XLV.—*Optical Activation of Racemic Acid by l-Malic Acid.*

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WITH reference to the existence of optically active substances in nature, van't Hoff predicted the possibility of their formation "bei unsymmetrischen Versuchsbedingungen, bei Umwandlungen z.B. die durch die Wirkung des rechts-oder links-cirkularpolarisierten Lichtes stattfinden oder durch aktive Verbindungen veranlasst werden, vielleicht sogar in aktiven Lösungsmitteln" ("Die Lagerung der Atome im Raume," 2nd edition, 1894, p. 30). Those words are highly suggestive, and undoubtedly have been the incentive to much research.

Although asymmetric synthesis in Fischer's interpretation of the term was not experimentally realised with compounds of known constitution until 1904, it is more than probable that the idea may also have occurred independently to van't Hoff when he uses the phrase "durch aktive Verbindungen" in the above quotation. The one-sided manner in which nature builds up substances possessing molecular asymmetry has been imitated by Rosenthaler, for example when he synthesised *d*-mandelonitrile from benzaldehyde and hydrogen cyanide through the agency of one of the enzymes of emulsin. Whether in this case *d*-mandelonitrile was formed with the exclusion of the *l*-nitrile is an open question, but on the assumption that both nitriles were synthesised to different extents, the preponderance of the *d*-nitrile must certainly have been very great. Again, the recent work of Neuberg on carboligase renders it clear that combination between benzaldehyde and acetaldehyde to form an optically active ketol takes place in a very one-sided manner. As contrasted with such results achieved by enzyme action, the asymmetric syntheses accomplished by the aid of the directing influence of compounds of known constitution, for example, *l*-menthol, *l*-borneol, or *d*-amyl alcohol, lead only to a mixture of unequal amounts of the two enantiomorphous forms. Thus in the asymmetric synthesis of *l*-atrolactic acid from benzoylformic acid, where the activating agent is *l*-menthol:

the resulting acid had $[\alpha]_D - 9.5^\circ$ in ethyl-alcoholic solution
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(T., 1904, **85**, 1249), whereas the pure *l*-acid has $[\alpha]_D - 37.7^\circ$ in the same solvent (T., 1910, **97**, 1016). As a matter of fact, in no single case has an asymmetric synthesis been effected with compounds of known constitution where one enantiomorphous form alone has been synthesised.* Still such experiments give the definite proof that only asymmetry can beget asymmetry, and they afford a rational interpretation of the manner in which optical activity can be propagated in nature from one compound to another when once an optically active complex is available at the start. But on the genesis of optical activity in the living plant or animal this ontogenetic method throws no light whatsoever.

Van't Hoff's suggestion of the possibility of a medium like circularly-polarised light exerting a directing influence deals with the bigger problem, and it is interesting to recall that Pasteur himself was also alive to the fundamental importance of this question, for he provided himself with powerful electromagnets for the purpose of testing the influence of a strong magnetic field on an externally-compensated compound (*Revue scientifique*, 1884, [iii], 7, 3). His results were presumably negative, and there is no record of them. Boyd (*Inaug. Diss.*, Heidelberg, 1896) investigated two reactions in each of which a compound containing an asymmetric

* Recently Weiss (*Monatsh.*, 1919, **40**, 391) drew the conclusion that *l*-menthyl *d*-phenyl-*p*-tolylacetate is obtained apart from its diastereoisomeride by the interaction of phenyl-*p*-tolylketen and *l*-menthol :

McKenzie and Miss Widdows (T., 1915, **107**, 702) had previously shown, however, that this ester could not be saponified so as to give the optically pure *d*-acid after the removal of the menthol. Accordingly, when Weiss saponified his ester, he obtained the inactive acid. He is thus in error when he states that he accomplished an asymmetric synthesis, but he has proved the guiding influence of the menthol in its action on the keten, even although the liquid menthyl ester which he obtained may not have been quite homogeneous.

Much confusion would be avoided if the term "asymmetric synthesis" were always used in the restricted sense to which Fischer gave precision (*Ber.*, 1894, **27**, 3231; *Sitzungsber. K. Akad. Wiss. Berlin*, 1902, **28**, 597; *Ber.*, 1903, **36**, 2575. Compare Marckwald, *Ber.*, 1904, **37**, 349; McKenzie, T., 1904, **85**, 1249). In this connexion the misleading statement is made by Jaeger ("Lectures on the Principle of Symmetry," 1917, p. 290) that the first positive results on partial asymmetric synthesis were obtained by Marckwald and McKenzie in the fractional esterification of *r*-mandelic acid by *l*-menthol (*Ber.*, 1899, **32**, 2130). It must be emphasised, however, that the latter authors themselves do not regard this and subsequent work carried out by them on the fractional esterification and hydrolysis of stereoisomerides as examples of asymmetric synthesis at all, since at the very outset a compound is employed which already contains an asymmetric carbon atom.

carbon atom was synthesised in a strong magnetic field. However, neither the stilbene dibromide formed by adding bromine to stilbene nor the mandelic acid prepared by reducing benzoylformic acid with sodium amalgam exhibited any optical activity. According to J. Meyer (*Chem. Ztg.*, 1904, **28**, 41), no positive result could have been expected from Boyd's experiments, since in a homogeneous magnetic field there is a plane of symmetry perpendicular to the lines of force. Meyer accordingly polarised the light before submitting it to the influence of the magnetic field, but his experiments also failed. It may also be mentioned that one of the present authors carried out in 1895 some fruitless experiments on the action of circularly polarised light on aqueous solutions of silver *dl*-lactate and silver *dl*-mandelate. Again, Cotton (*Ann. Chim. Phys.*, 1896, [vii], **8**, 373) investigated the action of circularly polarised light on *dl*-Fehling's solution with negative results, so far as optical activation is concerned, but he made the noteworthy observation that the blue *d*- and *l*-Fehling's solutions possessed different coefficients of optical absorption for circularly polarised light of definite sign. This observation becomes of real importance if Byk (*Z. physikal. Chem.*, 1904, **49**, 641) is correct in his surmise that a constant source of asymmetric circularly polarised light is available on the earth's surface by the reflection of the plane-polarised rays of sunlight from the surface of the sea and the subsequent rotation of those reflected rays by the earth's magnetism. Finally, Henle and Haakh (*Ber.*, 1908, **41**, 4261) deal with the conversion of methylethylcyanoacetic acid into methylethylacetoneitrile, and of *s*-dichlorodimethylsuccinic acid into dichlorodimethylpropionic acid. Both reactions were induced by submitting the solutions in the presence of uranium salts to light which was either circularly polarised or was rotated by a magnetic field after having previously been polarised. The results were negative (compare Byk, *Ber.*, 1909, **42**, 141; Freundler, *Ber.*, 1909, **42**, 233).

The third suggestion made by van't Hoff in the lines quoted at the beginning of this paper deals with the possible influence of an optically active solvent as an activating medium, and attempts have been made in various directions to obtain experimental evidence in its favour. Thus Tolloczo (*Z. physikal. Chem.*, 1896, **20**, 412) distributed a racemic compound between two solvents (one of which was optically active) sparingly soluble in one another in order to find out if the compound, when recovered from both solvents, was optically active. *r*-Mandelic acid was distributed between ether and a concentrated aqueous solution of *d*-fructose, but no activity of the mandelic acid regenerated from each of those solvents was observed. Presumably, therefore, *d*-mandelic acid

has the same solubility as its *l*-isomeride in the solution of fructose employed. Similarly, racemic acid was not activated when it was distributed between water and lævorotatory amyl alcohol. Again, after van't Hoff had suggested to Goldschmidt that *d*- and *l*-isomerides might possess different solubilities in an optically active solvent, the solubility of *d*- and *l*-carvoximes in *d*-limonene was measured, when no difference in solubility of the oximes was noted (Goldschmidt and Cooper, *Z. physikal. Chem.*, 1898, **26**, 714). Further, Walden (*Ber.*, 1899, **32**, 1846) examined the displacement of chlorine in *r*-chlorosuccinic acid by the action of potassium hydroxide in the presence of lævorotatory amyl alcohol. The resulting malic acid was optically inactive. Kipping (*P.*, 1900, **16**, 226) prepared benzoin from potassium cyanide and benzaldehyde, a solution of camphor in alcohol being used as the solvent; pyruvic acid was also reduced to lactic acid with aqueous *d*-glucose as the solvent; in each case the products were inactive. Again, E. and O. Wedekind (*Ber.*, 1908, **41**, 456) combined benzylmethylaniline and allyl iodide in an optically active medium such as *l*-menthol or *d*-limonene, but the product in every case was the inactive quaternary iodide.

A positive result was obtained when potassium hydrogen racemate was crystallised from an aqueous solution of *l*-malic acid (T., 1915, **107**, 440). The resulting crystals were dextrorotatory, and consisted of potassium hydrogen racemate with a small admixture of potassium hydrogen *d*-tartrate. The study of this peculiar observation has now been resumed.

When *l*-malic acid was added to an aqueous solution of potassium racemate, the crystals which separated were dextrorotatory, and consisted essentially of potassium hydrogen racemate together with some potassium hydrogen *d*-tartrate (*loc. cit.*). The behaviour of *l*-malic acid towards sodium racemate has now been found to be similar.

Attempts were next made to find out if optical activation could be effected by acids other than *l*-malic acid. No fewer than fifteen other optically active acids were separately tested, and in every case the crystals which were deposited by the addition of the acid to an aqueous solution of potassium or sodium racemate consisted of the acid racemate. Accordingly, of the active acids examined, *l*-malic acid is exceptional in being the only one which caused activation. Racemic acid may possibly also be exceptional, although this point has not been examined in much detail. When *r*-mandelic acid (1 mol.), for example, was neutralised by aqueous sodium hydroxide, and *l*-malic acid ($\frac{1}{2}$ mol.) then added, the resulting crystals of sodium hydrogen mandelate exhibited no optical activity.

Similarly, *r*-dimethoxysuccinic acid could not be activated by *l*-malic acid.

The optical rotatory power of the dextrorotatory product from the action of *l*-malic acid on potassium racemate can be enhanced by neutralising with potassium hydroxide and then adding a fresh quantity of *l*-malic acid. After this treatment was repeated several times, the separated crystals were found to possess about double the activity of the initial deposit.

When sodium hydrogen racemate was crystallised from an aqueous solution of *l*-malic acid, it separated from the cold solution in admixture with sodium hydrogen *d*-tartrate. In a similar manner, both rubidium hydrogen racemate and caesium hydrogen racemate can be activated. On the other hand, when potassium hydrogen racemate was crystallised from an aqueous solution of *l*-mandelic acid, no optical activation was observed, and negative results were also obtained with four other active acids.

So far as the inquiry has gone, there is not sufficient evidence for the conclusion to be drawn that the partial activation of racemic acid by *l*-malic acid is actually due to a resolution of the acid. It is perhaps significant, however, that when an aqueous solution of sodium racemate was mixed with *l*-malic acid and then polarimetrically examined before crystallisation began and after crystallisation ceased, the *lævo*-value had intensified. If we have to deal with a partial resolution of racemic acid, the case is interesting as providing the first example of the partial resolution of an inactive acid by an active acid instead of by an active base or alcohol. On the other hand, those chemists who are prepared to agree with Erlenmeyer in his recent ingenious claims will find in the present paper several admirable examples of "asymmetric induction."

EXPERIMENTAL.

Addition of l-Malic Acid to Sodium Racemate.

An aqueous solution of 10 grams of racemic acid (1 mol.) was neutralised by sodium hydroxide, and 7.97 grams of *l*-malic acid (1 mol.) were added, the solution being made up to 100 c.c. Immediately after the preparation of this solution and before it had started to crystallise, it was polarimetrically examined at the ordinary temperature and found to be *lævorotatory*, giving $\alpha_D - 0.94^\circ$ ($l = 2$). This value remained constant after the solution had been heated on a boiling water-bath for fifteen minutes and the original volume then adjusted when the solution had cooled. The solution was concentrated by evaporation and, on cooling, glassy prisms (6.87 grams) gradually separated, the filtrate (33 c.c.) giving

$\alpha_D - 2.41^\circ$ ($l = 2$). The solid was dextrorotatory in aqueous solution:

$$l = 2, c = 5, \alpha_D + 0.19^\circ, [\alpha]_D + 1.9^\circ.$$

The air-dried solid on analysis gave $H_2O = 9.5$, whereas $C_4H_5O_6Na, H_2O$ requires $H_2O = 9.5$ per cent. The anhydrous salt gave $Na = 13.4$; calc. $Na = 13.4$ per cent.

In another experiment where 5 grams of racemic acid and 4.8 grams of *l*-malic acid were employed, the separated crystals (3.9 grams) were dissolved in water, and the solution (16 c.c.) was examined before crystallisation started, 15 c.c. of it giving $+0.69^\circ$ in a 2-dcm. tube.

Since the conclusion was drawn from those results and from others which need not be quoted that sodium hydrogen *d*-tartrate crystallises along with its racemic isomeride from solutions prepared in the manner described, it seemed possible that if the original lævorotatory solution obtained by the addition of *l*-malic acid to sodium racemate were allowed to crystallise, polarimetric examination of the liquid in contact with the separated crystals might exhibit an enhanced value in the lævo-direction. Accordingly, an aqueous solution (20 c.c.) of sodium racemate prepared by the neutralisation of 2 grams of racemic acid was quickly mixed with an aqueous solution (20 c.c.) of 1.6 grams of *l*-malic acid, and the resulting solution then polarimetrically examined; the value $\alpha_D - 0.47^\circ$ ($l = 2$) was noted. As crystallisation had started only slightly, the solution was evaporated to smaller bulk, and part of it examined before crystallisation started, giving $\alpha_D - 0.90^\circ$ ($l = 2$). On remaining over-night in the polarimeter tube, glassy crystals had separated, but the supernatant liquid was clear, so that polarimetric readings of it could be taken with ease; the lævorotation had perceptibly increased to $\alpha_D - 1.20^\circ$. After an additional three days this value had increased to $\alpha_D - 1.37^\circ$, which latter value was again observed a day later.

Activation of Alkali Hydrogen Racemates by Crystallisation from an Aqueous Solution of l-Malic Acid.

Sodium Hydrogen Racemate.—8.1 Grams of this salt were added to 32 c.c. of an aqueous solution containing 5.71 grams of *l*-malic acid. After heating on the water-bath for half an hour, the clear solution was cooled, and crystallisation started. The crystals were drained and washed with 10 c.c. of water. The air-dried product amounted to 6 grams, and the analysis conducted with a portion dried at $120-130^\circ$ gave $Na = 13.2$ (calc. 13.4) per cent. It was dextrorotatory; 2.5 grams of it were neutralised with sodium

hydroxide and the whole of the solution was examined in a 2-dcm. tube, when the value $\alpha_D + 0.37^\circ$ was observed. The numerical value of this dextrorotation was increased by the addition of boric acid. 1.57 Grams of the crystals were mixed with 1.5 grams of boric acid, and the aqueous solution of the mixture gave $\alpha_D + 0.77^\circ$ ($l = 2$).

Rubidium Hydrogen Racemate.—This salt was prepared by neutralising racemic acid with rubidium hydroxide and then adding the calculated amount of *N*-sulphuric acid to the hot solution; crystallisation of the acid salt started quickly on cooling. Rubidium hydrogen racemate (9.8 grams) was dissolved by boiling with 130 c.c. of an aqueous solution containing 5.6 grams of *l*-malic acid. The crystals which separated from the cold solution amounted to 7.9 grams, and an analysis of the air-dried salt gave $Rb = 36.6$ ($C_4H_5O_6Rb$ requires $Rb = 36.4$ per cent.). The aqueous solution prepared by neutralising 4 grams of this salt with rubidium carbonate gave $\alpha_D + 0.34^\circ$ when examined in a 2-dcm. tube.

In order to make certain that the activity noticed was actually caused by the agency of malic acid, rubidium hydrogen racemate was crystallised from boiling water, and the optical inactivity of the crystals which separated determined.

Cæsium Hydrogen Racemate.—Ten grams of this salt were heated with 100 c.c. of an aqueous solution containing 4.6 grams of *l*-malic acid. 4.8 Grams separated (Found: $Cs = 47.1$; calc., $Cs = 47.1$ per cent.). 3.5 Grams were added to water and neutralised by cæsium carbonate; when polarimetrically examined, the solution gave a distinct shadow in the dextro-direction, the value noted being $\alpha_D + 0.11^\circ$ ($l = 2$).

No optical activation of racemic acid was observed to have taken place when the following optically active acids were substituted for *l*-malic acid: *l*-lactic acid, *l*-mandelic acid, *l*-acetylmandelic acid, *d*-ethoxysuccinic acid, *d*-dimethoxysuccinic acid, *d*-dimethoxysuccinamic acid, *l*-phenylmethoxyacetic acid, *l*-tropic acid, *l*- β -hydroxy- β -phenylpropionic acid, *d*- β -hydroxy- β -phenylpropionic acid, *l*-quinic acid, *d*-camphoric acid, *l*-camphanic acid, *l*-asparagine, *l*-aspartic acid. The procedure was on the lines which gave positive results with *l*-malic acid, the active acid in each case being added to the aqueous solution of potassium or sodium racemate. The resulting crystals exhibited no distinct optical activity when examined in alkaline solution. Moreover, when potassium hydrogen racemate was dissolved in an aqueous solution of *l*-mandelic acid, the crystals which separated were optically inactive when examined in the usual way. A similar result was obtained when aqueous

solutions of *d*-camphoric acid, *l*-aspartic acid, *d*- β -hydroxy- β -phenyl-propionic acid, and *d*-dimethoxysuccinic acid were respectively employed as the solvent for the potassium hydrogen racemate.

Mandelic acid has the property of forming acid salts, for example, barium hydrogen *r*-mandelate (T., 1899, 75, 969). Potassium hydrogen *r*-mandelate can be easily prepared by neutralising mandelic acid by potassium hydroxide and adding to the aqueous solution an amount of mandelic acid equal to that neutralised. The acid salt separates from water in glassy prisms, and mandelic acid is obtained from its aqueous solution by extraction with ether. The acid sodium salt, prepared in a similar manner, separates from water in prisms grouped in rosettes. Mandelic acid, unlike racemic acid, undergoes no optical activation whatsoever when examined in its behaviour towards *l*-malic acid. The salt obtained by adding *l*-malic acid ($\frac{1}{2}$ mol.) to the solution of sodium mandelate prepared from mandelic acid (1 mol.) was found to be optically inactive in aqueous solution, and it gave *r*-mandelic acid on extraction with ether. Analysis of this salt gave Na = 6.9.

requires Na = 7.0 per cent.

Neither acid sodium mandelate nor acid potassium mandelate is activated by crystallisation from an aqueous solution of *l*-malic acid. The acid sodium mandelate obtained by the addition of the requisite quantity of *d*-tartaric acid to an aqueous solution of sodium *r*-mandelate was also devoid of optical activity.

Finally, in place of racemic acid, *r*-dimethoxysuccinic acid was taken. Barium *r*-dimethoxysuccinate (12 grams) was converted into the potassium salt, to the aqueous solution of which *l*-malic acid (4 grams) was added. 3.6 Grams of potassium hydrogen *r*-dimethoxysuccinate were isolated, and when this was neutralised no optical activity at all could be detected.

Addition of l-Malic Acid to Potassium Racemate.

16.8 Grams of racemic acid (1 mol.) were neutralised by aqueous potassium hydroxide, and the solution was made up to 840 c.c. To the warm solution *l*-malic acid (13.4 grams, 1 mol.) was added, and crystals soon began to separate from the clear solution. The crystals (17.7 grams) were neutralised by potassium hydroxide, and the solution (177 c.c.) was examined in a 2-dm. tube containing about 15 c.c. The value $\alpha_D + 0.30^\circ$ was observed. The potassium salt contained in this solution corresponded with 15.8 grams of racemic acid, and the solution after dilution was accordingly treated with 12.6 grams of *l*-malic acid (1 mol.). The resulting crystals were again neutralised, and after polarimetric examination of a

portion of the solution the whole of the latter was treated with a fresh quantity of malic acid. This process was repeated several times, with the results tabulated below. The volume relationships were comparable throughout; in the crystallisation of the sparingly soluble acid salts the concentration corresponded with 1 gram of racemic acid (hydrated) in 50 c.c. of solution, whilst for the polarimetric estimation the acid salts were neutralised by potassium hydroxide and the volume adjusted so that 1 gram of acid salt was contained in 10 c.c. of the neutral solution. The crystals in each case were weighed after having been dried at 100° for one hour.

In the following table, A = equivalent weight of racemic acid (hydrated), calculated from the weight of crystals; B = weight of malic acid (1 mol.); C = total volume; D = weight of crystals; E = rotation of crystals after neutralisation by potassium hydroxide, $c = 10$.

A.	B.	C.	D.	E.
15.8 grams	12.6 grams	790 c.c.	14.7 grams	$\alpha_D + 0.37^\circ$
13.13 "	10.47 "	656 "	12.52 "	0.54
11.18 "	8.92 "	559 "	9.96 "	0.62
8.9 "	7.1 "	445 "	7.62 "	0.68
6.81 "	5.43 "	340 "	5.97 "	0.66
5.34 "	4.26 "	267 "	4.68 "	0.60
4.18 "	3.34 "	209 "	3.41 "	0.60

The solution (34.1 c.c.) containing the final product (3.41 grams) was evaporated and the whole of it examined in a 2-dcm. tube, when the value $\alpha_D + 1.35^\circ$ was observed. This dextrorotation was intensified by the addition of boric acid to the solution.

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