

REVIEW ARTICLE

SOME STEPS IN THE DEVELOPMENT OF STEREOCHEMISTRY*

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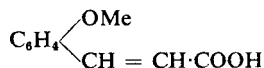
INTRODUCTION

STEREOCHEMISTRY, now a branch of science of the first rank, deals with the spatial arrangement of the atoms composing the molecule. It had its inception in Pasteur's work on the optically active forms of tartaric acid, begun in 1848. The theoretical conceptions of Le Bel and van 't Hoff, advanced in 1874, were founded mainly upon the experimental observations of Pasteur. Their Theory of Molecular Configuration (sometimes called the Space Theory) assumes a distribution in three-dimensional space of the four groups attached to the carbon atom; this atom is depicted at the centre of a tetrahedron, instead of at the centre of a square, according to the tacit assumption of Kekulé's Theory of Molecular Structure, which had been put forward in 1858. Briefly, the theory of 1874 conferred solidity upon the flat, two-dimensional structural formulæ of Kekulé. The Space Theory was viewed with a certain scepticism until Emil Fischer, in the following decade, used it as a guide in his astonishingly successful researches on sugars. Since then the theory has responded to the growing demands of chemical research in a manner almost without precedent, and indeed later physical methods dealing with the effect of X-rays and electron rays on organic compounds have shown the conception to possess an essential truth probably unimagined by its authors. It has even proved possible to measure bond-lengths, or actual distances between the carbon atom at the centre of the tetrahedron of van 't Hoff and the atoms at its corners, as, for example, the bond-length C-H in the molecule of methane, CH₄.

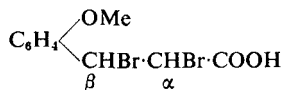
The birth of van 't Hoff, in 1852, coincided closely with the foundation of stereochemistry by Pasteur. It is therefore appropriate that this Review, written in van 't Hoff's centenary year of 1952, should take the form of an account at first-hand of a variety of researches illustrating some of the important stereochemical advances of the last half-century.

METHYLCOUMARIC AND METHYLCOUMARINIC ACIDS

A simple example of a stereochemical research¹ is afforded by the methylcoumaric and methylcoumarinic acids, a pair of ethylene isomers having the common structural formula (I):



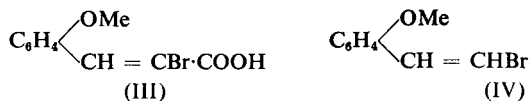
(I)



(II)

* Based on the Inaugural Sessional Address delivered to the Pharmaceutical Society of Great Britain, at Edinburgh, on November 21, 1952.

When the two stereoisomeric acids (I) are brominated, the symmetric molecule passes in each case into an asymmetric molecule containing two dissimilar asymmetric carbon atoms (α and β). Therefore each acid (I) should be able to furnish the same two optically inactive dibromides (*dl*-forms). Each dibromide should then be resolvable into optically active components (*d*- and *l*- forms). Apart from an examination of these formal stereochemical relationships, an unexpected chemical distinction was found to exist between the two *dl*-dibromides (II). When treated with concentrated aqueous potassium hydroxide in the cold, one of these (m.pt. 134° C.) lost hydrogen bromide, while the other (m.pt. 170° C.) lost carbon dioxide in addition, the respective products being (III) and (IV):



Cold dilute alkali yielded only the product (IV) in both instances. The exceptional reactivity of the β -halogen atom was borne out further in both of the dibromides, and also in a dichloride, through its easy replacement by methoxyl or ethoxyl on warming the dihalogenide with the corresponding alcohol containing a little hydrogen chloride.

SIMPLE ASYMMETRIC MOLECULES

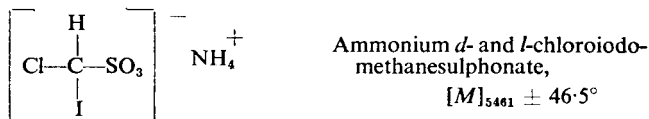
According to the Space Theory, any molecule of the type *abcd*, having four different kinds of atoms or radicals (*abcd*) attached to a common carbon atom—a so-called “asymmetric carbon atom”—should be capable of existing in right- and left-handed (*d*- and *l*-) forms, distinguished by equal and opposite optical rotatory powers. For many years after the advent of the Space Theory it was not found possible to isolate optically active forms of any organic compound containing fewer than three carbon atoms in its molecule, such as occur, for example, in lactic acid, $\text{CH}_3\cdot\text{CH}(\text{OH})\cdot\text{COOH}$. It was suggested in 1898 that optical activity might not necessarily result from the presence of an asymmetric carbon atom in a molecule unless other carbon atoms were attached to the asymmetric centre²; but, as Werner pointed out in 1904, there was at that time little experimental evidence bearing on this question.³

Early attempts⁴ to resolve chlorosulphoacetic acid, $\text{CHCl}(\text{SO}_3\text{H})\cdot\text{COOH}$, and chlorobromomethanesulphonic acid, $\text{CHClBr}\cdot\text{SO}_3\text{H}$, containing respectively only two and one carbon atoms in the molecule, failed. A later attempt, using the hitherto unknown chloriodomethanesulphonic acid, $\text{CHClI}\cdot\text{SO}_3\text{H}$, was successful.⁵

The first indication of resolution was obtained by using a new optically active base, *d*- and *l*-hydroxyhydrindamine, which had been recently synthesised (*vide infra*); but a satisfactory result was not reached until the introduction of a new idea, namely, repeated fractional precipitation of the very sparingly soluble brucine salt. The novel process furnished ammonium *d*-chloriodomethanesulphonate having $[\text{M}]_{5461} + 43.1^\circ$ in dilute aqueous solution. Thus was achieved a settlement of what was

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then called one of "the most fundamental stereochemical problems that have hitherto remained unsolved." Much later, in 1932, McMath⁶ succeeded in obtaining the *d*- and *l*- forms of the ammonium salt, having $[M]_{5461} + 46.5^\circ$ and -46.0° , respectively. Thus the enantiomeric relationship was fully established. The stable optical activity here displayed is due to an asymmetric system closely approaching the ideal molecular simplicity of a carbon atom attached to four other single atoms of different kinds:



The optically active anion is a structure of only eight atoms, containing less than 5 per cent. of carbon.

Previously, McMath⁷ had studied the optical resolution of four other substances with asymmetric molecules containing either one or two carbon atoms. Chloroiodoacetic acid, $\text{CHClI}\cdot\text{COOH}$, and chlorosulphoacetic acid, $\text{CHCl}(\text{SO}_3\text{H})\cdot\text{COOH}$, underwent normal optical resolution with brucine or hydroxyhydrindamine, but were found to racemise with great ease in presence of alkali. This configurational lability assumed a spectacular aspect in chlorobromomethanesulphonic acid, $\text{CHClBr}\cdot\text{SO}_3\text{H}$: for here the optical activity of the anion could be demonstrated only in the presence of a suitable optically active base. The following schemes represent (i) the normal optical resolution (according to Pasteur's Second Method) of an externally compensated acid (*dAlA*) by a levorotatory base (*lB*), and (ii) the optical resolution of *dl*-chlorobromomethanesulphonic acid by *l*-hydroxyhydrindamine in acetone solution:

- (i) $2lB + dAlA = lBIA$ (50 per cent.) + $lBdA$ (50 per cent.).
(ii) $2lB + dAlA = lBIA$ (81 per cent.) \rightleftharpoons $lBdA$ (19 per cent.).

In the second case the two diastereoisomeric salts exist in dynamic equilibrium in acetone solution, from which by careful crystallisation the whole of the original *dl*-acid may be obtained in the form *lBIA*. When the optically active base is removed from this salt, the acid at once racemises.

The production of a controlled optical activity resulting from the domination of a very mobile asymmetric system by an outside asymmetric influence has sometimes been termed "asymmetric induction." Here we have one of the earliest and most striking examples of this phenomenon. A similar effect was observed with chlorobromoacetic acid, $\text{CHClBr}\cdot\text{COOH}$. Some of these results are summarised in the following table:

<i>Order of Decreasing Optical Stability</i>	
(1) $\text{CHClI}\cdot\text{SO}_3\text{H}$	$[M]_D \pm 36^\circ$ (aq.)
(2) $\text{CHClI}\cdot\text{COOH}$	$\pm 60^\circ$
(3) $\text{CHCl}(\text{SO}_3\text{H})\cdot\text{COOH}$	$\pm 31^\circ$
(4) $\text{CHClBr}\cdot\text{SO}_3\text{H}$	asymmetric induction
(5) $\text{CHClBr}\cdot\text{COOH}$	asymmetric induction

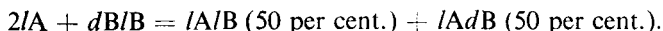
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The Space Theory was put forward in 1874; forty years elapsed before the preparation in an optically active form of any organic compound containing fewer than three carbon atoms in its molecule. From the foregoing investigations it is clear that the delay was due to the great configurational mobility of such simple asymmetric systems.

NEW OPTICAL RESOLVING AGENTS

Resolution of Bases: Oxymethylenecamphor

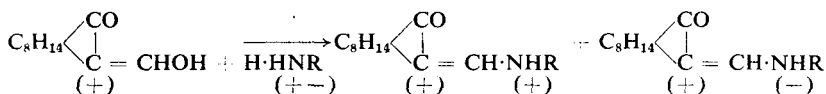
Pasteur's Second Method of optical resolution, in its original form, is illustrated by the following equation, the equimolecular mixture of diastereoisomeric salts being separated by a purely physical process of fractional crystallisation:



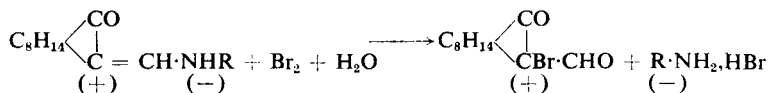
Externally compensated bases and acids may be resolved by using a suitable optically active acid or base, respectively.

This method often fails owing to the two salts forming solid solutions or partial racemates.⁸

It was thought that the formation of such inseparable complexes might be overcome, or at least minimised, when the equimolecular mixture consisted of two diastereoisomeric condensation products instead of two diastereoisomeric salts. For example, *d*-oxymethylenecamphor, which is readily prepared from *d*-camphor, condenses rapidly in aqueous ethanolic acetic acid with primary and secondary amines; and a *dl*-base should yield two diastereoisomers:



The product from *dl*- α -phenylethylamine, $\text{PhMeCH} \cdot \text{NH}_2$, was easily separated into its two pure constituents by fractional crystallisation⁹; but the products resisted hydrolysis, and there was some delay before it was discovered¹⁰ that they could be decomposed quantitatively by titration in cold ethanolic solution with bromine:



dl-Hydroxydrindamine was also resolved in this way; but *dl*-*ac*-tetrahydroquinaldine gave a partial racemate, inseparable by fractional crystallisation (*vide infra*).

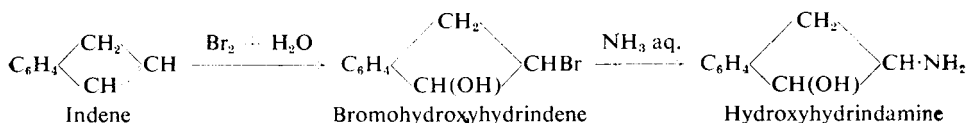
This method has since been widely used in the resolution of externally compensated primary and secondary amino-compounds.

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Resolution of Acids: Hydroxyhydrindamine

In resolving a *dl*-form by Pasteur's Second Method it is a great advantage to have both the *d*- and *l*- form of the resolving agent, as it is then possible, by using them successively, to effect a complete optical resolution. If only one form of the resolving agent is available, it is often impracticable to obtain the more soluble diastereoisomer in a state of purity. The commonest optically active bases used in work of this kind are the natural asymmetric alkaloids, such as brucine, strychnine and quinine, and these are usually obtainable only in one optically active form. The position is closely similar with menthylamine, bornylamine and other synthetic bases, prepared from menthone, camphor, and other natural optically active substances.

It came therefore as a welcome discovery, in 1911, that a hydrocarbon, indene, easily obtainable in bulk from coal tar, could be converted by successive treatment with bromine water and aqueous ammonia into a crystalline base, hydroxyhydrindamine¹¹:



Incidentally, the discovery that bromine water could act in this simple way as an effective source of hypobromous acid led to a long series of investigations on the formation of bromo- and chlorohydrins from ethylenic compounds by the use of bromine water and chlorine water.¹² At the present day, ethylene glycol, of great importance as an anti-freeze and as a chemical intermediate, is manufactured industrially from ethylene through treatment with chlorine water followed by hydrolysis of the resulting ethylene chlorohydrin: $\text{CH}_2:\text{CH}_2 \rightarrow \text{CH}_2\text{Cl}\cdot\text{CH}_2(\text{OH}) \rightarrow \text{CH}_2(\text{OH})\cdot\text{CH}_2(\text{OH})$.

dl-Hydroxyhydrindamine is readily resolved into *l*- and *d*- forms by successive treatment with *d*- and *l*- α -bromocamphor- π -sulphonic acid, the less soluble diastereoisomer being the salt *lBdA* (or *dB/A*). Originally the *d*-base could thus be obtained only by the use of the rare *l*-form of camphor. Much later,¹³ it was found possible to obtain the pure *d*-base by inoculating the mother liquor from the salt *lBdA*, under carefully prescribed conditions, with a seed of the pure salt *dBdA*. In the same investigation it was shown that by a similar method *dl*-tartaric acid could be completely resolved with cinchonine, and *dl*-camphor-10-sulphonic acid with brucine. The optically active forms of hydroxyhydrindamine have proved to be of considerable value in stereochemical work, as for example in investigations on asymmetric compounds of simple molecular structure (*vide supra*).

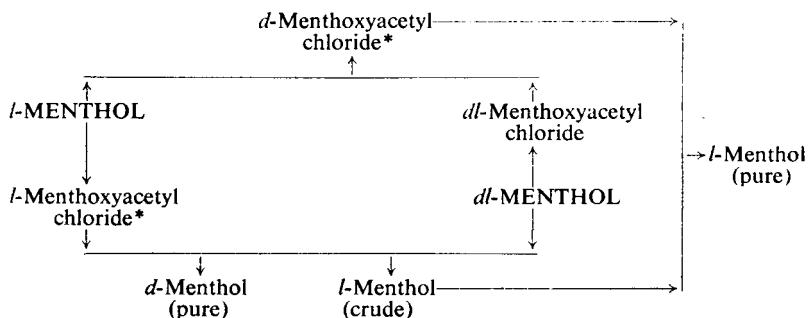
Resolution of Alcohols

1. In the course of work in the terpene series (*vide infra*), it became important to devise effective methods for resolving terpenic alcohols, particularly in the menthol series, since the known methods proved to

be quite inadequate. In the first place it was desired to obtain access to *d*-menthol, which had hitherto been unobtainable except in minute amounts.¹⁴ By esterifying *dl*-menthol in quinoline or pyridine with *l*-camphor-10-sulphonyl chloride it proved easy to isolate pure *d*-menthyl *l*-camphor-10-sulphonate (*l*-D) through fractional crystallisation of the equimolecular mixture of diastereoisomeric esters (*l*-D and *l*-L).¹⁵ The ester *l*-D (or its enantiomer, *d*-L) crystallises in magnificent prisms, readily attaining 6 to 8 cm. in length and 10 to 12 g. in weight. Upon hydrolysis, however, the ester gave a yield of only 10 per cent. of pure *d*-menthol, owing to the simultaneous production of menthene.

2. At this stage it was sought to use *l*-menthol as an agent for procuring *d*-menthol. *l*-Menthol, $C_{10}H_{19}\cdot OH$, by successive treatment with sodium, chloroacetic acid and thionyl chloride, passes into *l*-menthoxyacetyl chloride, $C_{10}H_{19}\cdot O\cdot CH_2\cdot COCl$, or $R^-\cdot O\cdot CH_2\cdot COCl$. This reagent reacts with *dl*-menthol in pyridine to yield the two diastereoisomers, $R^-\cdot O\cdot CH_2\cdot COOR^+$ and $R^-\cdot O\cdot CH_2\cdot COOR^-$. The first of these esters was less soluble than the second and readily separable. Preferential hydrolysis of the ester radical with hot dilute ethanolic alkali then yielded pure *d*-menthol in excellent yield: $R^-\cdot O\cdot CH_2\cdot COOR^+ + KOH = R^-\cdot O\cdot CH_2\cdot COOK + R^+\cdot OH$. The *l*-menthoxyacetyl chloride was then recovered and used again.

By an extension of this method a species of auto-catalytic process¹⁶ was devised, whereby a small initial quantity of *l*-menthol could be used as the sole optically active agent necessary for the separation of indefinitely large amounts of *dl*-menthol into pure *d*- and *l*-menthol, as shown in the following diagram :



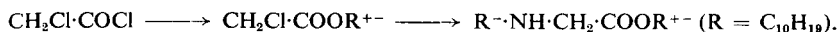
* Recovered and used again.

This method is a general one capable of wide application. For example, *l*- and *d*-menthoxyacetyl chloride have been used to prepare pure *l*- and *d*-neomenthol from *dl*-neomenthol¹⁷; further, *l*-menthoxyacetyl chloride has been used to effect the complete optical resolution of *dl*-*trans*-1:2-cyclohexanediol¹⁸; and *d*- and *l*-bornoxyacetyl chloride have been applied in preparing pure *d*- and *l*-borneol.¹⁹

3. In another process²⁰ *l*-menthylamine, prepared from *l*-menthone, by reducing its oxime, was used as the resolving agent. Chloroacetyl

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chloride, when treated successively with *dl*-menthol and *l*-menthylamine, readily yielded *dl*-menthyl *l*-menthylglycine:



Fractional crystallisation of this free ester and its sulphate, respectively, led quickly to pure *d*- and *l*-menthol in high yields (56 per cent. and 65 per cent.). Thus, one optically active reagent affords a complete resolution. The method is again a general one of wide applicability.

Structurally, the esters of menthylglycine are closely analogous to those of menthoxyacetic acid, the respective formulæ being $\text{R}\cdot\text{NH}\cdot\text{CH}_2\cdot\text{COOR}$ and $\text{R}\cdot\text{O}\cdot\text{CH}_2\cdot\text{COOR}$. In each case the less soluble ester is the one in which the two asymmetric radicals R are related as object and image; so that *l*-menthone or *l*-menthol is used in order to gain access to *d*-menthol.

PASTEUR'S FIRST METHOD OF OPTICAL RESOLUTION

All the methods of optical resolution which have been dealt with up to this point are based fundamentally upon Pasteur's Second Method. A reference may now be made to Pasteur's First Method. This depends upon the spontaneous separation from each other of two enantiomers through their passage into two kinds of crystals related enantiomorphously, when the externally compensated form of the substance is allowed to crystallise from solution under suitable conditions. Two particular queries arose for investigation²¹: (1) Are distinctive "hemihedral facets" always developed on a crystal composed of uniform asymmetric molecules (and therefore necessarily enantiomorphous in structure)? (2) If not, can Pasteur's First Method be applied when the "hemihedral facets" fail to appear on a crystal of this kind?

dl-isoHydrobenzoin, $\text{Ph}\cdot\text{CH}(\text{OH})\cdot\text{CH}(\text{OH})\cdot\text{Ph}$, appeared to be a suitable substance for investigation, in view of the fact that it had been reported to separate from solution as a conglomerate of *d*- and *l*-crystals.²² Pure specimens of *d*- and *l*-isohydrobenzoin were prepared by treating *d*- and *l*-isodiphenylhydroxyethylamine, $\text{Ph}\cdot\text{CH}(\text{OH})\cdot\text{CH}(\text{NH}_2)\cdot\text{Ph}$ (*vide infra*) with nitrous acid.

d-isoHydrobenzoin was found to crystallise from ethyl acetate at the ordinary temperature in the monoclinic system, most of the crystals being rendered enantiomorphous in external form by the development of a pair of *q*-facets at the right side (Fig. 1, top right). Under similar conditions, *l*-isohydrobenzoin deposited crystals which were non-coincident mirror-images of those of *d*-isohydrobenzoin (Fig. 1, top left). Crystallisation from chloroform at the ordinary temperature gave a different result, the normal form of crystal being apparently symmetric (Fig. 1, bottom), owing to a lack of the *q*-facets. A few such crystals were also deposited from ethyl acetate solutions.

Query (1) therefore receives the answer that "A crystal composed entirely of asymmetric molecules of one kind is not bound to reveal asymmetry of external form. Molecular asymmetry may, or may not, betray itself in the form of the crystal."

In order to find an answer to query (2), preparations of externally compensated (or *dl*-) *isohydrobenzoin*, made by mixing equal weights of *d*- and *l*-*isohydrobenzoin*, were crystallised from the same two solvents. From ethyl acetate, two enantiomorphous forms were deposited side by side (Fig. 2), and these were shown by polarimetric examination to consist

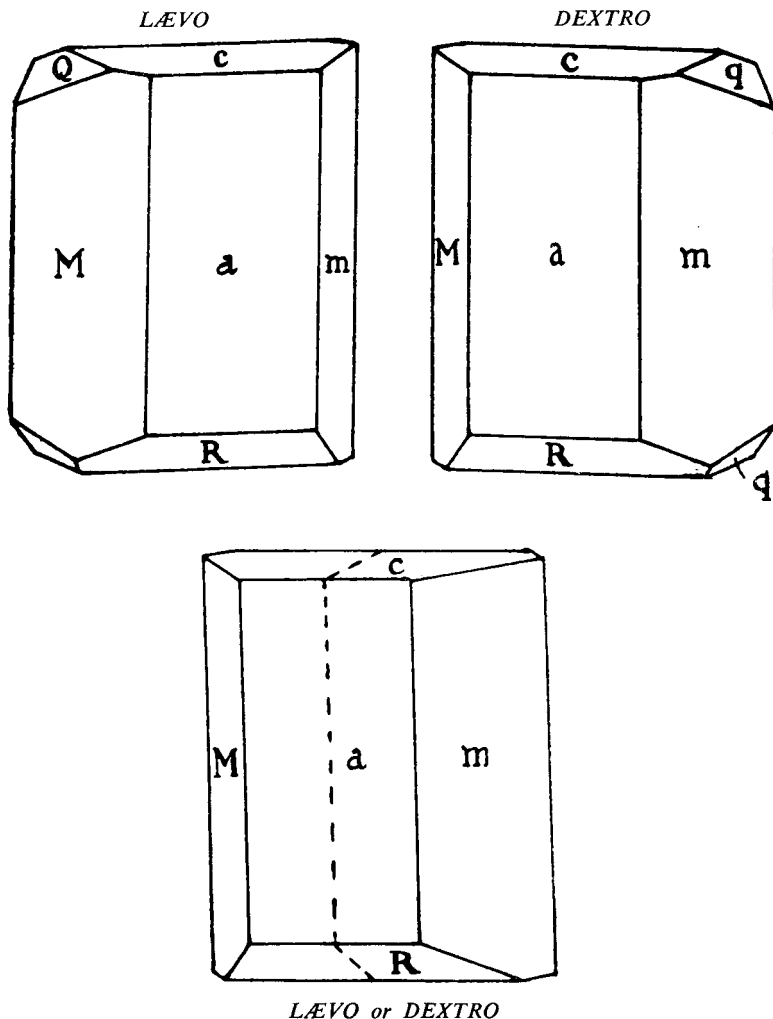


FIG. 1. *iso*Hydrobenzoin crystallised singly from ethyl acetate.

of pure *d*- and *l*-*isohydrobenzoin*, respectively. They differed, however, from the specimens which had been previously obtained by crystallising each pure form separately, in that the *q* and *m* faces showed a pronounced curvature. These curved faces, forming a marked contrast to the plane faces of Figure 1 (top right and left), were helpful in segregating the right- and left-handed crystals.

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Similar curved faces were developed upon crystals deposited from solutions of *dl*-isohydrobenzoin in chloroform, and this morphological distinction enabled the two kinds of crystals to be separated by inspection, in spite of the absence of the distinctive *q*-facets. The crystals obtained in this way were identical in form with the third crystal depicted in Figure 1, except for the curvature of their *m* faces. They showed the predicted sense and magnitude of optical rotation. Therefore the optical resolution had been accomplished by the method of spontaneous separation and manual selection of individual crystals, even in the absence of right- and left-handed *q*-facets.

To sum up:

First, enantiomorphism of crystal structure frequently unfolds itself on the surface of the crystal, but quite often it does not.

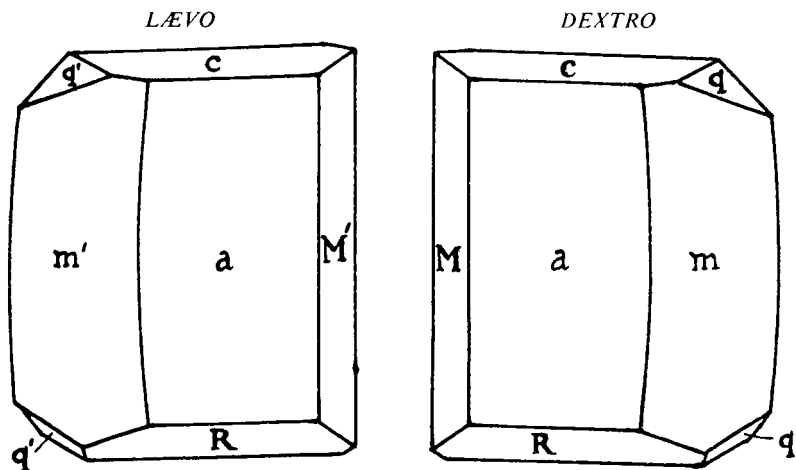


FIG. 2. *iso*Hydrobenzoin crystallised in company from ethyl acetate.

Secondly, in solutions of *dl*-isohydrobenzoin the differentiation of *d*- and *l*-forms is promoted by the presence of the opposite kind of molecule. It remains for further research to show whether this is a general proposition or not.

Thirdly, the possibility of separating right- and left-handed forms from a crystallising conglomerate depends mainly upon the amount of time the observer is prepared to spend in varying the conditions of crystallisation.

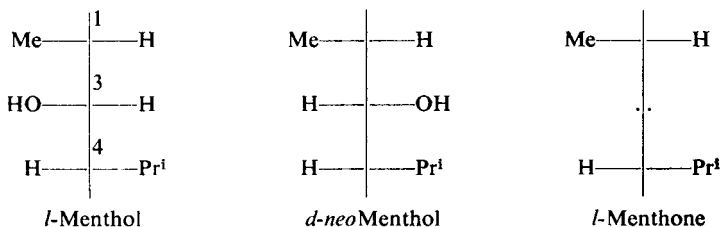
KINETIC STUDIES

1. Pasteur's three classical methods of optical resolution²³, devised between 1848 and 1858, underwent no fundamental development in principle until 1899. Pasteur's Second Method remained a static one, depending for its effect upon the purely physical process of fractional crystallisation when applied to the separation of two diastereoisomeric salts, such as *dA/B* and *lA/B* in the resolution of a *dl*-acid. In 1899, Marckwald and McKenzie²⁴ introduced the first effective modification of this method by devising a dynamic process in which the chemical reaction

became the resolving agent. They found that when *l*-menthol was heated with an excess of *dl*-mandelic acid, the unchanged acid was slightly λ evorotatory, thus showing that *l*-menthol had reacted more rapidly with the *d*- than with the *l*-acid. The new principle was fully established by much further work of the kind, undertaken largely by McKenzie and his collaborators.

Attention was focused upon slow reactions, notably partial esterification and partial saponification, since it seems to have been thought that the stereochemical preferences concerned would be unable to operate in a rapid reaction. A remarkable piece of rebutting evidence came to light in the course of the work on oxymethylenecamphor. As mentioned above, when *dl-ac*-tetrahydroquinaldine is condensed with oxymethylenecamphor the two diastereoisomers form a partial racemate inseparable by fractional crystallisation. Nevertheless, it proved possible to achieve with this reagent the optical resolution of the base.²⁵ When *l*-oxymethylenecamphor (represented below by L) was condensed with an excess of *dl-ac*-tetrahydroquinaldine, the recovered base was strongly λ evorotatory and the condensation product consisted of the two diastereoisomers, *d*-L and *l*-L, in the proportion of 60 per cent. to 40 per cent. When fractionally crystallised, this product readily separated into a partial racemate, *d*-L, *l*-L (80 per cent.), and the pure compound *d*-L (20 per cent.), from which the pure *d*-base was easily obtained. It was considered at the time "very remarkable that a reaction of the type of this condensation, which proceeds almost as rapidly as an ionic interaction, should yield the two products, *l*-L and *d*-L, with such very different velocities."

2. The different reaction-velocities of stereoisomers with a common reagent has been turned to striking practical use in devising the most efficient method yet known for the preparation of a pure optically active form of *neomenthol*.²⁶ As shown below, *d-neomenthol* is an epimer of *l*-menthol, the ordinary menthol of peppermint oil, and both of them are derived from *l*-menthone:



l-Menthol may be oxidised quantitatively to *l*-menthone. This ketone when reduced with *isopropanol* and aluminium *isopropoxide*, yields a mixture of about 70 per cent. of *d-neo*- and 30 per cent. of *l*-menthol. Competitive reaction with about half the calculated amount of *p*-nitrobenzoyl chloride in dry pyridine then leads rapidly to the preparation of stereochemically pure *d-neomenthol*: owing to the "protective" action of the *isopropyl* group upon the adjacent hydroxyl group, the *neomenthol* molecule reacts much more slowly than its epimer.

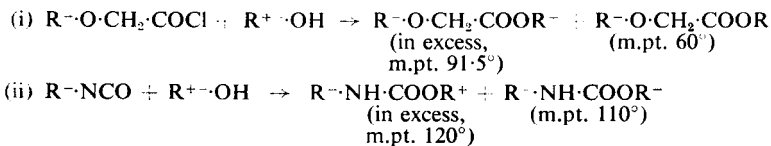
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In this process—which utilises, it should be noted, a symmetric agent in the separative operation—the $\cdot\text{CH}(\text{OH})\cdot$ group of *l*-menthol has been rotated through 180° in a very neat and effective way. The method is a general one, capable of wide application.

3. The above behaviour, being due to obvious stereochemical obstruction, was to be anticipated; but kinetic studies in this field abound in stereochemical preferences, for many of which there is at present no adequate explanation. Particular interest attaches to reactions in which both of the reactants are asymmetric. As a result of concurrent and long-continued work in the terpene series (*vide infra*) it has become possible to investigate highly specialised cases in which the two reactants are not only asymmetric, but also closely related in structure and even in spatial configuration. Very little work has been done in this difficult field—which in its broad aspect is one of great interest in Nature as well as in Art—but a beginning has been made.

A study of the different reaction-velocities of a pair of enantiomers with a common optically active reagent embodying one of the enantiomeric configurations concerned has brought forcibly to notice the tendency of an asymmetric molecule or radical to show a preference for its enantiomeric form; moreover in such reactions the major product has the higher melting point and is less soluble.

Thus, in reaction (i) below,²⁷ *d*-menthol reacts more rapidly than *l*-menthol with *l*-menthoxyacetyl chloride; and in (ii) *d*-menthol reacts more rapidly than *l*-menthol with *l*-menthyl isocyanate²⁸:



It has been shown²⁹ that *d*-menthyl *l*-menthylglycine, with its two enantiomeric menthyl radicals, has a higher melting point and is less soluble than *l*-menthyl *l*-menthylglycine; accordingly it may be anticipated (although the experiment has not been made) that the first of these compounds would be the predominating product of a reaction between *l*-menthylamine and *dl*-menthyl chloroacetate:



Interesting but quite unpredictable results have been obtained in studying the comparative reaction-velocities of a pair of enantiomers with an optically active reagent containing an epimeric (or doubly epimeric) configuration. For example, in reaction (ii) above,²⁸ *l*-menthol reacts much more rapidly than *d*-menthol with *d*-neomenthyl isocyanate; and *l*-isomenthol reacts much more rapidly than *d*-isomenthol with *l*-menthyl isocyanate. This last observation suggests a dynamic method for the optical resolution of *dl*-isomenthol, which has not yet been accomplished by any method.

SPECIAL ASYMMETRIC TYPES

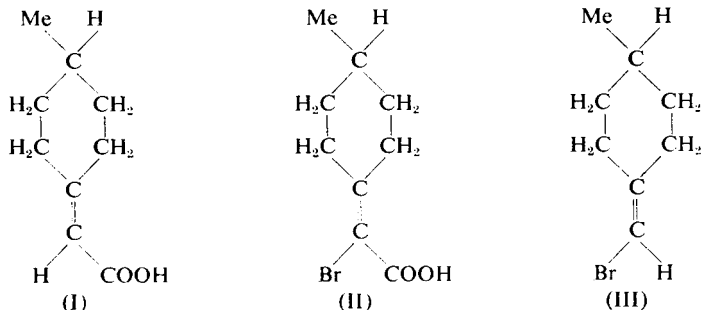
Organic Selenium Derivatives

In 1899, Pope, in collaboration with Peachey,³⁰ provided the first unquestionable example of an optically active organic compound in which the asymmetry was associated with an atom other than carbon. Benzylphenylallylmethylammonium iodide, corresponding to the general model $NabcdX$, was isolated in *l*- and *d*- forms, thus showing that the nitrogen atom could act as a so-called "asymmetric centre." During the next few years Pope and his collaborators provided an exciting serial story into which asymmetric atoms of tin, sulphur and selenium entered in succession as leading characters. The experimental proof that atoms of nitrogen, tin, sulphur and selenium could, like carbon atoms, act as centres of asymmetry and give rise to optically active organic molecules must be viewed as the greatest advance in stereochemistry that had been made since the days of Pasteur, Wislicenus, and van 't Hoff.

In 1900, Pope and Peachey³¹ had prepared the first optically active sulphur compound, $[MeEtS\cdot CH_2\cdot COOH]Br$, and in 1902 Pope and Neville³² obtained the first optically active selenium compound, $[MePhSe\cdot CH_2\cdot COOH]$. Attempts to prepare the selenium analogue of the sulphur compound, in order to ascertain the effect upon the optical rotation of exchanging a sulphur atom for a selenium atom in the two derivatives $[MeEtS\cdot CH_2\cdot COOH]Br$ and $[MeEtSe\cdot CH_2\cdot COOH]Br$, had to be abandoned owing to the revolting and distressful odour of methylethyl selenide and possible concomitants.³³

Centroasymmetry

As far back as 1875, van 't Hoff³⁴ had pointed to the possibility of the existence of asymmetric molecules possessing no particular asymmetric atom. He instanced the case of allene derivatives of the type $abC:C:Ccd$, in which, as a consequence of the tetrahedral theory, the groups *a* and *b* would lie in a plane at right angles to the plane occupied by *c* and *d*, thus giving rise to an asymmetric configuration with a non-superposable mirror-image. Allene derivatives of this fundamental type being difficult of access, it was necessary to synthesise a suitable substance of a modified type. In this substance, 1-methylcyclohexylidene-4-acetic acid (I), one of the double bonds of the allene is replaced by a cyclohexane ring (i.e., a 2-carbon ring is replaced by a 6-carbon ring):



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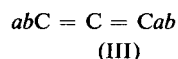
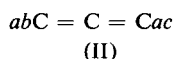
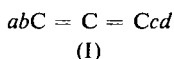
Perkin's attempts to resolve this acid (I) failed; but the complete optical resolution was eventually accomplished with the aid of brucine.³⁵ Structures of this type, which Pope termed "centroasymmetric," were thereby brought into line with the familiar type containing one or more formally asymmetric atoms in the molecule.

Treatment with bromine converted the optically active forms of (I) into optically active dibromides. These dibromides were found to react analogously to the methylcoumaric acid dibromides (*vide supra*) with concentrated and dilute alkali, respectively, thus yielding two other centroasymmetric compounds (II) and (III), each of which was optically active. Of these changes, Pope wrote: "We know of no other series of reactions in organic chemistry which shows so distinctly as this the persistence of mirror-image isomerism as revealed by the conservation of the optical activity throughout such profound disturbances of the molecular configuration as are here involved."

This optical resolution was described in 1940 as "the basis of all modern stereochemical investigation."³⁶ It provided a conclusive vindication of the broad view of van 't Hoff, that (a) any compound whose molecules have no plane of symmetry can exist in optically active forms, and (b) conversely, the molecules of a compound showing optical activity in the amorphous condition cannot have a plane of symmetry.

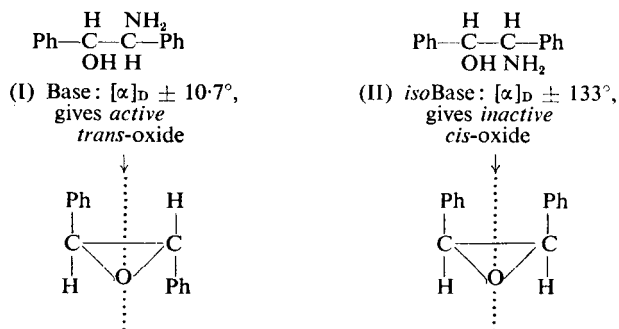
Dissymmetry

The following three types of allene derivatives possessing enantiomorphous molecular configurations may be foreseen:



The first two types are truly asymmetric, since they possess no element of symmetry: 1-methylcyclohexylidene-4-acetic acid is analogous to the second type. The third type differs from the other two in possessing a twofold axis of symmetry, and is described as "dissymmetric," rather than "asymmetric."³⁷ Since it has no plane of symmetry and gives a non-superposable mirror-image, this configuration is still enantiomorphous and capable of existing in right- and left-handed forms. The first true allene derivative to be prepared in optically active forms belonged to this type, van 't Hoff's prediction of 1875 being fulfilled by Maitland and Mills³⁸ in 1935, after the passage of 60 years.

A dissymmetric substance of a simpler type, *trans*-2:3-diphenylethylene oxide, is also of interest from other points of view. The hydrobenzoin, of which the optically active forms have been mentioned above, may be obtained by the action of nitrous acid on either of the isomeric bases, diphenylhydroxyethylamine (I) and *isodiphenylhydroxyethylamine* (II), shown in the appended projection formulae. These bases may be synthesised easily in their *dl*-forms and resolved in each case into *d*- and *l*-components.³⁹ When the derived quaternary ammonium iodides are steam distilled with silver oxide they yield the corresponding 2:3-diphenylethylene oxides, as indicated overleaf:



The *cis*-oxide has a plane of symmetry in its molecule (shown by the broken line in the bottom right-hand projection formula), and is therefore incapable of exhibiting optical activity. In striking contrast, the molecule of the *trans*-oxide is dissymmetric, since it has a twofold axis of symmetry (shown by the broken line in the bottom left-hand projection formula), and it should therefore be capable of existing in *d*- and *l*-forms, exhibiting optical activity.

In fact,⁴⁰ as shown in the diagram, *d*-diphenylhydroxyethylamine, m.pt. 143° , $[\alpha]_D + 10.7^\circ$, gave rise to the *l*-*trans*-oxide, m.pt. 69.7° , $[\alpha]_D - 306^\circ$; and *l*-isodiphenylhydroxyethylamine, m.pt. 115° , $[\alpha]_D - 133^\circ$, gave the optically inactive *cis*-oxide, m.pt. 42° .

Since the yields of pure oxides were almost quantitative, the occurrence of configurational changes during their formation is unlikely. Therefore the relative configurations (I) and (II) above were assigned to the base and *isobase*, respectively.

RELATIVE MOLECULAR CONFIGURATION

These results show that in certain cases the persistence or loss of optical activity in a common chemical process may be used to throw light upon the relative molecular configurations of stereoisomers. A first glance at the projection formulae derived above might suggest that formula (II), with its appearance of greater symmetry, should be that of the compound of lower rotatory power. A clearer picture of the spatial relationships is obtained, however, by projecting the tetrahedral model (one of the two asymmetric carbon atoms being situated above the other on a vertical axis) on to a plane surface. Taking into account the probable mutual repulsion of the two electronegative phenyl radicals, the relative mean positions will be as shown below, the bracketed groups occupying the lower plane:



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In (I) the mean positions of the oscillating groups are such that one H atom lies approximately in a mean position below the other, while the NH_2 group lies similarly below the OH group. Remembering the close stereochemical equivalence of OH and NH_2 in the menthols and menthylamines, in their effects upon the magnitude of the optical rotation,⁴¹ it will be seen that system (I) approaches the symmetrical, whereas system (II) departs widely therefrom. The much larger optical rotation of the *isobase* (II) is thereby explained.

The determination of the relative molecular configurations of these two asymmetric $\alpha\beta$ -hydroxyamines is of much interest, because of their relationship to a series of structurally similar substances of great physiological interest.

Such configurational determinations are much more difficult in open-chain systems, with free rotation of asymmetric carbon atoms about the single bond, than in cyclic systems devoid of this possibility.

STEREOCHEMICAL STUDIES IN THE TERPENE SERIES

Stereochemistry originated from a study of certain naturally occurring substances, in particular the tartaric and lactic acids. Since then its principles have been elucidated to a large extent as a result of researches upon purely artificial compounds, as will indeed be evident from the foregoing discussions. It must not be forgotten, however, that stereochemistry permeates the whole great corpus of organic nature, in which is found its deepest and fullest expression.

Nowhere does this fundamental truth receive a greater emphasis than in a chemical study of the Australian flora. The genus *Eucalyptus* alone numbers its species in hundreds, and each species secretes its individual essential oil, always consisting of a complex mixture of organic substances, many of which are asymmetric and optically active. Prominent among these constituents are terpenes and terpene derivatives; these provide a fascinating and almost limitless field of study for the stereochemist.

Space does not allow me to enter into details of many such researches of which integrated accounts have been published from time to time.⁴² All that can be done here is to give a mere indication of some of the outstanding features of this work, most of which is strongly charged with a stereochemical interest. Many of the published papers in question have dealt directly with piperitone, the *lævorotatory* ketone of certain eucalyptus oils.⁴³ Another sequence, devoted to researches in the menthone series,⁴⁴ has completely elucidated the relative molecular configurations of the menthones, menthols and menthylamines, besides throwing light on the stereochemistry of certain menthenes and other related compounds. There have been parallel researches in the carvone series⁴⁵; still other communications record work on phellandrenes,⁴⁶ while diosphenol,⁴⁷ pulegone,⁴⁸ thujones,⁴⁹ and many other terpene derivatives have also been investigated stereochemically.

Prolonged investigations of this kind bring home to the stereochemist a vivid realisation of an all-pervading asymmetric influence presiding over

the manifold operations of organic Nature. The stereochemist can accomplish much in his laboratory; but he remains powerless to effect many of the subtle stereochemical differentiations of Nature.

Many species of Australian eucalypts produce piperitone, invariably in the levorotatory form; whereas certain Indian grasses give rise to its mirror-image form, *dextro*-piperitone.⁵⁰ The excessively delicate control of the molecular mechanism in these and an infinity of other natural stereochemical processes appears to be a prerogative of the living organism. Although the stereochemist has travelled so far on his way in the first century of the science, it is clear that the finer manifestations of stereochemical synthesis still remain beyond his control and inseparable from the vital processes of organic Nature.

Nearly a century ago, in 1860, Pasteur said: "If the mysterious influence to which the asymmetry of natural products is due should change its sense or direction, the constitutive elements of all living beings would assume the opposite asymmetry. Perhaps a new world would present itself to our view. Who could foresee the organisation of living things if cellulose, right as it is, became left; if the albumin of the blood, now left, became right? These are mysteries which furnish much work for the future, and demand henceforth the most serious consideration from science."⁵¹

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