongly to the right in opposite sign to the rotations of the beta glucosides that may be prepared from them."

Additional evidence that the halogen-acetyl and nitro-acetyl sugars of Table II (with the exception of the second chloro-acetyl galactose) are alpha rather than beta compounds, is the increase in dextrorotation of the end asymmetric carbon atom with increasing weight of the attached group. This is strikingly shown in the regular progression, $A_F = +9,800$, $A_{Cl} = 37,800$, $A_{Br} = +59,300$, $A_I = +85,400$, which is the direction of change that is to be expected for a series of alpha compounds. A similar series of beta compounds, for example, the numerous beta glucosides, always shows the opposite direction of change of A with increasing weight of the attached group;[33] thus the specific rotations of the beta glucosides of urea, methylurea, dimethylurea and phenylurea are —24, —30, —33 and —55, respectively, showing a progression in the levo direction which is even more pronounced if the molecular rotations are compared.

In the case of nitro-acetyl glucose it appears that the alpha and beta forms may both have been prepared in crystalline condition. Skraup and Kremann[34] report the existence of a crystalline nitro-acetyl glucose, of specific rotation +1.5 in chloroform, and mention that it readily isomerizes on recrystallization from alcohol to the stable form of specific rotation +149 mentioned in Table II. If these forms do constitute an α,β pair of common ring structure, which seems probable because of the

[31] Ref. 3. See also Fischer, *Ber.*, **43**, 2521 (1910). Fischer and von Mechel, *Ber.*, **49**, 2813 (1916).

[32] E. Fischer, *Ann.*, **381**, 123 (1911).

[33] Ref. 5, p. 84.

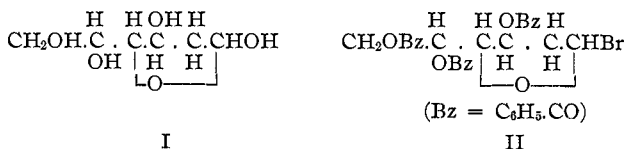[34] Skraup and Kremann, *Monatsh.*, **22**, 1043 (1901).

apparently easy transformation, the well-known stable isomer must be named the alpha form on account of its higher dextrorotation, thus confirming the conclusion previously reached. The calculated specific rotation in chloroform of the β-nitro-acetyl glucose is $(B_{glucose} - A_{NO_2})$ ÷ mol. wt. = $(20,700 - 37,100) ÷ 393 = -42$, a value which suggests that Skraup and Kremann's preparation may have contained some of the alpha form.

Chloro-acetyl maltose has a specific rotation of $+159$ in chloroform Table (II) and we have shown that it is the alpha form. The rotation of the corresponding beta form is calculated to be $(B_{maltose} - A_{Cl})$ ÷ mol. wt. = $(62,700 - 37,800) ÷ 654 = +38$. Freudenberg and Ivers[35] have recently described a chloro-acetyl maltose which they prepared by the action of a solution of hydrogen chloride in ether on maltose octa-acetate. Its specific rotation in chloroform was to the right, $+ 67.5$. On first sight it seems possible that the substance may be the unknown beta form (new nomenclature) of chloro-acetyl maltose containing some of the alpha form, but Freudenberg and Ivers found that the percentage of chlorine in it corresponded with the formula of a chloro-*octa*-acetyl maltose better than with that of a chloro-*hepta*-acetyl derivative. The present considerations are therefore given with reserve, but in their support it may be mentioned that the theoretical difference of the chlorine content for the two substances is less than 0.5%.

Classification of Various Acyl and Halogen-Acyl Derivatives of the Aldoses

1.   The Value of A_{Br} for Bromo-tribenzoyl-glucodesose

It is possible to calculate the value of A_{Br} for this derivative of glu-codesose from the rotations of some compounds that have been described recently by Bergmann, Schotte and Leschinsky.[36] From glucodesose, the structure of which is I,
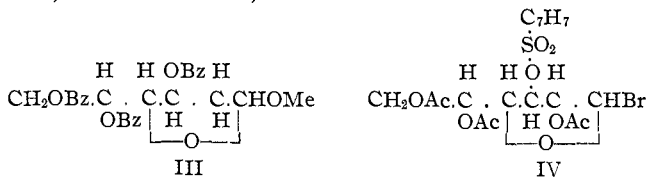

$$\begin{array}{cc} \text{H \ \ HOH H} & \text{H \ \ H OBz H} \\ \text{CH}_2\text{OH.C . C.C . C.CHOH} & \text{CH}_2\text{OBz.C \ \ C.C . C.CHBr} \\ \text{OH | H \ H |} & \text{OBz| H \ \ H |} \\ \text{L—O———} & \text{L—O———} \end{array}$$

$$(\text{Bz} = \text{C}_6\text{H}_5.\text{CO})$$

$$\text{I} \qquad\qquad \text{II}$$

they prepared the tetrabenzoate and from it bromo-tribenzoyl-glucodesose, of Structure II, showing $[\alpha]_D = +121$ in acetylene tetrachloride. From this bromo compound (mol. wt., 539) they prepared tribenzoyl-methyl-

[35] Freudenberg and Ivers, *Ber.*, **55**, 941 (1922).

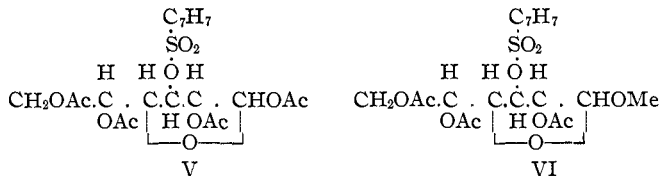[36] Bergmann, Schotte and Leschinsky, *Ber.*, **56**, 1052 (1923).

glucodesoside, of Structure III,

$$\begin{array}{cc}
 & \begin{array}{c} C_7H_7 \\ \dot{S}O_2 \end{array} \\
\begin{array}{c} \text{H\ \ H OBz H} \\ \text{CH}_2\text{OBz.C\ .\ C.C\ .\ C.CHOMe} \\ \text{OBz} \mid \text{H}\ \ \text{H} \mid \\ \llcorner\text{—O—}\lrcorner \end{array} &
\begin{array}{c} \text{H\ \ H}\dot{\text{O}}\text{ H} \\ \text{CH}_2\text{OAc.C\ .\ C.\dot{C}.C\ .\ CHBr} \\ \text{OAc} \mid \text{H OAc} \mid \\ \llcorner\text{—O—}\lrcorner \end{array} \\
\text{III} & \text{IV}
\end{array}$$

showing $[\alpha]_D = -34.3$ in acetylene tetrachloride. The molecular rotation of III (mol. wt., 490) may be written, on the very probable assumption that the substance is a β-glucoside from analogy with the similarly prepared derivatives of other sugars, $(B_{glucodesose} - A_{Me}) = (-34.3) 490 = -16,800$. The value of A_{Me} is half the difference of the molecular rotations of the alpha and beta forms of methyl-glucoside tetra-acetate, which has been found to be[37] $+26,900$; hence $B_{glucodesose} = +10,100$. The molecular rotation of bromo-tribenzoyl-glucodesose (II) may be written $(B_{glucodesose} + A_{Br}) = (121) 539 = +65,200$; hence, subtracting the value of $B_{glucodesose}$, $A_{Br} = +55,100$. This agrees with the values of A_{Br} shown in Table II and indicates that the principle of optical superposition may be applied to the derivatives of glucodesose. It also proves that the bromo compound is an alpha form and that the glucodesoside that is prepared from it is a beta derivative. Glucodesose thus conforms with glucose in these reactions.

2. The Value of A_{Br} for Bromo-tri-acetyl-toluenesulfo Glucose

From this derivative of glucose, of Structure IV, of mol. wt. 523 and specific rotation $+164$ in acetylene tetrachloride, Freudenberg and Ivers[35] have prepared tetra-acetyl-toluenesulfo glucose, of Structure V,

$$\begin{array}{cc}
\begin{array}{c} C_7H_7 \\ \dot{S}O_2 \end{array} & \begin{array}{c} C_7H_7 \\ \dot{S}O_2 \end{array} \\
\begin{array}{c} \text{H\ \ H}\dot{\text{O}}\text{ H} \\ \text{CH}_2\text{OAc.C\ .\ C.\dot{C}.C\ .\ CHOAc} \\ \text{OAc} \mid \text{H OAc} \mid \\ \llcorner\text{—O—}\lrcorner \end{array} &
\begin{array}{c} \text{H\ \ H}\dot{\text{O}}\text{ H} \\ \text{CH}_2\text{OAc.C\ .\ C.\dot{C}.C\ .\ CHOMe} \\ \text{OAc} \mid \text{H OAc} \mid \\ \llcorner\text{—O—}\lrcorner \end{array} \\
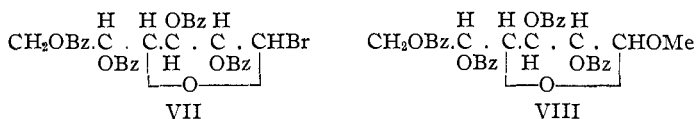\text{V} & \text{VI}
\end{array}$$

of mol. wt. 502 and specific rotation $+13.6$ in acetylene tetrachloride, and likewise tri-acetyl-toluenesulfo-methyl glucoside, of Structure VI, of mol. wt. 474, and specific rotation -17.1 in the same solvent. The molecular rotation of V may be written, on the probable assumption that it is a beta compound from the method of its synthesis, $(B_x - A_{Ac}) = (13.6) 502 = +6,800$. The value of A_{Ac} is one-half the difference between the molecular rotations of the alpha and beta forms of glucose pentaacetate, which is known[7e] to be 19,100; hence $B_x = +25,900$. The molecular rotation of IV may be written $B_x + A_{Br} = (164) 523 = + 85,800$ (Equation I), and hence $A_{Br} = +59,900$, in good agreement with

[37] Ref. 7e, p. 1265.

previous values.   In a similar manner the molecular rotation of VI may be written $B_x - A_{Me} = (-17.1)$ 474 $= -8,100$, and subtracting the value of A_{Me} previously mentioned (26,900) leaves $B_x = +18,800$.   Using this value of B_x in Equation I gives $A_{Br} = +67,000$.   While the agreement here is not so good as in the case of the acetate the result leaves no doubt that again the bromo compound is an alpha derivative and the acetate and glucoside are both beta forms.

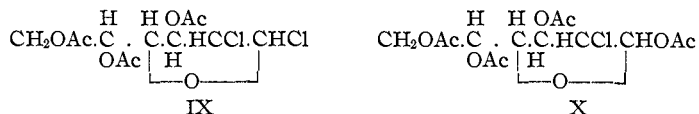### 3.   The Value of A_{Br} for Bromo-tetrabenzoyl Glucose

The specific rotation of this substance (mol. wt., 659) was measured by Fischer and Helferich[88] in toluene solution, $[\alpha]_D = +145$.   They state that the compound is quite soluble in chloroform but no measurement of the rotation in this solvent is recorded.   In the usual manner they prepared from it tetrabenzoyl-methyl glucoside (mol. wt., 610), showing $[\alpha]_D = +31$ in chloroform.   The structure of the bromo compound is doubtless VII,

<pre>
      H   H OBz H   H   H OBz H
CH₂OBz.C . C.C . C . CHBr   CH₂OBz.C . C.C . C . CHOMe
     OBz | H   OBz | OBz | H   OBz |
        L—O———┘   L—O———┘
         VII   VIII
</pre>

and that of the glucoside, VIII.   Writing the molecular rotation of the glucoside, VIII, which is assumed to be a beta form on account of its production from a bromo-acyl sugar, $[M]_D = B_y - A_{Me} = (31)$ 610 $= +18,900$, and using the value of $A_{Me} = +26,900$ previously mentioned, B_y is $+45,800$.   Writing the molecular rotation of the bromo compound VII, $B_y + A_{Br} = (145)$ 659 $= +95,600$, and subtracting the value of B_y leaves $A_{Br} = +49,800$, which indicates by its normal magnitude and sign that the bromo compound is an alpha form and the glucoside a beta derivative.   For a more accurate measurement of the value of A_{Br} it is necessary that the rotation of the bromo compound be measured in chloroform solution.

4.   The Value of A_{Cl} for Tri-acetyl-(1,2)dichloro Glucose (Tri-acetyl-glucal Dichloride)

From this crystalline addition product of chlorine to glucal, of Structure IX,

<pre>
      H   H OAc   H   H OAc
CH₂OAc.C . C.C.HCCl.CHCl   CH₂OAc.C . C.C.HCCl.CHOAc
     OAc | H | OAc | H |
        L—O———┘   L—O———┘
         IX   X
</pre>

of mol. wt. 343, and of specific rotation $+200$ in acetylene tetrachloride, Fischer, Bergmann and Schotte[39] prepared tetra-acetyl-2-chloro glucose

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

[39] Fischer, Bergmann and Schotte, *Ber.*, **53**, 509 (1920).

(tetra-acetyl-glucose-2-chlorohydrin), of Structure X, of mol. wt. 367, and of specific rotation +51 in acetylene tetrachloride, and also tri-acetyl-2-chloro-methyl-glucoside (tri-acetyl-methyl-glucoside-2-chlorohydrin), of Structure XI,

$$\begin{array}{cc}
\text{H \ H OAc} & \text{H \ H OAc} \\
\text{CH}_2\text{OAc.C . C.C.HCCl.CHOMe} & \text{CH}_2\text{OAc.C . C.C.CHNH}_2\text{.CHBr} \\
\text{OAc | H} \qquad \qquad & \text{OAc | H} \qquad \qquad \\
\text{L—O——} & \text{L—O——} \\
\text{XI} & \text{XII}
\end{array}$$

of mol. wt. 339 and of specific rotation +40 in acetylene tetrachloride. In these compounds the space positions of the hydrogen and chlorine atoms about Carbon 2 are not yet known, but since X and XI were prepared from IX the configuration of this carbon atom is the same in the three substances or, in other words, they have the same basal chain, and consequently the usual method of calculation of A_{Cl} may be applied to their rotations. Assuming from the method of their preparation that X and XI are beta forms, the molecular rotation of X is $B_w - A_{Ac} = (51)$ $(367) = +18,700$, and $B_w = 18,700 + 19,100 = 37,800$. The molecular rotation of XI is $B_w - A_{Me} = (40) (339) = +13,600$ and $B_w = 13,600 + 26,900 = +40,500$. The average of these two values of B_w is +39,100. The molecular rotation of IX is $B_w + A_{Cl} = (200) (343) = 68,600$, and subtracting the average value of B_w leaves $A_{Cl} = +29,500$. This value is in fair agreement with those previously obtained for A_{Cl}, proving that the dichloro compound, IX, is an alpha form, and that its acetate (X) and methyl glucoside (XI) are beta derivatives.

5. The Value of A_{Br} for an Acyl Derivative of Glucosamine, 1-Bromo-2-salicylidene-3,5,6-tri-acetyl-glucosamine

By condensing bromo-tri-acetyl-glucosamine,[40] of Structure XII, with salicyl aldehyde, Irvine and Hynd[41] prepared a crystalline substance which Irvine and Earl[42] have lately shown to be a salicylidene derivative, of Structure XIII,

$$\begin{array}{cc}
\text{H \ H OAc} & \text{H \ H OAc} \\
\text{CH}_2\text{OAc.C. \ C.C.CHN \quad . \quad CHBr} & \text{CH}_2\text{OAc.C. \ C.C.CHN \quad . \quad CHOMe} \\
\text{OAc | H} \qquad \| \qquad & \text{OAc | H} \qquad \| \qquad \\
\qquad \text{HC.C}_6\text{H}_4\text{.OH} & \qquad \text{HC.C}_6\text{H}_4\text{.OH} \\
\text{L—O———} & \text{L—O———} \\
\text{XIII} & \text{XIV}
\end{array}$$

Its molecular weight is 471 and its $[\alpha]_D$ in methyl alcoholic solution is +242. From it Irvine and Earl have prepared in the usual way a methyl glucosidic derivative, (mol. wt. 422, and $[\alpha]_D = +76$ in methyl alcohol),

[40] (a) Irvine, McNicoll and Hynd, J. Chem. Soc., 99, 250 (1911). (b) Hamlin, THIS JOURNAL, 33, 766 (1911). The configuration of the second carbon, CHNH₂, for glucosamine is not known with certainty.

[41] Irvine and Hynd, J. Chem. Soc., 103, 41 (1913).

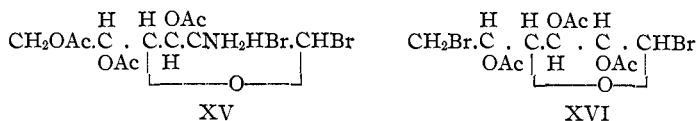[42] Irvine and Earl, ibid., 121, 2370 (1922).

of Structure XIV. Assuming as before that the substitution of the bromine atom by the methoxy group yields in this case a β-glucoside, the molecular rotation of XIV is $(B_s - A_{Me}) = (76) (422) = +32,100$, and $B_s = +32,100 + 26,900 = +59,000$. Writing the molecular rotation of the bromo compound XIII $(B_s + A_{Br}) = (242) (471) = +114,000$, and subtracting the value of B_s leaves $A_{Br} = +55,000$ in methyl alcoholic solution. This value conforms fairly well with those of A_{Br} in Table II; possibly a better agreement will be found when the rotations in chloroform are measured, but the present data show clearly that these salicylidene compounds of glucosamine fall in line with the general observation that the bromo compound is an alpha form and the methyl glucoside derivative a beta modification. The principle of optical superposition apparently applies to very diverse derivatives of glucosamine; in addition to its application to these salicylidene derivatives, it is to be recalled that Irvine and Earl have shown that the alpha and beta forms of glucosamine hydrochloride differ in molecular rotation in water by $+16,160$, conforming closely with the similar difference for the alpha and beta forms of glucose, $+16,920$, and Hudson and Dale[43] have shown that the alpha and beta forms of glucosamine penta-acetate show nearly the same difference in molecular rotation in chloroform $(+35,900)$ as do the alpha and beta forms of glucose penta-acetate $(+38,100)$. Irvine and Earl have expressed the view that these agreements may be taken to indicate a closer structural relationship of glucosamine to glucose than to mannose because the similar difference for the forms of mannose penta-acetate is considerably less $(+31,200)$.

6.   The Value of A_{Br} for Bromo-tri-acetyl-glucosamine Hydrobromide

The conclusion from the preceding section that bromo-tri-acetyl-glucosamine yields a salicylidene derivative which is an alpha form makes it very probable that the parent substance is likewise an alpha modification, because a change from alpha to beta on carbon Atom 1 would not be expected in this condensation which takes place on carbon Atom 2. Better evidence, leading to the same result, may be obtained from a comparison of the rotation of bromo-tri-acetyl-glucosamine with those of the glucosamine α- and β-penta-acetates. If the rotation of bromo-tetra-acetyl glucosamine were known in chloroform solution an accurate determination of A_{Br} for this important compound, which is the parent substance for the known aldosides of glucosamine, could be obtained by the usual comparison with the glucosamine penta-acetates. I can find no record of the preparation of this substance, but the specific rotation of bromo-tri-acetyl-glucosamine hydrobromide (mbl. wt., 449) is given by Irvine, McNicoll and Hynd[40a] as $+136°$ in pure dry acetone, increasing during 2 hours

[43] Hudson and Dale, THIS JOURNAL, **38**, 1431 (1916).

to the constant final value of 148. The question of the nature of this mutarotation will be discussed later; for the present the final value $+148$ will be taken as the specific rotation of bromo-tri-acetyl-glucosamine hydrobromide, of Structure XV. The molecular rotation of the com-

$$\begin{array}{c} \text{H} \quad \text{H OAc} \\ \text{CH}_2\text{OAc.C . C.C.CNH}_2\text{HBr.CHBr} \\ \text{OAc} \underbrace{\begin{array}{c} \text{H} \end{array}}_{\text{O}} \\ \text{XV} \end{array} \qquad \begin{array}{c} \text{H} \quad \text{H OAc H} \\ \text{CH}_2\text{Br.C . C.C . C . CHBr} \\ \text{OAc} \underbrace{\begin{array}{c} \text{H} \quad \text{OAc} \end{array}}_{\text{O}} \\ \text{XVI} \end{array}$$

pound is $(B_l + A_{Br}) = (148)(449) = +66,500$, and I assume, as a first approximation, that the molecular rotation of its acetyl derivative has the same value. This is made very probable by the fact that the molecular rotations of the hydrochloride and hydrobromide of methyl glucosamine[44] are almost exactly alike (Irvine and Hynd), and those of the similar halide salts of 6-amino-methyl-glucoside (Fischer and Zach[45]) are likewise almost identical in value. The rotation of the acetylated basal chain of glucosamine, which is here assumed to have the same value as in the hydrobromide derivatives, is one-half the sum of the molecular rotations of the α- and β-glucosamine penta-acetates, or $B_l = +18,400$ (in chloroform solution).[46] Subtracting this value from the value 66,500 found

TABLE III

CLASSIFICATIONS ON THE BASIS OF ROTATORY POWER

Alpha forms	$[\alpha]_D$	Beta forms	$[\alpha]_D$
The known halogen-acetyl derivatives of xylose, glucose, mannose, rhamnose, lactose, maltose and cellobiose.............		The second chloro-acetyl galactose.......................	−78
		Tribenzoyl - methyl - glucodesoside.......................	−34
The known stable nitro-acetyl derivatives of glucose, galactose and maltose................		Tetra - acetyl - toluenesulfo glucose....................	+13.6
		Tri - acetyl-toluenesulfo-methyl-	
The first chloro-acetyl galactose..	+212	glucoside....................	−17.1
Bromo-tribenzoyl glucodesose....	+121	Tetrabenzoyl-methyl-glucoside..	+31
Bromo - tri - acetyl - toluenesulfo glucose.....................	+164	Tetra-acetyl-2-chloro glucose....	+51
		Tri - acetyl - 2 - chloro - methyl-	
Bromo-tetrabenzoyl glucose......	+145	glucoside....................	+40
Tri - acetyl - (1,2)dichloro glucose	+200	1 - Methyl - 2 - salicylidene, - 3,5,-	
Bromo - tri - acetyl - glucosamine hydrobromide................	+148	6-tri-acetyl-glucosamine......	+76
1 - Bromo - 2 - salicylidene - 3,5,6- tri-acetyl-glucosamine.........	+242		

[44] This compound seems to be of a different type of structure from methyl glucoside [Ref. 41, 1913, p. 42], the methyl radical being attached to the nitrogen atom, but this abnormality does not affect the present argument since the peculiar grouping is present in both the hydrochloride and the hydrobromide.

[45] Fischer and Zach, Ber., 44, 132 (1911).

[46] Ref. 43, p. 1434.

in the equation above leaves $A_{Br} = 48,100$, which indicates that bromo-tri-acetyl-glucosamine is an alpha form.

The slight mutarotation of this substance when dissolved in pure dry acetone, from 136 to 148, mentioned previously, is very noteworthy. Possibly it is caused by a slow combination with the solvent. Another possibility is that the crystalline substance, which seems to be the alpha form of high dextrorotation, may have contained a small amount of the unknown beta form, which changed slowly to the alpha form in solution, or again the solid material may have been the beta form, this having changed so rapidly in solution to the alpha form that only the last portion of the mutarotation was observed. The subject must be discussed with caution as the existing experimental evidence is capable of various interpretations and additional data are much to be desired.

Summarizing this section and the previous one, the classifications of Table III have been made on the basis of rotatory power.

Calculation of the Rotations of Several Halogen-Acetyl Aldoses

The values for the rotations of the terminal asymmetric carbon atom now known for so many types of derivatives allow the calculation of the rotations of a large number of halogen-acyl, nitro-acyl and mixed acyl derivatives of various sugars and glucosides. It does not seem desirable to burden the literature with these calculated values, as the typical examples which have been given will illustrate the method of applying the appropriate coefficients in particular cases. However, I wish to record the calculated rotations of four substances which are of immediate interest.

The Calculated Rotation of β-Chloro-acetyl Glucose.—This is the unknown isomer of the common, or α-, chloro-acetyl glucose. Its specific rotation in chloroform is calculated to be $[\alpha]_D = (B_{glucose} - A_{Cl}) \div$ mol. wt. $= (20,700 - 37,800) \div 366 = 47°$. In like manner the specific rotation in chloroform of the unknown β-bromo-acetyl glucose is calculated to be $[\alpha]_D = (B_{glucose} - A_{Br}) \div$ mol. wt. $= (20,700 - 59,300) \div 411 = -94°$. Amé Pictet and Castan[47] have lately prepared by the action of strong hydrochloric acid on glucosan an amorphous substance which they name α-glucosyl chloride and have stated that on acetylation it yielded the long sought β-chloro-acetyl glucose (new nomenclature), and that on treatment with sodium methylate it yielded α-methyl-glucoside. No rotations of any of these substances were recorded and the identifications were made from melting-point determinations alone; under these conditions a definite conclusion as to whether the unknown β-chloro-acetyl glucose was really obtained cannot be made and the question must await the production of more accurate experimental evidence.

[47] Amé Pictet and Castan, *Helv. Chim. Acta*, **4**, 319 (1921).

The Calculated Rotation of 1,6-Dibromo-tri-acetyl Glucose (Aceto-1,6-dibromo Glucose)

This substance was discovered by Fischer and Armstrong and has been used by Fischer as the starting point of many syntheses, but there appears to be no record of a measurement of its specific rotation. The value can be calculated from the rotation of 1-benzyl-2,3,5-triacetyl-6-bromo glucose (XVII) which was synthesized by Fischer and Zach.[48] The structure of aceto-1,6-dibromo glucose is XVI. By the interaction of XVI with benzyl alcohol, the corresponding acyl-benzyl-glucoside was produced, of Structure XVII, mol. wt. 459 and $[\alpha]_D = -47$ in chloroform

$$\begin{array}{cc}
\text{H \ \ H OAc H} & \text{H \ \ H OAc H} \\
\text{CH}_2\text{Br.C . C.C . C . CHOCH}_2.\text{C}_6\text{H}_5 & \text{CH}_2\text{OAc.C . C.C . C . CHOCH}_2.\text{C}_6\text{H}_5 \\
\text{OAc} | \text{ H \ \ OAc} | & \text{OAc} | \text{ H \ \ OAc} | \\
\overline{\quad\text{—O}\quad} & \overline{\quad\text{—O}\quad} \\
\text{XVII} & \text{XVIII}
\end{array}$$

solution. Now the specific rotation of tetra-acetyl-benzyl-glucoside, of Structure XVIII and mol. wt. 438, has been found by Fischer and Helferich[38] to be $[\alpha]_D = -50$ in alcoholic solution. This acetylated glucoside was prepared from bromo-acetyl glucose by Koenigs and Knorr's method and is doubtless a member of the β-glucosidic series, which is confirmed by the fact of the easy hydrolysis by emulsin of the benzyl glucoside that is produced from it after the removal of the acetyl groups. Writing the molecular rotation of XVIII accordingly ($B_{glucose} - A_x$) = $-50\ (438) = -21,900$, and substituting the value of $B_{glucose}$ (from Table I) in this equation leaves $A_x = 42,600$. The molecular rotation of XVII, doubtless also a beta compound on account of its synthesis by Koenigs and Knorr's method, is written ($B'_{glucose} - A_x$) = (-47) (459) = $-21,600$, and subtracting A_x leaves $B'_{glucose} = 21,000$. Then the specific rotation of XVI becomes ($B'_{glucose} + A_{Br}$) ÷ mol. wt. = $(21,000 + 59,300)$ ÷ $474 = +169$ on the probable view that the substance is an alpha derivative. It is desirable for this calculation to know the specific rotation of XVIII in chloroform rather than in alcohol.

Calculation of the Rotation of Bromo-acetyl Gentiobiose

As there is much evidence that the biose of amygdalin may be gentiobiose,[49] and the synthesis of amygdalin is likely to be accomplished accordingly through bromo-acetyl gentiobiose, the specific rotation of this substance is here calculated. The molecular rotation of the acetylated basal chain of gentiobiose ($B_{gentiobiose}$) is one-half the sum of the molecular rotation in chloroform of the α and β forms of gentiobiose octa-acetate,

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

[49] Haworth and Leitch, *J. Chem. Soc.*, **121**, 1921 (1922). Kuhn, *Ber.*, **56**, 857 (1923). See also number 3 of the present series of articles, THIS JOURNAL, **46**, 483 (1924).

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

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

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).