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OPTICAL ROTATION AND ATOMIC DIMENSION. V

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Experimental evidence already reported¹ supports the following rule: a comparison of compounds differing only in having an asymmetry-producing halogen atom replaced by an atom of another halogen (these halogens being immediately attached to an asymmetric carbon atom) shows that the differences in *specific* rotation, Cl comp.-F comp., Br comp.-Cl comp., and I comp.-Br. comp., are approximately proportional to the differences of the respective atomic diameters recorded by Bragg.

The present paper gives a comparison of compounds that differ also in having an atom of one halogen replaced by an atom of another halogen, with the difference that the halogens in these compounds are attached to an asymmetric carbon atom, not directly, but *through a chain of atoms*. Although this investigation is only in the preliminary stage, in that the author has not yet succeeded in obtaining a full series of this kind of derivatives, the results clearly support the rule that *in the latter kind of derivatives the molecular rotation differences are approximately proportional to the differences in atomic diameter recorded by Bragg*.

Whether this change from the first to the second rule is abrupt or takes place gradually when a chain of one or more atoms is introduced between halogen and asymmetric carbon atoms, has not yet been investigated. Moreover, the corresponding hydrogen derivatives (replacement of halogen by hydrogen) can now be drawn into the comparison and brought into relation with the atomic diameter differences.

Two sets of derivatives have been prepared and their rotations measured: (I) salicin (H derivative), chloro-, bromo- and iodosalicin; and penta-acetyl-salicin (H derivative), with penta-acetyl derivatives of chloro-, bromo- and iodosalicin (the preparation of these derivatives has been described in the literature, but their rotations have not been recorded); and (II) α -penta-acetyl-glucose (H derivative), together with α -fluoro-, α -chloro- and α -bromo-acetyl-tetra-acetyl-glucose.

The halogen derivatives in the second set are new compounds, similar to the mixed acyl compounds prepared by Brigl.²

The preparation and investigation of these salicin derivatives showed that errors regarding these compounds are recorded in the literature.

Visser³ stated that chloro-, bromo- and iodosalicin contain two mole-

¹ THIS JOURNAL, 45, 2381 (1923); 46, 1484 (1924); 47, 1280 (1925).

² Brigl, *Z. physiol. chem.*, 116, 20 (1921).

³ Visser, *Arch. Pharm.*, 235, 544 (1897).

cules of water of crystallization and that chloro- and iodosalicin lose both molecules of water of crystallization at 100°, whereas bromosalicin loses at this temperature only one molecule. The experiments here reported prove that this statement regarding the behavior of bromosalicin is incorrect. In an air-dry condition, chloro-, bromo- and iodosalicin all contain two molecules of crystallization water.

These results show, further, that the regularity in chemical behavior, which can be expected in a series of this kind and which makes these compounds comparable, is also maintained in respect to conditions under which water of crystallization is lost.

Difficulties arise when salicin (H derivative) is included in the comparison of the halogen derivatives. No solvent in which all four compounds are fairly soluble could be found; and salicin does not contain water of crystallization. Complication is avoided, however, when the comparison is made in absolute alcoholic solution, as the substances are then measured in water-free form, although unfortunately only in low concentration.

Another erroneous statement in the literature regarding salicin and its halogen derivatives concerns the so-called tetra-acetyl derivatives. Schiff⁴ prepared an acetyl derivative of salicin and, using an inaccurate method of determination of acetyl groups, called it a *tetra-acetyl-salicin*. Visser,³ applying the same acetylation procedure and the same method of analysis to the halogen derivatives of salicin, obtained data agreeing with the required values for *tetra-acetyl-halogen-salicin*. The author has found by accurate analysis, however, that the compounds are *penta-acetyl derivatives*. For this reason acetylation with acetic anhydride is not incomplete, as heretofore believed, but leads to the fully acetylated derivatives, just as methylation of salicin leads to a fully methylated penta-methyl-salicin.⁵

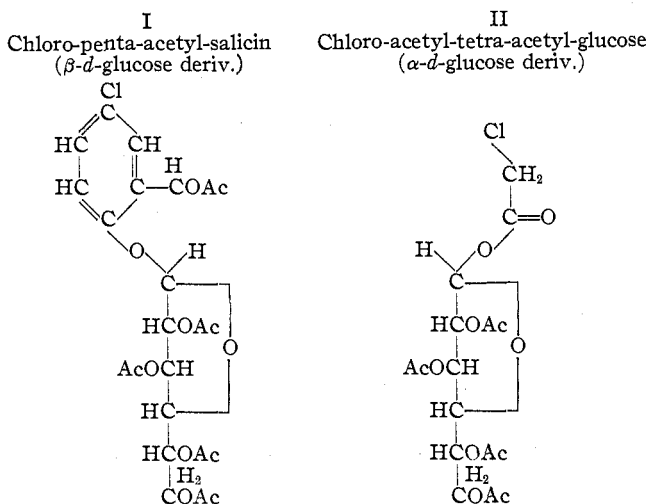
The penta-acetyl derivatives of salicin and the corresponding chloro, bromo and iodo derivatives and also the second series of derivatives (the α -halogen-acetyl-tetra-acetyl-glucose derivatives) do not contain water of crystallization and are easily soluble in chloroform, so that no difficulty is involved in obtaining a comparison of their rotations.

A consideration of the structural formulas of the compounds investigated shows that in Case I the halogen has replaced the only H atom attached to a carbon atom, whereas in Case II two hydrogen atoms are still attached to the carbon atom which is involved in the substitution, and for this reason a complication for including the hydrogen derivative in the comparison may be involved in Case II.⁶

⁴ Schiff, *Ann.*, **154**, 9 (1870).

⁵ Irvine and Rose, *J. Chem. Soc.*, **89**, 817 (1906).

⁶ A discussion of the replacement of one halogen by another has been made. *THIS JOURNAL*, **45**, 2382 (1923).



In Table I the radii of the halogen atoms, as estimated from the graphic table given by Bragg,⁷ are compared with the values given by Wherry.⁸ A third ratio, valuable for comparison, is obtained from the differences in specific rotation of the halogen-tetra-acetyl-glucose derivatives reported in the fourth article of this series.

TABLE I

ATOMIC RADII IN Å. FOR HYDROGEN AND HALOGENS AND RATIO OF THEIR DIFFERENCES

	H	F	Cl	Br	I	F-H	Ratio of differences			Cl-H
							Cl-F	Br-Cl	I-Br	
Bragg	?	0.6-0.7	1.0-1.1	1.2-1.3	1.4-1.5	?	+41	+16	+24	?
Wherry	0.95 ^a	0.85	1.35	1.50	1.70	-10	+50	+15	+20	+40
Ratio derived from spec. rotat. diff. of halogen 4-ac.-glucoses						?	+41	+17.1	+21.4	?

^a Wyckoff [*Proc. Nat. Acad. Sci.*, **9**, 33 (1923)] gives 0.55 for H, while his values for the halogens agree with those of Bragg. Subsequent estimates of the radius of H give the higher average used by Wherry.

^b Only the ratio has a meaning in this comparison, not the separate magnitude of its factors.

The salicin derivatives require the Cl-H value (as the corresponding fluoro derivatives are lacking) for comparison with the Br-Cl and I-Br value. *The Br-Cl value, therefore, has been used as the common value to be equalized for comparing the results of the investigation in Tables II, III and IV.*

With but few exceptions, the solutions were made up in the same flask. As the volume of the flask at 20° is 24.9767 cc., the quantity of substance must be multiplied by the factor 4.0038 to give the concentration of the substance in 100 cc. The same observation tube (4 dm.) was used through-

⁷ Bragg, *Science Progress*, **16**, 45 (1921).

⁸ Wherry, *Am. Mineralog.*, **9**, 165 (1924).

out the investigation. The rotations are in circular degrees. The molecular rotations are divided by one hundred. The concentration used for a comparison of one set of compounds, kept approximately the same, is stated separately for each table. Other conditions of measurement are identical. The figures in small type are outside the limits of accuracy.

TABLE II
COMPARISON OF MOLECULAR ROTATIONS OF SALICIN AND HALOGEN DERIVATIVES OF SALICIN IN ABSOLUTE ALCOHOL WITH ATOMIC DIAMETERS

	Salicin	Chlorosalicin	Bromosalicin	Iodosalicin
Mol. wt.	286	321	365	412
α	-1.10 ⁹	-1.26 ⁵	-1.59 ⁴	-1.17 ⁸
$[\alpha]_D^{20}$	-45.6 ⁰	-52.6 ⁶	-49.7 ⁷	-47.9 ⁵
$[M]_D^{20}$	-130 ⁶	-168 ⁸	-181 ⁷	-197 ⁶
	Cl-H	Br-Cl	I-Br	
Diff. of mol. rotat.	-38	-13	-16	
Bragg	?	+16	+24	
Diff. of mol. rotat. of subst. of this table reduc. to Bragg's Br-Cl		-16	-20	
Wherry	+40	+15	+20	
Diff. of mol. rotat. of subst. of this table reduc. to Wherry's Br-Cl	-44	-15	-18	
Spec. rotat. diff. of halog.-4-ac.-gluc.	?	+17.1	+21.4	
Diff. of mol. rotat. of subst. of this table reduc. to above Br-Cl		-17	-21	

Remarks.—The magnitude of the differences not the sign must of course be compared; the sign needs to be considered only if it changes on the same horizontal row of figures, as occurs in Table IV.

The $[\alpha]_D^{20}$ values for the halogen derivatives are based on the anhydrous substance, the molecular rotation being obtained by multiplying with the water-free molecular weight.

The final rotation for salicin was obtained by dissolving 0.6000 g. of substance in 98.6643 cc. of absolute alcohol at 20°. The final rotations for chloro-, bromo- and iodosalicin were obtained by dissolving, respectively, 0.1668; 0.2197 and 0.1668 g. of the dihydrate (corresponding, respectively, to 0.1500, 0.20000 and 0.1534 g. of anhydrous substances) to a volume of 24.9767 cc. with absolute alcohol at 20°.

TABLE III
COMPARISON OF MOLECULAR ROTATIONS OF PENTA-ACETYSALICIN AND PENTA-ACETYL DERIVATIVES OF HALOGEN-SALICIN IN CHLOROFORM SOLUTION WITH ATOMIC DIAMETERS

	Penta-ac.-salicin	Penta-ac.-chlorosalic.	Penta-ac.-bromosalic.	Penta-ac.-iodosalic.
Mol. wt.	496	531	575	622
α	-5.87 ⁴	-7.14 ⁶	-7.03 ⁵	-6.93 ⁵
$[\alpha]_D^{20}$	-18.3 ⁴	-22.3 ¹	-21.9 ⁵	-21.6 ⁵
$[M]_D^{20}$	-91.0	-118.4	-126.3	-134.7

TABLE III (Concluded)

	Cl-H	Br-Cl	I-Br
Diff. of <i>mol. rotat.</i>	-27.4	- 8.1	- 8.4
Bragg	?	+16	+24
Diff. of <i>mol. rotat. of</i> subst. of this table re- duc. to Bragg's Br-Cl		-16	-17
Wherry	+40	+15	+20
Diff. of <i>mol. rotat. of</i> subst. of this table re- duc. to Wherry's Br-Cl	-51	-15	-16
Spec. rotat. diff. of halog. 4-ac.-gluc.	?	+17.1	+21.4
Diff. of <i>mol. rotat. of</i> subst. of this table re- duc. to above Br-Cl		-17	-18

Remarks.—The first remark under Table II applies here also. All derivatives crystallize without water of crystallization. The rotations for all derivatives were obtained by dissolving 2.000 g. of substance to a volume of 24.9767 cc. with chloroform at 20° and polarized in the 4dm. tube. Sufficient accuracy is obtained in this way for allowing the inclusion of the first decimal of the *mol. rotat. differences.*

TABLE IV

COMPARISON OF MOLECULAR ROTATIONS OF α -PENTA-ACETYL-GLUCOSE AND α -HALOGEN ACETYL-TETRA-ACETYL-GLUCOSES IN CHLOROFORM SOLUTION WITH ATOMIC DIAMETERS

	α -Penta- acetyl-gluc.	α -Fluoro- acetyl deriv.	α -Chloro- acetyl deriv.	α -Bromo- acetyl deriv.
Mol. wt.	390	408	425	469
α	+21.24 ⁸	+12.13 ⁶	+13.36 ⁶	+12.32 ⁶
$[\alpha]_D^{20}$	+101.1 ⁷	+92.6 ⁵	+100.8 ²	+94.8 ¹
$[M]_D^{20}$	+394 ⁷	+378 ²	+428 ¹	+444 ⁷
	I-H	Cl-F	Br-Cl	
Diff. of <i>mol. rotat.</i>	-17	+50	+17	
Bragg	?	+41	+16	
Diff. of <i>mol. rotat. of</i> subst. of this table re- duc. to Bragg's Br-Cl		+47	+16	
Wherry	-10	+50	+15	
Diff. of <i>mol. rotat. of</i> subst. of this table re- duc. to Wherry's Br-Cl	-15	+44	+15	
Spec. rotat. diff. of halog. 4-ac.-gluc.	?	+41	+17.1	
Diff. of <i>mol. rotat. of</i> subst. of this table re- duc. to above Br-Cl		+50	+17	

Remarks.—All derivatives crystallize without crystallization water. The final rotation for α -penta-acetyl-glucose was obtained by dissolving 1.3114 g. to a volume of 24.9767 cc. with chloroform at 20°; for the fluoro-acetyl compound by dissolving

0.8175 g., for the chloro-acetyl compound 0.8274 g., and for the bromo-acetyl compound 0.8114 g. to the same volume under the same conditions.

Discussion of Results

The following conclusions are drawn by the author from these tables.

1. The *molecular* rotations and not the specific rotations must be considered for obtaining a relationship between the sets of compounds investigated.

2. The *molecular* rotation differences of these sets of compounds bear the same proportion to the atomic diameter differences as did the *specific* rotation differences of the compounds previously investigated.

These conclusions were obtained by the following considerations.

As reported in the preceding articles of this series,¹ the specific rotations of halogen-acetyl-derivatives of *d*-glucose, *d*-xylose and *l*-arabinose (the glucose and xylose compounds being α -*d* derivatives and the arabinose compounds being β -*l* derivatives and similar in structure as well as in sign and magnitude of rotation to α -*d*-galactose derivatives as shown by Hudson⁹) *increase in rotation to the positive side from the fluoro to the iodo compound*, in a regular way. The specific rotations of the halogen-acetyl derivatives of *d*-fructose (shown by Hudson¹⁰ to be β -*d*-derivatives) *increase in rotation to the negative side from the fluoro to the iodo compound* in the same regular way. This regularity holds now for the *molecular rotations* of the halogen derivatives¹¹ herein discussed. These *molecular rotations increase to the positive side* in Table IV, leaving at first the magnitude out of consideration, the halogen-acetyl-tetra-acetyl-glucoses being α -*d* compounds, and *increase to the negative side* in Tables II and III, the salicin derivatives being β -*d* compounds (Fischer,¹² Hudson and Paine¹³). When we consider the *specific* rotations, however, *every* series of the compounds investigated forms an exception to this regularity. In Tables II and III the specific rotations *increase* to the positive side from the chloro to the iodo compound, which is abnormal, and in Table IV the specific rotation first rises from the fluoro to the chloro compound and then drops from the chloro

⁹ Hudson, *THIS JOURNAL*, **46**, 462 (1924).

¹⁰ Hudson, *ibid.*, **46**, 479 (1924).

¹¹ The rotational values for the *hydrogen* derivatives have not been used to reach these conclusions. Structural considerations applying to the α -*d* glucose derivatives, the unestablished atomic dimension value for hydrogen and the lack of the fluoro-salicin derivative prevent the application of the rotational values of the hydrogen derivatives to these constructive conclusions. The atomic dimension value for hydrogen given by Wherry agrees, however, with the respective rotation differences.

¹² Fischer [*Ber.*, **27**, 2990 (1894)] found that salicin is hydrolyzed by emulsin but not by invertase in conformity with synthetic β -glucosides.

¹³ Hudson and Paine [*THIS JOURNAL*, **31**, 1242 (1909)] calculated the specific rotation of the freshly liberated glucose from salicin by the action of emulsin from the change in rotations with and without the presence of alkali, conclusively showing that β -glucose is split off by emulsin.

to the bromo derivatives, which is also abnormal for the stated regularity.

Coming now to the second conclusion, the differences of the specific rotations of the compounds here described are much smaller than those of the compounds previously described. This peculiarity makes it difficult to attain the degree of accuracy possible in the case of the former compounds. The result of a determination of mean error¹⁴ has been used here to judge the magnitude of dependable figures, as the determinations described were carried out with the same care. Small quantities of impurities which may be present are here a *much greater source of error* than for the derivatives compared in previous papers, where the considered differences are much larger. Special care was taken that the rotation finally adopted should agree as closely as possible with the rotation of the preceding crystallization, which often required for the salicin derivatives five recrystallizations. The records of the specific rotations of the recrystallizations of the individual compounds in the experimental part will give an idea of the purity obtained.

That the molecular rotations of the first class of compounds are not comparable with the molecular rotations of the second class of compounds follows from a consideration of the magnitude of the differences. The ratio of the differences of the molecular rotations of the first class of compounds for F-Cl to Cl-Br may be taken as 3 to 2, whereas this ratio for the second class of compounds as seen from Table IV is 3 to 1. This large difference in ratio cannot be explained by errors in observation or the presence of impurities in the second class of compounds.

To reach the second conclusion especial attention must be given to the comparison of the found molecular differences with the differences of the specific rotations of the first class of investigated compounds, which differ in the I-Br value from Bragg's atomic diameter differences. These are given in the last row of figures in each table. Tables II and III show that the ratio of these specific rotation values of the first class of compounds is in the best agreement with the ratio of the experimental values. Bragg's and Wherry's values also agree for Table II, but not so well for Table III, not considering the hydrogen values and taking into account the possible errors. The results in Table IV show the *typical high Cl-F value* in its ratio to the Br-Cl value, verifying the second conclusion. The outlook for including the hydrogen derivatives in the comparison is favorable, but is awaiting other comparisons.

In conclusion, it is to be emphasized that we have recognized *two* classes among asymmetric compounds of similar structure (glucose derivatives) containing substituted halogens. The compounds of the first class contain asymmetric carbon atoms in which the halogen is directly attached to this carbon atom so that the halogen itself is a seat of production of asym-

¹⁴ THIS JOURNAL, 46, 1486 (1924).

metry. In this first class of compounds, containing different halogens, *every molecule acts on polarized light in the ratio of its weight, yielding quantities of activity, which increase in proportion to the atomic dimensions of the halogens.*

The compounds of the second class contain asymmetric carbon atoms in which the halogens modify an asymmetry-producing group attached to this asymmetric carbon atom. In this class of compounds, containing different halogens, *every molecule acts as a unit in yielding the increase in activity proportional to the atomic dimensions of the halogens.*

It is still undecided whether the change from Class 1 to Class 2 when a chain of one to more atoms is introduced between asymmetric carbon and halogen is abrupt or gradual. It is possible that the principle of alternately induced polarity, diminishing in effect from a center [(C. F. van Duin, *Chem. Weekblad.*, **22**, 146 (1925))] may be applied in this connection, although this cannot be done without further experimental work. The relationship between *molecular* rotation and atomic magnitude shown to hold in the second class, is more readily understandable in physical terms than the same relationship in the first class, and in order to make sure that the latter relation was not merely a function of some peculiarity in configuration or structure of the compounds investigated, it is the author's intention to prepare other kinds of derivatives belonging to this class.

An explanation of all the observed facts does not appear to lie at hand and it seems well to collect first more data for other sets of halogen derivatives to establish the validity of the foregoing as rules.

Experimental Part

Salicin.—This was recrystallized from hot water. The second recrystallization gave a substance of constant rotation, m. p. 201°, agreeing with the value recorded by Visser³ and Schiff.¹⁵ The final value for the specific rotation was obtained by dissolving 0.6000 g. of substance and bringing to a volume of 98.6643 cc. with absolute alcohol at 20°. This solution produced a rotation in the 4dm. tube of 1.109 circular degrees to the left; hence, $[\alpha]_D^{20} = -45.60$, which is taken as the specific rotation of the pure substance, as a rotation of nearly identical magnitude was obtained with the former crystallization.

Chlorosalicin (Monochlorosalicin).—The method of preparation described by Piria¹⁶ (compare also Visser³), with certain modifications, was used. Several crystallizations are necessary to obtain an absolutely pure preparation. To remove a slight turbidity, especially noticeable in a water solution, an absolute alcoholic solution was filtered through a hardened filter until the solution was clear; m. p. of water-free substance, 164° (Visser,³ 154°). The final value for the specific rotation was obtained by dissolving 0.1668 g. of the dihydrate corresponding to 0.1500 g. of anhydrous substance to a volume of 24.9767 cc. with absolute alcohol at 20°, which produced a rotation in the 4dm. tube of 1.265 circular degrees to the left; hence, $[\alpha]_D^{20} = -52.66$, which is taken as the specific rotation of the pure substance. (Repeating the same estimation

¹⁵ Schiff, *Gazz. chim. ital.*, **11**, 111 (1881).

¹⁶ Piria, *Ann.*, **56**, 52 (1845).

yielded the identical value, and the former recrystallization gave the values -52.85 and -52.47 .) The water of crystallization was estimated by drying 0.5g. samples first in a desiccator over fresh sodium hydroxide. After this drying no more loss of weight was observed, by drying in a vacuum desiccator or by heating in a tube which was heated at 100° and evacuated to 2mm. pressure while connected to a container with phosphorus pentoxide.

Anal. Calcd. for $C_{18}H_{17}ClO_7 \cdot 2H_2O$: H_2O , 10.10. Found: 10.10, 10.12.

Two Carius determinations confirmed the results of previous investigators (Piria,¹⁶ and Visser³) that monochlorosalicin of the formula given had been prepared.

Anal. Subs., 0.2961, 0.3000: $AgCl$, 0.1200, 0.1205. Calcd. for $C_{18}H_{17}ClO_7 + 2H_2O$: Cl , 9.95. Found: 10.02, 9.93.

Bromosalicin.—The methods of preparation described by O. Schmidt¹⁷ were used. The preparation was recrystallized in the same manner as described for chlorosalicin until a constant-rotating product was obtained; m. p. of water-free substance, 171° (Visser,³ 170°). The final value for the specific rotation was obtained by dissolving 0.2197 g. of the dihydrate corresponding to 0.2000 g. of anhydrous substance to a volume of 24.9767 cc. with absolute alcohol at 20° , which produced a rotation in the 4dm. tube of 1.594 circular degrees to the left; hence, $[\alpha]_D^{20} = -49.77$ which is taken as the specific rotation of the pure substance as a former recrystallization gave the value $[\alpha]_D^{20} = -49.41$ and a subsequent recrystallization with a somewhat higher concentration gave the value $[\alpha]_D^{20} = -49.55$. The determination of the water of crystallization showed that Visser's results are erroneous and that bromosalicin behaves in the same manner as the corresponding chloro and iodo compounds.

Anal. Calcd. for $C_{18}H_{17}BrO_7 \cdot 2H_2O$: H_2O , 8.98. Found: 8.98, 8.72.

Subs., 0.2043: CO_2 , 0.2936; H_2O , 0.0955. Subs., 0.2989, 0.2956; $AgBr$, 0.1329, 0.1385. Calcd. for $C_{18}H_{17}BrO_7 + 2H_2O$: C , 38.89; H , 5.28; Br , 19.92. Found: C , 39.18; H , 5.23; Br , 19.78, 19.94.

Iodosalicin.—The method of preparation described by Visser³ was used. The method for separation and recrystallization of the iodosalicin was the same as that described for the chloro compound; m. p. of anhydrous substance 191° (Visser,³ 192°). The final value for the specific rotation was obtained by dissolving 0.1668 g. of the dihydrate (corresponding to 0.1534 g. of anhydrous substance) to a volume of 24.9767 cc. with absolute alcohol at 20° . This produced a rotation in the 4dm. tube of 1.178 circular degrees to the left; hence, $[\alpha]_D^{20} = -47.95$, which is taken as the specific rotation of the pure substance. A somewhat higher concentration of the same pure substance gave the value $[\alpha]_D = -48.23$ and a product of a former crystallization, $[\alpha]_D^{20} = -48.10$. The water of crystallization was determined by the method given for the chloro and bromo compounds.

Anal. Calcd. for $C_{18}H_{17}IO_7 \cdot 2H_2O$: H_2O , 8.04. Found: 8.08, 7.86.

Subs., 0.2976, 0.2938: AgI , 0.1557, 0.1544. Calcd. for $C_{18}H_{17}IO_7 + 2H_2O$: I , 28.33. Found: 28.27, 28.41.

Penta-acetyl-salicin was first prepared according to the method described by Schiff.¹⁸ Afterwards it was found that boiling under a reflux condenser with acetic anhydride¹⁹ for two hours instead of six hours yields the same product. The crystalliza-

¹⁷ Schmidt, *Zeitschr. f. Chem.*, **8**, 516 (1865).

¹⁸ Schiff, *Ann.*, **154**, 9 (1870).

¹⁹ The acetic anhydride was obtained by redistilling commercial acetic anhydride in a distilling apparatus, the parts of which were connected by ground joints. The use of this anhydride materially improved the yield of pure product. Undoubtedly, the

tion from alcohol had to be repeated several times before a constant rotation value was obtained. After a fifth (final) recrystallization, 2.000 g. of substance dissolved in chloroform under identical conditions produced a rotation of 5.874 circular degrees to the left; hence, $[\alpha]_D^{20} = -18.34$, which is taken as the specific rotation of the pure substance, as subsequent recrystallization did not materially change this figure, and a third and fourth recrystallization gave, respectively, the values $[\alpha]_D^{20} = -18.90$ and -18.53 ; m. p., 131–132° (Visser,³ 130°). To determine the acetyl groups, Schiff adopted for the estimations a prolonged boiling of the substance with magnesium hydroxide in water suspension. The author employed the following procedure. A mixture of 0.5000 g. of the very finely powdered compound with 100.13 cc. of 0.25 *N* sulfuric acid was boiled for five hours under a reflux condenser in a quartz flask. For neutralization, 300.39 cc. of 0.1 *N* sodium hydroxide solution was required; hence, 300.39 – 250.33 = 50.06 cc. of 0.1 *N* sodium hydroxide solution was used for neutralizing the acetic acid produced. Experiments with salicin made under the same conditions showed that necessary corrections for this prolonged heating are very small, as after boiling for five hours only 0.52 cc. of 0.1 *N* sodium hydroxide less was used for neutralizing the acid than would have been necessary before the boiling. Other experiments with acetyl-salicin showed that boiling for 4.5–5 hours is necessary to obtain complete hydrolysis. Applying the necessary small correction it was found, therefore, that the acetic acid produced by 0.5000 g. of the compound required 50.58 cc. of 0.1 *N* sodium hydroxide for neutralization. In a similar experiment 0.5000 g. of substance boiled for four and a half hours required 50.42 cc. of 0.1 *N* sodium hydroxide solution, whereas the formula requires for penta-acetyl-salicin 50.38 cc. of 0.1 *N* sodium hydroxide solution and for tetra-acetyl-salicin 44.03 cc. of 0.1 *N* sodium hydroxide solution.

Anal. Subs., 0.2147, 0.2111: CO₂, 0.4372, 0.4298; H₂O, 0.1093, 0.1074. Calcd. for C₁₃H₁₄O₃(C₂H₃O₂)₄: C, 55.48; H, 5.77. Calcd. for C₁₃H₁₃O₂(C₂H₃O₂)₅: C, 55.62; H, 5.69. Found: C, 55.53, 55.52; H, 5.69, 5.69.

Penta-acetyl-chlorosalicin.—The method of preparation described by Visser³ was followed. The recrystallization from absolute alcohol had to be repeated several times before a constant rotation value was obtained. After a fifth (final) recrystallization 2.000 g. of substance dissolved with chloroform to a volume of 24.9767 cc. produced a rotation of 7.146 circular degrees to the left; hence, $[\alpha]_D^{20} = -22.31$, which is taken as the specific rotation of the pure substance as the third and fourth recrystallization measured under similar conditions gave the values $[\alpha]_D^{20} = -22.43$ and -22.29 ; m. p., 157° (Visser,³ 142°). The acetyl determination was performed as has been described for penta-acetyl salicin.

Anal. Subs., 0.2111, 0.2218: CO₂, 0.4027, 0.4218; H₂O, 0.1005, 0.1022. Subs., 0.2948, 0.3003: AgCl, 0.0796, 0.0803. Subs., 0.5000: 100.38 cc. of 0.25 *N* H₂SO₄; 297.65 cc. of 0.1 *N* NaOH + corr. 0.52 cc. of 0.1 *N* NaOH. Calcd. for C₁₃H₁₃ClO₂(C₂H₃O₂)₄: C, 51.57; H, 5.36; Cl, 7.26; 40.93 cc. of 0.1 *N* NaOH for AcOH. Calcd. for C₁₃H₁₂ClO₂(C₂H₃O₂)₅: C, 52.01; H, 5.13; Cl, 6.68; 47.10 cc. of 0.1 *N* NaOH for AcOH. Found: C, 52.02, 51.87; H, 5.32, 5.16; Cl, 6.68, 6.61; 47.22 cc. of 0.1 *N* NaOH.

Penta-acetyl-bromosalicin.—This derivative was prepared according to the method used for the corresponding chloro derivative. It was necessary to repeat the recrystallization from absolute alcohol several times before a constant rotating substance was obtained. After a fifth (final) recrystallization, 2.000 g. of substance dissolved with

use of a catalyst (Na acetate) would give a better yield of the pure product, making the many recrystallizations unnecessary. It was interesting to prove, however, that by exactly following the methods of the previous investigators only *penta-acetyl* derivatives can be obtained.

chloroform to a volume of 24.9767 cc. produced a rotation of 7.035 circular degrees to the left; hence, $[\alpha]_D^{20} = -21.96$, which is taken as the specific rotation of the pure substance as a third and fourth recrystallization measured under similar conditions gave the values $[\alpha]_D^{20} = -22.18, -21.97$; m. p., 146° (Visser, ³ 148°).

Anal. Subs., 0.2040, 0.1915: CO_2 , 0.3597, 0.3378; H_2O , 0.0869, 0.0844. Subs., 0.2991, 0.2949: AgBr, 0.0954, 0.0972. Subs., 0.5000: 100.13 cc. of 0.25 *N* H_2SO_4 ; 292.98 cc. of 0.1 *N* NaOH + corr.: 0.52 cc. of 0.1 *N* NaOH. Calcd. for $\text{C}_{13}\text{H}_{13}\text{BrO}_8$ ($\text{C}_2\text{H}_3\text{O}_2$)₄: C, 47.27; H, 4.73; Br, 14.99; 37.52 cc. of 0.1 *N* NaOH for AcOH. Calcd. for $\text{C}_{13}\text{H}_{12}\text{BrO}_2(\text{C}_2\text{H}_3\text{O}_2)_5$: C, 47.99; H, 4.73; Br, 13.90; 43.47 cc. of 0.1 *N* NaOH for AcOH. Found: C, 48.09, 48.11; H, 4.80, 4.93; Br, 13.57, 14.02; 43.17 cc. of 0.1 *N* NaOH.

Penta-acetyl-iodosalicin.—This derivative was also prepared according to the method used for the corresponding chloro derivative. After a fourth (final) recrystallization 2.000 g. substance dissolved with chloroform to a volume of 24.9767 cc. gave a rotation of 6.935 circular degrees to the left; hence, $[\alpha]_D^{20} = -21.65$, which is taken as the specific rotation of the pure substance, as a second and third crystallization measured under similar conditions gave the values $[\alpha]_D^{20} = -21.64, -21.67$; m. p., 122° (Visser, ³ 119°).

Anal. Subs., 0.2516, 0.2345: CO_2 , 0.4106, 0.3836; H_2O , 0.0974, 0.0899. Subs., 0.2993, 0.3070: AgI, 0.1118, 0.1159. Subs., 0.5000: 100.13 cc. of 0.25 *N* H_2SO_4 ; 289.97 cc. of 0.1 *N* NaOH + corr. 0.52 cc. of 0.1 *N* NaOH. Calcd. for $\text{C}_{13}\text{H}_{13}\text{IO}_8$ ($\text{C}_2\text{H}_3\text{O}_2$)₄: C, 43.44; H, 4.34; I, 21.88; 34.48 cc. of 0.1 *N* NaOH for AcOH. Calcd. for $\text{C}_{13}\text{H}_{12}\text{IO}_2(\text{C}_2\text{H}_3\text{O}_2)_5$: C, 44.36; H, 4.37; I, 20.40; 40.15 cc. of 0.1 *N* NaOH for AcOH. Found: C, 44.50, 44.61; H, 4.33, 4.29; I, 20.19, 20.41; 40.16 cc. of 0.1 *N* NaOH.

α -Fluoro-acetyl-tetra-acetyl-glucose.²⁰—To prepare this compound, 5 g. of tetra-acetyl-glucose was dissolved in a solution of 0.5 g. of zinc chloride in 20 g. of fluoro-acetic anhydride and heated for a few minutes on the steam-bath. The reddish-brown solution was poured into ice water, and the gummy semi-crystalline product was taken up in ether.²¹ The ether solution was dried with anhydrous sodium sulfate, filtered and allowed to evaporate in the air, whereupon small needles separated. It was recrystallized in the same way and the separated crystals were filtered by suction. This recrystallization was repeated until further crystallization did not change the melting point or specific rotation. The yield is small (about 2 g. from 5 g. of glucose-tetra-acetate), but may no doubt be increased by repeating the preparation under different conditions. After three recrystallizations of the fluoro compound a fraction melting at 119 – 120° was obtained; 0.2518 g. of this fraction dissolved to a volume of 24.9767 cc. with chloroform produced a rotation in a 4dm. tube at 20° of 3.736 circular degrees to the right; hence, $[\alpha]_D^{20} = +92.64^\circ$. Another fraction of this recrystallization, which melted a little lower, at 118° , gave $[\alpha]_D^{20} = +91.89$. This last fraction was recrystallized, yielding a preparation melting at 119° , and $[\alpha]_D^{20} = +92.27$. A second fraction of the preceding re-

²⁰ Also corresponding beta derivatives may be obtained. Preliminary experiments for obtaining *β*-chloro-acetyl-tetra-acetyl-glucose with chloro-acetic anhydride and sodium acetate as catalyst have resulted in the separation of a crystalline derivative having a less positive specific rotation than the alpha compound, proving that the designation *α* derivatives, which had been derived from their preparation with zinc chloride as a catalyst, is the correct nomenclature. As some of the intermediates necessary for the preparation of fluoro-acetic anhydride are obtained in small yields, this preparation was available only in small amounts and was used up for the study of the *α* derivative. The preparation of the corresponding *β* derivatives for testing the atomic dimension relationship will be taken up later.

²¹ The water solution was saved for recovering the excess of fluoro-acetic acid.

crystallization, melting at the same temperature, gave $[\alpha]_D^{20} = +92.55$. The three preparations of specific rotations $+91.89^\circ$, $+92.27^\circ$ and $+92.55^\circ$ were combined and recrystallized; 0.3052 g. of the first fraction of this recrystallization, melting at 119° , gave a rotation of 4.509 circular degrees to the right under identical conditions; hence, $[\alpha]_D^{20} = +92.25^\circ$.

To obtain a specific rotation from a higher concentration, as used for the comparison, this last fraction was combined with that of $[\alpha]_D^{20} = +92.64$; 0.8175 g. of this preparation gave a rotation of 12.130 circular degrees to the right under identical conditions; hence, $[\alpha]_D^{20} = +92.65$, which has been taken as the specific rotation of the pure substance. The magnitude of the values ranging from $+92.25$ to $+92.65$ represents values within the limits of error²² for the pure compound. This determination of error could not be made for this compound, as not enough of the pure substance was available.

The substance melting at 119° is slightly bitter and is readily soluble in ordinary solvents, fairly soluble in benzene and little soluble in water and petroleum ether. The rotation of a solution of the compound in acetic anhydride did not change when some zinc chloride was dissolved and the solution heated for a few minutes on the steam-bath. The original compound could be recovered. This experiment indicates that the pure alpha compound has been separated.

The data obtained on analysis include also the results of the saponification, which was performed by shaking 0.5000 g. of the substance with an excess of 0.1 *N* sodium hydroxide solution at 0° for five and half hours. After the solution had been titrated, it was evaporated to a small volume and a few drops of acetic acid and calcium chloride solution were added. No precipitate was obtained after one night, indicating that fluoro-acetic acid had been formed under these conditions of saponification.

Anal. Subs., 0.2212: CO_2 , 0.3804; H_2O , 0.1053. Subs., 0.5000: CaF_2 , 0.0439. Subs., 0.5000: 140.6 cc. of 0.1 *N* NaOH; 80.15 cc. of 0.1 *N* H_2SO_4 . Subs., 2.029, 2.534: C_8H_6 , 100; ΔT , 0.233°, 0.290°. Calcd. for $\text{C}_{16}\text{H}_{21}\text{O}_{11}\text{F}$; C, 47.04; H, 5.18; F, 4.65; 61.27 cc. of 0.1 *N* NaOH for AcOH and CH_2FCOOH ; mol. wt., 408. Found: C, 46.99; H, 5.32; F, 4.23; 60.45 cc. of 0.1 *N* NaOH; mol. wt., 435, 437.

The intermediates needed were obtained as follows.

Tetra-acetyl-glucose was prepared according to the method of Fischer and Hess.²³ Fluoro-acetic acid by the procedure: chloro-acetyl chloride (Eastman) \longrightarrow methylester of chloro-acetic acid²⁴ \longrightarrow methylester of iodo-acetic acid²⁵ \longrightarrow methylester of fluoro-acetic acid²⁶ (using AgF^{27}) \longrightarrow fluoro-acetic acid.⁴ Fluoro-acetic anhydride has not been described in the literature, but its preparation is not especially difficult, if the general method of Bischoff and Walden²⁸ for converting halogenated acids to the respective anhydrides is followed. Fifty g. of phosphorus pentoxide was quickly mixed with 30 g. of powdered fluoro-acetic acid and distilled from a 1-liter distilling flask in the vacuum of an oil pump (2–3 mm.). The distillate was redistilled under the same conditions, and the acetylation (see before) was performed directly in the tared receiver, after the weight of the distillate had been determined (from 20–25 g.). Analysis was not made, and no physical constants were determined on the fluoro-acetic anhydride (which was obtained as a semi-solid crystalline mass at ordinary temperature), because not much of this reactive substance was available.

²² THIS JOURNAL, 46, 1486 (1924).

²³ Fischer and Hess, *Ber.*, 45, 912 (1912).

²⁴ Meyer, *Ber.*, 8, 1152 (1875).

²⁵ Aronstein and Kramps, *Ber.*, 14, 604 (1881).

²⁶ Moissan, *J. pharm. Chim.*, [5] 23, 329 (1891).

²⁷ Swarts, *Bull. Acad. Roy. Belgique*, 31, 675 (1896).

²⁸ Bischoff and Walden, *Ber.*, 27, 2949 (1894).

α -Chloro-acetyl-tetra-acetyl-glucose.—Three g. of tetra-acetyl-glucose was dissolved in a solution of 0.5 g. of zinc chloride in 10 g. of chloro-acetic anhydride,²⁹ heating the solution for eight minutes on the steam-bath and pouring the reaction product into a little cold water. The preparation solidified within half an hour. The crystalline lumps were broken and the crystals were filtered by suction. It was recrystallized from hot absolute alcohol. On allowing the solution to cool slowly, long, well-defined needles separated out. On recrystallizing the compound a few times, a pure product is obtained; yield, 2.5 g. of pure substance. After two recrystallizations, 0.8144 g. dissolved in chloroform to a volume of 24.9767 cc. produced a rotation in a 4dm. tube of 13.117 circular degrees to the right; hence, $[\alpha]_D^{20} = +100.57$. A third recrystallization gave almost the same results as a fourth recrystallization, which also agreed within a few hundredths of a degree with the final rotation of another preparation of the same compound; 0.8274 g. of the fourth recrystallization gave a rotation of 13.360 circular degrees to the right under identical conditions; hence, $[\alpha]_D^{20} = +100.82$, which is taken as the specific rotation of the pure substance; m. p., 128°. It is very slightly bitter and readily soluble in ordinary solvents, fairly soluble in benzene and slightly soluble in water and petroleum ether. The rotation of a solution of the compound in acetic anhydride did not change when some zinc chloride was dissolved and the solution was heated for a few minutes on the steam-bath. The original compound could be recovered. This experiment indicates that the pure alpha compound has been prepared. The saponification was performed in the same way as that for the corresponding fluoro compound. After the solution had been titrated, a few drops of nitric acid and silver nitrate solution were added, but not even a turbidity was observed. After boiling this solution for some time a precipitate of silver chloride was formed. This experiment shows that chloro-acetic acid has been formed in the saponification.

Anal. Subs., 0.2197: CO₂, 0.3629; H₂O, 0.0971. Subs., 0.3039: AgCl, 0.1026. Subs., 0.5000: 140.95 cc. of 0.1 N NaOH; 81.87 cc. of 0.1 N H₂SO₄. Subs., 2.1294: C₆H₆, 100; ΔT 0.250°. Calcd. for C₁₆H₂₁O₁₁Cl: C, 45.21; H, 4.98; Cl, 8.35; 58.82 cc. of 0.1 N NaOH for AcOH and CH₂ClCOOH; mol. wt., 425. Found: C, 45.05; H, 4.94; Cl, 8.35; 59.08 cc. of 0.1 N NaOH; mol. wt., 426.

α -Bromo-acetyl-tetra-acetyl-glucose.—The procedure of preparation and purification was the same as that for the analogous chloro compound, except the heating on the steam-bath, which was reduced to about five minutes. The necessary bromo-acetic anhydride was obtained from bromo-acetic acid in the same way as for the analogous chloro compound. The yield is 2 g. of pure product from 3 g. of tetra-acetyl-glucose; m. p., 116°. Two preparations of this compound yielded nearly the same end value for the specific rotation; 0.8190 g. of the fourth recrystallization of the first preparation dissolved to a volume of 24.9767 cc. with chloroform produced a rotation in a 4dm. tube at 20° of 12.421 circular degrees to the right; hence, $[\alpha]_D^{20} = +94.70$, nearly agreeing in value with the result of the third recrystallization (+94.40). A fifth recrystallization of this preparation produced for 0.8114 g. under identical conditions a rotation of 12.320 circular degrees to the right; hence, $[\alpha]_D^{20} = +94.81$, which is taken as the specific rotation of the pure substance. The end value of the other preparation gave a specific rotation of +94.78. It is slightly bitter and is readily soluble in ordinary solvents except water and petroleum ether. In conformity with the other compounds, the rotation of a solution in acetic anhydride did not change when zinc chloride was dissolved and the solution heated for a few minutes on the steam-bath. The saponification was performed

²⁹ Chloro-acetic anhydride was obtained by the method of Bischoff and Walden (Ref. 29) using the same procedure and the same proportions of P₂O₅ and chloro-acetic acid as were used for the analogous fluoro-acetic anhydride.

in the same way as that for the fluoro and chloro compounds. The titrated solution did not show any turbidity after the addition of nitric acid and silver nitrate solution. Silver bromide precipitated only after boiling, showing that bromo-acetic acid had been formed in the saponification.

Anal. Subs., 0.2177: CO₂, 0.3264; H₂O, 0.0904. Subs., 0.1623: AgBr, 0.0647. Subs., 0.5000: 140.60 cc. of 0.1 *N* NaOH; 87.28 cc. of 0.1 *N* H₂SO₄. Subs., 1.633, 2.6542, 3.2058: C₆H₆, 100; ΔT 0.181°, 0.283°, 0.355°. Calcd. for C₁₆H₂₁O₁₁Br: C, 40.93; H, 4.51; Br, 17.04; 53.30 cc. of 0.1 *N* NaOH for AcOH and CH₂BrCOOH; mol. wt., 469. Found: C, 40.89; H, 4.65; Br, 16.96; 53.32 cc. of 0.1 *N* NaOH; mol. wt., 451, 469, 451.

Summary

Two classes of asymmetric compounds containing substituted halogens are recognized:

(I) A class in which the halogens are directly attached to the asymmetric carbon atom; here every molecule acts in the ratio of its weight, yielding quantities of activity which increase with the respective atomic dimensions of the halogens. (II) A class in which the halogens modify an asymmetric group attached to the asymmetric carbon atom; in this class every molecule acts as a unit for yielding the same result as in the first class.

It has not yet been determined whether an abrupt or a gradual change from Class I to Class II exists when a chain of one or more atoms is introduced between asymmetric carbon and halogen. The behavior of the compounds in Class I, however, is unexpected and this class will first be investigated for other kinds of derivatives.

The outlook for including the hydrogen derivatives in the comparison is favorable, but such inclusion must await further experimental data. Data for substantiating these above regularities will be collected.

The specific rotations of halogen derivatives of salicin and their penta-acetates are measured, and the methods of preparation, properties and analyses of α -fluoro-, chloro- and bromo-acetyl-tetra-acetyl-glucose are given.

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