Asymmetric Transformations in Salts of Phenylmalonamic and Phenylmalonanilic Acids. The Kinetics of Racemisation of Phenylmalonamic Acid

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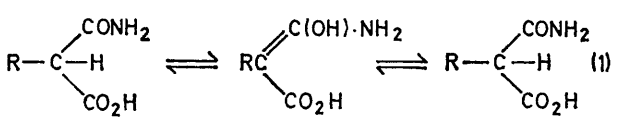
Phenylmalonamic acid may be obtained in active form by treatment with (−)-cinchonidine in ethanol, chloroform, or acetone, the latter solvent yielding acid with the highest activity $[\alpha]_D^{25}$ 45°. Cinchonine also gave optical activation but quinine and brucine did not. Phenylmalonanilic acid, was only obtained active in the form of its salt with cinchonidine. The kinetics of racemisation of phenylmalonamic acid are first order.

DURING attempts at their resolution the substituted malonamic acids were found to be optically labile in certain cases. Experiments were, thereupon, initiated with a view to studying the asymmetric transformations concerned.

It is clearly likely that the optical lability of these acids is due to a keto–enol change which involves the asymmetric carbon atom [process (1)]. In the presence



(1)

of an activating agent, such as an alkaloid, the reversion to the keto-form may be preferential, giving either only one diastereoisomer, or an excess of it. Alternatively since the two diastereoisomers formed on the addition of the activating agent will have different free energies, and therefore solubilities, crystallisation of the salt may result in the deposition of the least soluble diastereoisomer. The equilibrium in the solution would thus be momentarily, or notionally, disturbed as the process proceeds but would be restored to its normal value at the expense of the more soluble diastereoisomer, a process termed ' asymmetric transformation by crystallisation ' by Harris.[1]

Although there are numerous asymmetric transformations in which the optical lability is due to relaxation in the restriction of rotation about single bonds [1-3] the

[1] M. M. Harris, *Progr. Stereochem.*, 1958, **2**, 157.
[2] M. M. Jamison, *Trans. Faraday Soc.*, 1945, 696.
[3] E. E. Turner and M. M. Harris, *Quart. Rev.*, 1947, **1**, 299.

number of reported cases in which the optical lability results from the tautomeric process is much smaller.[4-7]

EXPERIMENTAL

Syntheses.—(i) Alkylmalonamic acids were prepared by the monoalkylation of ethyl cyanoacetate [8,9] followed by stepwise hydrolysis of the ester [10] and cyano-groups.[11]

(ii) Benzylmalonamic acid was obtained by the method of Baker and Lapworth.[12]

(iii) Phenylmalonamic acid was prepared by the ethoxycarbonylation of benzyl cyanide [13] followed by stepwise hydrolysis of the ester and cyano-groups.

(iv) Alkyl and phenylmalonanilic acids were prepared by the method of Redmon.[14]

Activation Experiments.—Equivalent quantities of the racemic acid and the alkaloid were used throughout. Polarimetric readings were taken on a Bellingham and Stanley polarimeter using a 1 dm tube with methanol as the solvent unless otherwise stated. The decomposition of the alkaloidal salts was effected by treatment with 4N-HCl; this resulted in the crystallisation of the free acid. The acid was then filtered off, thoroughly washed with water, and dried under vacuum. The yield was 60—80%.

Activation experiments with the first three alkylmalonamic acids (I; R = Pr^i, Bu^i, and Bu^n) using brucine, quinine, cinchonidine, and cinchonine, in solvents in which either the acid or the activating agent was soluble to some extent (*e.g.*, methanol, ethanol, acetone, chloroform, dioxan, and dimethyl sulphoxide) gave negative results. The salts with quinine, cinchonidine, and cinchonine were highly insoluble in the above mentioned solvents and were, therefore, deposited in nearly quantitative yields. When decomposed, these salts gave the original inactive acid. It was observed that the salt from any particular pair of acid and base crystallised from different solvents with nearly the same specific rotation (for example, the cinchonidine salt of butylmalonamic acid separated from acetone, chloroform, and acetone–ether solutions with $[\alpha]_D^{20}$ −76·0, −78·0, and −77·0° respectively).

On the other hand, the brucine salts of these acids were highly soluble in the above mentioned solvents. Complete removal of the solvent left an oil which solidified on the usual treatment and gave the original inactive acid on decomposition. The equivalent quantities of brucine (0·098 g) and any of these acids in acetone or chloroform (10 ml) showed a constant rotation of α −0·50 and −0·26° respectively. These rotations were found to be quite close to the rotations of the solutions of the same amount of brucine and an equivalent quantity of two similar but inactive acids, *i.e.* malonamic acid [α −0·53 (in acetone) and −0·26° (in chloroform)] and di-isopropylmalonamic acid [α −0·55 (in acetone) and −0·26° in (chloroform)]. Thus it was concluded that the solutions represent the partial racemate and that no optical activation was taking place.

Benzylmalonamic acid gave similar results.

Cinchonidinyl D-*phenylmalonamate.* (±)-Phenylmalonamic acid (2·25 g) and cinchonidine (3·65 g) were dissolved in acetone (125 ml). The solution was concentrated, under vacuum, to *ca.* 50 ml. Crystallisation of the salt was completed by the addition of water. The salt (5·8 g, 97%), m.p. 115—117°, $[\alpha]_D^{20}$ −58·0° (*c* 2), gave, on decomposition, the active *acid*, m.p. 121°, $[\alpha]_D^{20}$ +45·0° (*c* 2) (Found: C, 60·4; H, 5·1; N, 7·7. $C_9H_9O_3N$ requires C, 60·3; H, 5·1; N, 7·8%).

Similar experiments using ethanol (100 ml) or chloroform (200 ml) and acetone (25 ml) yield salts with $[\alpha]_D^{20}$ −78·0 and −66·0° respectively, which on decomposition yielded acid with m.p. 120—121°, $[\alpha]_D^{20}$ +5·0 and +32·0° (*c* 2), respectively.

Cinchoninyl L-*phenylmalonamate.* The racemic phenylmalonamic acid (3·2 g) was suspended in ethyl acetate (200 ml) and dimethyl sulphoxide was added dropwise till a clear solution was obtained; to this solution was added cinchonine (5·2 g). The salt separated in the form of thick jelly (7·5 g, 90%) (dried), $[\alpha]_D^{20}$ +110·0° (*c* 2). This salt gave *acid*, m.p. 120—121°, $[\alpha]_D^{20}$ −32·5° (*c* 2), on decomposition (Found: C, 60·3; H, 5·0; N, 7·7%).

Similar experiments using cinchonine and the (±)-acid in dioxan (200 ml) or chloroform (100 ml) (containing the alkaloid) and acetone (100 ml) (containing the acid) gave on decomposition acids with $[\alpha]_D^{20}$ −28·5 and −15·0° respectively.

Quininyl (±)-*phenylmalonamate.* To a solution of quinine (3·2 g) in chloroform (20 ml) [or acetone (50 ml) or 1 : 1 ethanol–water (50 ml)] was added (±)-phenylmalonamic acid (1·8 g) which on standing gave crystals of the salt (*ca.* 90%) in each case, $[\alpha]_D^{20}$ −122·5° (*c* 2). Decomposition of the salt gave the original inactive acid, m.p. 122—123°.

Activation Experiments on Phenylmalonanilic Acid.—(i) *Using quinine.* A solution of quinine (4·6 g) in chloroform (200 ml) [or acetone (150 ml)] was treated with the racemic acid (2·6 g). The solutions did not yield any solid and therefore the salt was precipitated by the addition of ligroin (b.p. 40—60°). It had $[\alpha]_D^{20}$ −127·0° (*c* 2) and gave in each case the inactive acid, m.p. 125°, on decomposition.

(ii) *Using cinchonine.* A solution of the (±)-acid (5·1 g) in ethyl acetate (300 ml) [or acetone (200 ml) or dioxan (150 ml)] and dimethyl sulphoxide (20 ml) was treated with cinchonine (5·9 g). Addition of ligroin (b.p. 40—60°) caused the separation of an oil which solidified on scratching (90—100%) with constant rotations of $[\alpha]_D^{20}$ +160 (in methane) and +76·0° (in acetone). On decomposition it gave the original inactive acid, m.p. 126°.

(iii) *Using cinchonidine.* (a) The racemic acid (2·6 g) and cinchonidine (3·0 g) were dissolved separately in acetone (50 ml) and chloroform (50 ml) respectively. The two solutions were mixed and ligroin (b.p. 40—60°) added which gave 4·9 g (99%) of the salt, $[\alpha]_D^{20}$ −76° (*c* 2). The use of acetone as the solvent gave similar results. The salts obtained in either case gave on decomposition the original inactive acid, m.p. 126°.

(b) A solution of the racemic acid (2·6 g) in acetone (25 ml) was treated with cinchonidine (3·0 g). The solution was immediately chilled in a dry ice–acetone bath, decomposed with cold aqueous 2N-HCl, and extracted with cold chloroform. The organic layer was separated and a portion of it

[4] H. Leuchs and J. Wutke, *Ber.*, 1913, **46**, 2460.
[5] H. Leuchs, *Ber.*, 1921, **54**, 830.
[6] W. C. Ashley and R. L. Shriner, *J. Amer. Chem. Soc.*, 1932, 4410.
[7] E. M. Davidson and E. E. Turner, *J. Chem. Soc.*, 1945, 843.
[8] J. C. Hessler, *Amer. Chem. J.*, 1899, **22**, 169.
[9] J. Kenner and E. Witham, *J. Chem. Soc.*, 1921, **119**, 1452.
[10] J. C. Hessler and W. F. Henderson, *J. Amer. Chem. Soc.*, 1921, 627.
[11] E. Testa, *Il Farmaco*, 1962, **17**, 168.
[12] W. Baker and A. Lapworth, *J. Chem. Soc.*, 1924, 2333.
[13] J. C. Hessler, *Amer. Chem. J.*, 1904, **32**, 119.
[14] B. C. Redmon, U.S.P. 2,782,231 (*Chem. Abs.*, 1957, **51**, 10,571).

was quickly filtered through dried $CaCl_2$ into a polarimeter tube. This solution showed an initial rotation, α of $+0.05°$ which gradually disappeared. The remaining chloroform solution was evaporated under vacuum to give inactive phenylmalonanilic acid, m.p. 126° (Found: C, 70·5; H, 5·1; N, 5·6. Calc. for $C_{15}H_{13}O_3N$: C, 70·6; H, 5·1; N, 5·5%).

Kinetic Experiments. Racemisation of Active Phenylmalonamic Acid.—General procedure. Active phenylmalonamic acid (0·20 g) was directly weighed in a graduated flask (10 ml) which was then left in a thermostatted bath maintained at the desired temperature. The solvent, previously brought to the same temperature, was introduced into the flask. The solution was immediately filtered into a jacketted polarimeter tube (1 dm), the temperature of which was maintained by circulating water by a Shandon Circhotherm pump. The readings were taken as soon as the temperature gradient had been eliminated. They were continued until the rotation was very small. A final observation was made to check that the rotation had reached zero. The solution under examination was then evaporated under vacuum and the original inactive acid recovered (confirmed by i.r. spectroscopy and mixed m.p.). The study was repeated as various temperatures.

Results.—The racemisation obeyed first-order kinetics so that the rate constant k was obtained from the slope of the log plot of α_t/t and the Arrhenius parameters from the slope of the straight line plot of log k against T^{-1} following the simplified form [15] of the absolute rate equation.[16] The rate constants and the corresponding half-life periods are given in Table 1 and the Arrhenius and transition state parameters are shown in Table 2.

TABLE 1

The racemisation of active phenylmalonamic acid

Solvent	Temp (°C)	k/min^{-1}	$t_{\frac{1}{2}}$/min
Methanol	20·0	$9·24 \times 10^{-4}$	765
	30·0	$3·43 \times 10^{-3}$	200
	37·4	$8·36 \times 10^{-3}$	83
1% Pyridine (in methanol)	20·0	$9·69 \times 10^{-2}$	7
1% Aniline (in methanol)	20·0	$8·75 \times 10^{-2}$	8

TABLE 2

The Arrhenius and transition state parameters for the racemisation of active phenylmalonamic acid in methanol

E_A = 23·3 kcal mol^{-1}
log A = 14·3 s^{-1}
ΔS^* = −3·3 cal mol^{-1} K^{-1}
ΔH^* = 22·6 kcal mol^{-1}
ΔG^* = 23·6 kcal mol^{-1}

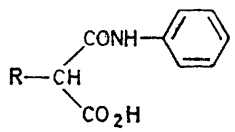
The (+)- and (−)-forms of the acid gave identical values of the rate constants and therefore of the Arrhenius and transition state parameters

DISCUSSION

The failure of alkylmalonamic acids to undergo asymmetric transformations may be attributed to the inductive or electron-releasing effect of the alkyl group resulting in a slight negative charge on the central carbon atom which prevents the mobility of the α-hydrogen atom.

If the relative stabilities of alkylmalonamic acids are due to the $+I$ effect of the alkyl groups then the replacement of these by phenyl or benzyl groups could result in compounds in which asymmetric transformations take place. It was observed that while the benzylmalonamic acid gave results similar to those obtained with the alkylmalonamic acids, phenylmalonamic acid underwent ' asymmetric transformation by crystallisation ' when the cinchonidinyl D-phenylmalonamate and cinchoninyl L-phenylmalonamate crystallised out of various solvents with varying optical rotations, in nearly quantitative yields. The active forms of phenylmalonamic acid with highest specific rotations, +45·0 and −32·5° (methanol), were obtained from the decomposition of the salts, obtained from acetone and ethyl acetate–dimethyl sulphoxide solutions, respectively.

The study was extended to alkylmalonanilic acids (II; R = Me and Et) in order to link this work with that of Davidson and Turner on benzylmalonanilic acid.[7]



(II)

A mixture of equivalent quantities of these acids with brucine, quinine, cinchonidine, and cinchonine did not exhibit any mutarotation in acetone, methanol, and chloroform solutions. The alkaloidal salts formed by these acids were found to be highly soluble in the various solvents tried. Ligroin (b.p. 40—60°) was, therefore, used to precipitate the salts. They gave back the original inactive acid on decomposition. It was therefore again concluded that these acids are not undergoing asymmetric transformations (see, however, below). The effect of the *N*-phenyl group on the optical lability in the phenylmalonamic acid and the rather difficult later work on phenylmalonanilic acid (II; R = Ph) help to elucidate the situation. Phenylmalonanilic acid with cinchonidine, cinchonine, and quinine gave results similar to those obtained with the alkylmalonanilic acids and no asymmetric transformation by crystallisation was detected. It did, however, show a sign of activation when the experiments were conducted in solution. During these experiments, the racemic acid was treated with cinchonidine in acetone. The solution was chilled, decomposed with cold aqueous HCl, and finally extracted with ice cold chloroform. The chloroform extract was quickly filtered through dried $CaCl_2$ into a polarimeter tube (1 dm). This solution showed an initial rotation α +0·05° which gradually disappeared. The observation of this fleeting optical activity indicated that the placement of a phenyl group on the nitrogen atom of (I) (which is already labile) has made it optically unstable to such an extent that it looses optical activity as soon as it is removed from combination with the activating agent. In the case of alkylmalonanilic acids, the

[15] D. M. Hall and M. M. Harris, *J. Chem. Soc.*, 1960, 490.
[16] S. Glasstone, K. J. Laidler, and H. Eyring, ' The Theory of Rate Processes,' McGraw-Hill, New York, 1941.

introduction of an *N*-phenyl group failed to yield an asymmetric transformation perhaps because although the *N*-phenyl group is contributing towards the optical instability of these acids, its effect is at too great a distance from the asymmetric carbon atom. Thus Davidson and Turner's benzylmalonanilic acid was an intermediate case where the effect was neither too strong nor too weak.

Kinetic Studies.—Active phenylmalonamic acid showed a tendency to racemise in solution, in water, even at room temperature. The racemisation was therefore followed kinetically in methanol at three different temperatures (Tables 1 and 2). In the presence of traces of alkali racemisation was instantaneous. The effect of added organic bases on the rate of racemisation was studied by following the rates in methanol containing 1% (v/v) pyridine or aniline. Table 1 reveals that in the presence of these bases the rate of racemisation is accelerated by about a hundred times with a corresponding reduction in the half-life. The observation that the rate constants are nearly the same in aniline and pyridine solutions is in line with the pK_b values (9·38 and 8·96 respectively) of these bases.

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