THE CONFIGURATIONAL RELATIONSHIPS OF THE SUGARS, HYDROXY ACIDS, AMINO ACIDS AND HALOGEN ACIDS

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In recent years, chemists have devoted much attention to the configurational relationships of monosaccharides, α-amino, α-hydroxy and α-halogen acids.

The field of chemistry in which the achievements of stereochemistry have been the greatest is undoubtedly that which deals with the configurational relationships of monosaccharides. The name of Fischer is preeminent among all workers in this field, but the name of Kiliani should also be remembered in this connection as he was the one to furnish a method for the synthesis of a higher monosaccharide from a lower one and Fischer made much use of this method.

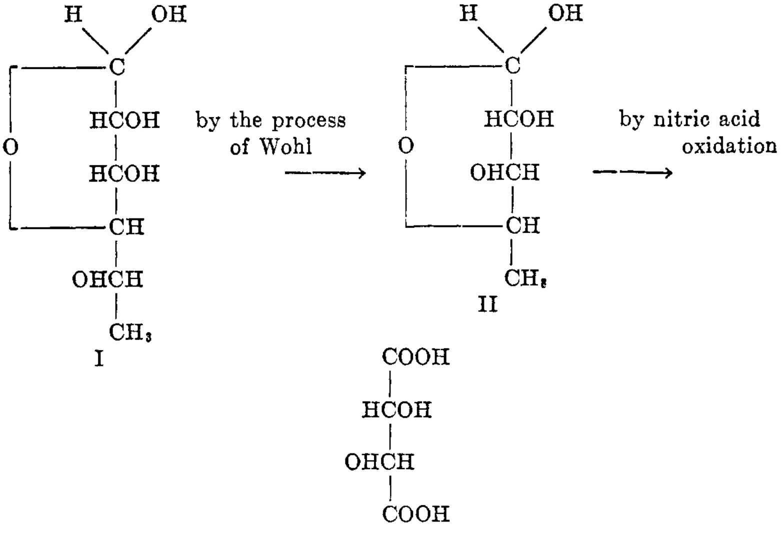
The relationships of simple carbohydrates is a matter of common knowledge and need not be reviewed here. The most rational and clearest presentation of these relationships is found in the article of Rosanoff. A comprehensive summary on simple sugars in general is to be found in the monograph of Armstrong.

Fischer, in his day the greatest master of stereochemistry and also the greatest authority on sugar chemistry, was the first to point out the possibility of correlating the configuration of hydroxy acids with the configuration of monosaccharides. The pioneer work in this direction was done by Fischer himself and further progress was made by workers who received their training and inspiration from him. Fischer also realized the importance of correlating the configurations of amino acids with those of hydroxy acids and made some efforts towards that end but soon realized that the usual chemical methods were inadequate for that purpose. This problem received considerable attention in other laboratories and substantial progress towards its solution has been made in recent years. This review will be devoted principally to these achievements. A brief review, however, will be given of the work on the correlation of the configurations of hydroxy acids with those of the sugars and of the mutual relationships of the configuration of individual amino acids.

The work on the two last-mentioned problems was accomplished by purely chemical methods. The chemical reactions employed were such that did not involve the asymmetric carbon atom.

CORRELATION OF HYDROXY ACIDS WITH SUGARS

The first effort of a comprehensive treatment of this subject is that by Fischer. Prior to Fischer, isolated attempts were made in this direction. The first important contribution by Fischer was the one which established the configuration of d-tartaric acid, which was prepared by the degradation of l-rhamnose through the following steps:



dextro-tartaric acid.

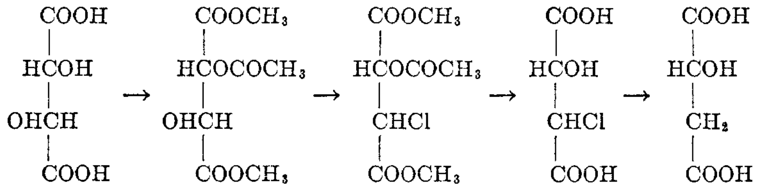
III

In 1875 Bremner converted by the action of hydroiodic acid dextro-tartaric into dextro-malic acid and in this he saw conclusive evidence of the similarity of the allocation of the hydroxyl in dextro-malic and dextro-tartaric acids.

Prior to the time of Fischer's work, it had been shown that dextro-malic acid could be obtained from levo-aspartic acid. Fischer, in the early days of his work, thought that these three independent observations justified the conclusion that dextro-tartaric, dextro-malic and levo-aspartic acids are configurationally related.

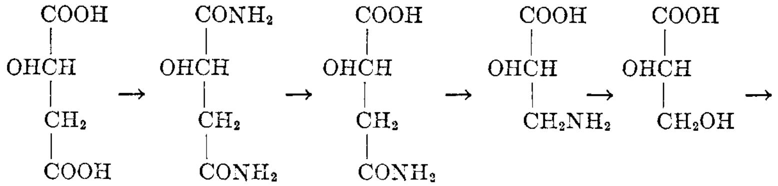
But in 1893, the phenomenon of Walden Inversion was discovered and thereupon Fischer, in 1896, qualified the conclusions regarding the configuration of the four substances by a proviso that a Walden Inversion had not taken place in the course of the reactions which led from one to the other. As it happened, subsequent and more reliable methods which excluded the possibility of Walden Inversion established the same relationships which were formulated by Bremner.

The following figures, IV, V, VI, VII, VIII illustrate the set of reactions by which dextro-tartaric acid was converted into dextro-malic acid by K. Freudenberg and F. Braun.

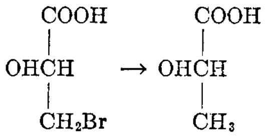


dextro IV; V; VI; VII; dextro VIII

In an investigation which preceded the one just mentioned, K. Freudenberg correlated the configurations of malic, glyceric and lactic acids by the following set of reactions.



natural, levo IX; malamid X; malaminic acid XI; levo iso-serine XII; dextro-glyceric acid. XIII

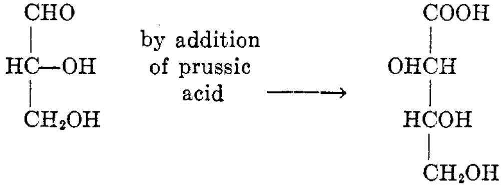


$$\begin{array}{c}\mathrm{COOH}\\|\\\mathrm{OHCH}\\|\\\mathrm{CH_2Br}\end{array}\rightarrow\begin{array}{c}\mathrm{COOH}\\|\\\mathrm{OHCH}\\|\\\mathrm{CH_3}\end{array}$$

dextro-3-bromo lactic acid. XIV

dextro-lactic acid. XV

In a very ingenious and laborious way, Wohl and his coworkers correlated on the one hand, the configuration of glyceric aldehyde with tartaric acid and on the other, that of glyceric aldehyde with glyceric acid. Thus, in coöperation with Momber, he established the relationship between dextro-glyceric aldehyde and levo-tartaric acid in the following way:

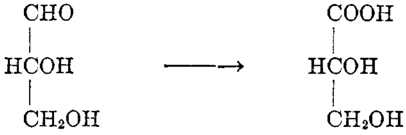


$$\begin{array}{c}\mathrm{CHO}\\|\\\mathrm{HC{-}OH}\\|\\\mathrm{CH_2OH}\end{array}\xrightarrow{\text{by addition of prussic acid}}\begin{array}{c}\mathrm{COOH}\\|\\\mathrm{OHCH}\\|\\\mathrm{HCOH}\\|\\\mathrm{CH_2OH}\end{array}$$

dextro-glyceric aldehyde XVI

levo-tartaric acid. XVII

With R. Schellenberg he oxidized glyceric aldehyde to the corresponding acid,

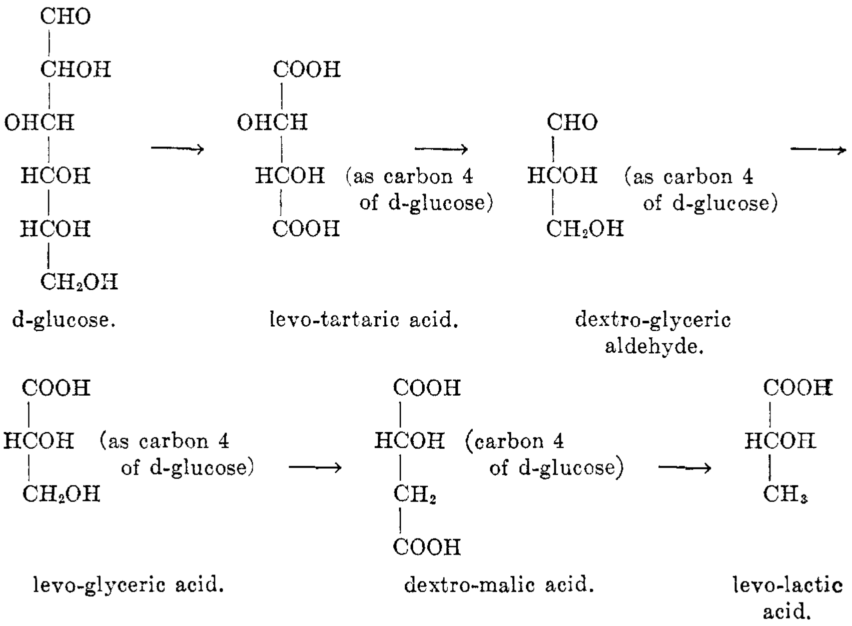


$$\begin{array}{c}\mathrm{CHO}\\|\\\mathrm{HCOH}\\|\\\mathrm{CH_2OH}\end{array}\longrightarrow\begin{array}{c}\mathrm{COOH}\\|\\\mathrm{HCOH}\\|\\\mathrm{CH_2OH}\end{array}$$

dextro-glyceric aldehyde,

levo-glyceric acid. XVIII

Thus, on the basis of all this very ingenious and technically difficult work the following relationships are established. Carbon atoms 3 and 4 of glucose are taken as points of reference.



$$\begin{array}{c} CHO \\ | \\ CHOH \\ | \\ OHCH \\ | \\ HCOH \\ | \\ HCOH \\ | \\ CH_2OH \end{array} \longrightarrow \begin{array}{c} COOH \\ | \\ OHCH \\ | \\ HCOH \\ | \\ COOH \end{array} \longrightarrow \begin{array}{c} CHO \\ | \\ HCOH \\ | \\ CH_2OH \end{array} \longrightarrow$$

$$\begin{array}{c} COOH \\ | \\ HCOH \\ | \\ CH_2OH \end{array} \longrightarrow \begin{array}{c} COOH \\ | \\ HCOH \\ | \\ CH_2 \\ | \\ COOH \end{array} \longrightarrow \begin{array}{c} COOH \\ | \\ HCOH \\ | \\ CH_3 \end{array}$$

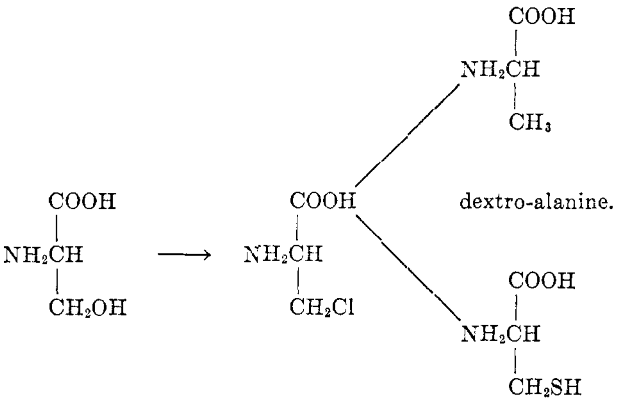
XIX

The dextro and levo, refer only to the direction of rotation whereas the letter *d*, as in *d-glucose*, indicates that the sugar belongs to the d series. Rosanoff's classification of the d and l series should be generally accepted. On the basis of this classification, dextro-tartaric, dextro-malic, levo-glyceric and levo-lactic belong to the d series. The designation of d and l series is a matter of convention; the relationship given in figure XIX are facts and correlate the other substances with d-glucose, if carbon atom (2) of d-glucose is taken as point of reference.

STEREOCHEMICAL RELATIONSHIPS OF 2-AMINO ACIDS

The pioneer work in this direction was also done by E. Fischer. In coöperation with K. Raske, he converted levo-serine into levo-1-amino-2-chloropropionic acid and this into dextro-alanine and later, also in coöperation with Raske, he converted levo-1-

amino-2-chloropropionic acid into levo-cystine. The reactions involved are presented in the following figures:



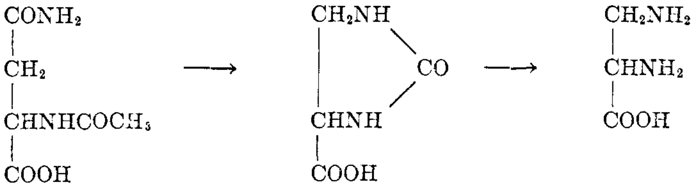
levo-serine

levo-1-amino-2-chloro-propionic acid

levo-cystine.

FIG. XX

It is evident that all these amino acids belong to one and the same series although they rotate in opposite directions. More recently, Karrer in coöperation with Schlosser converted levo-asparagine into dextro-diamino-propionic acid through the following set of reactions.



levo-asparagine.

XXI

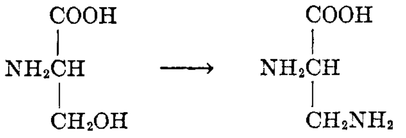
levo-glyoxalidon 2-carbonic acid-5.

XXII

dextro-diamino propionic acid.

XXIII

Later, Karrer converted dextro-serine into levo-diamino-propionic acid, thus having correlated levo-aspartic acid with levo-serine.



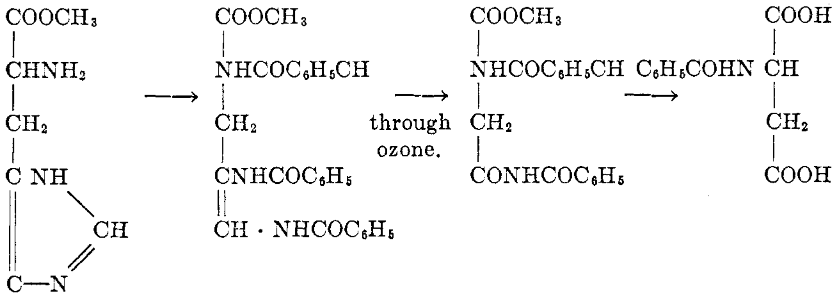
$$\begin{array}{c} COOH \\ | \\ NH_2CH \\ | \\ CH_2OH \end{array} \longrightarrow \begin{array}{c} COOH \\ | \\ NH_2CH \\ | \\ CH_2NH_2 \end{array}$$

levo-serine dextro-diamino propionic

XXIV

Mention also should be made of the work of E. Waser and E. Brauchli, who advanced evidence in favor of configurational relationship between l-tyrosine and l-phenylalanine.

The latest contribution to the correlation of amino acids is the work of W. Langewhick from the laboratory of K. Freudenberg. This author converted histidine into benzoyl-levo-aspartic acid by the following set of reactions.



Hystidine methyl ester

benzoyl-levo-aspartic acid.

XXV

This concludes the list of amino acids of which the mutual stereochemical relationships have been established by chemical reactions which did not involve the asymmetric carbon atom.

While the work thus far reviewed was in progress, new problems came to the fore of which the solution at that time and still now seems unapproachable by the purely chemical method. Prominent among these were: The differentiation between dynamic isomers such as α- and β-sugars, ring isomers in the sugars, and above all, the problems which arise from the phenomenon of Walden Inversion.

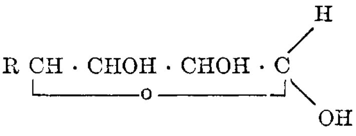
For the solution of these new problems, recourse was taken to physical methods and the review which is to follow will be devoted to a survey of efforts in this direction. Several authors were engaged on these problems. The methods employed in each were in certain respects similar but not identical and the results obtained by different methods, in the majority of instances, were mutually corroborative. For clearness it may be advantageous to sketch separately the progress brought about by each individual method.

CONCLUSIONS BASED ON VAN'T HOFF'S SUPERPOSITION THEORY

First phase

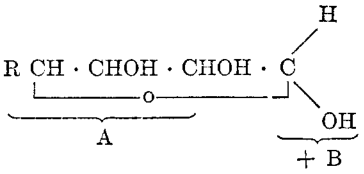
The pioneer work on the application of van't Hoff's theory for the purpose of bringing out configurational relationships was done by C. S. Hudson. A complete review of this work will not be attempted in this place for several reasons. It would occupy more space than the scope of the article permits. To some extent, it is being reviewed by Hudson himself. In this sketch only an outline of Hudson's method of reasoning is given.

The first paper by Hudson on this subject bears the title "The Significance of Certain Numerical Relations in the Sugar Group" and is concerned principally with the configuration of carbon atom (1) of the simple sugars and of their glycosides. The deductions made in that paper are based on two fundamental principles: one is that of van't Hoff, postulating that the molecular rotation of a substance with more than one asymmetric group is equal to the algebraic sum of the rotations of the individual groups. The second refers to the structure of simple sugars. The discovery of α- and β-isomers of simple sugars and of their glycosides led E. Fischer and other sugar chemists to accept for simple sugars the structure suggested by Tollens and now known as the oxidic structure, namely,



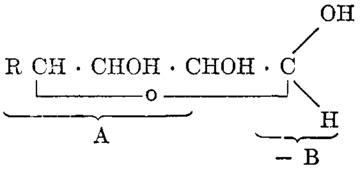
$$\mathrm{R}\,\underbrace{\mathrm{CH\cdot CHOH\cdot CHOH\cdot C}}_{\mathrm{O}}{<}^{\mathrm{H}}_{\mathrm{OH}}$$

Here R stands either for H, (C_nH_{2n+1}) or for $CH_2OH(CHOH)_n$. Hudson pointed out that the molecular rotation of a simple sugar may be regarded as the algebraic sum of the rotations of carbon atom (1) and of that of the rest of the molecule. Thus, designating the α-isomer



$$\underbrace{\text{R CH}\cdot\text{CHOH}\cdot\text{CHOH}}_{A}\cdot\text{C}\begin{matrix}\text{H}\\ \underbrace{\text{OH}}_{+\,B}\end{matrix}$$

the β-isomer will have to be expressed



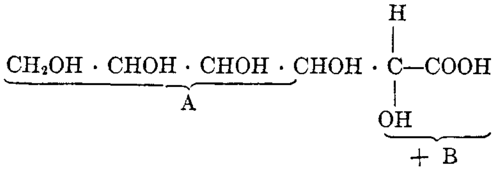
$$\underbrace{\text{R CH}\cdot\text{CHOH}\cdot\text{CHOH}}_{A}\cdot\text{C}\begin{matrix}\text{OH}\\ \underbrace{\text{H}}_{-\,B}\end{matrix}$$

Thus, the sum of the molecular rotation represents the value of 2 A and the difference that of 2 B.

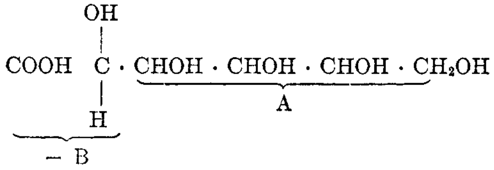
By the use of this method, Hudson succeeded in establishing important relationships concerning the configuration of carbon atom (1) of simple sugars and of their glycosides; later, he extended the method for exploring the structure of several di- and trisaccharides as regards the α- or β-character of their glycosidic unions. The work has been both stimulating and important.

Second phase

This phase relates to stereochemical relationships of hydroxy acids. In search for a clue to the solution of the problem of the allocation of the amino group in 2-aminohexonic acids, P. A. Levene was led to test whether the superposition theory of van't Hoff holds also for hexonic acids. The reasoning of Levene was analogous to that of Hudson. The molecular rotation of a hexonic acid may be regarded as the sum of rotations of two parts: one consisting of carbon atoms (1) and (2) and the other including carbon atoms (3), (4), (5) and (6). Thus, taking a pair of epimeric hexonic acids, each isomer may be represented as follows:



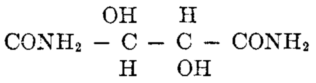
$$\underbrace{CH_2OH \cdot CHOH \cdot CHOH}_{A} \cdot CHOH \cdot \underbrace{\overset{H}{\underset{OH}{C}}—COOH}_{+\,B}$$



$$\underbrace{COOH \quad \overset{OH}{\underset{H}{C}}}_{-\,B} \cdot \underbrace{CHOH \cdot CHOH \cdot CHOH \cdot CH_2OH}_{A}$$

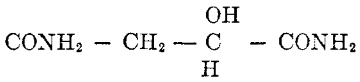
Here then the sum of the molecular rotations of the two acids is equal to 2A, and the difference to 2B.

Analysis of the data published by different writers but principally by Nef on the rotations of metal salts, alkaloidal salts and of phenylhydrazides of a number of sugar acids revealed the regularity in the direction of rotation of the carbon atoms (2) of the entire group of substances, namely, it was found that in all acids which had the allocation of the hydroxyl of carbon atom (2) as in the d-gluconic acid, the rotation of B was to the right and in those with the configuration of carbon (2) as in d-mannonic acid, the rotation of B was to the left. Later in coöperation with G. M. Meyer, Levene prepared a series of metal salts of sugar acids and later a series of phenylhydrazides. The original conclusions of Levene were substantiated by the more comprehensive analysis. Hudson also lent his attention to the optical behavior of sugar acids and noted that the rotation of B in the phenylhydrazides of sugar acids was quantitatively higher than that of A, and that therefore the direction of rotation of carbon atom (2) is in the same direction as that of the phenylhydrazide. Hence, according to Hudson, it was not necessary to possess a pair of epimers in order to determine the direction of rotation of carbon atom (2). Later Weerman and also Hudson and his co-workers directed their attention to the amides of sugar acids. Hudson further extended his observations to acids of simpler structure, namely, to tartaric and malic, the configurations of which were established by chemical means and he found that also in the case of these acids the rule held, namely, d-tartaric acid amide



$$CONH_2 - \overset{OH}{\underset{H}{C}} - \overset{H}{\underset{OH}{C}} - CONH_2$$

in agreement with the prediction rotated to the right and l-malic



$$CONH_2 - CH_2 - \overset{OH}{\underset{H}{C}} - CONH_2$$

to the left. Hudson then applied the rule to levo-mandelic acid and attributed to it the configuration of the l-acids. Freudenberg, however, later modified the rule of Hudson to read that all such acids are to be designated as d-acids of which the amides have a higher dextro-rotation than the free acids. When so formulated, the rule held for all acids of known configuration and also for mandelic acid.

The case of levo-mandelic acid is important for the following reason. Mandelic acid is levo-rotatory (−153°) and forms a levo-rotatory amide (−95.5°) and hence, according to the rule of Hudson, should be regarded as an l-acid. On the other hand, hexahydromandelic acid obtained by the hydrogenation of levo-mandelic acid is levorotatory (−26.6°) and forms a dextrorotatory amide. Thus, according to the original rule of Hudson, different configurations should be assigned to the two acids but according to the rule as modified by Freudenberg, the same configuration of *d*-acids is assigned to both.

Thus, in regard to the configuration of hydroxy-acids, the work of Levene, Hudson, Weerman and Freudenberg led to the formulation of definite rules which permit the determination of the configuration of a hydroxy acid on the basis of its optical behavior. It must be emphasized, however, that all the work thus far reviewed was concerned principally with developing a physical method for ascertaining configurational relationships of hydroxy derivatives only. The next task was to discover a way for coördinating configurations of amino and hydroxy derivatives. The work of Levene on hexosaminic acids had that aim. Similar was the aim of the work of Clough. The methods employed by Clough were the outgrowth of much important work on the relationship of chemical structure and optical rotation which was done by many very prominent chemists, namely, Frankland, Armstrong, McKenzie, Patterson, Pickard and Kenyon and others. The principal contributions bearing on the topic under discussion are reviewed in the following section.

INFLUENCE OF EXTERNAL CONDITIONS SUCH AS TEMPERATURE AND CHARACTER OF SOLVENT AND OF SUBSTITUTION ON OPTICAL ROTATION

It may be well to begin the survey of the work on this topic by reference to the publication by Frankland and Wharton in 1896. The investigation was concerned with the influence of chemical structure on the optical activity. In that, the rotatory powers of dibenzoyl and ditoluyltartrates are discussed. The unexpected observation made in the course of the work is contained in the following quotation: "This is a very remarkable series of rotations, exhibiting, as it does, a phenomenon which, as far as we are aware, has not hitherto been observed, namely, the passage through a maximum in the change of rotation, brought about by change of temperature, or, in other words, a change in the sign of the sensitiveness of the rotation due to the temperature."

The results are given in table 1.

In a more extensive way the influence of solvent and of temperature on rotation was investigated by T. S. Patterson. At the outset of his work, Patterson was engaged in searching for the causes of the variation of the rotatory power of a substance n different solvents. The method employed by this author onsisted in comparing the curves expressing the changes of rotations with respect to changes of temperature. Patterson discarded the then-prevailing theory that the cause of the variation of rotation was due to the differences in the state of aggregation in different solvents and instead was inclined to accept the view that the principle variable was the molecular solution volume. Soon, however, the work assumed a broader aspect, namely, the search for such peculiarities or singular points in the temperature rotation (T.R.) curves which could offer a basis of comparison between structurally related substances. Patterson was impressed by the fact first noted by Frankland and Wharton that every T.R. curve had a sinuous form exhibiting a maximum and a minimum. This author then concentrated his attention on the position of the maximum point with the change of concentration and of temperature. Figure XXVII presents the results of measurements of the molecular rotation of aqueous solutions of potassium ethyltartrate. In these experiments the

TABLE 1

Rotation of ethylic dibenzoyltartrate

(Length of polarimeter tube in each case was 44 mm.)

$$\text{At } 1.3^\circ\ [\alpha]_D = \frac{-30.06^\circ}{0.44 \times 1.2121} = -56.36^\circ;\ [\delta]_D = -477.5.$$

$$\text{At } 18.0^\circ\ [\alpha]_D = \frac{-31.29^\circ}{0.44 \times 1.1979} = -59.36^\circ;\ [\delta]_D = -499.0.$$

$$\text{At } 38.0^\circ\ [\alpha]_D = \frac{-32.06^\circ}{0.44 \times 1.1809} = -61.70^\circ;\ [\delta]_D = -514.0.$$

$$\text{At } 44.0^\circ\ [\alpha]_D = \frac{-32.10^\circ}{0.44 \times 1.1758} = -62.05^\circ;\ [\delta]_D = -515.0.$$

$$\text{At } 53.5^\circ\ [\alpha]_D = \frac{-32.00^\circ}{0.44 \times 1.1677} = -62.28^\circ;\ [\delta]_D = -514.5.$$

$$\text{At } 60.0^\circ\ [\alpha]_D = \frac{-31.85^\circ}{0.44 \times 1.1622} = -62.28^\circ;\ [\delta]_D = -513.0.$$

$$\text{At } 77.5^\circ\ [\alpha]_D = \frac{-31.37^\circ}{0.44 \times 1.1472} = -62.15^\circ;\ [\delta]_D = -507.0.$$

$$\text{At } 100.0^\circ\ [\alpha]_D = \frac{-30.16^\circ}{0.44 \times 1.1280} = -60.77^\circ;\ [\delta]_D = -490.5.$$

$$\text{At } 109.5^\circ\ [\alpha]_D = \frac{-29.51^\circ}{0.44 \times 1.1199} = -59.89^\circ;\ [\delta]_D = -481.0.$$

$$\text{At } 136.5^\circ\ [\alpha]_D = \frac{-27.38^\circ}{0.44 \times 1.0970} = -56.72^\circ;\ [\delta]_D = -450.0.$$

$$\text{At } 182.5^\circ\ [\alpha]_D = \frac{-24.03^\circ}{0.44 \times 1.0571} = -51.66^\circ;\ [\delta]_D = -399.5.$$

position of the maximum varied with concentration of the solute. It varied also with the solvent and with the character of the chemical group introduced into the tartaric acid.

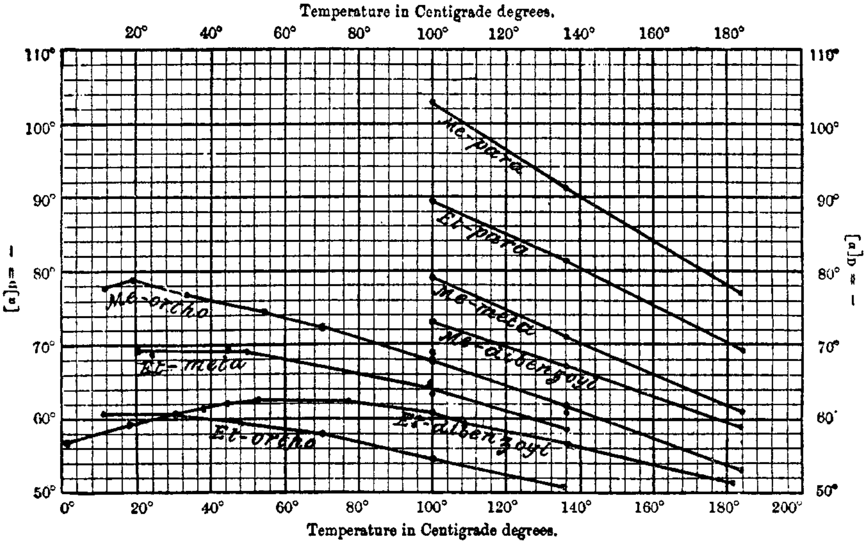


FIG. XXVI. INFLUENCE OF TEMPERATURE ON THE SPECIFIC ROTATION OF METHYLIC AND ETHYLIC DITOLUYLTARTRATES, AND OF METHYLIC AND ETHYLIC DIBENZOYLTARTRATES

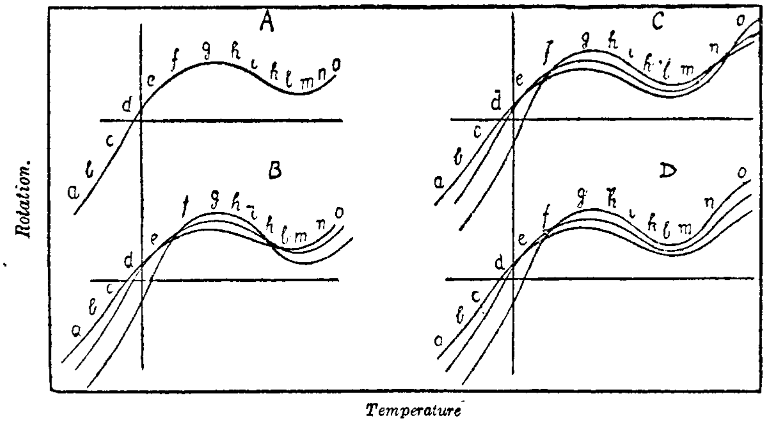


FIG. XXVII

Patterson, after work which extended over many years and which embraces a great number of substances, came to the conclusion that closely related chemical substances such as esters of tartaric acid exhibit similar temperature rotation curves, although the maximum rotation may occur at different temperatures and at different rotations.

The significance of the temperature rotation curve as a basis of comparison of configurationally similar substances was further demonstrated by Pickard and Kenyon in a long series of investigations on the derivatives of simple secondary carbinols.

As experience and data accumulated, it became evident that another important factor had to be considered in comparing configurationally related substances, namely, the color of the light employed for the measurement of the rotation. In this connection a very important discovery was made by Armstrong and Walker. These authors suggest that the specific rotations of substances for light of different refrangibilities can be arranged diagrammatically and, what they term a "characteristic diagram" is formed by configurationally related substances. Armstrong and Walker describe the construction of the diagram in the following words:

> To construct the diagram characteristic of a substance, a reference line is drawn with a slope of unity and on this are plotted the various specific rotations of light of any of the refrangibilities observed. The points for other refrangibilities are then plotted on the ordinate passing through the points previously located on the reference line. The observations may be those made either in different solvents or at different concentrations.

Figure XXVIII represents the characteristic diagram for d-fructose in different concentrations. The measurements were made by Armstrong and Walker. In Figure XXIX specific rotations are plotted as functions of solvent.

The application of rotatory dispersion was further advanced by the very important work of T. M. Lowry who demonstrated that for the majority of organic substances, the rotatory dispersion can be expressed by Drude's formula

$$\alpha = \frac{K}{\lambda^2 - \lambda^2_0} \qquad (I)$$

He termed the form of dispersion which can be expressed by this formula, "simple dispersion," in distinction from "complex dispersion" which could not be expressed by the simple formula

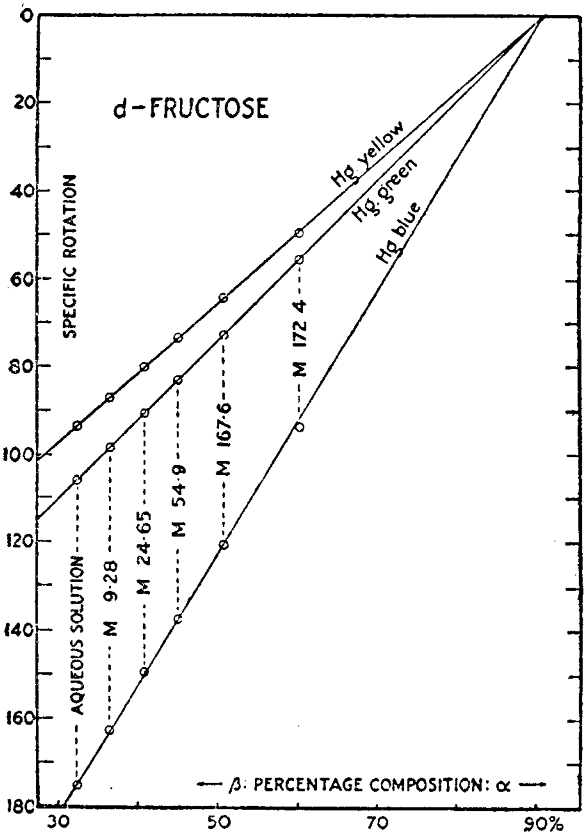


Fig. XXVIII. Characteristic Diagram of d-Fructose

Equilibrium between α and β forms altered by the addition of alcohol to the aqueous solution. Reference color, Hg green.

and which required for its expression the two membered formula containing four constants:

$$\alpha = \frac{K_1}{\lambda^2 - \lambda^2_1} - \frac{K_2}{\lambda^2 - \lambda^2_2} \qquad \text{(II)}$$

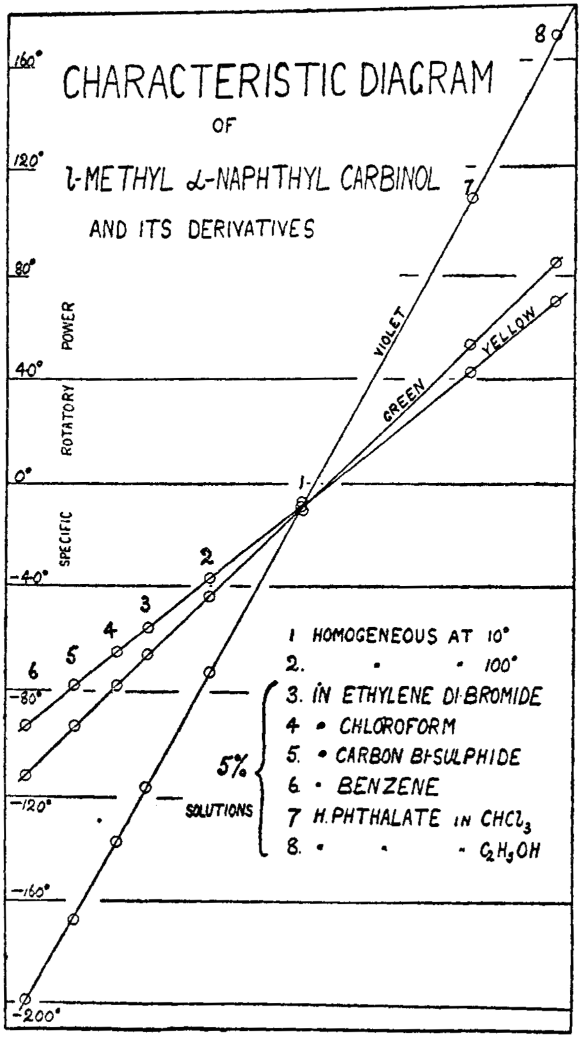


Fig. XXIX. Characteristic Diagram for l-Methyl-α-Naphthyl Carbinol and its Derivatives

The measurements were made by Pickard and Kenyon

It is evident that K, in all cases where formula (I) holds for lights of all refrangibilities, is independent of the wave length, and hence K- the rotation constant, expresses better the rotatory properties of a substance than the value of the specific rotation at one given wave length.

Very useful information was obtained when rotatory dispersion was measured at varying temperatures. Namely, it was observed that certain substances exhibited complex dispersion up to a certain range of temperature changes and then followed the simple law. This indicates that the complexity of the solution is smaller at the temperatures exhibiting the simple dispersion and hence comparisons made at those temperatures are more serviceable.

To sum up, the studies in temperature rotation changes and those in rotatory dispersion, aimed at a method of expressing those rotatory powers of a substance which were, as far as possible, free from external influences. The methods here reviewed were particularly useful in correlating the configurational relationships of carbinols but were also applied to work which constitutes the main theme of this review and to which the following two sections are devoted.

CONFIGURATIONAL CORRELATION BETWEEN AMINO ACIDS AND HYDROXY ACIDS

Chronologically, after the discovery of Walden Inversion, the systematic effort of correlating the configuration of amino acids with hydroxy acids was made by Levene, but the publication of Clough had a more comprehensive scope and for this reason, the discussion will begin with a review of his article, published in 1918. The principles developed by Frankland, Patterson, Pickard and Kenyon were accepted by Clough and made the basis for a comparison of the configurational relationships of hydroxy, amino and halogen acids.

Hydroxy acid

Clough began his discussion by the analysis of the influences of external conditions such as temperature, solvent and certain substituents on a series of acids of known configuration, namely, on levo-lactic, levo-glyceric, dextro-malic and dextro-tartaric. These acids, as developed in the earlier part of this review, are configurationally identical and because of their relationship to d-glucose may be designated d-acids.

Clough then extended his analysis to hydroxy acids of which the configuration had not been known. Thus he examined the

TABLE 2

The influence of sodium bromide on the optical rotatory power of levomalic acid, dextro-tartaric acid, methyl-levo-lactate, methyl-levo-malate, and methyl-dextro-tartrate in methyl alcoholic solution

COMPOUND	$[\alpha]^{15}_{gr.}$ (IN METHYL ALCOHOL C = 10)	$[\alpha]^{16}_{gr.}$ (IN METHYL ALCOHOLIC SODIUM BROMIDE N. C = 10)
Levo-malic acid	−5.9	+21.8°
Dextro-tartaric acid	+2.6	−9.0
Methyl-levo-lactate	+5.4	−5.8
Methyl-levo-malate	−9.4	+9.1
Methyl-dextro-tartrate	+2.7	−12.6

TABLE 3

The influence of sodium haloids on the optical rotatory powers of dextro-β-phenyl-lactic acid and methyl-dextro-β-phenyl-lactate in solution

COMPONENT	SOLVENT	$\hat{C}$	t°	$\alpha^{t}_{gr.}$ (l=2)	$[\alpha]^{t}_{gr.}$
Dextro-β-phenyl lactic acid	Water	2.505	20°	+1.28°	+25.5
	Aqueous sodium chloride (4N)	0.665	20°	+0.18	+13.5
	Methyl alcohol	10.0	20°	+4.20	+21.0
	Methyl alcoholic sodium bromide (N)	10.0	20°	−0.41	−2.0
Methyl-dextro-β-phenyl lactate	Methyl alcohol	10.0	18°	−0.90	− 4.5
	Methyl alcoholic sodium bromide	10.0	18°	−4.46	−22.3

influence of sodium chloride (or bromide) on dextro-β-phenyl lactic acid and its methyl ester. On the basis of similarity of the action of these salts on this acid and on the derivatives of levo-malic, levo-lactic and dextro-tartaric acids, he assigned to dextro-β-phenyl lactic acid the configuration of the d-series. Of the many tables relating to the hydroxy acids the two pertaining to this case are given by way of an illustration of Clough's procedure.

In a similar way the behavior of levo-α-hydroxyisohexoic, levo-α-hydroxyglutaric and levo-α-hydroxyisovaleric acids was analyzed.

The conclusions regarding the configurations of hydroxyacids suggested by Clough are: "levo-lactic acid, levo-glyceric acid, dextro-malic acid, dextro-α-hydroxy butyric acid, dextro-α-hydroxyisovaleric acid, dextro-α-hydroxyisohexonic acid, dextro-α-hydroxyglutaric acid and dextro-β-phenyl lactic acid all possess the same relative configuration as dextro-tartaric acid."

2-Amino acids

Clough then proceeded to investigate the influence of inorganic salts and of different solvents on the optical rotatory power of amino acids.

The following tables contain the data of such information as was obtained by Clough or as collected by him from literature.

Applying to the analysis of the optical behavior of amino acids the same mode of reasoning as was used in connection with the hydroxy acids, Clough formulated the following conclusion regarding the configuration of naturally occurring amino acids.

> Naturally occurring amino acids, commonly denoted as dextro-alanine, levo-serine, levo-aspartic acid, dextro-valine, levo-leucine, dextro-isoleucine, dextro-aminobutyric acid, dextro-glutamic acid, levo-phenylalanine, and levo-tyrosine all possess the same configuration. The configuration of these compounds has been denoted by the symbol "l."[1]

In a similar manner, Clough has analyzed the behavior of α-halogen acids. In connection with this class of compounds,

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[1] Clough denotes by "d" such acids that have the configuration of d-tartaric acid and as "l" those having the configuration of levo-tartaric acid. The present writer suggests the indication of the direction of rotation by the words "dextro," or "levo," and those having the configuration of d-tartaric acid as d-acids. This practice would be in harmony with the designations now in use in the sugar acids.

TABLE 4

The influence of inorganic salts on the optical rotatory power of d-glutamic acid in aqueous solution

SOLVENT	p	d^{25}	$\alpha^{25}_{\text{gr.}}$ $(l = 4)$	$\left[\alpha\right]^{25}_{\text{gr.}}$
Water	1.50	1.003	+0.80°	+13.3°
Aqueous sodium chloride (*N*)	1.50	1.043	0.90	14.4
Aqueous sodium chloride (4*N*)	1.51	1.152	1.10	15.8
Aqueous potassium chloride (*N*)	1.53	1.050	0.95	14.8
Aqueous barium chloride (*N*)	1.53	1.092	0.96	14.4
Aqueous barium bromide (4*N*)	1.51	1.500	1.64	18.1
Aqueous sodium hydroxide (1 mol.)	12.25	1.075	−1.88	−3.6
Aqueous sodium hydroxide (2 mols.)	6.55	1.050	+3.22	+11.7
Aqueous hydrogen chloride (1.5 mols.)	8.75			+37.4

TABLE 5

The influence of solvents on the optical rotatory power of ethyl l-aspartate

SOLVENT	c	$\alpha^{15}_{gr.}$ $(l = 2)$	$[\alpha]^{15}_{gr.}$
None		−6.34° (1 = 0.5)	−11.7°
Benzene	10.92°	−2.75	−12 6
Chloroform	11.02	−2.13	−9 7
Acetone*	20.0	−3.50	−8.8
Water	21.7	+1.83	+4.2
Water	12.25	1.03	4.2
Aqueous sodium chloride (4*N*)	10.81	1.44	6.7
Aqueous barium bromide (4*N*)	14.50	3.34	11.5
Aqueous calcium chloride (5*N*)	13.21	3.84	14.5
Aqueous hydrogen chloride (*N*)	11.37	2.73	12.0
Methyl alcohol	20.0	$\alpha^{20}_{gr.}$ −0.19	$[\alpha]^{20}_{gr.}$ −0.5
Methyl-alcoholic sodium bromide (*N*)	20.0	$\alpha^{20}_{gr.}$ +1.72	$[\alpha]^{20}_{gr.}$ +4.3

* Ethyl *l*-aspartate reacts with acetone, the rotation changing from $\alpha_{gr.}$ − 3.50° to $\alpha_{gr.}$ −56.6° (c = 20) in fifteen hours.

TABLE 6

The optical rotatory powers ($[\alpha]_D^{20}$) *of α-amino acids and of certain derivatives from them*

AMINO-ACID	WATER	HYDRO-CHLORIC ACID	BENZOYLAMINO-ACID (IN KOH, AQ)	AMINOACYLGLYCINE (IN WATER)	GLYCYLAMINO-ACID (IN WATER)	HYDANTOIN*
d-Alanine[1]	+2.7°	+14.3°	+36.5°	+50.2°	−50.0°	+50.6° (water)
l-Serine[2]	−6.8	+14.4	+43.6 (in NaOH, aq.) (p-nitrobenzoyl)	—	—	—
l-β-Chloro-α-aminopropionic acid[3]	−15.5	+0.9	—	—	—	—
d-α-Aminobutyric acid[4]	+8.0	+19.6	+30.7 (in NaOH, aq.)	+86.4 (K) +26.8 (A & C)	−20.3	—
d-Valine[5]	+6.4	+28.7	—	+90	−19.7	−97.5 (phenyl-hydantoin in alcohol).
d-α-Aminohexoic acid[6]	—	+23.0	+21.9	—	—	—
l-Leucine[7]	−10.3	+15.6	+6.6 (in NaOH, aq.)	+85.5	−35.0	−68.2 (in NaOH, aq.)

[*] Hydantoins, Dakin & Dudley, J. Biol. Chem., 1913, **17**, 29; 1914, **18**, 48; T., 1915, **107**, 434.

[1] Fischer, Ber., 1905, **38**, 2914; 1906, **39**, 453; 1907, **40**, 943.

[2] Fischer and Jacobs, Ber., 1906, **39**, 2942; Fischer and Raske, Ber., 1907, **40**, 3717.

[3] Fischer and Raske, loc. cit.

[4] Fischer and Mouneyrat, Ber., 1900, **33**, 2383; Koelker, Zeitsch. physiol. Chem., 1911, **73**, 312; Abderhalden and Chang, ibid., 1912, **77**, 471.

[5] Fischer, Ber., 1906, **29**, 2320; Fischer and Scheibler, Annalen, 1908, **363**, 136.

[6] Fischer and Hagenbach, Ber., 1901, **34**, 3764.

[7] Fischer, Ber., 1900, **33**, 2370; Ber., 1906, **39**; 2893; Fischer and Steingroever, Annalen, 1909, **365**, 167.

TABLE 7

The optical rotatory powers ($[\alpha]_D^{20}$) *of α-amino-acids and of certain derivatives from them*

AMINO-ACID	WATER	HYDROCHLORIC ACID	BENZOYLAMINO-ACID (IN KOH, AQ.)	AMINO-ACYLGLYCINE (IN WATER)	GLYCYLAMINO-ACID (IN WATER)	HYDANTOIN*
d-iso Leucine[8]	+11.3°	+40.6°	+26.4° (in NaOH, aq.)	+33.6°	−14.7°	—
l-Asparagine[9]	−4.9	+28.5	—	—	−6.4	—
l-Aspartic acid[10]	+4.3	+25.7	+37.4	—	+11.1	−125 (in NaOH, aq.)
d-Glutamic acid[11]	+9.9	+30.8	+18.7	—	−6.3	−79 (in NaOH, aq.)
l-Phenylalanine[12]	−35.3	−7.1	+17.1	+54.2	+41.4	−96.4 (in 50 per cent alcohol).
l-Tyrosine[13]	—	−8.6	+19.2	—	—	−143 (in NaOH, aq.)

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[*] Hydantoins, Dakin and Dudley, J. Biol. Chem., 1913, **17,** 29; 1914, **18,** 48; T., 1915, **107,** 434.

[8] Locquin, Bull. Soc. chim., 1907 [iv], **1,** 595; Abderhalden, Hirsch, and Schuler, Ber., 1909, **42,** 3394.

[9] Fischer and Koenigs, Ber., 1904, **37,** 4585.

[10] Fischer, Ber., 1899, **32,** 2451; Fischer and Fiedler, Annalen, 1910, **375,** 181.

[11] Fischer, Kropp, and Stahlschmidt, Annalen, 1909, **365,** 189.

[12] Fischer and Mouneyrat, loc. cit.; Fischer and Schoeller, Annalen, 1907, **357,** 1.

[13] Fischer, Ber., 1899, **32,** 3638.

the available data were very meagre. Nevertheless, Clough felt justified in drawing the following conclusion:

> The dextrorotatory α-halogen acids which have been isolated are assumed to be configurationally similar compounds. A comparison of the rotatory powers of the optically active α-bromoacylamino acids with those of the α-aminoacylamino acids leads to the view that the halogen acids mentioned above are configurationally related "l" amino-acids.

Thus, according to Clough, the naturally occurring amino acids have the configurations of l-tartaric acid and the dextro halogen acids have the same configurations. Clough, however, states that further investigations are desirable in order that a definite decision may be reached.

Simultaneously with Clough, Karrer, in coöperation with Kaase, measured the optical rotatory dispersion of dextro-glutamic acid, and of several of its derivatives, the ethyl ester, levo-chloroglutaric and dextro-hydroxyglutaric. The amino acid, the hydroxy acid and several other derivatives exhibited a rise in dextrorotation with the decrease in the wave length; the chloroderivative exhibited an increase to the left. Karrer and Kaase drew the conclusion that the hydroxy and the amino acids examined by them were configurationally related, whereas the levo-chloroacid was enantiomorphously related to the former two. With respect to the amino and chloroacid, the conclusions of Karrer and Kaase coincided with that of Clough.

Very recently, Freudenberg and Rhino measured the rotation constant of several derivatives of dextro-alanine with similar derivatives of dextro-lactic acid. The calculations were made by the Ackerman formula which is Drude's rotatory dispersion formula. Its applicability for the measurement of rotatory dispersion of organic compounds was first demonstrated by Lowry. Table 8 contains the results of the observations of Freudenberg and Rhino.

On the basis of these results, Freudenberg and Rhino consider dextro-alanine and dextro-lactic acids configurationally similar and denote the two acids l-acids.

Thus, practically every one of the methods introduced by Frankland, Patterson, Armstrong, Pickard and Kenyon for the study of stereochemical relationships was made use of in the investigations of configurational relationships between hydroxy acids, halogen acids and amino acids. Thus far, the conclusions have been mutually corroborative.

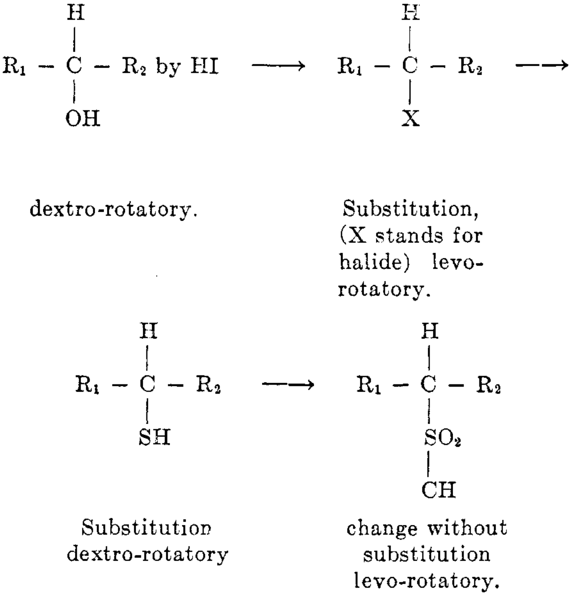
TABLE 8

	K_M NATURAL (DEXTRO) ALANINE	K_M DEXTRO LACTIC ACID
1. Amide of the benzoyl derivative	<+29	+36
2. Ethyl ester benzoyl derivative	+3	+10.5
3. Methyl ester benzoyl derivative	0 (±1)	+7.5
4. Ethyl ester of the hexahydrobenzoyl derivative	−19 (±4)	−15
5. Ethyl ester of the acetyl derivative	−22	−25
6. Amide of Toluolsulfo derivative	−26 (±8)	−28 (±3)
7. Ethyl ester Toluolsulfo derivative	−26	−39

THE INFLUENCE ON THE OPTICAL ROTATION OF THE CHANGE OF POLARITY OF ONE OF THE GROUPS ATTACHED TO THE ASYMMETRIC CARBON ATOM BROUGHT ABOUT WITHOUT THE PROCESS OF SUBSTITUTION

It was pointed out in the early section of this review that the correlations in the group of hydroxy acids were to a large extent established by methods of pure organic chemistry. Also those that have not yet been correlated by these methods undoubtedly will be some day in the not distant future. Many of the amino acids have been mutually correlated by purely chemical methods. It is not impossible that the halogen substituted acids will be mutually correlated by such methods. However, there is little hope that hydroxy, amino and halogen acids will be correlated by purely chemical methods. The cause of the difficulty lies in the phenomenon of Walden Inversion. When the condition under which the Inversion takes place will be discovered, then the correlation between the configuration of the three groups of substances will become apparent of itself. The work on Walden

Inversion done up to the present remains without practical value for the investigations into configurational relationships. Recently, Levene has undertaken a series of investigations which promises to throw some light on the circumstances under which the phenomenon of Walden Inversion occurs. The plan of the work consists in observing the changes in the optical activity of a substance which are brought about by changes in the polarity of one group attached to the asymmetric carbon atom when the change is accomplished without substitution. Levene, in cooperation with Mikeska, observed the changes in the optical behavior of secondary thioderivatives and of the corresponding sulfonic acids. The results of the observations are the following. In the derivatives of normal secondary alcohols, the changes in direction of rotation are as follows:



$$\begin{array}{c}H\\|\\R_1-C-R_2\\|\\OH\end{array}\text{ by HI}\longrightarrow\begin{array}{c}H\\|\\R_1-C-R_2\\|\\X\end{array}\longrightarrow$$

dextro-rotatory.

Substitution, (X stands for halide) levo-rotatory.

$$\begin{array}{c}H\\|\\R_1-C-R_2\\|\\SH\end{array}\longrightarrow\begin{array}{c}H\\|\\R_1-C-R_2\\|\\SO_2\\|\\CH\end{array}$$

Substitution dextro-rotatory

change without substitution levo-rotatory.

Thus, in this group of substances, the last change of the direction of rotation is brought about under conditions which exclude the possibility of a Walden Inversion and therefore, one is justified in concluding that normal aliphatic dextrorotatory secondary alcohols are configurationally related to the levorotatory halides and that the above conversion of the alcohol into the halide has taken place without Walden Inversion.

Levene and Mikeska then extended their observations to α-substituted acids.

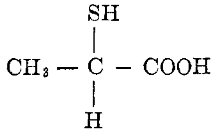
In this group of substances the change from the thio to the sulfonic acid derivative is not accompanied by the same change of rotation that was characteristic of the derivatives of the normal secondary alcohols. A decrease in dextro-rotation, perhaps, is exhibited by the sulfonic acid derivatives. This needs confirmation. The important fact, however, is that in the thio acid and in the sulfonic acid, there is observed the same character of change of rotation when the acid is converted into a metallic salt. Thus, dextro-thiolactic acid forms a levorotatory sodium salt, and the configurationally related sulfopropionic acid shows a similar change of rotation when it is transformed into a metallic carboxylic salt. The results of the measurements are given in table 9.

TABLE 9

Optical activity of the salts of thio and sulfo acids

SUBSTANCE	FREE ACID $[M]_D$	MONO-SALT $[M]_D$	DI-SALT $[M]_D$	TRI-SALT $[M]_D$
l-Xanthopropionic acid	+107.68°	+45.05°		
l-Thiolactic acid	+58.98°	−5.58°	+7.32°	
l-Sulfopropionic acid	+13.76°	+12.84°	−3.28°	
l-Xanthosuccinic acid	+95.05°	+43.86°	+8.65°	
l-Thiosuccinic acid	+73.06°	+41.58°	+48.57°	+41.09°
l-Sulfosuccinic acid	+44.25°	+43.43°	+29.22°	+25.67°
d-Sulfobutane	−4.38°	−6.29°		

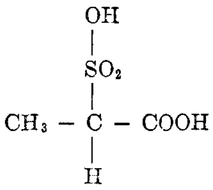
At first glance the results summarized in this table seem confusing. Thus the dextrorotatory thiolactic acid forms a levorotatory monobasic salt. It behaves in this respect similarly to dextro-lactic acid. The direction of rotation, however, is again changed when a second equivalent of sodium hydroxide is added to the solution. Thus the neutral salt is dextrorotatory. In the sulfopropionic acid the direction of rotation is unaltered when the acid is converted into a monobasic salt, and is reversed in the dibasic salt. This apparently puzzling difference in the behavior of the two substances, however, can be readily explained. In dextro-thiolactic acid



$$\begin{array}{ccc} & SH & \\ & | & \\ CH_3 - & C & - COOH \\ & | & \\ & H & \end{array}$$

the carboxyl is the stronger acidic group. When the hydrogen of this group is replaced by a metal ion, the substance behaves as dextro-lactic acid, namely, the salt is levorotatory. When a second equivalent of the base is added, it replaces the hydrogen atom of the sulfide rest and then the direction of the rotation turns to the right.

In the sulfopropionic acid



$$\begin{array}{ccc} & OH & \\ & | & \\ & SO_2 & \\ & | & \\ CH_3 - & C & - COOH \\ & | & \\ & H & \end{array}$$

the stronger acidic group is the SO_2OH rest. The neutralization of this group brings about a slight change in the direction toward the left, as is the case when the thio group is neutralized in dextro-thiolactic acid. When a second equivalent of base is added, this forms a salt with the carboxyl group and then the direction of the rotation is shifted to the left as is the case when the carboxyl group is neutralized in the dextro-thiolactic or in the dextro-lactic acids.

In a similar way, the changes in rotations of the thio- and sulfosuccinic acids may be analyzed.

These observations are instructive inasmuch as the configurational relationships of the substances are known from the methods of their preparation and hence the observations show that substituted acids configurationally related exhibit similar changes of optical rotation when the acids are converted into the metallic salts even though the polarity of one of the groups attached to the asymmetric carbon atom is changed. Thus, dextro-lactic acid and dextro-alanine should also be regarded as configurationally related for the reason that in both, the free acid has a higher dextrorotation than the metallic salt. The same conclusions regarding dextro-lactic acid and dextro-alanine were reached by Clough and by Freudenberg on other grounds. The evidence of Levene and Mikeska is more direct than that of the other writers.

THE STEREOCHEMICAL RELATIONSHIPS OF HEXOSES AND HEXONIC ACIDS TO 2-AMINOHEXOSES AND 2-AMINOHEXONIC ACIDS

Work on this problem was undertaken prior to any other systematic investigation into the configurational relationship of amino and hydroxy derivatives. The original plan of the work was a comprehensive one. It was hoped first to correlate the simple sugars and sugar acids with aminohexoses and hexosaminic acids, then to reduce the latter to α-amino acids and thus to establish the configuration of amino acids by purely chemical methods. Work on aminopentonic acids also was contemplated. Unfortunately, the attempts to reduce the 2-aminohexonic acids to optically active 2-aminocaproic acids were not successful. Nevertheless, the work on hexosamines and on aminohexonic furnished very important data for the elucidation of the configurational relationship of hydroxy and of amino acids.

The advantages which the sugar acids offer for the study of stereochemical relationships are the following: A pair of enantiomorphous substances differ from one another by only one property, the direction of the optical rotation. Two sugar acids enantiomorphous only with regard to carbon atom (2) differ, as a rule, in other physical properties in addition to the optical and often differ also in their chemical behavior. Furthermore, the acids can be reduced to the corresponding sugars, and these again differ markedly from one another. Thus, gluconic and mannonic acids are characterized not only by the optical behavior of the free acids and their salts, amides, and phenylhydrazides, but also by their solubilities, their tendencies to form crystalline lactones, etc., and in addition, by the physical and chemical properties of glucose and of mannose to which they can be reduced respectively.

Levene and his co-workers synthetically completed the series of 2-aminohexonic acids (only one had been known prior to their work). Making use of the van't Hoff superposition theory in a manner similar to that applied by Hudson to sugars, they classified the eight d-2-aminohexonic acids into two groups, namely,

Group I	*Group II*
Chitosaminic	Epichitosaminic
Chondrosaminic	Epichondrosaminic
Levo-xylohexosaminic	Dextro-xylohexosaminic
Levo-ribohexosaminic	Dextro-ribohexosaminic

The substances in each group are configurationally related in regard to carbon atom (2). The substances in group I and group II are enantiomorphously related in regard to carbon atom (2). The basis for this classification is the comparison of the values of the optical rotations of carbon atom (2) in the hydrochlorides of the amino acids. The next problem was to establish the allocation of the amino groups in these acids. The configuration of carbon atom (2) in hexonic acids has been definitely established by chemical methods. It thus became necessary to establish the genetic relationships between the hexonic and the amino hexonic acids.

Table 10 represents the values and the direction of the rotation of carbon atom (2) in the hexonic and hexosaminic acids when the rotation of the hydrochlorides of the latter are compared with those of the phenylhydrazides of the former.

The similarity of the specific rotations is striking. However, this property alone is not sufficient to establish the configurational relationships of the two groups of substances. Therefore additional proof was needed. For this reason, the following points were investigated: first, the equilibrium between the two epimeric hexonic acids formed by the addition of prussic acid to a pentose;

second, the equilibrium between the corresponding two hexosaminic acids formed through the addition of prussic acid to

TABLE 10

ACID HYDROCHLORIDES	$[\alpha]_D$ OF CARBON ATOM (2)	$[M]^{20}_D$	PHENYLHYDRAZIDE	$[\alpha]_D$ OF CARBON ATOM (2)	$[M]^{20}_D$
Epichitosaminic	+12.5	+24.37	Gluconic	+14.25	+42.18
Chitosaminic	−12.5	−24.37	Mannonic	−14.25	−42.18
Dextro-xylohexosaminic	+12.5	+24.37	Gulonic	+14.25	+42.18
Levo-xylohexosaminic	−12.5	−24.37	Idonic	−14.25	−42.18
Epichondrosaminic	+12.5	+24.37	Galactonic	+8.25	+24.42
Chondrosaminic	−12.5	−24.37	Talonic	−8.25	−24.42
Dextro-ribohexosaminic	+19.12	+37.28	Allonic	+20.8	+61.56
Levo-ribohexosaminic	−19.12	−37.38	Altronic	−20.8	−61.56

TABLE 11

FROM	ROTATION OF CARBON ATOM 2 IN PREDOMINATING FORM	FROM	ROTATION OF CARBON ATOM 2 IN PREDOMINATING FORM
Arabinose	Levo	Aminoarabinoside	Levo
Lyxose	Levo	Aminolyxoside	Levo
Xylose	Dextro	Aminoxyloside	Dextro
Ribose	Levo	Aminoriboside	Levo

TABLE 12

Chitosaminic acid	2-aminomannonic acid
Epichitosaminic acid	2-aminogluconic acid
Chondrosaminic acid	2-aminotalonic acid
Epichondrosaminic acid	2-aminogalactonic acid
Dextro-d-xylohexosaminic acid	2-aminogulonic acid
Levo-d-xylohexosaminic acid	2-aminoidonic acid
Dextro-d-ribohexosaminic acid	2-aminoallonic acid
Levo-d-ribohexosaminic acid	2-aminoaltronic acid

amino-pentoses. The two equilibria were then compared and found as given in table 11.

On the basis of the analogies recorded in tables 10 and 11, the relationships as given in table 12 could be formulated.

Further, it was found that when chitosaminic acid was deaminized, it gave gluconic acid (as the 2-5 anhydro form) but not mannonic. This was in agreement with Fischer's assumption that on deamination of α-amino acids with nitrous acid, a Walden Inversion occurs.

If, in addition, it is remembered that it was customary to designate as "d-amino acids" all such acids which rotate to the right in hydrochloric acid solution, and as "d-hydroxy acids" all acids of which the salts rotate to the right, it will become evident how the relationships expressed in table 12 for a time seemed logical and correct.

Doubts as to the rationality of this mode of comparison came to the fore when the directions of rotations of carbon atom (2) were determined not from the behavior of the sugar acids but from that of the sugars themselves. On the basis of van't Hoff's superposition theory it is possible, as was shown by Hudson, to determine the direction of the rotation of carbon atom (2) of two epimeric sugars when the rotations of the α- β-forms of each are known. When, on the one hand, two hexoses, glucose and mannose, were taken for comparison and on the other hand, two 2-aminohexoses; chitosamine and epichitosamine (all may be taken in the form of pentacetates) then it was found that carbon atoms (2) in glucose and in chitosamine rotated in the same direction, namely, to the right, and mannose and epichitosamine both to the left. On the basis of these observations, chitosamine should be considered configuratively related to glucose, and epichitosamine to mannose. Thus, a contradiction arose between the conclusions reached on the basis of the optical rotations of the epimeric hexosaminic acids and those reached on the basis of the epimeric aminohexoses. Further inquiry became necessary in order that a decision could be reached in favor of one or the other conclusion. It may be added here that the preponderance of evidence was found in favor of the second of the two named relationships.

It was known from the work of Hudson and his co-workers that the difference in the molecular rotations of the α- and β-glucoses had a normal value, and from the calculations of

Hudson and Yanowsky and from the experimental work of Levene it was definitely proved that in the case of the α- and β-mannoses, the corresponding value was abnormal. Some time ago, Irvine prepared the α- and β-isomers of chitosamine hydrochloride and found that the difference of the molecular rotation of the two forms was normal and therefore suggested that chitosamine was configurationally related to glucose. This evidence alone would scarcely be sufficient to establish the configuration of chitosamine. The molecular rotations of sugars are determined largely by the character of the oxidic ring and it is possible that in a simple sugar and in the corresponding 2-amino sugar the predominating form may have a different ring structure.

However, though insufficient in itself, the conclusion of Irvine found confirmation in the above-mentioned result of the evaluation of the rotation of carbon atom (2) of chitose on the basis of the rotations of α- and β-chitose pentacetates and α- and β-epichitose pentacetates. A third point of evidence favorable to this conclusion is found in the consideration of the properties of epichitosamine. The difference of the optical rotations of the α- and β-forms of this sugar was found abnormal, resembling mannose in this respect, and if the structure of 2-amino mannose is attributed to epichitose, then the structure of 2-aminoglucose should be assigned to chitose. For this theory, then, three points of evidence have accumulated.

There still remained the puzzle of the discrepancy between the conclusions following from the observations made on the properties of the sugars and those of the acids. However, a wholly harmonious theory is reached when a different basis is chosen for connecting the configurations of hexonic and aminohexonic acids than the one taken for table 10.

A scrutiny of tables 13 and 14 showing the direction of the rotation of the hexonic acids in solution of dilute hydrochloric acid and the rotations of the metallic salts, phenylhydrazides or amides brings to light certain regularities. From these tables it is seen that all hexonic and all 2-aminohexonic acids can be

TABLE 13

Showing the specific rotations of the free acids and of their derivatives
(All of the d series)

	FREE ACIDS $[\alpha]_D^0$	Na SALTS $[\alpha]_D^{20}$	PHENYLHYDRAZIDES $[\alpha]_D^{20}$	AMIDES $[\alpha]_D$
Gluconic	0.0	+11.78	+18.0	+31.2
Mannonic	+15.6	−8.82	−10.5	−17.3
Idonic	+	−2.52	−15.1	–
Gulonic	−1.6	+12.68	+13.45	+15.2
Galactonic	−8.0	+0.40	+12.2	+30.0
Talonic	?	?	+4.35	–
Allonic	−10.0	+4.30	+25.88	–
Altronic	+8.0	−4.05	−15.8	–

TABLE 14

ACIDS	IN 5 PER CENT NaOH $[\alpha]_D^0$		IN 2.5 PER CENT HCl $[\alpha]_D^0$
Chitosaminic	+1.3°	c = 5.0	−15.0°
Epichitosaminic	−5.0°	c = 5.0	+10.0°
Dextro-d-xylo-2-aminohexonic	−16.°	c = 2.5	+14.0°
Levo-d-xylo-2-aminohexonic	+2.0°	c = 2.5	−11.0°
Chondrosaminic	−15.0°	c = 2.5	−17.0°
Epichondrosaminic	+1.8°	c = 2.5	+8.0°
Dextro-d-ribo-2-aminohexonic	+2.0°	c = 2.5	+12.5°
Levo-d-ribo-2-aminohexonic	−15.0°	c = 2.5	−26.0°

TABLE 15

First group	
Chitosaminic acid	Gluconic acid
Chondrosaminic acid	Galactonic acid
d-Levo-xylohexosaminic acid	Gulonic acid
d-Levo-ribohexosaminic acid	Allonic acid
Second group	
Epichitosaminic acid	Mannonic acid
Epichondrosaminic acid	Talonic acid
d-Dextro-xylohexosaminic acid	Idonic acid
d-Dextro-ribohexosaminicacid	Altronic acid

divided into two groups as given in table 15. In the first group, the metallic salts exhibit a higher dextrorotation than the free acids; in the second, the order is reversed. Thus, accepting as a basis for classification the *sign* of the difference of the molecular rotations of the free acid and of its metallic salt, the contradiction is removed which existed between the conclusions reached on the basis of the properties of the aminohexonic acids and those on the basis of the properties of aminohexoses.

It was shown in the previous sections of this paper that the same rule is applicable for the classification into the d and l series of the simple amino and hydroxy acids as well as of the thio and sulfo acids. The observations on sugars and amino sugars, and on sugar acids and amino sugar acids, place this rule on a firmer basis.

The practical results of all the investigations in this field of endeavor, then, are the following:

1. All natural amino acids are configurationally related to l-hydroxy acids which, in their turn, are configurationally related to l-tartaric acid. The amino or hydroxyl groups in these acids have the same allocation as the hydroxyl on carbon atom (2) of mannose.
2. 2-Amino hexoses occurring in nature, chitosamine and chondrosamine, have the configurations of 2-amino glucose and of 2-aminogalactose respectively.
3. In α-amino acids, the deamination by means of nitrous acid takes place without Walden Inversion.

The evolution of these views was very gradual and many schools of thought contributed to it. Fischer's classical work and the work of Wohl and Freudenberg and Karrer have established by purely chemical methods the configurational relationships between members of the same classes of substances. Levene and Mikeska have studied the influence on the optical rotation of the polarity of the groups attached to the asymmetric carbon atom. Frankland and others have studied the influence of structure on optical rotation. Clough, Karrer, Freudenberg and Levene have made use of these different methods and have added some new ones in order to correlate the configuration of α-amino acids and α-halogen acids with that of α-hydroxy acids and of nitrogenous sugars with simple sugars.

REFERENCES

On configurational relationships of hydroxyacids

BREMER, G. J. W.: *Ber. d. deut. chem. Ges.*, 8, 861 (1875).
FISCHER, E.: *Ber. d. deut. chem. Ges.*, 29, 1377 (1896). (Configuration of tartaric acid.)
FREUDENBERG, K.: *Ber. d. deut. chem. Ges.*, 47, 2027 (1914).
FREUDENBERG, K., AND BRAUN, FRITZ: *Ber. d. deut. chem. Ges.*, 55, 1339 (1922).
WOHL, A., AND MOMBER, F.: *Ber. d. deut. chem. Ges.*, 50, 455 (1917).
WOHL, A., AND SCHELLENBERG: *Ber. d. deut. chem. Ges.*, 55, 1404 (1922).
WALDEN, P.: Optische Umkehrerscheinungen, Fried. Vieweg and Sohn Braunschweig, 1919.

On configurational relationships of aminoacids

FISCHER, E., AND RASKE, K.: *Ber. d. deut. chem. Ges.*, 40, 3717 (1907); 41, 893 (1908).
KARRER, P., AND KAASE, W.: *Helv. Chim. Acta*, 2, 436 (1909); 3, 244 (1920).
WASER, E., AND BRAUCHLI, E.: *Helv. Chim. Acta*, 7, 740 (1924).

The influence of external conditions on configurationally related substances

ARMSTRONG, H. E., AND WALKER, E. E.: *Proc. R. Soc.*, A 88, 388 (1913).
CLOUGH, G. W.: *Trans. Jour. Chem. Soc.*, 113, 526 (1918).
FRANKLAND, P., AND WHARTON, F. M.: *Trans. Chem. Soc.*, 69, 1587 (1896).
FREUDENBERG, K., AND RHINO, F.: *Ber. d. deut. chem. Ges.*, 57, 1547 (1924).
KARRER, P., AND KAASE, W.: *Helv. Chim. Acta*, 2, 436 (1919); 3, 248 (1920).
LOWRY, T. M.: *Trans. Chem. Soc.*, 103, 1067 (1913).
PATTERSON, T. S.: Trans. 77, 1106 (1900); 85, 1142 (1904); 93, 1843 (1908); 95, 323 (1909); 109, 1145 (1916); etc.
PICKARD, R. H., AND KENYON, J.: *Trans. Chem. Soc.*, 99, 45 (1911); 101, 620, 1427 (1912); 103, 1923 (1913); 105, 830 (1914); 105, 1115, 2226 (1914); etc.
RUPE, H., AND ACKERMANN: *Ann. d. Chem.*, 420, 1 (1919).

Influence on the optical rotation of the change of polarity of one of the groups attached to the asymmetric carbon atom

LEVENE, P. A., AND MIKESKA, L. A.: *Jour. Biol. Chem.*, 59, 473 (1924); 60, 1, 685 (1924); 63, 85 (1924).

Configurational relationships in 2-aminohexoses and 2-aminohexonic acids

LEVENE, P. A., AND CO-WORKERS: Monographs of The Rockefeller Institute for Medical Research, No. 18 (1922).
LEVENE, P. A.: *Jour. Biol. Chem.*, 59, 123 (1924); 63, 95 (1924).

Configurational relationships of simple sugars and sugar acids established on the basis of van't Hoff's Superposition Theory

Freudenberg, K., Brauns, F., and Siegel, H.: *Ber. d. deut. chem. Ges.*, 56, 193 (1923).

Hudson, C. S. *J. Amer. Chem. Soc.*, 31, 66 (1909); 38, 1566 (1916); 39, 462 (1917); 40, 813 (1918).

Hudson, C. S., and Yanowski, E.: *J. Amer. Chem. Soc.*, 39, 1013 (1917).

Hudson, C. S., and Komatsu, S.: *J. Amer. Chem. Soc.*, 41, 1141 (1919).

Levene, P. A.: *Jour. Biol. Chem.*, 23, 145 (1915).

Levene, P. A., and Meyer, G. M.: *Jour. Biol. Chem.*, 26, 355 (1916); 31, 623 (1917).

Weerman, R. A.: Dissertation published by A. Kruyt, Amsterdam (1916).