CCXXI.—*A Study of the Anomalous Rotatory Dispersion of Configuratively Related Compounds.*

By CHARLES EDMUND WOOD and SYDNEY DIGGARY NICHOLAS.

IT has been indicated (this vol., p. 1671) that when anomalous rotatory dispersion is exhibited by *d*-tartaric acid and its derivatives, the anomaly always occurs in the positive region of rotation and crossing of the axis takes place in one way only ($d\alpha/d\lambda$ being positive). A survey of the literature indicates that, when anomaly is realisable for a compound of *d*-configuration, it is confined to the positive region of rotation, and for a compound of *l*-configuration to the negative region; the significance of anomaly, in this respect, has not hitherto been realised. The rule is that anomaly, when realisable, is an absolute guide to relative configuration.

Clough (J., 1918, **113**, 526) has studied the effect of certain halide salts on the optical rotatory powers of *l*-lactic acid, methyl *l*-lactate, *d*-glyceric acid, *l*-malic acid, methyl *l*-malate, *d*-tartaric acid, and methyl *d*-tartrate; he also considered the influence of substituents on the rotatory power of these four acids. Clough assumes that " the optical rotatory powers of similarly constituted compounds possessing the same configuration are in general influenced similarly by the same changes in the external conditions and also by the introduction of the same substituent into a given radical attached to the asymmetric carbon atom."

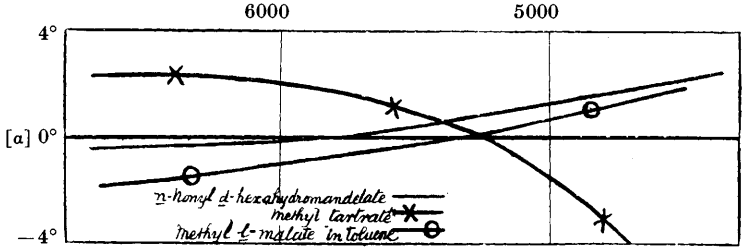
Application of the Criteria of Anomaly to Organic Acids.

Three of the acids, *l*-lactic, *l*-malic, and *d*-tartaric, or their simple esters, exhibit anomalous rotatory dispersion.

Methyl l*-lactate in aqueous solution.* The anomaly becomes more pronounced on dilution, it is confined to the positive region of rotation, and crossing of the axis occurs in one way only.

p.	$[\alpha]^{20°}_{D}$.	$[\alpha]^{20°}_{gr.}$.	$[\alpha]^{20°}_{vi.}$.
20	+1·8°	+1·8°	−0·2°
10	+1·3	+1·4	−0·5 (Clough, *loc. cit.*)
5·36	+1·3	+1·4	−0·9

FIG. 1.



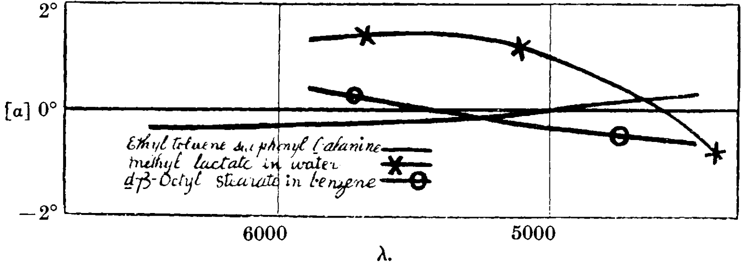


FIG. 2.

The anomaly of this ester for 5·36% concentration is shown in Figure 2.

Methyl l*-malate.* The anomaly is well defined in benzene, toluene, *m*-xylene, *p*-xylene, mesitylene, etc., solution at different concentrations (Grossmann and Landau, *Z. physikal. Chem.*, 1910, **75**, 144).

Conc.	Solvent.		r.	y.	gr.	l.bl.	dk.bl.
2·5	Benzene	$[\alpha]_{\lambda}$	−0·79°	−0·40°	0·00°	0·40°	0·79°
2·5	Toluene	$[\alpha]_{\lambda}$	−1·17	−0·39	0·00	1·17	1·95
2·5	*m*-Xylene	$[\alpha]_{\lambda}$	−1·69	−2·11	−1·69	−1·27	−0·84

Even a 5% solution of methyl *l*-malate in gylcerol shows the anomaly occurring in the negative region (Grossmann, *Trans. Faraday Soc.*, 1914, **10**, 18). The rotatory dispersion of a 5% solution of the ester in toluene is given in Fig. 1.

	r.	y.	gr.	l.bl.	dk.bl.	vi.
$[\alpha]_\lambda$	−1·76°	−0·78°	0·00°	+0·78°	+1·37°	+1·95°

Winther (*Z. physikal. Chem.*, 1902, **41**, 161) also showed that malic acid in aqueous solution was anomalous in the negative region.

Methyl d-*tartrate.* In the homogeneous condition at the ordinary temperature (Lowry and Abram, J., 1915, **107**, 1187) and at high temperatures (Wood and Nicholas, *loc. cit.*), in solution (Lowry and Abram, *loc. cit.*), and in the form of derivatives in the homogeneous condition (Wood and Nicholas, *loc. cit.*), the ester retains its characteristic anomaly. The dispersion curve plotted from the data below is given in Fig. 1.

λ	6708	6563	6152	5893	5324	5086	4678	4359
$[\alpha]_\lambda^{17\cdot7^\circ}$	+2·32°	+2·36°	+2·19°	+1·87°	+0·34°	−0·85°	−4·10°	−9·17°

Whenever anomaly is exhibited by *d*-tartaric acid and its derivatives either in the homogeneous condition or in solution, the anomaly occurs in the positive region of rotation (for data on the tartrates, see Patterson, J., 1916, **109**, 2, 1139, etc.; Lowry and Austin, *Phil. Trans.*, 1921—22, *A*, **221**, 249).

Anomaly occurs for methyl *l*-lactate in the positive region, for methyl *l*-malate in the negative region, and for methyl *d*-tartrate in the positive region of rotation. Hence *l*-lactic acid is configuratively related to *d*-malic and *d*-tartaric acids and belongs to the "*d*"-series of α-hydroxy-acids. There are no available dispersion data for application of the rule to glyceric acid and its esters (Frankland and McGregor, J., 1893, **63**, 512).

In a later paper, Clough (J., 1925, **127**, 2808) discusses the relative configuration of hexahydromandelic acid; he assigns, on considerations of a similar nature to those given in his earlier paper, the *l*-acid to the "*d*"-series.

The following data (Wood and Comley, J., 1924, **125**, 2631) show the anomaly of two normal esters :

	λ	6708	5893	5461	4359
n-Octyl *l*-hexahydromandelate ...	$[\alpha]_\lambda^{199\cdot3^\circ}$	+0·99°	+0·53°	−0·15°	−2·35°
n-Nonyl *d*-hexahydromandelate ...	$[\alpha]_\lambda^{201\cdot8^\circ}$	−0·43°	+0·02°	+0·42°	+2·42°

Since the anomaly of *n*-octyl *l*-hexahydromandelate is in the positive region, the acid belongs to the "*d*"-series, whereas the anomaly of the *n*-nonyl *d*-hexahydromandelate assigns this acid to the "*l*"-series. The anomaly was realised in both cases at a high temperature. In Fig. 1, the anomaly of the *n*-nonyl ester is indicated.

This independent proof of the relative configuration of the enantiomorphs of hexahydromandelic acid is important.

Comparison of the rotatory power of the amides and esters of *l*-mandelic acid and *l*-hexahydromandelic acid has enabled both Clough (*loc. cit.*) and Freudenberg (*Ber.*, 1923, **56**, 193), by reference to the relative configuration of *l*-hexahydromandelic acid, to assign *l*-mandelic acid to the " *d* "-series, and to show that Hudson's rule, *viz.*, that all hydroxy-acids which yield dextrorotatory amides and hydrazides belong to the " *d* "-series (*J. Amer. Chem. Soc.*, 1918, **40**, 813), requires modification. No derivatives of mandelic acid exhibiting anomaly have been studied, so far, by the authors.

Freudenberg (Freudenberg and Rhino, *Ber.*, 1924, **57**, 2, 1547, etc.), on similar lines to Clough, bases his method for the determination of relative configuration on the assumption that analogous compounds of like configuration undergo corresponding changes of rotatory power under similar conditions. The important feature of his method is the avoidance of factors (solvents, compounds with free hydroxyl, carboxyl, or amino-groups, etc.) which induce anomaly. Where the use of solvents cannot be avoided, extrapolation methods have to be resorted to in order to eliminate solvent effect. A modification of the use of the one-term Drude equation is employed, whereby that part of the dispersion curve is chosen for comparison which differs least from simplicity. Thus comparison of different derivatives with one another is based on the values of K_{M} deduced from the equation $[M]_n = K_{\mathrm{M}}/(\lambda_n^2 - \lambda_0^2)$ (Rupe and Ackermann, *Annalen*, 1919, **420**, 1).

This method, which attempts to eliminate conditions of anomaly and complexity, is in striking contrast with the rule stated, which requires only the dispersion curves showing visible anomaly. An instance of anomaly from which the configuration could be inferred immediately is ethyl toluenesulphonyl-*l*-alanine, which is anomalous in the negative region (see Fig. 2) (Freudenberg, *loc. cit.*).

Solvent.	Conc.	$\lambda =$	6490	5780	5460	4440
Acetylene tetrachloride	19·62	$\alpha_{\lambda}^{19^\circ}$ (0·5 dcm.)	−0·33°	−0·27°	−0·17°	+0·29°

Another example, methyl benzoyl-*l*-alanine, taken from the work of Freudenberg is of importance, for it illustrates anomaly by a maximum in the negative region, but crossing of the axis does not occur :

Solvent.	Conc.	$\lambda =$	6490	5780	5460
Pyridine	48·5	$\alpha_{\lambda}^{20^\circ}$ (0·5 dcm.)	−0·23°	−0·33°	−0·30°

As an additional example, Hewitt (*Biochem. J.*, 1927, **21**, 1, 216) has shown that tyrosine in 20% hydrochloric acid is anomalous in the negative region :

$\lambda =$	6660	5780	5461	4359
$[\alpha]_{\lambda}^{20^{\circ}}$	−7·2°	−9·3°	−9·6°	−7·8°

In the case of ethyl monobenzoyltartrate (Wood and Nicholas, *loc. cit.*), anomaly of this type occurs at low temperatures, but at higher temperatures a point of inflexion only is realised in the dispersion curve. From the varied examples quoted, it is clear that a maximum, a crossing of the axis, and a point of inflexion, which are indicative of anomaly (compare Lowry, J., 1915, **107**, 1195), together or separately, are sufficient criteria for determining the relative configuration of an asymmetric compound. The theoretical considerations which led to these conclusions are given in another paper.

Karrer and Kaase (*Helv. Chim. Acta*, 1919, **2**, 436), in studying certain reactions in the glutaric acid series with special reference to the measurement of the rotatory dispersion of the products obtained, suggest that the symbols *d*- and *l*- should be given to those compounds which tend to give positive and negative maxima respectively. This tendency refers to rotational values for short wave-length in the positive or negative region; *l*-malic acid is regarded as a d-*acid*, for its dispersion curve (compare Fig. 1, methyl *l*-malate) attains a positive rotational value or tends to a "positive maximum" in the blue region. This conclusion is erroneous. The rotations of *l*-aspartic acid and its ethyl ester tend to a "positive maximum" and the above authors suggest that the acid should be called a "*d*"-acid, which is opposed to the expressed views of Clough that the naturally occurring α-amino-acids, *e.g.*, *l*-aspartic acid, *l*-tyrosine, possess the configuration denoted by "*l*."

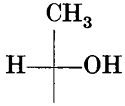
	$\lambda =$	6563	5493	5463	4990	4861
l-Aspartic acid ...	$[\alpha]_{\lambda}$	−3·54°	−2·48°	−2·13°	−1·18°	—
Ethyl *l*-aspartate...	$[\alpha]_{\lambda}$	+0·98	+1·73	+2·25	—	+3·38

(Karrer and Kaase, *loc. cit.*)

From the rotations given, anomaly is seen to occur in the negative region, and it is assumed that *l*-aspartic acid is configuratively related to *l*-tartaric acid. The "maxima" referred to above are, of course, not real maxima exhibited by anomalous dispersion curves, but simply denote ascent of the dispersion curves for short wave-lengths in (or to) the positive or the negative region. Since *d*-α-hydroxyglutaric acid, ethyl *d*-pyroglutamate, and *d*-butyrolactone-γ carboxylic acid (compare Karrer and Kaase, *loc. cit.*, for designation "*d*"-) all exhibit anomaly in the negative region, they should be considered to be configuratively related to *l*-tartaric acid.

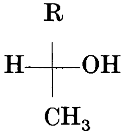
Configuratively Related Alcohols.

The application of the rule to optically active alcohols is of interest. The authors regard the "*d*"- and "*l*"-methyl- and "*d*"- and "*l*"-ethyl-carbinols as two distinct series, quite as distinct as are the series of esters derived from "*d*"- and "*l*"-lactic [$CH_3{\cdot}CH(OH){\cdot}CO_2H$] and from "*d*"- and "*l*"- α-hydroxybutyric [$CH_3{\cdot}CH_2{\cdot}CH(OH){\cdot}CO_2H$] acids. For reasons discussed later the "*d*"- and "*l*"- methyl series are represented by the space formulæ (I) and (II).



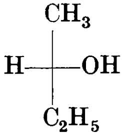
$$\begin{array}{ccc} & CH_3 & \\ H & - & OH \\ & R & \end{array}$$

"*d*-Methyl" series.
(I.)



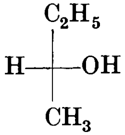
$$\begin{array}{ccc} & R & \\ H & - & OH \\ & CH_3 & \end{array}$$

"*l*-Methyl" series.
(II.)



$$\begin{array}{ccc} & CH_3 & \\ H & - & OH \\ & C_2H_5 & \end{array}$$

"*d*"-Methyl-ethylcarbinol.
(III.)



$$\begin{array}{ccc} & C_2H_5 & \\ H & - & OH \\ & CH_3 & \end{array}$$

"*l*"-Methyl-ethylcarbinol.
(IV.)

The first member, dimethylcarbinol, is inactive. The second members are (III) and. (IV). The members of the "*d*-methyl" series are all dextrorotatory (Pickard and Kenyon, J., 1911, **99**, 49) and therefore the members of the enantiomorphic series, *viz.*, the "*l*-methyl" series, are all lævorotatory.

The experimental grounds (effect of temperature is considered in another section) for this view are :

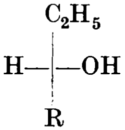
(1) "*d*"-Methylethylcarbinol has been proved to have the above space formula from its relationship to *d*-butane-αγ-diol, which is configuratively related to *d*-lactic acid (Levene, Walti, and Haller, *J. Biol. Chem.*, 1927, **71**, 465) belonging to the "*l*"-series of α-hydroxy-acids, and also to *l*-α-hydroxybutyric acid (Levene and Haller, *ibid.*, **74**, 343) belonging to the "*d*"-series of α-hydroxy-acids. This paradox will be discussed later. In the methyl series the alkyl radicals differ only in the length of the normal chains. The bottom radical for the "*d*"-series being the longer, for *d*-methylethylcarbinol has been proved experimentally to be configuratively related to "*d*"-α-hydroxybutyric acid, the replacement of the carboxyl group (top group) by the methyl radical causes no change in configuration.

(2) Certain esters of the higher *d*-alcohols exhibit visible anomaly in the positive region. Data for three typical esters are :

Ester.	Solvent.	$[\alpha]_D$.	$[\alpha]_{gr.}$.	$[\alpha]_{vi.}$.
d-β-Octyl *n*-nonoate	Benzene	+0·28°	±0°	−1·89°
d-β-Octyl stearate	Benzene	+0·32°	±0°	−0·63°
		(Pickard and Kenyon, J., 1914, **105**, 830.)		
d-β-Octyl succinate	Ethyl alcohol	$[\alpha]^{18^\circ}_{5893} = +1{\cdot}77^\circ$	$[\alpha]^{18^\circ}_{5461} = +1{\cdot}67^\circ$	
		$[\alpha]^{18^\circ}_{4358} = -0{\cdot}29^\circ$		
		(Hall, J., 1923, **123**, 43.)		

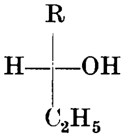
Further instances of the anomaly of these esters are : β-octyl, β-nonyl, β-decyl, β-undecyl, and β-tridecyl acetates, also β-undecyl propionate (Pickard and Kenyon, *loc. cit.*). The dispersion curve for *d*-β-octyl stearate is given in Fig. 2.

Similarly the ethyl series is formulated as in (V) and (VI). R can be equal to or greater than, but never less than, C_2H_5, for if it were less the alcohol would belong to the methyl series. The first member, diethylcarbinol, is inactive; the second members are (VII) and (VIII). The members of the " *d*-ethyl " series are all dextrorotatory (Pickard and Kenyon, J., 1913, **103**, 1923) and therefore the members of the enantiomorphic series, *viz.*, the " *l*-ethyl " series, are all lævorotatory.



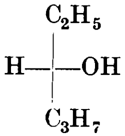
$$\begin{array}{c} \mathrm{C_2H_5} \\ \mathrm{H}-|-\mathrm{OH} \\ \mathrm{R} \end{array}$$

" *d*-Ethyl "
series.
(V.)



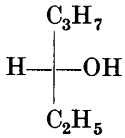
$$\begin{array}{c} \mathrm{R} \\ \mathrm{H}-|-\mathrm{OH} \\ \mathrm{C_2H_5} \end{array}$$

" *l*-Ethyl "
series.
(VI.)



$$\begin{array}{c} \mathrm{C_2H_5} \\ \mathrm{H}-|-\mathrm{OH} \\ \mathrm{C_3H_7} \end{array}$$

" *d* "-Ethyl-
propylcarbinol.
(VII.)

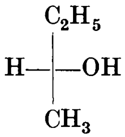


$$\begin{array}{c} \mathrm{C_3H_7} \\ \mathrm{H}-|-\mathrm{OH} \\ \mathrm{C_2H_5} \end{array}$$

" *l* "-Ethyl-
propylcarbinol.
(VIII.)

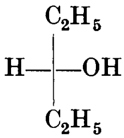
The grounds for the above formulation are :

(1) *l*-Methylethylcarbinol is a member of the " *l* "-methyl series; *d*-ethylpropylcarbinol is a member of the " *d* "-ethyl series, and the relationship is as follows :



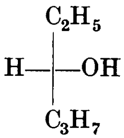
$$\begin{array}{c} \mathrm{C_2H_5} \\ \mathrm{H}-|-\mathrm{OH} \\ \mathrm{CH_3} \end{array}$$

" *l* "-Methylethyl-
carbinol.



$$\begin{array}{c} \mathrm{C_2H_5} \\ \mathrm{H}-|-\mathrm{OH} \\ \mathrm{C_2H_5} \end{array}$$

(Inactive.)



$$\begin{array}{c} \mathrm{C_2H_5} \\ \mathrm{H}-|-\mathrm{OH} \\ \mathrm{C_3H_7} \end{array}$$

" *d* "-Ethylpropyl-
carbinol.

etc.

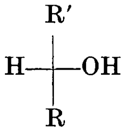
Rotation : Negative. Zero. Positive.

This passage from the *l*-methylethylcarbinol (configuration " *l* ") by increasing the bottom group through inactive diethylcarbinol to the dextrorotatory ethyl series involves a change of configuration, for the dextrorotatory members of the ethyl series are of " *d* "-configuration from the consideration of region of anomaly, temperature–rotation curves, molecular rotation, etc. Thus on experimental grounds in the " *d* "-alkyl series R is greater than R′; when R is equal to R′ asymmetry disappears, and when R is less than R′ the " *l* "-enantiomorphs of the R series are obtained [see (IX)].

From the graphical (space model) conception the distinction between a " *d* "- and " *l* "-configuration depends on the relative length of the normal chains represented by R and R′, two assumptions being possible for a " *d* "-configuration, namely R<R′ and R>R′.

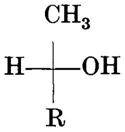
If R is originally less than R′, then on increase of R the alcohol passes through zero rotation to an "*l*"-configuration which is not in accordance with the "*d*"-configuration assigned to these alcohols on general grounds.

(2) Two instances of anomaly with regard to the "*d*"-ethyl series (Kenyon, J., 1914, **105**, 2246, 2254) could be inferred from the tabulated data, but the facts that no mention of anomaly is given in the text and that these two cases do not appear to be in harmony with the rest of the data, point to their being typographical errors. From characteristic diagrams for certain of the esters, however, the region of anomaly is inferred to be in the positive region (compare diagram, Kenyon, *loc. cit.*, p. 2234); further, the temperature–rotation curves for certain of the *d*- and *l*-alcohols exhibit maxima and minima of positive and maxima and minima of negative rotation, respectively, the presence of which is confirmatory though not conclusive evidence for the configurations.



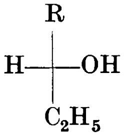
$$\begin{array}{ccc} & R' & \\ H & + & OH \\ & R & \end{array}$$

(IX.)



$$\begin{array}{ccc} & CH_3 & \\ H & + & OH \\ & R & \end{array}$$

"*d*-Methyl" series.
(X.)

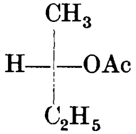


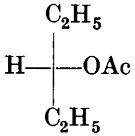
$$\begin{array}{ccc} & R & \\ H & + & OH \\ & C_2H_5 & \end{array}$$

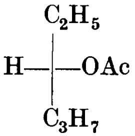
"*d*-Ethyl" series.
(XI.)

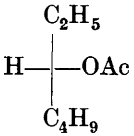
(3) The rotation data are in accord with this classification. The first optically active member, ethylpropylcarbinol, has a rotation $[\alpha]_D^{20^\circ} = +1{\cdot}97^\circ$, and as the series is ascended the molecular rotation *increases* in a normal manner. Kenyon (J., 1914, **105**, 2226) formulated the series as in (X) and (XI) and regarded dextrorotatory methylethylcarbinol as the first member of each series. According to his classification, this carbinol is the first member of the ethyl series (on our classification it is the first optically active member of the methyl series) and has rotation value $[\alpha]_D^{20^\circ} = +13{\cdot}87^\circ$, which is not in accordance with the rotational values of the "*d*-ethyl" series, the molecular rotation of which increases from zero rotation. Kenyon's view also leads to difficulties in considering the acetates of the "ethyl" series of carbinols. Kenyon (*loc. cit.*, p. 2231, Fig. 2) finds that the acetate of γ-butanol (dextrorotatory methylethylcarbinol) has a positive rotation. The acetate of diethylcarbinol is, of course, inactive, whereas the acetate of ethylpropylcarbinol is dextrorotatory. All the higher acetates of the series are of negative rotation, so there is an *unexplained* second zero between the acetates of γ-hexanol and γ-heptanol.

On the view put forward, no such irregularities occur, for (1) the acetate of methylethylcarbinol belongs to the methyl series, (2) the first zero denotes the discontinuous transition from the “ methyl ” to the “ethyl” series, (3) the acetate of ethylpropylcarbinol is the first member of the “ ethyl ” series, and (4) the second zero relates to the ethyl series only, the acetate of the first optically active member, ethylpropylcarbinol, being positive, and as the alkyl chain increases so the acetates pass normally from the positive to the negative region of rotation.


$$\begin{array}{c}\mathrm{CH_3}\\ \mathrm{H}-\!\!|\!\!-\mathrm{OAc}\\ \mathrm{C_2H_5}\end{array}$$


$$\begin{array}{c}\mathrm{C_2H_5}\\ \mathrm{H}-\!\!|\!\!-\mathrm{OAc}\\ \mathrm{C_2H_5}\end{array}$$

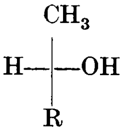

$$\begin{array}{c}\mathrm{C_2H_5}\\ \mathrm{H}-\!\!|\!\!-\mathrm{OAc}\\ \mathrm{C_3H_7}\end{array}$$

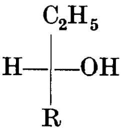

$$\begin{array}{c}\mathrm{C_2H_5}\\ \mathrm{H}-\!\!|\!\!-\mathrm{OAc}\\ \mathrm{C_4H_9}\end{array}$$

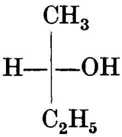
Rotation :	Positive.	Zero.	Positive.	Negative.
Configuration :	“ *d* ”		“ *d* ”	“ *d* ”

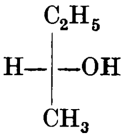
$\underbrace{\qquad\qquad\qquad\qquad\qquad\qquad}_{\text{“ }d\text{ ”-ethyl series.}}$

Clough (P., 1913, **29**, 357) represents the “ *d* ”-methyl and “ *d* ”-ethyl series as in (XII) and (XIII) and considers that similarity in the sign of rotation accompanies similarity of configuration so long as $R > CH_3$ and $R > C_2H_5$ for the two series respectively. When he considers the first optically active member of each series, *viz.*, (XIV) and (XV), he arrives at the “ paradox that the simplest members of the two configuratively similar series are enantiomorphic forms of the same substance.” The issue has been confused by allowing R to have values not only equal to and greater than, but also less than, C_2H_5, *viz.*, CH_3, and so erroneously *l*-methylethylcarbinol is made a member of the ethyl series.

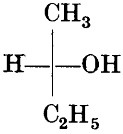

$$\begin{array}{c}\mathrm{CH_3}\\ \mathrm{H}-\!\!|\!\!-\mathrm{OH}\\ \mathrm{R}\end{array}$$
(XII.)

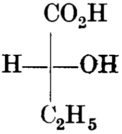

$$\begin{array}{c}\mathrm{C_2H_5}\\ \mathrm{H}-\!\!|\!\!-\mathrm{OH}\\ \mathrm{R}\end{array}$$
(XIII.)

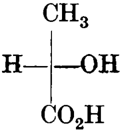

$$\begin{array}{c}\mathrm{CH_3}\\ \mathrm{H}-\!\!|\!\!-\mathrm{OH}\\ \mathrm{C_2H_5}\end{array}$$
(XIV.)


$$\begin{array}{c}\mathrm{C_2H_5}\\ \mathrm{H}-\!\!|\!\!-\mathrm{OH}\\ \mathrm{CH_3}\end{array}$$
(XV.)

The restricted definition of configuration as applied to the α-hydroxy-acids no longer serves when the alcohols are considered; methylethylcarbinol is a compound of relative configuration “ *d* ” on comparison with “ *d* ”-hydroxybutyric acid, but of relative configuration “ *l* ” on comparison with “ *l* ”-lactic acid.

(XVI.)

$$\begin{array}{c}\mathrm{CH_3}\\ \mathrm{H}-\!\!|\!\!-\mathrm{OH}\\ \mathrm{C_2H_5}\end{array}$$


$$\begin{array}{c}\mathrm{CO_2H}\\ \mathrm{H}-\!\!|\!\!-\mathrm{OH}\\ \mathrm{C_2H_5}\end{array}$$
(XVII.)


$$\begin{array}{c}\mathrm{CH_3}\\ \mathrm{H}-\!\!|\!\!-\mathrm{OH}\\ \mathrm{CO_2H}\end{array}$$
(XVIII.)

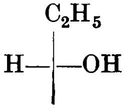
The configuration of a compound is regarded as “ *d* ” or “ *l* ” when the electron frequencies of the four pairs of coupling electrons are in the order of magnitude corresponding to a " *d* "- or " *l* "-α-hydroxy-acid, the sign of the high-frequency term in the Drude equation being taken as a criterion of the order. In (XVII) and (XVIII) the frequencies will be in the reverse order. On the assumption that the frequencies corresponding to the linkages decrease in the order $C–H > C–OH > C–CO_2H > C–CH_3 > C–C_2H_5$, (XVI) will have the same order as (XVII) but the reverse of (XVIII); accordingly the configuration of (XVI) is " *d*." Certain derivatives of higher members of the series (XVI) show anomaly in the positive region, *i.e.*, the high-frequency term is positive.

Configuration as at present defined has no meaning outside the series of related compounds to which it is applied. The above extension applies to all series, and accordingly all series are designated as " *d* "- or " *l* "- series. This designation not only implies the same order of frequencies but also a corresponding similarity of shape (compare Thomson, *Phil. Mag.* 1920, **40**, 713), *i.e.*, the geometrical distribution of the groups in space.*

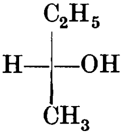
In the α-hydroxy-acids, two methods of determining relative configuration have been employed : (1) Proof of the correspondence of the three groups by processes of synthesis and degradation; (2) deductions from factors influencing optical rotatory powers. Only in those cases where the former has been adopted and in which no Walden change has been involved can the space formula be regarded as absolutely proved. The latter method is open to criticism, yet space formulæ are in all probability assigned correctly, for the electron frequencies of the linkages C–H, C–OH, $C–CO_2H$ are very likely far removed from the normal, and so the order of the frequencies is not altered by substitution of a group R (higher alkyl, $CH_2·CO_2H$, *cyclo*hexyl, phenyl, etc.) for CH_3 in lactic acid. Stated in another way, the fourth group R modifies but does not change the shape typical of " *d* "- or " *l* "-compounds.

The case is quite different when we replace the carboxyl group in " *d* "-lactic acid by the ethyl group and pass to the alcohols. The grouping (XIX) of the methyl series does not possess the characteristic of resisting change of configuration by a fourth group R. The " *l* "-alcohol (XX) has the geometrical asymmetry of the " *l* "-series.

(XIX.)

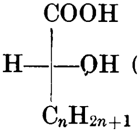


$$\begin{array}{c} C_2H_5 \\ H—|—OH \\ | \end{array}$$



$$\begin{array}{c} C_2H_5 \\ H—|—OH \\ CH_3 \end{array}$$

(XX.)



$$\begin{array}{c} COOH \\ H—|—OH \\ C_nH_{2n+1} \end{array}$$

(XXI.)

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* Neither the electrons nor the atomic groups are regarded as situated at the corners of a regular tetrahedron (compare Lindman, *Ann. Physik*, 1924, **74**, 6, 541, etc.).

On replacement of the methyl group first by C_2H_5 and then by C_3H_7, the alcohol passes through the regular tetrahedron to the geometrical asymmetry of the " *d* "-series.

Zero rotation for all wave-lengths due to passage of the shape through the regular tetrahedron to the enantiomorph is quite distinct from zero rotation for one particular wave-length; for passage through anomaly involves modification but not change in the typical shape. Although anomaly indicates when compounds have a similarity of geometrical asymmetry, yet the assignment of space formulæ, even when compounds with the linkages C–H and C–OH in common are being considered, requires a knowledge of the order of the frequencies of the four groups involved (that is, the order of the deflexion of the groups), *i.e.*, a knowledge as to which of the groupings in the derived compound deflect similarly to those in the original compound.

The synthetical work of Levene and Haller (*loc. cit.*) has been taken as the decisive factor in assigning space formulæ to the " *d* "-methyl and " *d* "-ethyl series of carbinols which may be considered as derived from the acids (XXI)—the " *d* "-methyl series by replacement of carboxyl by methyl, provided $C_nH_{2n+1} > CH_3$; similarly, the " *d* "-ethyl series, provided $C_nH_{2n+1} > C_2H_5$.

Influence of Radicals and Temperature.

Consider " *d* "-lactic and " *d* "-α-hydroxybutyric acids, the esters of which form two distinct homologous series which are structurally related. If we select a corresponding ester, *viz.*, the R ester from each series, these two esters are also members of an homologous series of " *d* "-α-hydroxy-esters, the first two members being $CH_3{\cdot}CH(OH){\cdot}CO_2R$ and $C_2H_5{\cdot}CH(OH){\cdot}CO_2R$.

Removal from the region of possible anomaly proceeds by increase of the *n*-alkyl chain of the ester grouping in the esters of " *d* "-lactic acid, this removal being indicated by the approach to and formation of maxima in the temperature–rotation curves of the esters.*

Increase of the alkyl group attached to the asymmetric carbon

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* A point of further importance is that the maximum rotation for a definite wave-length is at a lower temperature for the octyl than for the butyl ester. A more recent determination of the maxima for *n*-octyl *l*-lactate has been made with the following results (compare Wood, Such, and Scarf, J., 1923, **123**, 600):

Maxima occur at	103—105°	for	λ 6708
	108°	„	6563
	113—115°	„	6438

atom decreases the rotation and brings a particular ester nearer to the anomalous region :

Ethyl hydroxybutyrate	$[\alpha]_D^{15}$	+1·9°	(Guye and Jordan, *loc. cit.*)
,, *l*- ,,	$[\alpha]_D^{22°}$	−3·83°	(Levene and Haller, *J. Biol. Chem.*, 1927, **74**, 343.)
,, lactate	$[\alpha]_D^{15°}$	+8·64°	

In the case of the carbinols, a particular alcohol is a member of a series of structurally related alcohols, besides being a member of the "*d*"-methyl, "*d*"-ethyl series, etc. In this series R is the constant group and R′ the changing alkyl group. Increase of R′ ultimately brings the carbinol to the axis :

Methylpropylcarbinol	$[\alpha]_D^{20°}$	+13·70°	(Pickard and Kenyon, *loc. cit.*)
Ethylpropylcarbinol	,,	+ 1·97°	

(The third member being inactive, further increase of R′ would give the first optically active member of the "*l*"-propyl series.)

Thus a transition from the positive to the negative region takes place with change of configuration, the middle member, which separates the "*d*"- from the "*l*"-series, being inactive. They form a simple series of optically active compounds restricted with respect to the "*d*"-compounds to the positive region, which is not the case with the hydroxy-acids, where the upper and lower groupings never become identical. Passage into the negative region may be attained by acylation of the hydroxyl group or acylation and subsequent solution, but this depression of the rotation of the asymmetric carbon atom, forced, as it were, to give negative rotations, results generally in an ill-defined anomaly, or the derivative is situated in a particular part of the negative region where anomaly cannot be attained in the visible region either by change of temperature or by solution.

The following points are of interest with respect to the increase of the alkyl group R in the "*d*"-ethyl series, positive numerical values of the molecular rotation being considered (Pickard and Kenyon, J., 1913, **103**, 1934) : (*a*) The rotation increases with increasing temperature for the propyl and butyl members; (*b*) the amyl, hexyl, and heptyl members exhibit maxima in their temperature–rotation curves, the maxima for a particular wave-length moving to a *lower temperature* with increase of the alkyl chain, the octyl member, though showing maxima, being exceptional [compare the movements of maxima with increase of the alkyl grouping in the tartrates, certain of the members being exceptional (Patterson, J., 1913, **103**, 173; 1904, **85**, 765; Frankland and Garner, J., 1919, **115**, 643)]; (*c*) the nonyl, decyl, and undecyl members exhibit minima, the minima moving to a *higher temperature* and higher rotation with increase of the alkyl chain, the dodecyl member being exceptional [compare the movement of minima for members of the " *d* "-methyl series (Pickard and Kenyon, J., 1912, **101**, 626)]; (*d*) the rotatory powers of the tridecyl and pentadecyl members decrease with temperature as far as they have been investigated. From these considerations it is assumed that increase of R removes the alcohol in a direction away from the approach to the zero axis, certain members being exceptional. Just as minima are displaced to a higher temperature, so maxima are displaced to the lower temperature.

Increase of the R′ group has in general the reverse effect. Methylamylcarbinol exhibits minima (temperature–rotation curves), and ethylamylcarbinol maxima, minima being more removed, relatively, from the approach to a zero axis than maxima. The temperature–rotation curves for methylpropylcarbinol decrease with temperature; those for ethylpropylcarbinol increase with temperature, and it is assumed from analogy with the tartrates that the former are situated with reference to the approach to the zero axis, on a more remote, and the latter on the nearer part of a maximum rotation surface. Consideration of the data given by Pickard and Kenyon (J., 1911, **99**, 45; 1913, **103**, 1934; 1912, **101**, 620) shows that increase of R′ from the method to the ethyl grouping causes the minima to move to a lower temperature :

	Temp. of minimum rotation for $[\alpha]_D$.
Methyl-*n*-nonylcarbinol	178° (about) (calculated by authors).
Ethyl- ,, ...	100—120° (Pickard and Kenyon).
Methyl-*n*-decylcarbinol	169° (about) (calculated by authors).
Ethyl- ,, ...	120—140° (Pickard and Kenyon).
Methyl-*n*-undecylcarbinol	189° (about) (calculated by authors).
Ethyl- ,, ...	140—160° (Pickard and Kenyon).

In the above the temperature–rotation–wave-length surface for each individual member is compared, and the relative displacements of the surfaces, although discontinuous with each other, are considered.

l-α-Naphthylmethylcarbinol and *d*-α-naphthyl-*n*-hexylcarbinol are anomalous in the negative and positive regions respectively, and are considered to be of " *l* "- and " *d* "-configurations respectively :

	$[M]_D^{\text{Max.}}$.	Temp. of maximum.	$[M]_D^{10°}$.
Naphthylmethylcarbinol*	67·50°	140°	21·19°
α-Naphthyl-*n*-hexylcarbinol	106·8°	180°	27·24°

(Pickard and Kenyon, J., 1914, **105**, 1115; Kenyon and Pickard, 1914, **105**, 2644.)

* Comparable numerical values for $[M]_D$.

Increase of the alkyl chain results in (*a*) an increased rotation at the maximum, (*b*) movement of the maximum for a particular wave-length to a *higher* temperature, and (*c*) passage across the zero axis into the negative region.

The cases of phenyl-methyl- and -ethyl-carbinols are particularly interesting :

	$[M]_D^{Max.}$.	Temp. of maximum.	$[M]_D^{20°}$.	$[M]_D^{140°}$.
Phenylmethylcarbinol	—	—	50·94°	46·98°
Phenylethylcarbinol*	48·28°	120°	35·17°	46·74°

(Pickard and Kenyon, *loc. cit.*)

* Comparable molecular numerical values.

Neither of these alcohols shows visible anomaly. Phenylmethylcarbinol does not exhibit maxima in its temperature–rotation curves —its rotation continually decreases with temperature. Since the molecular rotation change from 20° to 40° is 0·3°, and that from 120° to 140° is 0·98°, it is inferred that the alcohol is tending to maximum rotation at low temperature and, in addition, that increase of the methyl to the ethyl group has brought the maximum into the visible region, *viz.*, to a *higher* temperature. Increase of the alkyl group results in (*a*) a decreased rotation at the lower temperature, (*b*) the realisation of a part of a surface of maximum positive rotation (for the compound of " *d* "-configuration). From analogy with the naphthylcarbinols, the region of possible anomaly is to the left (temperature–rotation diagram), and this deduction is supported by (*c*) complexity of character. Phenylmethylcarbinol is simple and phenylethylcarbinol complex below 40° (approx.) (Pickard and Kenyon, *loc. cit.*) (Characteristic diagram—intersection of violet and green lines in positive region.)

It is assumed from these considerations that both the dextrorotatory alcohols are of " *d* "-configuration, and that the movement of the maxima is due to the change in the alkyl group. Absolute proof and unassailable evidence would be given by the higher alcohols of this series.

The data at present available are not sufficient to make a decision with respect to space formulæ.

For simplicity of treatment only four cases of series movements of maxima and minima, two for each, for a particular wave-length have been considered ; the discussion of other possible cases has been deferred. In all the cases here discussed, the anomalous region is towards the left (compare treatment of movement of maxima and minima, this vol., p. 1696).

A survey of the *iso*propyl series (Pickard and Kenyon, J., 1912, **101**, p. 623, diagram) indicates an increase of specific rotation as the methyl increases to the butyl grouping ; thereafter, as the alkyl group increases, a decrease of rotation is noted, with rather better definition of maxima in temperature–rotation curves. The maxima are considered to be moving to the higher temperature with increase of the alkyl chain; further, the curves appear to be approaching to minima on the right, and the approach to the anomalous region is considered then to be to the left. If these points are conceded, it follows from analogy with other carbinols that these carbinols also are of "*d*"-configuration.

In conclusion, as an application of the fundamental criterion, the configuration, "*d*" and "*l*" respectively, of the following alcohols is inferred from the anomalous dispersion of derivatives.

	$[\alpha]_{D}$.	$[\alpha]_{ye.}$.	$[\alpha]_{gr.}$.	$[\alpha]_{vi.}$.
d-Benzylmethylcarbinyl stearate ... (approx. 5% CS_2 solution)	+0·54°	+0·31°	+0·23°	−1·31°
	$[\alpha]_{D}$.		$[\alpha]_{gr.}$.	$[\alpha]_{vi.}$.
Sodium 1-*ac*-tetrahydronaphthyl phthalate (H_2O solution)	−1·24°		−1·02°	+1·10°

(Kenyon and Pickard, J., 1914, **105**, 2262, 2677.)

A Case involving Asymmetric Nitrogen.—Nicotine is lævorotatory and its salts are dextrorotatory. Lowry and Singh (*Compt. rend.*, 1925, **181**, 909) have shown that the alkaloid in the homogeneous condition at 20° exhibits simple rotatory dispersion in the negative region. Gennari (*Z. physikal. Chem.*, 1896, **19**, 130) observed that an equimolecular mixture of nicotine and glacial acetic acid, within certain limits of dilution with water, exhibits anomaly in the positive region ($d\alpha/d\lambda$ positive). Nicotine salts are therefore assumed to be of relative configuration "*d*."

The rotation of the base is due to the asymmetry of the α-pyrrolidine carbon atom; in the salts, however, a new centre, the asymmetric pyrrolidine nitrogen atom, is involved (Lowry, *Chem. and Ind.*, 1927, **46**, 102). No decision as to the configuration of the free base is at present possible, for the respective configurations and dominance of the two centres are unknown.

Patterson and Fulton (J., 1925, **127**, 2435) have shown that the rational zero (for nicotine and its sulphate) is + 3°, and if this rotation could be realised for the green rays, the rotatory dispersion would be visibly anomalous in the positive region. But a deduction as to the relative configuration of the *free* base from the data given would require careful consideration of the occurrence and movement of maxima in the negative region in the temperature–rotation curves for the homogeneous base at high temperature, and similarly for the base in inert solvents, and also the construction of separate characteristic diagrams, as well as a composite one.

The fact that nicotine sulphate and nicotine in various solvents fit on the same characteristic diagram, suggests that the α-pyrrolidine carbon atom is of relative configuration " *d*."

Summary.

(1) Anomalous rotatory dispersion is a trustworthy criterion for determining relative configuration.

(2) The configurations of *l*-lactic, *l*-malic, *d*-hexahydromandelic, and *d*-tartaric acids, as shown by their anomalies, are " *d*," " *l*," " *l*," and " *d* " respectively, which is in agreement with the configurations assigned to these acids by other workers.

(3) The non-empirical nature of this criterion is illustrated by (*a*) *l*-alanine, *l*-tyrosine, and *l*-aspartic acid, which are configuratively related to *l*-tartaric acid, and (*b*) certain series of alcohols.

(4) The distinction between "*d*"- and "*l*"-alcohols containing normal straight chains depends only on their relative lengths, since all other factors are eliminated.

(5) Movement of maxima and minima for a particular wave-length in an homologous series of configuratively related compounds has been discussed.

(6) Series of alcohols have been considered with respect to: (*a*) Configuration; (*b*) rotation change with temperature for each individual member, particularly with regard to the region of approach of temperature–rotation curves to the zero axis and to a zero rotation–temperature–wave-length plane; (*c*) movements of maxima and minima as the series is ascended. A series, none of the members (or derivatives) of which exhibits anomaly, is then considered with respect to (i) temperature–rotation curves and (ii) movements of maxima and minima, as the series is ascended. From analogy, conclusions are drawn as to configuration relationship.

(7) The configuration of nicotine and its salts is considered.

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