CXCVIII.—*Optically Active Substances Containing no Asymmetric Atom.* 1 - Methylcyclohexylidene - 4-acetic Acid.

By WILLIAM HENRY PERKIN, WILLIAM JACKSON POPE, and
OTTO WALLACH.

A PERUSAL of van't Hoff's early work on optical activity makes it clear that he adopted the view, first advanced by Pasteur, that the optical activity of amorphous substances is due to enantiomorphism of molecular configuration. Van't Hoff and Le Bel developed Pasteur's conclusion by introducing a definite theory of the configuration of carbon compounds, and showed that the enantiomorphism of molecular configuration possessed by all known optically active substances could be correlated with the presence of asymmetric carbon atoms in the molecule.

The optical activity is, in fact, not, as is still sometimes stated, due to the presence of an asymmetric carbon atom, but originates in the enantiomorphous molecular configuration. The identification of a particular carbon atom in the molecule as asymmetric is merely a convenient method for recognising enantiomorphism of molecular configuration.

Van't Hoff realised that organic substances are capable of formulation which, whilst possessing enantiomorphous molecular configurations, contain no asymmetric atom, and quoted, as an instance, the formula $\begin{matrix} R_1 \\ R_2 \end{matrix} > C : C : C < \begin{matrix} R_3 \\ R_4 \end{matrix}$ as that of a substance which should be of enantiomorphous molecular configuration, and therefore capable of exhibiting optical activity in the amorphous state, although its molecule contains no asymmetric atom.

The statement is sometimes made that inosite, which is optically active in solution and has the configuration

contains no asymmetric carbon atom. This, however, seems to involve a misapplication of the definition of an asymmetric carbon atom. The carbon atom (1) is separately attached to the two systems,

which differ configurationally in the same way respectively as do the *d*-tartaric and mesotartaric acids; although these two groups thus differ in configuration, they are not enantiomorphously related. The carbon atom (1) being attached to these two configurationally dissimilar groups and to two others, namely, H and OH, is directly joined to four quite dissimilar groups, and is hence asymmetric; in the same way, it will be seen that the other five carbon atoms in the inosite molecule are also asymmetric.

No case has, in fact, been experimentally realised of a substance exhibiting optical activity in the amorphous state and containing no asymmetric carbon (nitrogen, sulphur, selenium, tin, or silicon) atom.

In view of the theoretical importance attaching to the discovery of substances exhibiting optical activity in the amorphous condition, and hence possessing enantiomorphous molecular configurations, but containing no asymmetric atom, it appeared desirable to attempt, by modern synthetic methods, the preparation of such compounds. The study of allene derivatives such as were considered by van't Hoff presented obvious disadvantages; the facility with which such substances undergo isomeric change and become converted into acetylene derivatives, and their tendency to combine with water, etc., to yield ethylene derivatives, might be expected to introduce experimental difficulties which would be desirably avoided. Perkin and Pope (Proc., 1906, 22, 107; Trans., 1908, 93, 1075) therefore synthesised the 1-methylcyclohexylidene-4-acetic acid,

which contains no asymmetric carbon atom, but which, in accordance with the van't Hoff conception, possesses an enantiomorphous molecular configuration, and attempted its resolution into optically active components. By a curious coincidence, Marckwald and Meth were at the same time engaged upon the synthesis of the same compound for the same purpose; they obtained an acid, melting at 40—41°, to which they assigned the constitution given above and effected its resolution into optically active components (*Ber.*, 1906, **39**, 1171). The acid melting at 40—41° was, however, quite different from that prepared by Perkin and Pope, which melts at 66°,* and the latter authors suggested (*Proc.*, 1906, **22**, 107) that Marckwald and Meth's acid is the isomeric 1-methyl- Δ^3 -cyclohexene-4-acetic acid of the constitution

As the carbon atom numbered (1) in the latter constitutional formula is obviously attached to four constitutionally dissimilar groups it is asymmetric in the ordinary sense; the resolution of such a synthetic product into optically active components therefore merely illustrates again the optical activity of substances which contain an asymmetric carbon atom in the molecule.

The difference of opinion briefly referred to above gave rise to a long controversy, and led to an extended series of experimental investigations (Marckwald and Meth, *Ber.*, 1906, **39**, 1171, 2035, 2404; Wallach, *Annalen*, 1907, **313**, 311; 1909, **365**, 255; Perkin and Pope, *Trans.*, 1908, **93**, 1075; Harding, Haworth, and Perkin, *Trans.*, 1908, **93**, 1943; Hope and Perkin, *Trans.*, 1909, **95**, 1360). The final result of this work has been to prove conclusively that the original view taken by Perkin and Pope was correct; the acid melting at 66° is the true 1-methylcyclohexylidene-4-acetic acid, whilst the acid melting at 40—41°, which Marckwald and Meth supposed to be the latter acid, is the 1-methyl- Δ^3 -cyclohexene-4-acetic acid, the graphic formula of which contains an asymmetric carbon atom. The resolution effected by Marckwald and Meth thus failed to yield a substance exhibiting optical activity and containing no asymmetric atom.

The close study devoted to the two isomeric acids under discussion led to simplifications in the preparation of 1-methylcyclohexylidene-4-acetic acid (Wallach, *Annalen*, 1909, **365**, 266), so that large quantities of this acid could be readily obtained for subjection to the treatment usually employed for the resolution of externally compensated acids into their optically active components. Owing to peculiarities in the behaviour of the substance, its resolution presented considerable difficulty, but we ultimately succeeded in separating the *d*- and

* The melting point, 70°, originally given is somewhat too high.

l-components of 1-methylcyclohexylidene-4-acetic acid in a state of purity. We are thus able to describe the first case of an optically active substance which possesses an enantiomorphous molecular configuration, although its constitutional formula contains no asymmetric atom.

In discussing the molecular configuration of 1-methylcyclohexylidene-4-acetic acid, it is convenient to adopt the rigid, but doubtless incorrect, view that the four valency bonds attached to the methane carbon atom in the molecule of a methane derivative are directed towards the apices of a regular tetrahedron, of which the carbon atom mentioned occupies the centre. The actual conditions, apart from the fact that they are dynamic and not static as just premised, are probably far less symmetrical than is indicated by our assumption; since, however, the space relations which give rise to the molecular enantiomorphism of the new acid can be readily elucidated on the basis of a symmetrical and rigid configuration for methane derivatives, nothing, for present purposes, is to be gained by introducing the more complicated, although doubtless more accurate, conditions indicated above.

The configuration of 1-methylcyclohexylidene-4-acetic acid may be represented in the following manner:

in which those bonds represented by unbroken lines all lie in one plane, and those represented by broken lines lie in a plane perpendicular to the first; if the continuous lines represent bonds which lie in the horizontal plane of the paper, the broken lines stand for bonds which lie in the vertical plane passing through the carbon atoms numbered 1, 4, and 7. It will now be seen that the plane of the paper which contains the continuous line bonds is not a plane of symmetry of the solid configuration, because the hydrogen atom marked (a), which lies outside that plane, is not repeated on the other side of the plane, the symmetrical position being occupied by the methyl group (b). Similarly, the vertical plane remarked above is not a plane of symmetry of the configuration, because the groups (c) and (d), of different compositions, occupy symmetrical positions on two sides of the plane; in the same way, it can be shown that no other plane is a plane of symmetry of the configuration as above represented. Further, no directions can be distinguished as axes of symmetry of the solid configuration, nor can any point be located within it as a centre of symmetry.

It is thus seen that, even when a highly symmetrical configuration is attributed to methane derivatives, the configuration assignable to 1-methylcyclohexylidene-4-acetic acid possesses neither planes, axes, nor a centre of symmetry. The absence of all these elements of symmetry is more than is requisite to determine the enantiomorphism of the configuration.

From the above discussion it will be observed that the configuration of 1-methylcyclohexylidene-4-acetic acid is enantiomorphous, even under the highly symmetrical condition represented by placing the carbon atoms numbered 1 to 8 and the hydrogen atom (*c*) in the plane of the paper and the carbon atom numbered 9 and the hydrogen atom (*a*) in the plane, perpendicular thereto, referred to above. The enantiomorphism would indeed persist if the hydrogen atoms (*a*) and (*c*) and the carbon atoms 8 and 9 were centred at the apices of a regular tetrahedron.

The conviction that the structural formulæ assigned to chemical substances imitate with considerable approximation to truth the real nature of molecular constitution was appreciably deepened by the introduction of the theory of the configuration of methane derivatives by van't Hoff and Le Bel; the development of the theory by Wislicenus, so as to embrace the configuration of ethylene derivatives, and by von Baeyer, in connexion with polymethylene derivatives, has strengthened the view that the constitutional formulæ of organic chemistry represent very closely the actual atomic arrangement of molecular complexes. The considerations which led to the work described in the present paper involved, as has been seen, the development of the original simple geometrical conception of the space configuration of methane and ethylene derivatives to an extent which may appear extreme. The fact that we have been able to show a close correspondence between the anticipations thus derived and the experimental results must be regarded as an independent demonstration of the fidelity with which constitutional formulæ picture molecular constitutions.

Resolution of 1-Methylcyclohexylidene-4-acetic Acid.

The resolution of externally compensated 1-methylcyclohexylidene-4-acetic acid into its optically active components is attended with some difficulty, owing, in the main, to the very feeble acidic properties of the substance. The inactive acid thus crystallises unchanged from solutions in the fairly powerful base, 1-tetrahydroquinoline, and can be extracted by appropriate neutral solvents from its mixtures with many of the optically active alkaloids. A clue to a successful mode of resolution was, however, ultimately derived from the observation that on

mixing aqueous solutions of brucine hydrochloride and sodium 1-methylcyclohexylidene-4-acetate a copious separation of an oil occurs; although this oily salt does not crystallise readily, the fact of its formation can be utilised for the isolation of the two enantiomorphously related acids.

As the result of a large amount of preliminary work, the following method was finally adopted for the resolution of the externally compensated acid. To a hot aqueous solution of two molecular proportions of externally compensated sodium 1-methylcyclohexylidene-4-acetate is added a hot aqueous solution of slightly less than one molecular proportion of brucine hydrochloride; during admixture, alcohol is added in just sufficient quantity to prevent the solution becoming turbid by the separation of an oily salt. On allowing the solution to cool slowly, an oil begins to separate, which, by persistent scratching with a glass rod, or better, by inoculation with crystalline salt obtained in a previous operation, may be caused to crystallise. In accordance with the experience of Pope and Peachey in connexion with the resolution of externally compensated bases (Trans., 1899, 75, 1066), it was to be expected that the crystalline salt which separated should be the least soluble of which the formation is possible in the system. The crystalline salt which separates under these conditions does, indeed, consist, in the main, of one product, namely, of brucine *l*-1-methylcyclohexylidene-4-acetate, so that the change can be expressed by the equation:

As will be pointed out later, however, a complicating factor is introduced, in that the two salts, *lB*/*lA* and *lB*/*dA*, behave as if they were partially isomorphous and form solid solutions.

The operation described above yields a crystalline separation, which has the composition of brucine *l*-1-methylcyclohexylidene-4-acetate, but which, on recrystallisation, is found to be by no means homogeneous; thus, in one case, on fractionally crystallising the separation obtained as described above from dilute alcohol in such a manner that the original separation was divided into five fractions, the consecutive fractions gave the following specific rotatory powers in 1 per cent. alcoholic solutions: $[\alpha]_D - 44.7^\circ$, $- 22.0^\circ$, $- 40.7^\circ$, $- 23.7^\circ$, and $- 33.6^\circ$.

The manner in which in these and a number of other trials the specific rotatory powers change from fraction to fraction indicates (1) that the original separation is a mixture of at least two substances, and (2) that the resolution of the mixture by recrystallisation does not follow the ordinary course; the separation is, in fact, complicated by the exhibition of behaviour somewhat similar to that observed with

mixtures of two substances which tend to form solid solutions, and readily yield supersaturated solutions. Since the two compounds present in the mixtures are presumably the *l*- and *d*-1-methylcyclohexylidene-4-acetates of *l*-brucine, it was, however, indicated by these results that some degree of separation could be effected by fractional crystallisation. Considerable quantities of the first separation of crystalline salt, obtained as above described, were therefore subjected to systematic fractional crystallisation from very dilute alcohol; the specific rotatory power of each fraction as it was separated was ascertained, and the numerous fractions were sorted into portions of approximately the same rotatory power. After a preliminary separation in this way into separate fractions of fairly uniform rotatory power, the systematic fractional crystallisation was repeated. As the final product of the prolonged application of this tedious process, a highly levorotatory salt was ultimately obtained, the rotatory power of which was unaltered by subsequent crystallisation. The material thus obtained gives all the ordinary indications of homogeneity, and separates from dilute alcoholic solution in elongated, colourless, rectangular prisms; it melts at 97—100° when dried in the air, and after expelling the water of crystallisation by heating at about 85°, commences to melt at 74°. As its properties appeared unaffected by further recrystallisation, it was regarded as the pure salt, *l*-brucine *l*-1-methylcyclohexylidene-4-acetate.

Brucine lævo-1-Methylcyclohexylidene-4-acetate,
 $C_{28}H_{26}O_4N_2 \cdot C_9H_{14}O_2 \cdot 2H_2O$.

A considerable quantity of salt answering to the above description having been accumulated, the whole was crystallised from dilute alcohol, and the following analyses and determinations of rotatory power made on the substance thus obtained:

0·3900, heated at 85°, lost 0·0242 H_2O . $H_2O = 6\cdot21$.

0·0790, air-dried salt, gave 0·1902 CO_2 and 0·0522 H_2O .

Subtracting $H_2O = 6\cdot21$; $C = 73\cdot00$; $H = 7\cdot14$.

$C_{32}H_{40}O_6N_2 \cdot 2H_2O$ requires $H_2O = 6\cdot17$; $C = 70\cdot02$; $H = 7\cdot35$ per cent.

For the determinations of the rotatory power, shown in the table below, the substance was made up to 20·05 c.c. with the solvent, and a 2-dcm. tube employed in each case.

Substance			
gram.	Solvent.	α_D .	$[\alpha]_D$.
0·1553	Absolute alcohol	-0·90°	-58·1°
0·1570	" "	-0·91	-58·1
0·3983	" "	-1·98	-49·8
0·5680	" "	-2·66	-46·9
0·1683	Methylal	-1·32	-78·6
0·1458	Water	-0·56	-38·6

It thus appears that the specific rotatory power diminishes with increasing concentration in alcoholic solution, that the specific rotatory power is much higher in methylal solution, and that in water, in which alone the salt may be supposed to be practically completely dissociated, the specific rotatory power has the lowest value.

In view of the difficulty which attends the preparation of the salt characterised by the above constants, it was deemed advisable to subject the whole mass of material to further fractional crystallisation from dilute alcohol in order to make quite sure that its rotatory power had attained a constant value. It was therefore crystallised four times from absolute alcohol, and the following determination of the rotatory power made with the product :

0.1528 gram, made up to 20.05 c.c. with absolute alcohol, gave $\alpha_D - 0.89^\circ$ in a 2-dcm. tube ; whence $[\alpha]_D - 58.4^\circ$.

The material was then subjected to another and fifth crystallisation from the same solvent, and the product found to give the following results on determination of its rotatory power :

0.1494 gram, made up to 20.05 c.c. with absolute alcohol, gave $\alpha_D - 0.87^\circ$ in a 2-dcm. tube ; whence $[\alpha]_D - 58.4^\circ$.

Since in a 0.75 per cent. alcoholic solution the salt exhibited the specific rotatory power $[\alpha]_D - 58.1^\circ$, as quoted above, and after four and five recrystallisations the values $[\alpha]_D - 58.4^\circ$ and -58.4° were obtained, these being experimentally identical with the first, little doubt seemed possible concerning the homogeneity of the substance. The following work, however, showed that this conclusion is incorrect.

On decomposing a small portion of the salt by addition of hydrochloric acid, a sample of acid was obtained which melted at $51-52^\circ$, and gave the following result on determination of its rotatory power :

0.1253 gram, made up to 20.05 c.c. with absolute alcohol, gave $\alpha_D - 0.97^\circ$ in a 2-dcm. tube ; whence $[\alpha]_D - 77.6^\circ$.

The main quantity of the salt, which was in the form of stout, crystalline prisms, was next treated with hydrochloric acid, and the precipitated acid filtered ; associated with it, however, was some brucine hydrochloride, which could not be conveniently washed out with water. The whole mass was therefore warmed with sodium carbonate solution, and, after filtration, the acid was precipitated by hydrochloric acid, collected, washed, and dried. The acid thus obtained melted at $47.5-49.5^\circ$, and gave the following results on determination of its specific rotation :

0.1509 gram, made up to 20.05 c.c. with absolute alcohol, gave $\alpha_D - 1.10^\circ$ in a 2-dcm. tube ; whence $[\alpha]_D - 73.7^\circ$.

The residue left after warming the crude acid with sodium carbonate

solution as above described still contained acid ; this was extracted by successive treatments with hydrochloric acid and sodium carbonate solution, and melted very sharply at 52·5—53°. It gave the following results on determination of its rotatory power :

0·1459 gram, made up to 20·05 c.c. with absolute alcohol, gave $\alpha_D - 1·18^\circ$ in a 2-dcm. tube ; whence $[\alpha]_D - 81·1^\circ$.

It is thus seen that the salt which yields acid of specific rotatory power $[\alpha]_D - 77·6^\circ$ gives, when the acid is separated in two fractions as described above, samples having the specific rotatory powers, $[\alpha]_D - 73·7^\circ$ and $- 81·1^\circ$ respectively.

In view of the unsaturated character of the acid, it seemed advisable to ascertain whether the above variations in rotatory power were caused by optical inversion during the liberation of the acid from the brucine salt. A quantity of the acid having the specific rotatory power $[\alpha]_D - 73·7^\circ$ was therefore distilled in a current of steam ; the acid separated from the distillate was found to have the specific rotatory power $[\alpha]_D - 74·0^\circ$. A further portion of the same sample of acid was next heated for ten hours on the water-bath with excess of a 10 per cent. sodium carbonate solution ; during this treatment the solution became brown in colour, but the acid subsequently separated from it was found to exhibit the specific rotatory power of $[\alpha]_D - 71·9^\circ$. These results indicate that the optical activity of the acid is practically unaffected by somewhat drastic treatment, and show that the observed variations in rotatory power cannot be attributed to the occurrence of optical inversion.

The explanation of the anomalous behaviour of the brucine salt appears to be as follows. It is seen that prolonged fractional crystallisation is necessary in order to obtain a brucine salt of constant rotatory power, namely, $[\alpha]_D - 58·1^\circ$ in a 0·75 per cent. absolute alcoholic solution ; it is also observed that the salt is not homogeneous, because the two fractions of acid separated from it have the rotatory powers of $[\alpha]_D - 73·7^\circ$ and $- 81·1^\circ$ respectively. Taken together, these facts indicate that the salt of specific rotatory power $[\alpha]_D - 58·1^\circ$ is an equilibrium mixture of brucine *l*- and *d*-1-methylcyclohexylidene-4-acetates which is not resolvable by further fractional crystallisation from dilute alcohol under the conditions established ; the slowness with which the maximum rotatory power $[\alpha]_D - 58·4^\circ$ is attained during prolonged fractional crystallisation suggests that the two salts form solid solutions. This is also in accordance with the facts that both contain the same proportion of water of crystallisation, and that an approximately complete resolution of the externally compensated acid is not effected by the original crystallisation with one-half a molecular proportion of brucine. It was also observed that on decom-

posing the salt of $[\alpha]_D - 58.4^\circ$, the first portion of acid separated has a lower rotatory power, $[\alpha]_D - 73.7^\circ$, than that which separated last, namely, $[\alpha]_D - 81.1^\circ$. This indicates that during the crystallisation of the brucine salt the salt with the lævo-acid first separated in a state of practical purity, and that subsequently the mixture of the two salts was deposited on the former as a kind of nucleus; since the crystals ultimately formed are quite massive, the outer layers were first decomposed by the hydrochloric acid, giving acid of the lower rotatory power, whilst the inner kernel was only decomposed by further treatment, and yielded acid of the higher rotatory power, $[\alpha]_D - 81.1^\circ$.

As no solvent other than dilute alcohol appears to be available for the fractional crystallisation of the brucine salt, it was useless, in view of the conclusions just derived, to attempt the further purification of the lævo-acid by the aid of the brucine salt. It is shown later, however, that the enantiomorphously related acid has the specific rotatory power $[\alpha]_D + 81.4^\circ$, so that the acid giving the value $[\alpha]_D - 81.1^\circ$ represents the pure *l*-1-methylcyclohexylidene-4-acetic acid.

The small difference in rotatory power between the pure lævo-acid of $[\alpha]_D - 81.1^\circ$ and that of $[\alpha]_D - 77.6^\circ$ yielded by the final crop of brucine salt, together with the large percentage of brucine contained in the brucine salt, rendered it certain that the specific rotatory powers observed with the brucine salt are practically the values appertaining to pure brucine *l*-1-methylcyclohexylidene-4-acetate. It seemed, however, desirable to check the numbers by preparing the latter salt from acid of $[\alpha]_D - 81.1^\circ$ by crystallising the components together from dilute alcohol. The pure salt was thus obtained in colourless, highly lustrous prisms having the properties already described in connexion with the slightly impure salt; the following determination of rotatory power was made:

0.1534 gram, made up to 20.05 c.c. with absolute alcohol, gave $\alpha_D - 0.89^\circ$ in a 2-dm. tube; whence $[\alpha]_D - 58.2^\circ$.

Brucine dextro-1-Methylcyclohexylidene-4-acetate,

After the separation of the lævo-acid from the externally compensated substance in the manner described above, the mother liquors are treated with hydrochloric acid and the crude *d*-1-methylcyclohexylidene-acetic acid separated; it is convenient to mix with it acid recovered from the fractions of brucine salt of low rotatory power to which reference has been made above. In this way a pure mixture of the *d*- and *l*-acids can be obtained which has a specific rotatory power of about

+30°, and, although the salt formed by brucine with the lævo-acid is much less soluble than that formed with the dextro-acid, the isolation of pure brucine *d*-1-methylcyclohexylideneacetate is possible. The acid of specific rotatory power of about $[\alpha]_D + 30^\circ$ is dissolved in dilute alcohol with the addition of an equivalent quantity of pure brucine, and the salt formed subjected to prolonged fractional crystallisation from the same solvent. It is advisable so to adjust the concentrations of the solutions that crystallisation does not occur until the liquid is cold; under these conditions the salt of the lævo-acid tends to separate in massive crystals, whilst that of the dextro-acid crystallises in aggregates of light feathery needles. It is thus possible to effect a partial separation by mechanical means, but the final purification of the salt of the dextro-acid must be completed by fractional crystallisation alone. In one series of fractionations a sample of salt was first isolated which exhibited the specific rotatory power $[\alpha]_D - 22.6^\circ$, in alcoholic solution. Eight subsequent crystallisations of this material yielded samples having the specific rotatory powers of $[\alpha]_D - 18.7^\circ$, -16.9° , -16.3° , -13.5° , -14.6° , -12.8° , -10.4° , and -11.5° respectively. The apparently irregular fluctuations of the specific rotatory powers of the successive crystallisations were at first difficult to understand, but were ultimately traced to the fact that the rotatory power of the pure salt diminishes very rapidly with increase of concentration of the solution. The last three values quoted above thus refer to pure brucine *d*-1-methylcyclohexylidene-4-acetate.

This salt crystallises in colourless, feathery needles from dilute alcoholic solution, and melts at 85–86°; after drying at 70–80°, it begins to melt at 76°, but the melting point is very indefinite. This is possibly to be attributed to the substance melting as a mere mixture of the component base and acid:

0.5530, heated at 70–80°, lost 0.0408 H₂O. H₂O = 7.38.

0.0806, air-dried salt, gave 0.1929 CO₂ and 0.0560 H₂O.

Subtracting H₂O = 7.38; C = 70.53; H = 7.50.

C₃₂H₄₀O₆N₂·2H₂O requires H₂O = 6.17; C = 70.02; H = 7.35 per cent.

For the determinations of the rotatory power, quoted in the table below, the substance was made up to 20.05 c.c. with the solvent, and a 2-dm. tube employed in each case.

Substance. gram.	Solvent.	α_D .	$[\alpha]_D$.
0.2348	Absolute alcohol	-0.27°	-11.5°
0.4015	" "	-0.16	-3.9
0.5548	" "	-0.08	-1.4
1.0404	" "	+0.25	+2.4
0.1404	Methylal	-0.31	-22.1
0.1404	Water	-0.04	-2.9

It is interesting to note that the specific rotatory power of this salt

varies with the concentration and the solvent in just the same directions as that of the brucine salt of the lævo-acid. In alcoholic solutions the lævorotation diminishes with increasing concentration until in a 5 per cent. solution the salt is dextrorotatory, just as in the previous case the rotatory power in methylal solution is much higher than that in aqueous solutions.

The two brucine salts are converted into oils by the addition of small proportions of alcohol, acetone, or ethyl acetate, and are extremely soluble in these and most other organic solvents.

lævo-1-Methylcyclohexylidene-4-acetic Acid,

As already indicated above, the purest samples of this acid separated from its brucine salt are still contaminated with traces of the enantiomorphously related isomeride; it forms minute, colourless, crystalline scales, and cannot be conveniently crystallised from any of the ordinary solvents. It melts very sharply at 52.5—53°, whilst the externally compensated acid melts at 66°, and its melting point is depressed by the presence of the externally compensated substance. Specimens of mixtures of the two active acids exhibiting the specific rotatory powers $[\alpha]_D$ 12.3°, 24.2°, 52.8°, 73.7°, and 77.6° melt respectively at 61°, 42—57°, 43—44.5°, 47.5—49.5°, and 51—52°, so that the eutectic mixture has a considerably lower melting point than either the pure active or the pure externally compensated acid; the melting point curve of mixtures of the dextro- and lævo-acid is thus of the type depicted in Roozeboom's Fig. 7 (*Zeitsch. physikal. Chem.*, 1899, 28, 508), and indicates that the partially compensated substances melt as mixtures of optically active and racemic compounds.

The following determinations of rotatory power were made, the substance being made up to 20.05 c.c. with the solvent, and a 2-dcm. tube being employed in each case:

Substance. gram.	Solvent.	α_D .	$[\alpha]_D$.
0.1459	Absolute alcohol	-1.18°	-81.1°
0.1471	" "	-1.19	-81.1
0.3195	" "	-2.48	-77.8
0.1505	Methylal	-1.12	-74.6
0.1616	Ether	-1.20	-74.4

dextro-1-Methylcyclohexylidene-4-acetic Acid.

This acid, as stated above, has been obtained more easily and in a state of slightly higher purity than its enantiomorphously related isomeride. It has the same melting point of 52.5—53°, and its mixtures with the externally compensated acid behave just as do those of

the *lævo*-isomeride. The following determinations of rotatory power were made, the substance being made up to 20.05 c.c. with the solvent, and a 2-dm. tube being employed in each case :

Substance gram.	Solvent.	α_D .	$[\alpha]_D$.
0.1453	Absolute alcohol	+1.18°	+81.4°
0.2957		+2.30	+78.0
0.1487	"Methylal"	+1.12	+75.5
0.1478	Ether	+1.11	+75.3

The fact that the above values are slightly higher than the corresponding figures for the enantiomorphously related acid is the only indication yet obtained of the rather greater degree of purity of the preparations of the *dextro*-acid.

On dissolving equal quantities of the two optically active acids melting at 52.5—53° in light petroleum and evaporating to dryness, the racemic acid was obtained melting at 62.5—63°; that this melting point is rather lower than that of the pure externally compensated acid, namely, 66°, is obviously due to the mixture, which weighed only a few milligrams, containing a slight excess of one of the component acids.

The fact, established by the work detailed in the foregoing pages, that substances of enantiomorphous molecular configuration can now be prepared which exhibit optical activity in solution but yet contain no asymmetric carbon atom, suggests a mode of investigating intramolecular change which should have interesting results. The *d*- and *l*-methylcyclohexylidene-4-acetic acids owe their optical activity to the possession of an enantiomorphous molecular configuration of the most general kind, namely, one not associated with the presence of an asymmetric atom, and should be convertible into the potentially active 1-methylcyclohexeneacetic acid described by Marchwald and Meth, the optical activity of which is to be correlated with the presence of an asymmetric carbon atom. This conversion has not hitherto been described, and we have made a number of experiments in order to establish the conditions under which it occurs.

After heating 0.5 gram of racemic 1-methylcyclohexylidene-4-acetic acid with 10 c.c. of water and 2 grams of sodium hydroxide for five hours on the water-bath, or with 10 c.c. of aniline for three hours at 100°, the original acid can be recovered unchanged. Similarly, on boiling 1 gram of the sodium salt of the inactive acid with 2 grams of aniline hydrochloride and 20 c.c. of alcohol during two hours, the original acid is found to be unaltered. On boiling 0.5 gram of 1-methylcyclohexylidene-4-acetic acid with 20 c.c. of dilute sulphuric acid for three hours, 0.4 gram of the original acid was recovered unchanged, together with traces of Marchwald and Meth's 1-methylcyclohexene-4-acetic acid, melting at 41°. In another experiment,

0.5 gram of the inactive hexylidene acid melting at 64° was boiled for three hours with 10 c.c. of dilute sulphuric acid with the addition of sufficient alcohol for solution; on subsequent distillation with steam, a mixture of acid and ester was obtained, which, when hydrolysed, gave a mixture of the original acid with traces of the acid melting at 41° .

Acting on the indications thus obtained, 0.5 gram of racemic 1-methylcyclohexylidene-4-acetic acid was heated for three hours on the water-bath with a mixture of 4 grams of sulphuric acid, 1 gram of water, and 5 c.c. of alcohol; approximately equal quantities of acid and ester were isolated from the product. The acid consisted in the main of Marckwald and Meth's 1-methyl- Δ^3 -cyclohexene-4-acetic acid, melting at 41° , and the ester also yielded, on hydrolysis with alcoholic soda, a product consisting principally of the same acid.

A method is thus now available for the conversion of 1-methylcyclohexylidene-4-acetic acid into the isomeric 1-methyl- Δ^3 -cyclohexene-4-acetic acid. We are now studying this conversion, using the optically active hexylidene acids, together with several chemical changes of an additive character, as a result of which the enantiomorphous molecular configuration, containing no asymmetric atom, becomes converted into an enantiomorphous configuration of the well-known type which is associated with the presence of one or more asymmetric carbon atoms.

Our thanks are due to Dr. John Read for the care with which he has carried out much of the experimental work involved in the present paper.

CHEMICAL DEPARTMENT,
THE UNIVERSITY,
MANCHESTER.

THE CHEMICAL LABORATORY,
THE UNIVERSITY,
CAMBRIDGE.

THE UNIVERSITY,
GÖTTINGEN.