OPTICAL ROTATION AND ATOMIC DIMENSION—HALOGENO-TETRA-ACETYL-DERIVATIVES OF MANNOSE. THEIR CONFIGURATIONAL PECULIARITIES

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ABSTRACT

The pure crystalline fluoro and iodo derivatives of acetylated mannose have been prepared. The specific rotation values in combination with the revised values of the chloro and bromo derivatives of acetylated mannose show a disagreement with the atomic dimension relationship established for the halogen derivatives of other monosaccharides.

An explantion of this behavior is obtained by model studies which show that the hydrogen of the first asymmetric carbon (to which the halogen is also attached) is influenced by atoms of the second carbon acetyl group, whereas, such an influence does not exist for the other investigated halogen derivatives of monosaccharides.

This result gives a suggestion for the configuration of other acetyl groups. These results show also that the study and testing of the principle of optical superposition should be carried out in the light of these configurational peculiarities.

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I. INTRODUCTION

NOTE.—This article is the ninth contribution to a series on optical rotation and atomic dimension which has appeared in the Journal of the American Chemical Society. The eighth article was published in Journ. Am. Chem. Soc., 51, p. 120; 1929.

The study of mannose has been impeded by the difficulty of obtaining its derivatives in crystalline form. This difficulty also delayed the comparison of the rotations of the halogeno-acetyl derivatives of this sugar. Only recently fluro-tetra-acetyl mannose was obtained in the form of crystals, whereas iodo-tetra-acetyl mannose crystallizes readily, if prepared according to the method described later in this paper. Bromo-tetra-acetyl mannose has been obtained in crystalline form by Micheel [1] and also by Levene and Tipson. [2] The compound has been prepared again and its rotation revised. Since the writer prepared crystalline α-chloro-tetra-acetyl mannose [3] several years ago a series of rotational values is available for comparison with the atomic dimension values. It has been established in the writers previous investigations on this subject that for all the investigated halogen derivatives of the mono-saccharides (glucose, fructose, xylose, and arabinose) the differences in specific rotations Cl–F, Br–Cl, and I–Br, have the same ratio 41 : 17 : 21, and further that this ratio agrees approximately with that for the respective differences in atomic diameter as given by Bragg (41 : 16 : 24). Later it was found [4]

[1] Micheel, Ber., 63, p. 390; 1930.
[2] Levene and Tipson, J. Biol. Chem., 90, p. 93; 1931.
[3] Brauns, J. Am. Chem. Soc., 44, p. 401; 1922.
[4] Brauns, J. Am. Chem. Soc., 49, p. 3170; 1927.

that close agreement is obtained by replacing Bragg's values of ionized halogens (in inorganic salts) by the values derived by van Arkel and de Boer[5] for the distance of the carbon to the halogen atoms as occurring in organic (homopolar) compounds. From these values the ratio 41 : 17 : 22.6 is found. Lately these values for neutral atomic diameters have been derived by Goldschmidt,[6] which yield as an average the ratio 41 : 14 : 20. If we take an average between these ratios of van Arkel and de Boer, and of Goldschmidt, we obtain 41 : 16 : 21, in close agreement with that for the differences in specific rotations of these four mono-saccharides. However, as seen from the compiled data in Table 1, the values for the mannose derivatives give an abnormal ratio 41 : 25 : 35. It is noteworthy, furthermore, that whereas for the β-bioses [7] an agreement is obtained by excluding the fluoro-derivatives, such an agreement is not obtained for the mannose derivatives, as the ratio is in this case 17 : 24.5 instead of 17 : 21.

TABLE 1.—*Comparison of the ratio of the differences of specific rotations with the ratio of the differences of neutral atomic diameters, for halogen derivatives of monosaccharides*

Specific rotations; derivatives of—						Specific rotation differences; derivatives of—						Reduced specific rotation differences; derivatives of—						Ratio of differences of neutral atomic diameter.
	Xylose	*l*-Arab.	Fruct.	Gluc.	Mann.		Xylose	*l*-Arab.	Fruct.	Gluc.	Mann.	Xylose	*l*-Arab.	Fruct.	Gluc.	Mann.	
1						2						3						4
F---	67.2	138.2	—90.4	90.1	21.5													
Cl--	171.2	244.4	—160.9	166.1	90.0	Cl-F--	104.0	106.2	70.5	76.0	68.5	41.0	41.0	41.0	41.0	41.0	41
Br--	211.9	287.1	—189.1	197.8	131.6	Br-Cl-	40.7	42.7	28.2	31.7	41.6	16.0	16.5	16.4	17.1	24.9	16
I---	------	339.1	-------	237.4	190.5	I-Br---	-----	52.0	-----	39.6	58.9	-----	20.0	-----	21.4	35.2	21

Explanation of table.—Sec. 1 gives the observed specific rotations of the halogen-acetyl derivatives of xylose, *l*-arabinose, fructose, glucose and mannose.

Sec. 2 gives the differences in specific rotation of sec. 1, between the Cl and F derivatives, the Br and Cl derivatives and the I and Br derivatives.

Sec. 3. The values given in this section have been obtained from those in sec. 2 by dividing each column by a factor which will reduce the first member of each column to the value 41. This value has been chosen in order to conform to the values given in sec. 4 for the ratio of the differences between the neutral atomic diameters.

Sec. 4. The ratio of the differences between the neutral atomic diameters of the halogens are obtained by averaging the values given by van Arkel and de Boer, and by Goldschmidt.

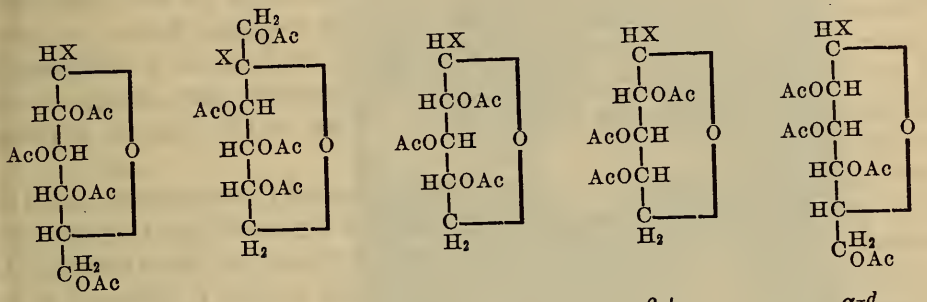
TABLE 2.—*Comparison of molecular rotations (divided by 100) of monosaccharide derivatives*

	Derivatives of—					Respective molecular rotation difference				
	Xylose	*l*-Arab.	Fruct.	Gluc.	Mann.	Xylose	*l*-Arab.	Fruct.	Gluc.	Mann.
F----------	187	384	—316	315	75					
Cl----------	504	720	—590	609	330	317	336	274	294	255
Br----------	718	973	—777	813	541	214	253	187	204	211
I----------	--------	1309	--------	1,087	873	--------	336	--------	274	332

[5] van Arkel and de Boer, Z. f. Physik, **41**, p. 27; 1927.
[6] See Wherry Am. Mineralogist, **14**, p. 54; 1929.
[7] J. Am. Chem. Soc., **51**, p. 1820; 1929.

II. DISCUSSION OF RESULTS AND CONCLUSIONS

In order to arrive at an explanation of the different results obtained r the halogeno-acetyl compounds of glucose, fructose, xylose, and ırabinose on the one hand and for the halogeno-acetyl derivatives mannose on the other, consider first their structural formulas (X representing a halogen).



α-d hal. tetra-acet. glucose | *β-d* hal. tetra-acet. fructose | *α-d* hal. tri-acet. xylose | *β-l* hal. tri-acet. arabinose | *α-d* hal. tetra-acet. mannose

As the index *d* refers to position of groupings on the last asymmetric arbon atom and *α* refers to the position of the hydroxyl group (or ts substituent) attached to the reducing carbon, *α-d* compounds ıust be similar in structure regarding the position of the groups ttached to these two carbon atoms. As a result of the system of ıomenclature and of the chemical behavior,[8] *β-d* halogeno-acetyl ırabinose is similar in structure to *α-d* halogeno-acetyl galactose, :onsequently in this compound also the halogen occupies the same)osition as it does in the *α-d* compounds. However, for the *β-d* lerivatives as represented by the fructose derivatives, the halogen nust take an opposite place in comparison with the other compounds ınder discussion. For that reason halogeno-acetyl fructose will not)e considered at this time, but will be discussed later. This is also warranted by its exceptional structure as a ketose. If we now com-)are the structural formulas for the halogeno-acetyl derivatives of glucose, xylose and *l*-arabinose on one hand and the structural formula for halogeno-acetyl mannose on the other, it is easily found that the difference in the position of the acetyl group of the second carbon is the only difference between the glucose and mannose derivatives, whereas additional differences in other groups have to be taken in account for the xylose, arabinose and fructose derivatives. The influence of the configuration or the direction[9] of the acetyl group of the second carbon can account for the different results for the glucose and mannose derivatives by considering the influence of the residual affinities of the double bond oxygen atom of the ring. The important part, which the residual affinities of this ring oxygen atom plays in the behavior of carbohydrates and their derivatives is illustrated by the frequent formation of the aldehyde form of the sugars as an intermediate in several reactions including the muta- rotation.[10]

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[8] Hudson and Phelps, J. Am. Chem. Soc., **46**, p. 2593; 1924.

[9] The written structure formula can give on the position of a group. The stereo-formula can clearly indicate position and also "configurational direction" or in short the "direction" of a group. The word direction will be used in that sense.

[10] Wolfrom, J. Am. Chem. Soc., **53**, p. 622; 1931. Lowry, Z. physik. Chem., **130**, p. 1928.

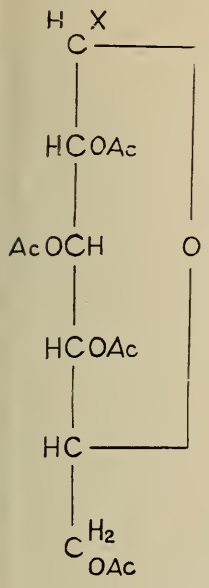
If we take the model of halogeno-tetra-acetyl glucose in which the second carbon acetyl group is represented in full by blocks, and turn this acetyl group in all possible directions, then we find that the hydrogen atoms of this acetyl group can come quite close to the ring oxygen atom (fig. 1, upper) and, therefore, possibly come under the influence of this atom. In this particular position of the acetyl group "all the atoms of this group are kept well away from the atoms attached to the first carbon atom." Thus we come to the conclusion that the atomic dimension relationship in its normal form, as previously described for halogeno-acetyl glucose, is due to a barrier-like action of the ring oxygen atom, which prevents the atoms of the second carbon acetyl group from coming close to the atoms attached to the first carbon.

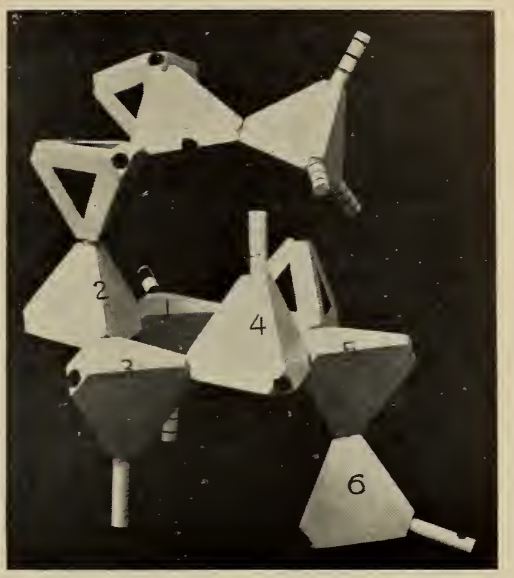
If we also take the model for halogeno-acetyl mannose, and attempt to use the ring oxygen as a barrier for preventing the atoms of the second carbon acetyl group from coming close to the atoms of the first carbon, we find that this can not be done as the hydrogen atoms of the second carbon acetyl group will never come closer than two carbon diameters to the ring oxygen atom for any direction of the acetyl group. If the abnormal atomic dimension relationship for halogeno-tetra-acetyl mannose is due to the action of other atoms in the vicinity of the first carbon, then these disturbing atoms must be those of the second carbon acetyl group.

The results of Freudenberg [11] and Haworth [12] (which will be discussed below) show that the double bond oxygen of the second acetyl group must be in the vicinity of the halogen as it yields derivatives with a ring formation (orthoacetic acid ring) between the first and second carbon atom. These facts gave the following clue. It was found probable that not only the hydrogen atoms of the second carbon acetyl group of halogeno-tetra-acetyl glucose are directed to a definite oxygen atom, but also that other acetyl groups influence each other by the same principle, the hydrogens of the one group being attracted by the double bond oxygen of another acetyl group.[13] It was possible to find the particular most probable position of the groups by trying out all possibilities and taking those configurational directions as the most probable, in which most of the active groups are saturated, preferably not allowing two CH_3 groups to act on the same oxygen atom. On this basis it was found that for halogeno-tetra-acetyl mannose the hydrogen atoms of the third carbon acetyl group are directed to the oxygen atom of the sixth carbon acetyl group; further, that the hydrogen atoms of the sixth carbon acetyl group are directed to the oxygen atom of the third acetyl group and the hydrogen atom of the fourth carbon to the ring oxygen atom. This arrangement left the oxygen affinities of the second carbon acetyl group still available and it seemed plausible that they are directed to the hydrogen atom of the first carbon atom, which brings the double bond oxygen atom in the vicinity of the halogen. This arrangement for halogeno-tetra-acetyl mannose is shown in Figure 1, lower.

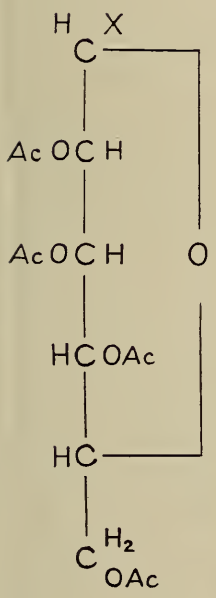
The following experimental facts lend support to the above conclusions. First consider the facts relating to the structural formula of

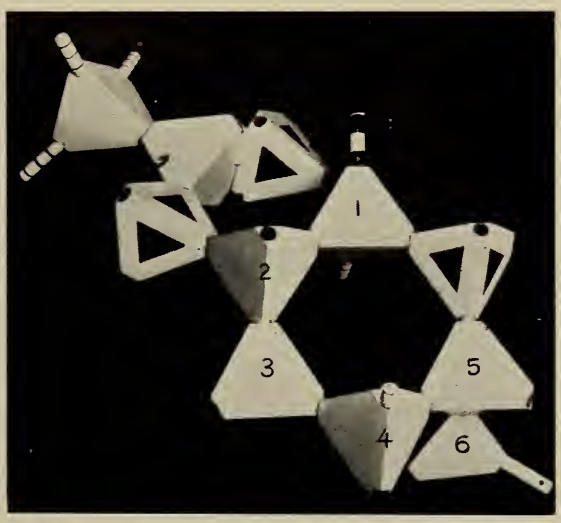
[11] Freudenberg, Naturwissenschaften, 18, p. 393; 1930.
[12] Haworth, J. Chem. Soc., p. 1395; 1930.
[13] In general, the direction of a group will be determined by the direction of the strongest secondary valence acting on it.





α-HALOGENO - TETRA-ACETYL- GLUCOSE





α-HALOGENO - TETRA-ACETYL-MANNOSE

CARBON ATOM

OXYGEN ATOM

ACETYL GROUP

HALOGEN (ALWAYS IN α-POSITION)

HYDROGEN ATTACHED TO THE FIRST CARBON AND SECOND CARBON-ACETYL-GROUP, ALL OTHERS OMITTED.

FIGURE 1

halogeno-acetyl-glucose and then to the structural formula of halogeno-acetyl mannose. Brigl [14] found that intense halogenation of acetylated glucose, maltose and cellobiose yields derivatives, which contain four chlorine atoms, the acetyl group of the first carbon being replaced by chlorine and also "the three hydrogen atoms of the second carbon acetyl group, which in our model come near to the ring atoms. This 1-chloro-2-tri-chloro-acetyl-glucose was shown by Brigl to be a stable β-derivative." The study of our model can account for this result as the three chlorine atoms are free from the attraction of the ring oxygen and consequently the double bond oxygen of the second carbon acetyl group can exert its action on the hydrogen of the first carbon and make it possible that a stable β derivative is formed. The mechanism of the Brigl reaction is undoubtedly of a complicated nature (see Brigl l. c.) as often found for similar reactions (Wolfrom l. c.), but "the β configuration of the final product as an equilibrium form of the affinities of all the groups support our stereo-formula." Further evidence in support of that formula is given by the following considerations and facts.

If it were possible to apply a certain halogenating reaction on glucoselike compounds, which could (if only temporarily) saturate the affinities of the ring oxygen atom, results should be obtained similar to those for the mannose compounds. Now Freudenberg [15] has found that maltose oct-acetate can be converted by an exceptional method of chlorination [16] to a compound with a ring formation which includes the chlorine and the acetyl group of the second carbon (ortho-acetic acid ring). However, chloro-hepta-acetyl maltose prepared by ordinary methods of chlorination (as applied for glucose and mannose derivatives) does not show a tendency for such a ring formation as it does not even yield derivatives with such a ring structure. It displays in combination with the fluorine and bromine derivatives of maltose an abnormal atomic dimension relationship.[17] Hence, an exceptional halogeno-acetyl maltose (with ortho-acetic acid structure) is obtained only by applying an extraordinary method of halogenation. However, a different result is obtained for the mannose derivatives. Freudenberg [18] and Haworth [19] came both to the conclusion that bromo-tetra-acetyl mannose [20] (prepared by the common method of halogenation) yields derivatives, which have a ring formation between the first and second carbon atom of the same type as the above-mentioned ortho-acetic acid ring structure. This shows then that the groups of the first and second carbon atoms for mannose can interact, which is in agreement with our conclusions of the proximity of the groups in the halogen derivatives.

Before making other conclusions, we will summarize as follows:

1. The "normal" ratio for the specific rotation differences of the halogeno-acetyl derivatives of glucose, as revealed by the atomic dimension relationship, can be displayed on account of the ring

[14] Brigl, Ber., **59**, p. 1588; 1926, and subsequent articles also Ber., **62**, p. 1717; 1929.
[15] Freudenberg, Naturwissenschaften, **18**, p. 393; 1930.
[16] The absolute ether used in the reaction of Freudenberg may have as active a part in it as in the Grignard reaction.
[17] Brauns, J. Am. Chem. Soc., **51**, p. 1820; 1929.
[18] See footnote 11, p. 576.
[19] See footnote 12, p. 576.
[20] Chloro-tetra-acetyl mannose behaves in the same manner as the bromo-derivative.

oxygen atom, which attracts the hydrogen atoms of the second carbon acetyl group, preventing the action of the double-bond oxygen of this group on the hydrogen of the first carbon.

2. The "abnormal" ratio for the specific rotation differences of the halogeno-acetyl derivatives of mannose as revealed by the atomic dimension relationship is due to the secondary valence action of the double-bond oxygen atom of the acetyl group attached to the second carbon atom upon the hydrogen of the first carbon atom.

The orientation of acetyl groups in the stereo-formula of all the discussed halogeno-acetyl derivatives are described below as a guide, but a clear insight can be obtained only by actually manipulating the models. Without models an idea can be obtained by viewing the picture of the ring structure. The acetyl group can be represented by four blocks, one for the binding oxygen, one for the double-bond oxygen, and two for carbons; the hydrogens can be omitted. The model of each compound is tested on its own possibilities, without taking into consideration the result of even closely-related substances. These will often give entirely different results, as illustrated by xylose tetra-acetate and glucose penta-acetate. The model of the definite six atomic ring structure described in Part VIII for glucose [21] will be kept, as it is interesting to see how far this arrangement can explain the facts.

III. DESCRIPTION OF STEREO-FORMULAS

α-d-halogeno-tetra-acetyl glucose: 2 CH_3 to ring O; 3 CH_3 to 6 O; 4 CH_3 to 2 O; 6 CH_3 to 3 O.

Remarks.—This means that the three hydrogen atoms of the second carbon acetyl group are directed to the vicinity of the ring oxygen atom. Further that the three hydrogens of the third carbon acetyl group are directed to the vicinity of the double bond oxygen atom of the sixth carbon acetyl group, etc. The acetyl residual affinities of the groups of the third and sixth carbon saturate each other. The discussion for obtaining the direction of the second carbon acetyl group has been made as well as the discussion for obtaining the directions of the others. The possibility of: 2 CH_3 to 4 O; 3 CH_3 to 6 O; 4 CH_3 to ring O and 6 CH_3 to 3 O also exists. This arrangement does not change the conclusions made, but does not explain the Brigl reaction.

α-d halogeno-tetra-acetyl mannose: 2 O to β hydrogen and α halogen; 3 CH_3 to 6 O; 4 CH_3 to ring O; 6 CH_3 to 3 O.

Remarks.—The discussion for obtaining the direction of the second carbon acetyl group has been made.

α-d halogeno-tri acetyl xylose: 2 CH_3 to 4 O; 3 CH_3 to ring O; 4 CH_3 to 2 O.

Remarks.—The atoms of acetyl groups do not come into the vicinity of the α-halogen.

β-l halogeno-tri-acetyl arabinose: 2 CH_3 to ring O; 3 CH_3 to 4 O; 4 CH_3 to 3 O.

Remarks.—The atoms of acetyl groups do not come into the vicinity of the β halogen, which has an upper position at the first carbon because the arabinose is an *l*-sugar.

β-d halogeno-tetra-acetyl fructose: 1 CH_3 to 4 O; 3 CH_3 to 1 O; 4 CH_3 to 3 O; 5 CH_3 to ring O.

Remarks.—The atoms of acetyl groups do not come into the vicinity of the β halogen, which has a lower position at the second carbon because the fructose is a *d*-sugar.

[21] Brauns, J. Am. Chem. Soc., 51, 1824; 1929.

We will now discuss the fully acetylated sugars.

In Hudson's method of studying the principle of optical superposition the first carbon is indicated by + A and − A for the α and β derivatives, respectively, and the rest of the molecule by B. The difference in the molecular rotations of the fully acetylated sugars is thus required to be equal (2A). The experimental results [22] for the mono-saccharides are given in Table 3.

TABLE 3.—*Molecular rotations of α and β forms of fully acetylated sugars*

	α	β	Difference
d-Glucose-penta-acetate	+39, 600	+1, 500	+38, 100
d-Mannose-penta-acetate	+21, 400	−9, 800	+31, 200
d-Galactose-penta-acetate(1 and 2)	+41, 600	+8, 900	+32, 700
d-Galactose-penta-acetate (3 and 4)	+23, 800	−16, 400	+40, 200
d-Xylose-tetra-acetate	+28, 300	−7, 900	+36, 200
l-Arabinose-tetra-acetate	+13, 400	+46, 800	−33, 400

It is seen from the table that the differences are not quite constant. We will consider this lack of constancy from a viewpoint which takes into account the influence of the direction of the acetyl groups.

If we view the model for α glucose as described, so that the ring is horizontal and the first carbon is situated farthest away from the observer with the second carbon at the left and the oxygen atom at the right, then it is not only assumed (as is generally done) that the upper position of an acetyl group (replacing a hydroxyl group of the original sugar) will make the particular carbon atom to which the acetyl group is attached positive rotating but also that the direction of the acetyl group to the right of the whole model has a positive rotating influence, and that a left direction has a negative rotating influence. The strongest positive influence, which an acetyl group can have is therefore to be up to the right and the strongest negative to be down to the left. Other intermediate values are dependent on the degree of left or right direction of the group.

The discussion is made easier, if we indicate the rotations of the first carbon for the α and β derivatives by A_α and A_β respectively, keeping in mind that A_α is the more positive rotating for the *d*-sugars and the more negative for the *l*-sugars. The rotations of the rest of the molecule are, respectively, B_α and B_β.

α-Glucose-penta-acetate: 1 CH_3 to ring O; 2 CH_3 to 4 O; 3 CH_3 to 6 O and to 4 O; 4 CH_3 to 2 O; 6 CH_3 to 3 O.

β-Glucose-penta-acetate: 1CH_3 to 3 O; 2 CH_3 to 4 O; 3 CH_3 to 4 O; 4 CH_3 to 2 O; 6 CH_3 to ring O.

Remarks.—The place of the first acetyl group for the α derivative changes to a diametrically opposite place for the β derivative, hence A_α and A_β can be represented by $+A$ and $-A$. The direction of the first acetyl group of the β derivative is also determined by the action of the hydrogen directly attached to the second column. The B_α value is not changed in comparison with the B_β value as the change of the sixth acetyl group which is not asymmetric does not change the rotation, hence the calculated difference (+38,100) truly represents $2A$.

α-Mannose-penta-acetate: 1 CH_3 to 2 O; 2 CH_3 to 1 O; 3 CH_3 to 6 O; 4 CH_3 to ring O; 6 CH_3 to 3 O.

β-Mannose-penta-acetate: The same as for the α compound. The first or β acetyl-group is here also directed to the second oxygen.

[22] Hudson, B. S. Sci. Paper, No. 533, p. 259.

Remarks.—It is seen that the arrangement in space of the groups attached to the first carbon is slightly more positive for the β form of the mannose compound than for the β forms of the glucose which will make the calculated difference for the mannose derivative smaller than for the glucose compound. Further, the direction of this acetyl group in the case of the α mannose compound (being up and to the left) is such as to give a more negative rotation to this first carbon atom than in the case of the α_2 glucose compound where the direction of the acetyl group is up and to the right thus making A_α for mannose-penta-acetate smaller than for glucose-penta-acetate, which will make again the calculated difference for the mannose derivatives (+31,200) smaller than the difference for the glucose derivatives, which agrees with experiment. (See Table 3.) The two pairs of galactose-penta-acetates are not considered on account of the uncertainty in their ring structure.

α-Xylose-tetra-acetate: 1 CH_3 to 3 O; 2 CH_3 to 4 O; 3 CH_3 to ring O; 4 CH_3 to 2 O.

β-Xylose-tetra-acetate: 1 CH_3 to 3 O; 2 CH_3 to 4 O; 3 CH_3 to ring O; 4 CH_3 to 2 O, or the same as for the α derivative.

Remarks.—The explanation for the discrepancy in the 2 A value for the xylose derivatives is the same as that given for the mannose derivatives, The $B\alpha$ and B_β value for the xylose derivatives is the same. The models also show that the discrepancy is here not as large as for the mannose derivatives as the $A\beta$ value is more negative for the xylose derivatives.

α-l Arabinose-tetra-acetate: 1 O to 5 H, 2 CH_3 to ring O; 3 CH_3 to 4 O; 4 CH_3 to 3 O.

β-l Arabinose-tetra-acetate: 1 CH_3 to ring O; 2 CH_3 to 1 O; 3 CH_3 to 4 O; 4 CH_3 to 3 O.

Remarks.—The α acetyl group of the first carbon, which has here a lower position at that carbon (because the arabinose is an *l*-sugar), has a direction which is more positive than the β acetyl group of the glucose compound, whereas the β acetyl group of the arabinose compound occupies the same place as the α acetyl group of the glucose compound. Hence the calculated difference must be smaller than for the glucose compounds. Further the $B\alpha$ value is different from the B_β value. The change in direction of the second carbon acetyl group makes the absolute value of the difference too low as found. (See Table 3.)

It is not intended to enter the field of investigation of the principle of optical superposition, however, the configurational peculiarities found by applying the atomic dimension relationship warrant the suggestion that the principle of optical superposition should be carefully tested and studied in the light of these results, taking into account the configurational peculiarities as illustrated for the acetylated sugars.

IV. EXPERIMENTAL PART

General remarks.—For all determinations of the specific rotation purified chloroform [23] was used. The volume of the solution was made up in the same flask to 24.9767 cc at 20°, which requires multiplication by the factor 4.0038 for obtaining 100 cc. The reading, which was made in the same 4 dm tube at 20°, is given in circular degrees.

β-Penta-acetyl mannose was prepared by acetylating mannose with acetic anhydride and zinc chloride according to the method of Hudson and Sawyer.[24] The time of reaction could be appreciably shortened (even when working with 80 g of mannose at a time) by taking the stoppered Erlenmeyer flask out of the cooling bath and rotating. As soon as the reaction mixture heated up it was cooled again. A

[23] Brauns, J. Am. Chem. Soc., **46**, p. 1486; 1924.
[24] See Hudson and Dale, J. Am. Chem. Soc., **37**, p. 1281; 1915.

few recrystallizations gave a product of constant specific rotation in chloroform of $-25.15°$ and m. p. 117° to 118° agreeing with the values reported by Hudson and Dale:[24] $[\alpha]_D^{20} = -25.3$; m. p. 117° to 118°.

α-Fluoro-tetra-acetyl mannose was prepared from β-penta-acetyl mannose in the manner previously described.[25] The distillation was finished in about 40 minutes and the reaction product was directly worked up. The sirup resulting from the extraction with chloroform did not crystallize by stirring with petroleum ether. After many unsuccessful attempts to crystallize the sirup it was kept in a vacuum desiccator over fresh sodium hydroxide and stirred repeatedly for removing the petroleum ether. After a few days the sirup crystallized. The solid mass was broken up and some of the substance saved for seeding. The larger part was dissolved in a small amount of absolute ether and filtered clear through a hardened filter paper. To the concentrated solution petroleum ether was added until a sufficient amount of crystals had separated. Many recrystallizations are required before a constant rotating pure substance is obtained. Large crystals can be separated by crystallizing from ether alone. The pure product crystallizes in prismatic needles and is stable colorless and slightly bitter. It is very soluble in most solvent except water and petroleum ether. m. p. 68° to 69°. The determination of the specific rotation in purified chloroform solution gave the following results:

Rotation.—Second recrystalization: Subs., 0.6695; $\alpha = +2.042°$; $[\alpha]_D^{20} = +19.05°$. Third recrystallization: Subs., 0.6049: $\alpha = +1.946°$; $[\alpha]_D^{20} = +20.08°$. Fourth recrystallization: Subs., 0.6220: $\alpha = +2.077°$; $[\alpha]_D^{20} = +20.85°$. Fifth recrystallization: Subs., 0.6166: $\alpha = +2.112°$; $[\alpha]_D^{20} = +21.38°$. Sixth recrystallization: Subs., 0.6184: $\alpha = +2.129°$; $[\alpha]_D^{20} = +21.50°$. Therefore, +21.50 is taken as the specific rotation of the pure substance.

Analyses.—Subs., 0.2171: CO_2, 0.3840; H_2O, 0.1083. Subs., 0.5000: CaF_2, 0.0524. Calcd. for $C_{14}H_{19}O_9F$: C, 47.98; H, 5.47; F, 5.43. Found: C, 48.24; H, 5.58; F, 5.10.

α-Chloro-tetra-acetyl-mannose.—This compound has been prepared and described before.[26] It was prepared again and the specific rotation measured under the same conditions as for the other halogen derivatives of mannose. The melting point (81°) and specific rotation were found identical with those recorded before. The specific rotation was determined in purified chloroform.

Rotation.—First recrystallization: Subs., 0.6027: $\alpha = +8.672°$; $[\alpha]_D^{20} = +89.84°$. Second recrystallization: Subs., 0.6140: $\alpha = +8.863°$; $[\alpha]_D^{20} = +90.13°$. Third recrystallization: Subs., 0.6202: $\alpha = +8.932°$ $[\alpha]_D^{20} = +89.92°$. Therefore $[\alpha]_D^{20} = +90.13$ is taken as the rotation of the pure substance.

α-Bromo-tetra-acetyl-mannose.—This compound has been prepared by Micheel and Micheel [27] and also by Levene and Tipson.[28]

The method by Micheel and Micheel was followed. Ten grams of powdered β penta-acetyl-mannose was added to 14.5 cc of a saturated solution of hydrobromic acid in glacial acetic acid, which had been

[25] Brauns, J. Am. Chem. Soc., **45**, p. 834; 1923.
[26] Brauns, J. Am. Chem. Soc., **44**, p. 401, 1922.
[27] Micheel and Micheel, Ber., **63**, p. 390, 1930.
[28] Levene and Tipson, J. Biol. Chem., **93**, p. 93, 1931.

cooled to 0° in a glass stoppered Erlenmeyer flask. After the substance had dissolved, the solution was allowed to stand for two hours at room temperature, then dissolved in 60 cc of chloroform and poured into 60 cc of ice water. The separated chloroform solution was shaken out three times with ice water; dried with calcium chloride and filtered and the chloroform evaporated with a current of dry air. The slightly yellow sirup, kept in a vacuum dessicator over fresh sodium hydroxide in the ice box solidified after a few weeks standing. Subsequent preparations crystallized easily by seeding. It was recrystallized by dissolving in a small amount of absolute ether, filtering through hardened filter paper and allowing the seeded solution to evaporate slowly in the ice box. Yield about 6 gm. A few recrystallizations gave a constant rotating pure product. The pure substance crystallizes in long colorless needles, which have a bitter taste. It is easily soluble in all ordinary solvents, except petroleum ether and water. m. p. 62°. Micheel and Micheel 48 to 50°. Levene and Tipson 53 to 54°. The rotation was measured in purified chloroform solution.

Rotation.—First recrystallization: Subs., 0.6690: $\alpha = +14.004°$; $[\alpha]_D^{20} = +130.70°$. Second recrystallization: Subs., 0.6392: $\alpha = +13.450°$; $[\alpha]_D^{20} = +131.38°$. Large clear crystals from a second separation of second recrystallization: Subs., 0.6506: $\alpha = +13.709°$; $[\alpha]_D^{20} = +131.57°$. Third recrystallization: Subs., 0.6230: $\alpha = +13.104°$; $[\alpha]_D^{20} = +131.33°$. Therefore, +131.57° is taken as the specific rotation of the pure substance. Micheel and Micheel found for the specific rotation in chloroform +122.1° and Levene and Tipson +123.1°.

Analyses.—Subs., 0.2136: CO_2, 0.3206; H_2O, 0.0908. Subs., 0.2200: AgBr, 0.1016. Calcd. for $C_{14}H_{19}O_9Br$: C, 40.87; H, 4.66; Br, 19.44. Found: C, 40.93; H, 4.76; Br, 19.65.

α-Iodo-tetra-acetyl-mannose.—Eight grams of β mannose-penta-acetate was dissolved in 14 cc purified chloroform in a Pyrex test tube and a minute amount of zinc chloride was added. The solution was cooled in an ice and salt bath. Hydriodic acid (which was first passed through asbestos mixed with red phosphorus, then through a calcium chloride tower, then through a phosphorus pentoxide tube and finally thorugh a spiral tube cooled in ice and salt) was passed in a slow stream through the mannose-penta-acetate solution for 10 to 15 minutes. The solution was poured into a dish and evaporated with a current of dry air under a belljar. A mixture of equal amounts of ether and petroleum ether was added and by scratching the sides of the dish crystallization started. The crystals were separated by suction and washed with ether—petroleum ether mixture. Recrystallization was produced by dissolving in a small amount of absolute ether adding half the amount of petroleum ether and seeding. Clear large size crystals were obtained by keeping the solution in a dessicator in a partial vacuum and cooling in the refrigerator. The pure compound crystallizes in short prisms and is slightly bitter and colorless. It is not stable but can be kept in pure condition for many months in a dessicator over sodium hydroxide in an ice box. It is readily soluble in ordinary solvents except water and petroleum ether. A sharp melting point can be obtained by quickly heating the substance

to near its melting point. It melts at 95° to a slightly yellowish liquid. The determination of the specific rotation in purified chloroform gave the following results:

Rotation.—First recrystallization: Subs., 0.6288: $\alpha = +18.799°$; $[\alpha]_D^{20} = +186.67°$. Second recrystallization: Subs., 0.6042: $\alpha = +18.418°$; $[\alpha]_D^{20} = +190.34°$. Third recrystallization: Subs., 0.6129: $\alpha = +18.608°$; $[\alpha]_D^{20} = +189.57°$. As other preparations gave final values of about +190.50, this value is taken as the specific rotation of the pure substance.

Analyses.—Subs., 0.2299: CO_2, 0.3088; H_2O, 0.0872, Subs. 0.2977 AgI, 0.1530. Calcd. for $C_{14}H_{19}O_9I$: C, 36.67; H, 4.18; I, 27.71. Found: C, 36.63; H, 4.24; I, 27,78.

Washington, June 30, 1931.