## 54. *The Optical Activation of Acids, and a New Resolution Process depending on it.*

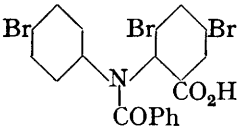
By Margaret M. Jamison and E. E. Turner.

In a previous paper (J., 1938, 1646) it was shown that the equilibrium in a non-hydroxylic solvent between the diastereoisomeric salts, base–*d*-acid and base–*l*-acid, of an optically active, optically stable base with an optically unstable acid is disturbed by adding an excess of the free acid. A technique was outlined for the detection, by means of "addition curves," of potential optical activity, even of a highly unstable kind. The evidence for the validity of the method has now been further analysed by the examination of acids of moderate optical stability, since this permits of the construction of curves showing both initial readings and final readings. Thus (Fig. 1), an acid of very low optical stability might give an addition curve *ABC*, whereas with an acid of moderate optical stability an initial curve *ADE* could *also* be constructed. In this way, effects other than those due to asymmetric transformation can be assessed.

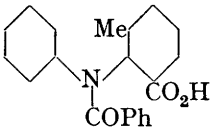
It has been shown that excess of acid, which always increases the *rate* of asymmetric transformation, may either accentuate or reverse a change occurring when base and acid are present in equivalent amounts. In the second case a method becomes available for the isolation, for the first time, of both dextro- and lævo-rotatory samples of an acid without the use of more than one resolving agent or the intermediate separation of a *solid* salt.

In a previous communication (*loc. cit.*) we outlined a new method for the examination of acids of low optical stability, one essential part of the method being to determine the optical rotation of a solution of a stable active base in presence of increasing quantities of the acid under investigation. The results were expressed by means of "addition curves," and in two instances deductions drawn from such curves led to the proof that at low temperatures the acids possessed measurable optical activity. On the other hand, although this afforded a satisfactory test of the general implication of the curves, the latter were incomplete, since information regarding the *initial* rotations for equilibrating solutions of different acid : base ratios was lacking.

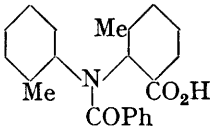
Of the acids studied, only 4 : 6 : 4′-tribromo-*N*-benzoyldiphenylamine-2-carboxylic acid (I) possessed sufficient optical stability for mutarotation due to activation to be observable at the ordinary temperature. With this acid and nor-*d*-$\psi$-ephedrine in chloro-



(I.)



(II.)



(III.)

form solution, activation was detectable even before the acid : base ratio 1 : 1 had been reached, and thereafter the extent of activation steadily increased. Two addition curves were thus obtained: the "initial" curve of type *ADE* (Fig. 1), representing rotations taken as soon as possible after mixing, and the "final" curve of type *ABC*, showing rotations after mutarotation had become complete. It is evident, therefore, that in the case of an optically very unstable acid the corresponding *ADE* curve could not be realised, since the mutarotational changes represented by *DB*, *EC*, and so on may be

almost instantaneous. Without the curve *ADE* as standard (*i.e.*, to include all extraneous effects of solvent, etc.) the value of the final curve *ABC* as a criterion of potential optical activity is materially lessened (except within a series of closely related acids; compare Jamison and Turner, *loc. cit.*). On the other hand, the acid : base ratio at which activation begins may vary from one example to another, *ABF* and *ABC* representing another possible pair of initial (but not realisable) and final (observable) addition curves. In order to obtain

FIG. 1.

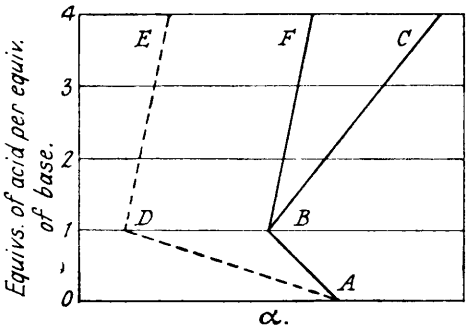
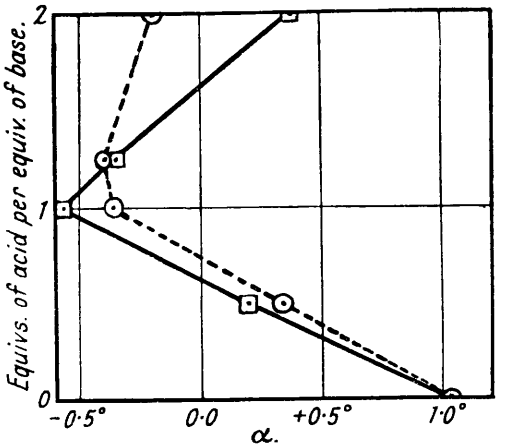


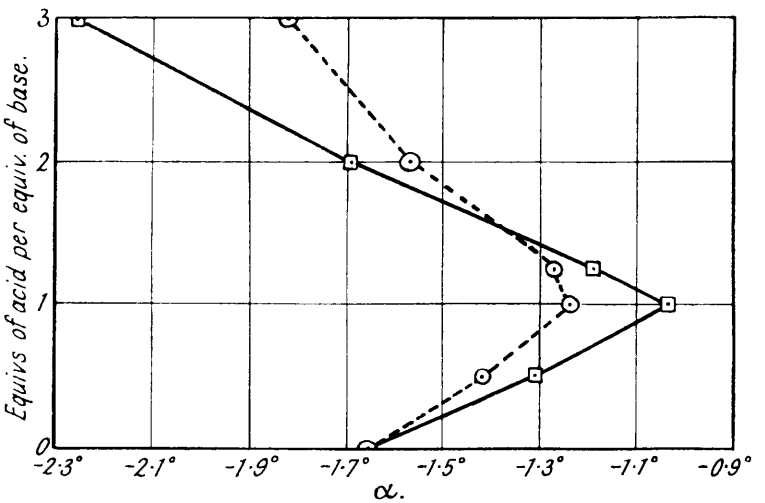

FIG. 2.




more information about these different types, it was essential to study a larger selection of acid–base pairs, and in particular it was important, in order to realise initial curves, to use acids, solution of which could be made up very quickly. The tribromo-acid had the disadvantage of dissolving slowly and to only a small extent in the solvent employed.

The first new acid synthesised for the purpose of this investigation was N-*benzoyl*-6-*methyldiphenylamine*-2-*carboxylic acid* (II). With nor-*d*-$\psi$-ephedrine in chloroform

FIG. 3.



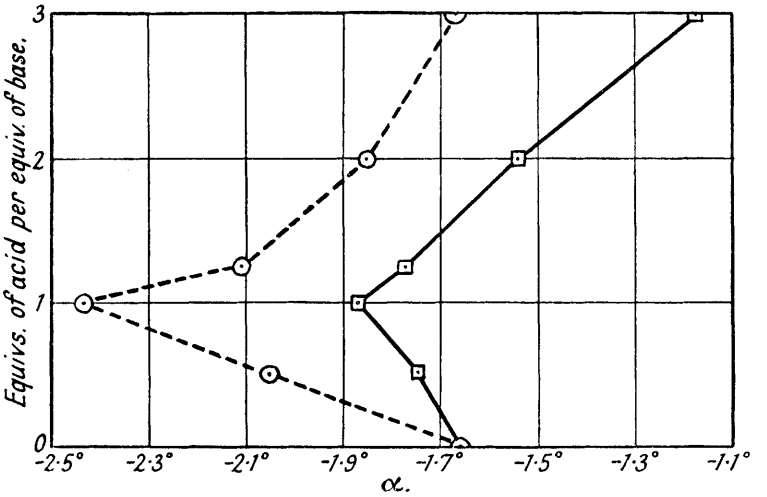

solution, mutarotation occurred when the acid : base ratio was 0·5 : 1, the rotation becoming less positive. At the ratio 1 : 1 the amount of change increased; at 1·25 : 1 it was relatively small, and at 2 : 1 extensive mutarotation occurred in the opposite sense, the positive rotation of the solution *increasing* (Fig. 2 *). A similar result was obtained with cinchoni-

* Addition curves 2—10 give $\alpha$ for $l = 2$ and $\lambda = 5461$. Initial rotations are shown by broken lines, and final by full lines.

dine (Fig. 3), the solvent ($X$) in this case being chloroform to which 1/40th of its volume of ethyl alcohol had been added: this mixture was found to be a better solvent than pure chloroform for all the acids used. The value for each rotation at the time of mixing acid and base in solution was obtained by following the mutarotation against time ($t$), and extrapolating to $t = 0$ the straight-line plot of log $(\alpha_t - \alpha_\infty)$ against $t$, this procedure being essential with rapidly mutarotating solutions.

From this result it appeared that a new and unexpected phenomenon had been observed, for in the case of both alkaloids the equilibrium, base–*d*-acid $\rightleftharpoons$ base–*l*-acid, had apparently been displaced in one direction at low acid : base ratios and in the other direction at high acid : base ratios. The mutarotational changes were, however, rather rapid, and it became desirable to seek a more optically stable acid with which a similar reversal of sign of mutarotation occurred.

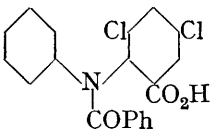
FIG. 4.

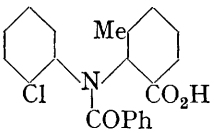



N-*Benzoyl*-2 : 6′-*dimethyldiphenylamine*-2′-*carboxylic acid* (III) was distinctly more stable optically than the 6-methyl acid (II), but was unsuitable in that it solvated with extreme readiness, particularly with water and hydroxylic compounds in general. Moreover, although with cinchonidine in solvent $X$, mutarotation occurred at all the acid : base ratios selected, it was greatest at 1 : 1, decreased up to 2 : 1, and then increased again at 3 : 1 (Fig. 4). Here, therefore, the change base–*l*-acid $\longrightarrow$ base–*d*-acid is quicker than the reverse change. Proof that each equilibrated solution contained excess of (combined or free) *d*-acid was obtained by removing the cinchonidine by rapid extraction with mineral acid. In each case, a chloroform solution was left with a *d*-rotation which rapidly diminished to zero.

The next acid examined was 4 : 6-*dichloro*-N-*benzoyldiphenylamine*-2-*carboxylic acid* (IV). This was considerably more soluble than the tribromo-acid (I) and was almost equally stable optically. With nor-*d*-$\psi$-ephedrine in chloroform it gave an addition curve

(IV.)



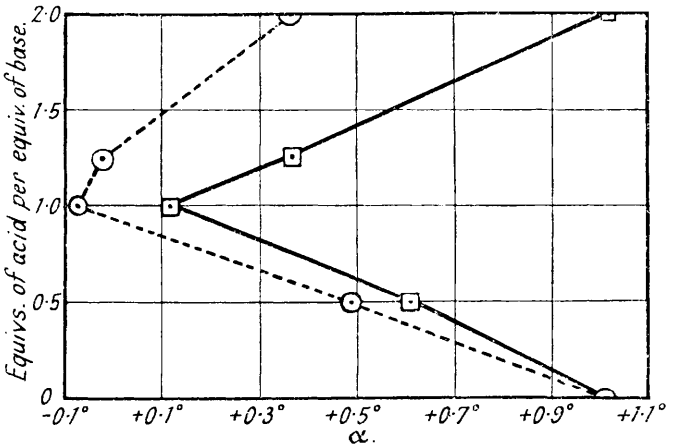

(V.)

(Fig. 5) strongly resembling that for the tribromo-acid and the same base. Activation began at quite small acid : base ratios and steadily increased in extent with further addition of acid. With cinchonidine and the dichloro-acid in solvent $X$ an effect similar to that found with the methyl acid (II) was observed (Fig. 6). At acid : base ratios 0·5 : 1, 1 : 1, and 1·25 : 1, dextromutarotation occurred, that at 1 : 1 being the most extensive, whilst at ratios 2 : 1 and 3 : 1 lævomutarotation occurred and was particularly marked at the 3 : 1

ratio. Extraction with mineral acid of the equilibrated solutions showed that at the 1 : 1 ratio *d*-acid, and at the 3 : 1 ratio *l*-acid, was present (free or combined) in excess.

The dichloro-acid was optically sufficiently stable to make it possible to determine the rate of racemisation of the *d*- and the *l*-acid, each of these being obtainable from the appropriate equilibrated solution. This was evaporated at a low temperature, and the

FIG. 5.




residual glass dissolved in pyridine at −20°. Addition of the solution to dilute mineral acid at −5° precipitated the free acid, which, although largely racemic, was active enough for rate measurements. The racemisation of the *d*- and the *l*-acid at 15° in solvent *X* gave $k = 0{\cdot}15 \pm 0{\cdot}02$ (min.$^{-1}$; $\log_{10}$).*

FIG. 6.

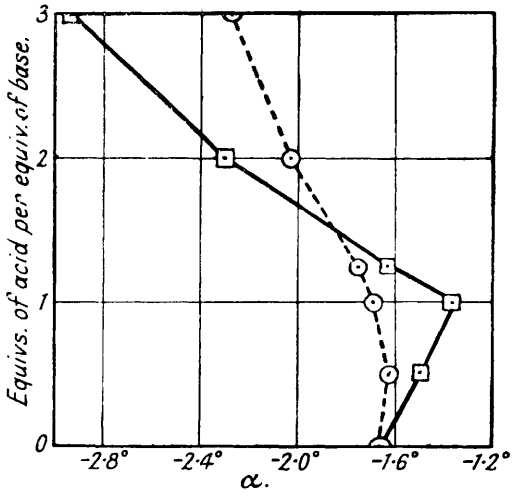
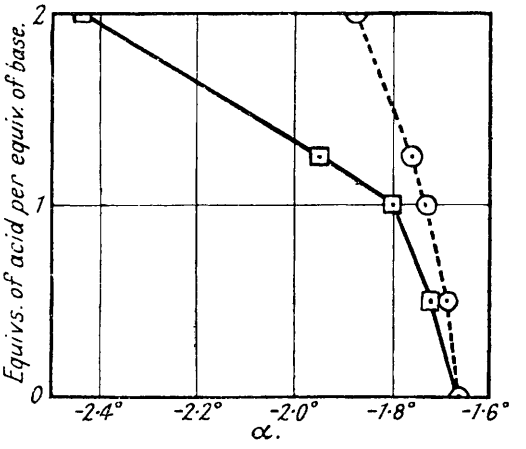



FIG. 7.




For comparison purposes the amount of activation for each stage of the addition of the tribromo-acid (I) to cinchonidine has been determined by the extrapolation method. Fig. 7 gives the results and shows that the amount of activation increases rapidly with increase in the acid : base ratio.

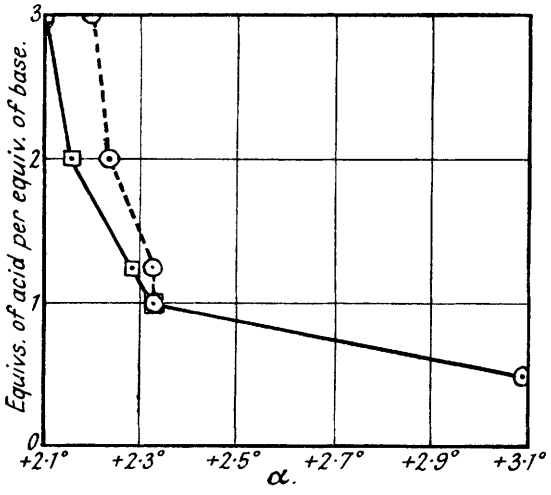
* These units are used throughout, unless otherwise stated, both in this and in the previous paper (*loc. cit.*).

The rates of equilibration for mixtures of the dichloro-acid (IV) and cinchonidine in solvent *X* gave the following mean results :

| Ratio of acid : base ..... | 1 : 1 | 2 : 1 | 3 : 1 |
|---|---|---|---|
| *k* ..... | 0·04 | 0·05 | 0·10 |

Here the mutarotation at 1 : 1 is towards the more positive, and that at 2 : 1 and 3 : 1 is towards the more negative, but the measured rate constant steadily increases.

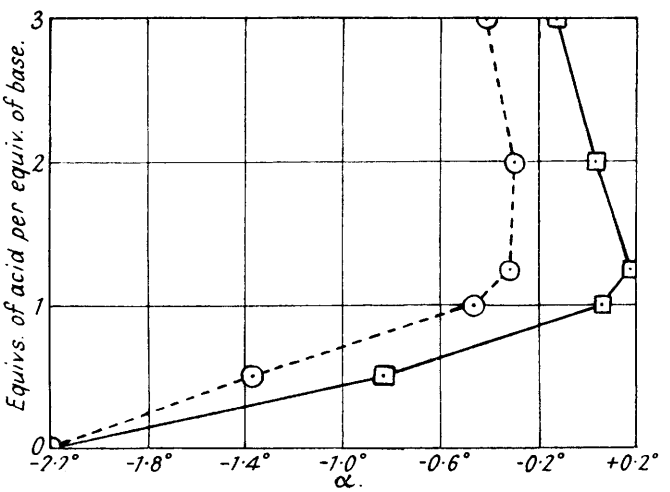
FIG. 8.




The last acid of the diphenylamine series to be investigated was 2-*chloro*-N-*benzoyl*-6'-*methyldiphenylamine*-2'-*carboxylic acid* (V). This proved to be excellent experimental material, since it was readily soluble, had little, if any, tendency to solvate, and had moderate optical stability. It was obtained in two crystalline forms, prisms and needle-clusters, both melting at 197—198°. In presence of acetone and light petroleum the prisms gradually grew at the expense of the needles, the latter entirely disappearing within a few weeks. Both forms invariably separated side by side, the needles predominating at first. The possibility was considered that the two forms might be two racemic stereoisomerides, such as are possible when two regions of restricted rotation are present in the same molecule. Examination in solvents in presence of active bases convinced us that this possibility had not been realised.

Addition curves have been worked out for the chloro-methyl acid (V) in solvent *X* with three different alkaloids. All these curves exhibit points of interest.

FIG. 9.




With cinchonine (Fig. 8) no mutarotation could be detected at the acid : base ratios 0·5 : 1 or 1 : 1. At higher ratios slight activation occurred, and increased with the proportion of acid. It is evident, of course, that the magnitude of an activation effect depends on a number of factors, including the absolute rotations of the individual components of the

system concerned, and a small rotational change in one case may be as significant as a large one in another.

With brucine and acid (V) (Fig. 9) there was considerable mutarotation at the 0·5 : 1 acid : base ratio and it increased at the 1 : 1 ratio. With higher proportions of acid it decreased, but remained of the same rotational sign, indicating that base–*d*-acid was more stable than base–*l*-acid. From this it should follow (van 't Hoff–Dimroth rule) that in solvent *X* and in related solvents, base–*l*-acid should be less soluble than base–*d*-acid, provided that solvation did not complicate matters. On addition of ether to an alcoholic solution of equivalent quantities of brucine and the *dl*-acid, second-order asymmetric transformation set in, and almost the whole of the salt in solution slowly crystallised out as the pure *brucine* l-*salt*, the specific rotation of which was found by the extrapolation method to be $[\alpha]^{20°}_{5461}$ — 383° in solvent *X*. It proved impossible entirely to remove the brucine from this salt by the usual pyridine method, but by pouring the solution of the salt in cold formic acid into cold dilute mineral acid and repeating this process twice, the partially racemised l-*acid* was obtained. For the racemisation of the acid in solvent *X* at 20°, *k* was found to be 0·068.

FIG. 10.

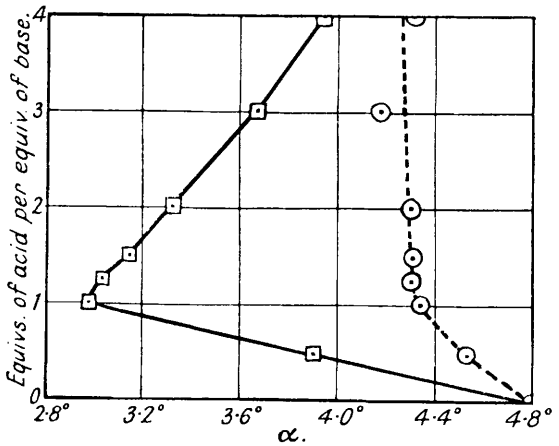
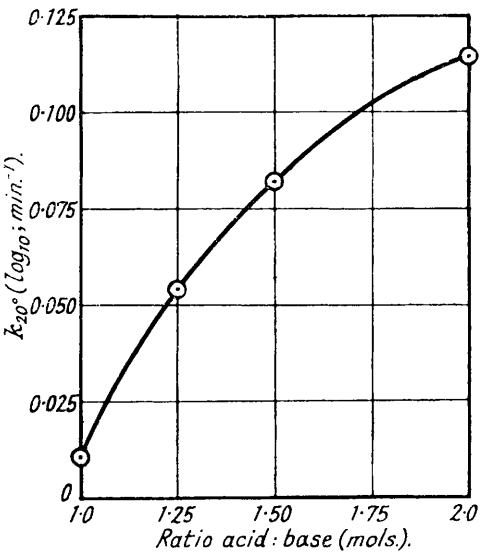



FIG. 11.




It was clear from the addition curves that neither the cinchonine nor the brucine mixtures with acid (V) were suitable for a kinetic study of the effect of varying the acid : base ratio on the speed of activation. It was found, however, that quinidine in solvent *X* provided a very satisfactory series of changes, the examination of which gave the following results :

For the addition experiments, 0·1620 g. of quinidine was used together with the appropriate amount of acid dissolved in 20 c.c. of solvent *X*. Readings are for 20·0°, $l = 2$, and $\lambda = 5461$.

| Acid : base ratio ... | 0 : 1 | 0·5 : 1 | 1 : 1 | 1·25 : 1 | 1·5 : 1 | 2 : 1 | 3 : 1 | 4 : 1 | ∞ : 1 |
|---|---|---|---|---|---|---|---|---|---|
| Initial α ..... | 4·80° | 4·53° | 4·35° | 4·31° | 4·31° | 4·30° | 4·23° | 4·31° | — |
| Final α ..... | — | 3·90° | 2·99° | 3·04° | 3·15° | 3·32° | 3·67° | 3·94° | — |
| Change in α ..... | — | 0·63° | 1·36° | 1·27° | 1·16° | 0·98° | 0·56° | 0·37° | — |
| *k* ..... | — | — | 0·0106 | 0·054 | 0·082 | 0·115 | — | — | 0·068 |

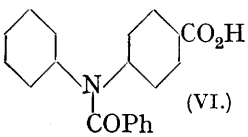
The addition results are shown in Fig. 10, and attention is directed to the almost " ideal " curve for initial rotations. This is probably due to the small solvating tendency of this particular acid.

These results are of great interest, for they show that as regards extent of activation the effect is greatest when the acid : base ratio is 1 : 1, but that the speed of activation increases as the proportion of acid is increased, as it does in every case so far examined. The combined results of the rate measurements are shown in Fig. 11. The most striking feature of

the results is that, although in our previous work (*loc. cit.*) it appeared probable that the fastest process in an equilibration would be less fast than the racemisation of the free acid, the equilibration of the chloro-methyl acid–quinidine mixtures is already faster than the acid racemisation at the acid : base ratio 1·5 : 1.

In order to obtain further information on this matter, we have determined the rate of racemisation of the chloro-methyl acid in solvent *X* in presence of (*a*) 0·5 mol. of quinoline, (*b*) 1 mol. of quinoline, and (*c*) 1 mol. of papaverine (this being selected as an optically inactive base approximating more to the type of active base used in the experiments). The values found for $k_{20°}$ were (*a*) 0·202, (*b*) 0·264, and (*c*) 0·168, so that in each case the rate constant is far greater than that for the free acid.

Nevertheless, it is known that sometimes the salt of a stably active base with an active acid is more easily racemised (or equilibrated) than the corresponding metallic salt. For instance, the sodium salt of 4-oximino*cyclo*hexanecarboxylic acid is optically more stable in solution than the quinine salt (Mills and Bain, J., 1910, **97**, 1866); the ammonium salt of *cyclo*hexanone-4-carboxylic acid benzoylphenylhydrazone is more stable than the quinine salt (*idem*, J., 1914, **105**, 64); and whereas the brucine salt of *N*-benzenesulphonyl-8-nitro-1-naphthylglycine has a half-life period of about 5 mins., the free acid has a half-life period of 16—17 mins. under similar conditions (Mills and Elliott, J., 1928, 1291). It would seem probable from space considerations that the salt of any of our diphenylamine acids with a bulky alkaloid molecule must have greater restriction of rotation than the free acid, but evidently the converse must be true in some cases, and the investigation of this point should throw light on the nature of such salts in solution.



(VI.)

The mechanism of the accelerative effect, on activation, of excess of free acid is still obscure. It is possible that the addition of excess of acid merely provides more molecules with which base–*d*-acid and base–*l*-acid can collide. Reactions of the type

$$\text{Base–}d\text{-acid} + l\text{-acid} \rightleftharpoons \text{base–}l\text{-acid} + d\text{-acid}$$

can also play a part, but the fact that all our changes are of the first order must be borne in mind. On the simple collision view, addition to a 1 : 1 mixture of chloro-methyl acid and quinidine of 1 mol. of an inactivable acid, *e.g.*, *N*-benzoyldiphenylamine-4-carboxylic acid (VI), should increase the rate of equilibration, and this we actually found to be the case, the velocity constants being (solvent *X*; 20°) :

| | |
|---|---|
| 1 mol. Quinidine + 1 mol. chloro-methyl acid ..... | $k = 0·0106$ |
| 1 mol. Quinidine + 1 mol. chloro-methyl acid + 1 mol. acid. (VI) ..... | $k = 0·084$ |

The extent of the activation is necessarily decreased, owing to the competition of the chloro-methyl acid and acid (VI) (chosen because of its similarity to the chloro-methyl acid in general properties) for the quinidine.

This pair of experiments also established another point. Since the initial rotations in the two experiments are the same, a reaction between the quinidine chloro-methyl acid salts and the second acid cannot be at all rapid. It is conceivable, though not probable, that if 1 mol. of an active base were added to a solution containing 2 mols. of an activable acid, the base might combine selectively with one form of the latter at the outset. It was found, however, that a solution containing 2 mols. of the chloro-methyl acid and 1 mol. of quinidine had the same initial rotation whether it was made by mixing 2 mols. of acid with one of base, or by adding 1 mol. of acid to a solution which had immediately beforehand been made to contain 1 mol. each of base and acid. The velocity constants of the two subsequent activation processes were respectively $k_{20°}$ 0·115 and 0·116.

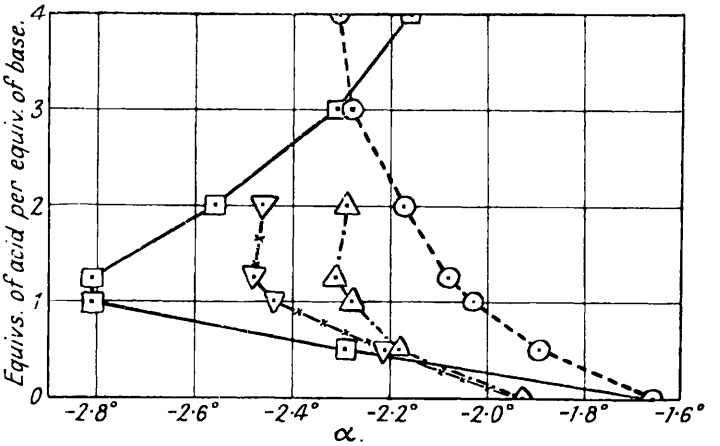
Hitherto, activation has been studied by the addition-curve method only with derivatives of *N*-benzoyldiphenylaminecarboxylic acids. We have now applied the method to the investigation of *N*-benzenesulphonyl-8-nitro-1-naphthylglycine (Mills and Elliott, *loc. cit.*). An interesting discovery was made during the preparation of the brucine *d*- and *l*-salts of this acid, for in addition to these salts, which were formed exactly as described by Mills and Elliott, the brucine *dl*-salt was obtained by cooling a warm solution in methyl

alcohol of equivalent proportions of brucine and the acid. For work with alkaloids other than brucine, we required one of the free active acids, which had not previously been prepared: the *l*-acid was therefore made from the brucine *l*-salt by the cold pyridine decomposition method.

The addition curve for the *dl*-acid and brucine in chloroform showed that mutarotational effects were relatively small, but with cinchonidine a number of observations of some interest were made. It was found in the first place that the rotation of the cinchonidine salt in " AnalaR " chloroform varied from sample to sample of the latter, and this was shown to be due to the presence of variable traces of alcohol in the chloroform. The acid was sparingly soluble in chloroform, but became readily soluble in presence of a little alcohol, *e.g.*, in solvent *X*. Mutarotation of the 1 : 1 mixture of the acid and cinchonidine in pure chloroform was so pronounced that it was of great interest to determine the equilibrium composition. This was done by determining the initial (extrapolation method) and final rotations of the two mixtures: (*a*) 1 mol. each of *dl*-acid and cinchonidine and (*b*) 1 mol. each of *l*-acid and cinchonidine. The initial and final specific rotations for salt in (*a*) were respectively $[\alpha]^{16°}_{5461}$ — 35·5° and — 87·3°, and in (*b*) — 255·5° and — 87·3°. From

FIG. 12.

O *and* □ *Solvent* X. Δ *Initial*; ∇ *final* EtOH.




these figures, negligible dissociation and strict additivity of rotations being assumed, it was calculated that the equilibrium was

Cinchonidine *d*-salt (38%) ⇌ Cinchonidine *l*-salt (62%)

Although these percentages cannot be more than approximate, it seems clear that the difference in free energy between the two salts is considerably greater than that between the two cinchonidine salts, previously investigated, of the tribromo-acid (I), for in this case the equilibrium composition under similar conditions was: cinchonidine *d*-salt, 49%; cinchonidine *l*-salt, 51% (Jamison and Turner, *loc. cit.*).

Although the Mills–Elliott acid was much more soluble in solvent *X* than in pure chloroform, mutarotation was less extensive in *X*. On the other hand, it was possible to study the effect on the extent of mutarotation, in *X*, of varying the acid : base ratio. The results are given in Fig. 12, which shows that activation produces a more negative rotation at the ratios 0·5 : 1, 1 : 1, 1·25 : 1, and 2 : 1, the extent of mutarotation being greatest at about 1 : 1. At 2 : 1 it is smaller, and at 3 : 1 it is almost zero, whilst at 4 : 1 mutarotation occurs, but produces a more positive rotation than that of the original 4 : 1 mixture. Extraction of the equilibrated solutions with mineral acid gave solutions of acid which, from the 1 : 1 and 2 : 1 mixtures, were *l*-rotatory; from the 4 : 1 mixture a *d*-rotatory solution of acid was obtained, whereas the acid from the 3 : 1 mixture was inactive.

It is intended later to deal with the effect of solvent on some typical activation equilibria.

As stated in our previous paper, it is probable that activation will be more pronounced in non-hydroxylic solvents. At present, we merely record some observations made with the Mills–Elliott acid in absolute ethyl alcohol. The results are given in Fig. 12, from which it is seen that activation does occur in alcohol, but to a very much smaller extent than in solvent *X*.

The present investigation has added considerably to our factual knowledge of activation phenomena. Attention may be directed to some aspects of activation of an acid of low optical stability in chloroform solution in presence of an optically stable, optically active base : (1) In some instances, increase in the acid : base ratio may at a certain point be accompanied by the disappearance of activation which was pronounced at lower acid : base ratios. At still higher ratios, activation will then usually reappear, but the accompanying mutarotation will be in the opposite sense to that observed at the lower acid : base ratios. (2) Sometimes the extent of activation is appreciable at the 0·5 : 1 ratio, attains a maximum at the 1 : 1 ratio, and thereafter remains almost constant. (3) In every example studied, increase in the acid : base ratio from 1 : 1 to 2 : 1 or 3 : 1 is accompanied by increase in the *speed* of activation, even when the initial and final curves intersect, as in Fig. 4. It must further be noted that all the mutarotational changes involved are kinetically of the first order.

Considerable interest attaches to the significance of the point of intersection of an initial and a final curve. Since it has been shown that addition of a base to excess of a *dl*-acid gives initially equal amounts of base–*d*-acid and base–*l*-acid, then, if activation depends solely on the change in the relative proportions of these two salts, the point of intersection must represent conditions under which the latter remain in equilibrium in equivalent quantities. On the other hand, the point of intersection usually is reached as a result of the diminution in an effect which attained its maximum extent at the 1 : 1 acid : base ratio. The diminution would then appear to be due to the beginning, at the 1 : 1 stage, of a new process which owes its inception and continuance to the presence of an excess of acid. If this were so, the point of intersection would represent a solution in which, as a result of the relative rates of the two changes

$$\text{Base–}d\text{-acid} \rightleftharpoons \text{base–}l\text{-acid} \quad \text{and} \quad \text{free } d\text{-acid} \rightleftharpoons \text{free } l\text{-acid}$$

optical compensation was brought about, so that, although on making up the initial mixture corresponding to this point no mutarotation was observable, this would be due to the mutual cancellation of the rotational changes occasioned by the two processes cited. The available facts do not allow us to analyse addition curves more precisely at present.

## Experimental.

The following syntheses were effected by the general method described by Jamison and Turner (J., 1937, 1954).

*Preparation of* N-*Benzoyl*-6-*methyldiphenylamine*-2-*carboxylic Acid*.—(*a*) *Phenylbenzimino*-2-*carbomethoxy*-6-*methylphenyl ether* crystallised from methyl alcohol in angular plates, m. p. 93° (Found : C, 76·4; H, 5·6. $C_{22}H_{19}O_3N$ requires C, 76·6; H, 5·5%).

(*b*) *Methyl* N-*benzoyl*-6-*methyldiphenylamine*-2-*carboxylate*. The above ether underwent isomerisation readily when heated at 260° and a 92% yield of ester was obtained. The *ester* crystallised from alcohol in prisms, m. p. 106—107° (Found : C, 77·2; H, 5·8. $C_{22}H_{19}O_3N$ requires C, 76·6; H, 5·5%).

(*c*) N-*Benzoyl*-6-*methyldiphenylamine*-2-*carboxylic acid* crystallised from alcohol in rectangular plates, and from acetone–light petroleum (b. p. 60—80°) in needles, m. p. 195—196° (with previous softening) (Found : C, 75·2; H, 5·3. $C_{21}H_{17}O_3N$ requires C, 76·1; H, 5·1%).

*Preparation of* N-*Benzoyl*-2 : 6′-*dimethyldiphenylamine*-2′-*carboxylic Acid*.—(*a*) N-o-*Tolyl*-*benzimino*-2′-*carbomethoxy*-6-*methylphenyl ether*. The iminochloride obtained from benz-*o*-toluidide and phosphorus pentachloride was condensed with the sodium derivative of methyl *o*-cresotate. The *ether* was crystallised from methyl alcohol and then from light petroleum (b. p. 60—80°). It formed prisms, m. p. 96—97° (yield, 60%) (Found : C, 76·7; H, 5·8. $C_{23}H_{21}O_3N$ requires C, 76·85; H, 5·9%).

(*b*) *Methyl* N-*benzoyl*-2 : 6′-*dimethyldiphenylamine*-2′-*carboxylate*. The above ether under-

went intramolecular change at 290°. The *methyl* ester formed prisms, m. p. 145°, from methyl alcohol (Found : C, 76·9; H, 5·8. $C_{23}H_{21}O_3N$ requires C, 76·85; H, 5·9%).

(*c*) N-*Benzoyl*-2 : 6′-*dimethyldiphenylamine*-2′-*carboxylic acid*. This acid solvates with extreme readiness. When crystallised from ethyl alcohol and air-dried, it contained 1 EtOH (3·5917 G. lost 0·4198 g. EtOH at 100°. Calc. for 1 EtOH : 0·4225 g.). After being dried over phosphoric oxide in a vacuum it gradually became free from solvent and had m. p. 184° (with previous softening) (Found : C, 75·7; H, 5·5. $C_{22}H_{19}O_3N$ requires C, 76·5; H, 5·5%).

*Preparation of* 4 : 6-*Dichloro*-N-*benzoyldiphenylamine*-2-*carboxylic Acid*.—(*a*) N-*Phenylbenzimino*-4 : 6-*dichloro*-2-*carbomethoxyphenyl ether*. The general method was modified in that the methyl dichlorosalicylate, being sparingly soluble, was added as a suspension in ethyl alcohol to the sodium ethoxide solution immediately before adding the ethereal solution of benzanilideiminochloride. The *ether* separated from alcohol in thick square plates, m. p. 112—113° (yield, 84%) (Found : Cl, 17·6. $C_{21}H_{15}O_3NCl_2$ requires Cl, 17·7%).

(*b*) *Methyl* 4 : 6-*dichloro*-N-*benzoyldiphenylamine*-2-*carboxylate*. The above ether underwent isomerisation with great ease, the change beginning at 220°. The *methyl* ester crystallised from ethyl alcohol in rhombohedra, m. p. 117—119° (yield, 89%) (Found : Cl, 17·6. $C_{21}H_{15}O_3NCl_2$ requires Cl, 17·7%).

(*c*) 4 : 6-*Dichloro*-N-*benzoyldiphenylamine*-2-*carboxylic acid* separated from alcohol in small prisms, m. p. 214—215° (with previous softening) and then from acetone–light petroleum (b. p. 40—60°) in prisms, m. p. 216—217° (with softening from 209°) (Found : Cl, 18·1. $C_{20}H_{13}O_3NCl_2$ requires Cl, 18·4%).

*Preparation of a specimen of the preceding acid containing excess of the* d-*form*. 0·7720 G. of the acid (1 mol.) and 0·5880 g. of cinchonidine (1 mol.) were dissolved in 20 c.c. of chloroform. After equilibration had been completed (2 hours), the solution was rapidly evaporated in a vacuum : no crystalline material separated during the evaporation. The glassy residue was dissolved in pyridine at −20°, and the solution poured into dilute hydrochloric acid containing ice. The precipitated acid was washed with water and dried in a vacuum, and 0·1470 g. was dissolved in solvent *X* (20 c.c.), whereupon the observed rotation ($l = 2$; $\lambda = 5461$) fell from +0·30° to zero. The racemisation was followed at 15° and the mean velocity constant, *k*, from two determinations was 0·15 ± 0·02.

*Preparation of a Specimen of* 4 : 6-*Dichloro*-N-*benzoyldiphenylamine*-2-*carboxylic Acid containing the* l-*Form in Excess*.—0·7720 G. (3 mols.) of the acid and 0·1960 g. (1 mol.) of cinchonidine were dissolved in 20 c.c. of chloroform, the solution left for one hour to equilibrate, and then evaporated to dryness in a vacuum without crystallisation intervening. The residue was decomposed with pyridine as described under the *d*-acid. 0·47 G. of the acid so prepared was dissolved in 20 c.c. of solvent *X*, whereupon the observed rotation at 15° rose from −0·25° to zero ($l = 2$). The mean velocity constant, *k*, for the racemisation was 0·15 ± 0·02.

*Measurement of the Velocity Constants for the Equilibration of* 4 : 6-*Dichloro*-N-*benzoyldiphenylamine*-2-*carboxylic Acid and Cinchonidine in Solvent* X *at Different Acid : Base Ratios*.—*Acid : base ratio* 1 : 1. Temp., 15°. 0·1930 G. of the *dl*-acid was dissolved to 20 c.c. in solvent *X*, and 0·1470 g. of cinchonidine added. Readings were begun within 2 mins. of mixing. Three different experiments gave the following results ($l = 2$; $\lambda = 5461$) :

| Observed change in α. | *k*. | |
|---|---|---|
| −1·65° to −1·36° | 0·041 | Mean 0·04 |
| −1·63° to −1·36° | 0·038 | |
| −1·64° to −1·36° | 0·036 | |

*Acid : base ratio* 2 : 1. Temp. 15°; $l = 2$. 0·1470 G. of cinchonidine was added to 0·3860 g. of the *dl*-acid dissolved to 20 c.c. in solvent *X*; *k* found, 0·05. The accuracy of this determination is smaller than that above, since the observable change in rotation is small, *i.e.*, from −2·03° to −2·31°, for the faster mutarotation.

*Acid : base ratio* 3 : 1. Temp., 15°; $l = 2$. 0·1470 G. of cinchonidine was added to 0·5790 g. of the *dl*-acid dissolved to 20 c.c. in solvent *X*. The results of two different determinations of *k* were :

| Observed change in α. | *k*. |
|---|---|
| −2·51° to −2·94° | 0·10 |
| −2·57° to −2·94° | 0·09 |

*Preparation of* 2-*Chloro*-N-*benzoyl*-6′-*methyldiphenylamine*-2′-*carboxylic Acid*.—(*a*) o-*Chlorophenylbenzimino*-2′-*carbomethoxy*-6′-*methylphenyl ether* crystallised from methyl alcohol in prisms,

m. p. 85—86° (yield, 75%) (Found : C, 69·4; H, 4·75. $C_{22}H_{18}O_3NCl$ requires C, 69·55; H, 4·8%).

The benz-*o*-chloroanilide required for this synthesis was prepared as follows : A mixture of 127 g. (1 mol.) of *o*-chloroaniline, 249 g. (1·1 mol.) of benzoic anhydride, and 300 c.c. of dioxan was boiled for ½ hour and then poured into a large bulk of dilute ammonia. The yield of crude benz-*o*-chloroanilide was 94%, and after crystallisation from alcohol was 82%.

(*b*) *Methyl 2-chloro-*N*-benzoyl-6′-methyldiphenylamine-2′-carboxylate* was obtained in 88% yield by heating the above ether at 260—270°. It crystallised from methyl alcohol in prisms, m. p. 168—169° (Found : C, 69·4; H, 4·75. $C_{22}H_{18}O_3NCl$ requires C, 69·55; H, 4·8%).

(*c*) *2-Chloro-*N*-benzoyl-6′-methyldiphenylamine-2′-carboxylic acid.* The purification of this acid in the usual manner by acidifying its solution in dilute sodium hydrogen carbonate was tedious owing to the sparing solubility of the sodium salt. When the *acid* was crystallised from acetone–light petroleum (b. p. 40—60°), it separated in two forms as described on p. 268. Both forms had m. p. 197—198°, with slight previous softening, but the m. p. varied with the rate of heating (Prisms. Found : C, 68·9; H, 4·35; Cl, 9·7. Needles. Found : C, 68·6; H, 4·5; Cl, 9·7. $C_{21}H_{16}O_3NCl$ requires C, 68·9; H, 4·4; Cl, 9·7%).

*Preparation of Brucine* l-2-*Chloro-*N*-benzoyl-6′-methyldiphenylamine-2′-carboxylate.*—To a solution of 4·3 g. of brucine dihydrate and 3·66 g. (1 mol.) of the *dl*-acid in 60 c.c. of absolute ethyl alcohol were added 250 c.c. of ether. After crystallisation had set in, a further 100 c.c. of ether were added, and after about 2 hours another 250 c.c. The microcrystalline salt was dried in a vacuum and weighed 6·65 g. (Found : C, 69·6; H, 5·8. $C_{44}H_{42}O_7N_3Cl$ requires C, 69·5; H, 5·6%). In solvent *X* 1 minute after wetting it had $[\alpha]_{5461}^{20°}$ — 346·2° (*c* = 0·983). The extrapolated value for *t* = 0 was $[\alpha]_{5461}^{20°}$ — 383°. A solution of the brucine salt (0·2000 g. in 20 c.c. of solvent *X*) at 20° mutarotated from — 6·49° to + 0·03°, the velocity constant for the mutarotation being 0·038.

*Preparation of* l-2-*Chloro-*N*-benzoyl-6′-methyldiphenylamine-2′-carboxylic Acid.*—The brucine salt was added with shaking to 20 parts of anhydrous formic acid at 0°. The solution was at once poured into excess of dilute hydrochloric acid and ice. The precipitated acid was quickly dried on a porous tile and submitted twice again to the above processes. It was finally dried in a vacuum.

*Racemisation in solvent* X *at* 20°. (*a*) The solution used contained 0·1666 g. of acid in 20 c.c. of solvent *X*. The first reading (*l* = 2) was made 2 minutes after wetting with solvent, and readings changed from —6·01° to zero; *k* = 0·069.

(*b*) The solution used contained 0·1150 g. of a different sample of acid in 20 c.c. Readings were begun 2 minutes after wetting with solvent, and changed from —3·94° to zero; *k* = 0·066.

*Quantitative Experiments on the Activation of 2-Chloro-*N*-benzoyl-6′-methyldiphenylamine-2′-carboxylic Acid in Solvent* X *in Presence of Quinidine at* 20°.—*Acid : base ratio* 1 : 1. (*a*) 0·1829 G. of acid was dissolved to 20 c.c. of solution and 0·1620 g. of quinidine added. Readings were begun 3·0 minutes after wetting and fell from +4·24° to + 2·99°. All readings given are the mean of three, taken at (*t* —0·5), *t*, and (*t* +0·5) minutes.

| Time after 3·5 mins. | $\alpha_t$. | $k \times 10^4$. | Time after 3·5 mins. | $\alpha_t$. | $k \times 10^4$. | Time after 3·5 mins. | $\alpha_t$. | $k \times 10^4$. |
|---|---|---|---|---|---|---|---|---|
| 0·0 | +1·23° | — | 17·0 | 0·81 | 107 | 47·0 | 0·37 | 111 |
| 4·0 | 1·11 | 112 | 21·0 | 0·74 | 105 | 52·0 | 0·33 | 110 |
| 7·0 | 1·03 | 110 | 26·0 | 0·65 | 106 | 58·0 | 0·29 | 108 |
| 10·0 | 0·96 | 108 | 32·0 | 0·55 | 109 | 64·0 | 0·26 | 105 |
| 14·0 | 0·87 | 107 | 42·0 | 0·44 | 106 | 70·0 | 0·22 | 107 |

whence mean *k* = 0·0107.

(*b*) Repetition of (*a*). Readings fell from +4·22° to +2·98° according to the unimolecular law; *k* = 0·0104 (limits, 0·0100 and 0·0107).

*Acid : base ratio* 1·25 : 1. (*a*) 0·2286 G. of acid and 0·1620 g. of quinidine in 20 c.c. of solution. Readings (*l* = 2) fell from +4·09° to +3·03°; *k* = 0·054 (limits 0·052 and 0·056).

(*b*) Repetition of (*a*). Rotation fell from +4·07° to +3·04°; *k* = 0·053 (limits, 0·051 and 0·058).

*Acid : base ratio* 1·5 : 1. (*a*) 0·2744 G. of acid and 0·1620 g. of quinidine in 20 c.c. of solution. Readings (*l* = 2) fell from +4·01° to +3·17°; *k* = 0·080 (limits, 0·076 and 0·082).

(*b*) Repetition of (*a*). Readings fell from +4·02° to +3·13°; *k* = 0·0845 (limits, 0·081 and 0·092).

*Acid : base ratio* 2 : 1. (*a*) 0·3657 G. of acid and 0·1620 g. of quinidine in 20 c.c. of solution. Readings (*l* = 2) fell from +3·91° to +3·32°; *k* = 0·110 (limits, 0·094 and 0·121).

(*b*) 0·9143 G. of acid in 50 c.c. of solvent. Added 0·3240 g. of quinidine; $l = 4$; $k = 0{\cdot}116$ (limits, 0·100 and 0·131).

(*c*) Repetition of (*b*); $k = 0{\cdot}115$ (limits, 0·105 and 0·134).

(*d*) As (*a*), but 1 mol. of acid mixed with 1 mol. of quinidine and the second mol. of acid added rapidly. Readings ($l = 2$) fell from +3·87° to +3·32°; $k = 0{\cdot}116$.

*Rate of Racemisation of* 1-2-*Chloro*-N-*benzoyl*-6′-*methyldiphenylamine*-2′-*carboxylic Acid in Presence of Quinoline* (*Solvent* X). *Temperature*, 20°.—*Acid* : *quinoline ratio* 1 : 1. To a solution of 0·0669 g. of quinoline in 20 c.c. of solvent *X* was added 0·1896 g. of the *l*-acid. Readings changed from −2·78° to zero; $k = 0{\cdot}264$.

*Acid* : *quinoline ratio* 2 : 1. To a solution of 0·0309 g. of quinoline in 20 c.c. of solvent *X* was added 0·1752 g. of *l*-acid. Readings changed from −2·76° to zero; $k = 0{\cdot}204$. Repetition of this experiment gave $k$ 0·199.

*Rate of Racemisation of the Papaverine Salt of* 1-2-*Chloro*-N-*benzoyl*-6′-*methyldiphenylamine*-2′-*carboxylic Acid*.—To a solution of 0·1545 g. of papaverine in 20 c.c. of solvent *X* was added 0·1666 g. of the *l*-acid. Readings ($l = 2$) changed from −2·64° to zero; $k$, 0·168.

*Rate of Equilibration of* 2-*Chloro*-N-*benzoyl*-6′-*methyldiphenylamine*-2-*carboxylic Acid* (1 *Mol.*) *and Quinidine* (1 *Mol.*) *in Presence of* N-*Benzoyldiphenylamine*-4-*carboxylic Acid* (1 *Mol.*). *Temperature* 20°.—0·1829 G. of the former acid was dissolved to 20 c.c. in solvent *X*. 0·1620 G. of quinidine was added, and rapidly thereafter 0·1585 g. of the second acid. Readings ($l = 2$) fell from +4·19° to +3·70°; $k = 0{\cdot}084$.

*Preparation of* N-*Benzenesulphonyl*-8-*nitro*-1-*naphthylglycine*.—The acid was prepared by the method described by Mills and Elliott (*loc. cit.*), but was crystallised, not from acetic acid, traces of which were tenaciously retained by the crystalline product, but from diluted methyl alcohol, blood-charcoal being used for the preliminary decolorisation. The prisms so obtained contained solvent and were therefore dissolved in chloroform, anhydrous sodium sulphate added, and the filtered solution treated with light petroleum (b. p. 40—60°). The very finely divided pure acid so obtained was suitable for making up solutions quickly.

*Resolution of* N-*Benzenesulphonyl*-8-*nitro*-1-*naphthylglycine*.—The formation of the brucine *l*-salt and its transformation into the *d*-salt took place exactly as described by Mills and Elliott. When, however, a warm solution of 4·30 g. of brucine dihydrate and 3·86 g. (1 mol.) of the *dl*-acid in 300 c.c. of absolute methyl alcohol was left, 6·3 g. of brucine *dl*-salt separated as clusters of soft needles, entirely different in appearance from the brucine-*d*-salt. Decomposition of the new salt gave an optically inactive acid.

The *l*-acid, which Mills and Elliott did not isolate, was obtained by dissolving the brucine *l*-salt in pyridine at −20° and pouring the solution into dilute hydrochloric acid and ice. The precipitate was collected, washed with dilute hydrochloric acid and water, and dried in a vacuum over magnesium perchlorate.

*Cinchonidine salts*. A crystalline salt of the acid with cinchonidine could not be obtained, and the salt was therefore prepared in solution as required.

(1) *dl*-Salt. A mixture of 0·1921 g. of *dl*-acid and 0·1463 g. of cinchonidine was dissolved to 20 c.c. in pure chloroform at 15°. Mutarotation followed the unimolecular law, and the straight-line plot of log of $\alpha_\infty - \alpha_t$ against time, when extrapolated to " zero " time, gave $\alpha^{15°}_{5461} - 1{\cdot}20°$, whence $[\alpha]^{15°}_{5461} - 35{\cdot}5°$. The final equilibrium rotation was $[\alpha]^{15°}_{5461} - 87{\cdot}3°$ ($l = 2$).

(2) *l*-Salt. A mixture of 0·1899 g. of *l*-acid and 0·1445 g. of cinchonidine under similar conditions gave initial $[\alpha]^{15°}_{5461} - 255{\cdot}5°$ and equilibrium $[\alpha]^{15°}_{5461} - 87{\cdot}3°$.

*Addition Curves : General Procedure*.—The acid to be used was dissolved to 20 c.c. in the solvent, and the base then added. The weight of base used was constant throughout one set of experiments. The following notes indicate the weight of base used in particular experiments. Figs. 2 and 5 refer to " AnalaR " chloroform as solvent. In all other cases solvent *X* was used. Initial readings were obtained by the extrapolation method for Figs. 3, 6, 7, 8, 9, and 12. The data for Fig. 10 were mainly obtained from rate determinations. For Figs. 2, 4, and 5 readings were taken, respectively, within 1·6, 2·0, and 1·6 mins. of adding base to acid.

Figs. 2 and 5. 0·1402 G. of nor-*d*-*ψ*-ephedrine.

Figs. 3, 4, 6, and 7. 0·1470 G. of cinchonidine.

Fig. 8. 0·1470 G. of cinchonine.

Fig. 9. 0·1970 G. of brucine (anhydrous).

Fig. 10. 0·1620 G. of quinidine.

Fig. 12. For both curves: cinchonidine, 0·1470 g. For ethyl alcohol curve, the first readings were made within 4 minutes of mixing.

All addition curve readings refer to $l = 2$ and the Hg line 5461.

*Errata.*—In Fig. 5 in our previous paper, curves I, II, III, and IV refer, respectively, to cinchonine, quinidine, nor-*d*-$\psi$-ephedrine, and $\psi$-ephedrine. Page 1649, line 14: for 0·5 g. read 0·1 g.

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